Immunology

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Immune reactions in serum and the middle-ear system play roles in the etiology, pathogenesis, and prevention of otitis media. The middle-ear mucosa has a secretory immune system similar to that of other areas of the respiratory tract but possesses few lymphocytes or organized lymphoid tissue (see Chapter 2, Figure 4). Immunologically active antigen interacts with immunocompetent cells in the lamina propria to produce a local immune response. The middle-ear effusion that results from acute or chronic infection or environmental antigens contains the major classes of immunoglobulins (Igs), complement, cells, immune complexes of antigen and antibody, and various chemical mediators of inflammation (Table 1). The immune

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<td>Leucyl aminopeptidase</td>
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response in the serum and middle ear to various antigens may prevent subsequent infection, assist in clearing the middle-ear effusion, or contribute to the accumulation and persistence of fluid in the middle-ear cavity. Although the middle ear is capable of local antibody production, the majority of evidence suggests that antibody detected in the middle-ear space comes primarily from the systemic circulation. Tissue factors, oxidative and hydrolytic enzymes, adherence to epithelial cells, and cytokines and inflammation are discussed in Chapter 3.

The immunology and host defenses of the middle ear are still relatively new areas of investigation. Many important questions remain unanswered. On the basis of results of placebo studies, 20% of acute otitis media (AOM) owing to Streptococcus pneumoniae and 50% owing to nontypeable Haemophilus influenzae resolve clinically and microbiologically without the use of antimicrobial drugs. Although no placebo studies are available with Moraxella catarrhalis as the pathogen, a spontaneous clearance rate (up to 75%) may be assumed on the basis of the efficacy of amoxicillin, a β-lactamase-susceptible penicillin, for infection caused by β-lactamase-producing organisms. Which host defense mechanism is responsible for ridding the middle ear of bacterial pathogens? What are the roles of specific antibody and complement? Are the bacteria opsonized, phagocyted by neutrophils, and killed intracellularly? The introduction of the conjugate pneumococcal vaccine sheds some light on the immunology of otitis media, but a lack of correlation of serotype-specific serum antibody with serotype-specific protection raises more questions about the immune defenses of the middle ear system. The interested reader is referred to Bernstein and colleagues for a contemporary review of topics about immunology and immunologic diseases of the ear.

METHODOLOGY IN STUDIES OF IMMUNE REACTIONS IN THE MIDDLE EAR

Immunologic studies of otitis media in the human are based on assays of serum, middle-ear effusion (obtained by needle aspiration through the tympanic membrane), and middle-ear mucosa (obtained by biopsy). Problems in methodology and limitations of data from human materials must be considered in evaluating the results of these studies:

1. Middle-ear effusion or mucosa is most readily obtained at operation. Therefore, most reports include patients with chronic disease who required an operative procedure. Only a few reports of materials obtained from patients with AOM are available.

2. Without information gathered prospectively, the investigator cannot identify the stage of disease when the material is obtained. In most reports, the stage of otitis media is identified grossly as acute or chronic by the character of the middle-ear effusion (serous, mucoid, purulent, or hemorrhagic). Few studies have results from more than one specimen or one observation per patient. Thus, there is little information on the sequence of immune events.

3. Techniques for assay of the same function vary in sensitivity and specificity. New techniques may provide results at variance with those of previously used methods.

4. The quantity of middle-ear fluid obtained by tympanocentesis is limited. The volume of most aspirates is 0.3 mL or less. Only a few studies can be performed with each sample. The quality of the fluid may be fibrinous, mucoid, or filled with cellular debris, making homogenization difficult.

5. Materials are not usually available from “normal” patients, and control subjects are difficult to define.

6. The investigator may not be able to identify the origin of the substance in the effusion. Trauma may occur during the course of aspiration and contaminate the effusion with blood and tissue products. The liquid represents the sum of substances derived from serum, inflamed middle-ear mucosa, degenerating white blood cells, and other cellular elements.

Experiments in animal models have provided important new information and stimulated new
concepts. Significant differences exist between species, however, and data derived from studies in animals must be viewed with caution. For the purposes of this chapter, data derived from studies of humans are cited; only a few references are made to animal experiments.

**IMMUNOLOGY OF THE PHARYNX**

Immunocompetent lymphoid tissue is present in the mucosa of the upper respiratory tract, the site of initial exposure for ingested and inhaled antigens. The lymphoid tissue of the pharynx includes the palatine tonsils and adenoids, the lymphoid tissue at the base of the tongue (lingual tonsil), the lymphoid tissue on the posterior wall of the pharynx (pharyngeal tonsil), and a circular ring of lymphoid tissue (Waldeyer’s ring). Plasma cells capable of producing all of the major classes of Igs have been identified in the tonsils. The immunologic aspects of the tonsils were reviewed by Wong and Ogra.3

The specific immunologic relationship of the tonsils and adenoids with the middle ear is unknown. The immunocompetent cells present in the tonsils and adenoids are an important defense in excluding microbial and environmental antigens from the systemic lymphoid system, thus performing a gatekeeper function. Because microbial organisms responsible for infection of the middle ear proliferate first in the throat or nasopharynx, the tonsils and adenoids may play a significant immunologic role in the host’s defense against otitis media.

**HUMORAL FACTORS**

The role of specific Igs in acute otitis media and otitis media with effusion is discussed briefly in this section and in the sections on immunology of AOM and immunology of otitis media with effusion.

**IgA and Secretory IgA**

IgA is secreted by plasma cells in lymphoid tissues lining the gastrointestinal, genitourinary, and respiratory tracts. The secretory component, a nonimmune glycoprotein formed by local epithelial cells, exists either in a bound state with IgA or in a free state in effusion fluids. Two IgA molecules combine with secretory component in the epithelium, and the complex (secretory immunoglobulin A [SIgA]) is transported through the cell and into the lumen. The production of SIgA begins when antigen is presented to immunocompetent cells in the mucosa.

IgA is the predominant Ig in middle-ear effusions. The ratio of IgA to IgG is higher in middle-ear effusion than in serum in most patients, and some patients have IgA in middle-ear fluid but not in serum. IgA is also found in nasopharyngeal secretions of patients with recent infection. Fluorescent antibody staining of middle-ear mucosa demonstrates SIgA in the epithelium. Small amounts of secretory component are free, but most of the secretory component in middle-ear effusions is bound to IgA.4 IgA subclasses differ in the amino acid sequence of the hinge region; both IgA1 and IgA2 have been identified in middle-ear effusions,5 but the functional significance of the subclasses in the middle ear is uncertain.

A specific IgA or SIgA response takes place in the middle-ear mucosa after exposure to antigen. IgA and SIgA specific for adenovirus, respiratory syncytial virus (RSV), and parainfluenza viruses have been identified in the middle-ear fluid of children with otitis media with effusion.6,7 The presence of specific IgA antibody for measles, mumps, rubella, and poliovirus in middle-ear fluid and its absence in some specimens of simultaneously obtained serum indicate that local antibody production takes place.8

Specific IgA can interfere with adhesion of bacteria to the mucous membrane and can neutralize viruses. SIgA and IgG coat bacteria and may be important in preventing microorganisms from attaching to mucosal cells and by promoting agglutination of bacteria.9,10

**Immunoglobulin G**

IgG is present in the middle-ear effusions of patients with both acute and chronic otitis media.
in concentrations, suggesting that local development of IgG occurs in the middle ear. IgG is divided into the subclasses IgG1, IgG2, IgG3, and IgG4 on the basis of differences in the structure of the \( \gamma \) heavy polypeptide chain. Data presented by Freijd and colleagues suggest an association between plasma IgG2 concentrations and susceptibility to otitis media in children.\(^{11}\) Otitis-prone children (8 to 17 episodes by the age of 30 months) had significantly lower plasma concentrations of IgG2 than did children who were not otitis prone (fewer than 2 episodes by the age of 30 months) at the ages of 12 and 32 months. Concentrations of IgG1, IgG3, and IgG4 were similar in the two groups.

**Immunoglobulin M**

IgM is produced in response to primary exposure to a microbial antigen. IgM is present in the middle-ear effusions of patients with both acute and chronic otitis media with effusion,\(^{12}\) but concentrations are lower than in serum, and studies of middle-ear mucosa obtained by biopsy in patients with chronic otitis media with effusion suggest that local synthesis of IgM does not occur.

**Immunoglobulin D**

IgD has been identified in the middle-ear effusions of patients with otitis media with effusion in excess of concentrations found in serum.\(^{13}\) IgD is found in serum in trace concentrations but has no identifiable function.

**Immunoglobulin E**

IgE is part of the external secretory system of antibody produced in the lymphoid tissue of the respiratory and gastrointestinal tracts. Increased concentrations of IgE have been found in the serum and secretions of patients with various atopic diseases. IgE antibody, when it is combined with appropriate antigen, causes release of histamine and chemotactic substances from mast cells and basophilic granulocytes. IgE-producing plasma cells have been identified on biopsy of mucosa of the middle ear, and IgE has been found in the middle-ear effusions of patients with both acute and chronic otitis media. The source of IgE in the middle-ear fluid of patients with otitis media with effusion may be the middle-ear mucosa in some patients\(^{14,15}\) and a transudate of serum in others.\(^{16,17}\)

**Complement**

The complement system includes 11 discrete but interacting proteins and possesses a wide variety of activities, such as microbial neutralization, phagocytosis, immune adherence, chemotaxis, and anaphylatoxin activities on smooth muscle and blood vessels; a cytotoxic effect may serve a protective function, leading to destruction of foreign cells.\(^{18}\) Activation of complement occurs by the classic or alternative pathway. The classic pathway is usually activated by antigen-antibody complexes and proceeds in sequence from C1 to C9. The alternative pathways do not require immune complex for activation but use materials such as endotoxin or bacterial polysaccharide. The early factors of the classic pathway (C1, C2, C4) are not required, but properdin and C3 are involved in activation.

Evidence for activation of complement in the middle-ear effusions of patients with acute and chronic otitis media has been reviewed by Bernstein and colleagues and Prellner and colleagues.\(^{19,20}\) Studies of middle-ear effusion show that levels of C2, C3, C4, and C5 are significantly depressed compared with corresponding levels in serum and that the amounts of C3 breakdown products are significantly elevated in the middle-ear fluid of children with otitis media with effusion,\(^{21}\) indicating use of complement in the middle ear during the course of the disease. Meri and colleagues suggested that activation of complement in middle-ear fluid may play a significant role in the pathogenesis of otitis media with effusion, either by decreasing local defenses against bacterial infection or by generating breakdown products that maintain and prolong the inflammatory process.\(^{21}\)
Rheumatoid Factor

Rheumatoid factor, an IgM that has the capacity to react with IgG in vitro, has been identified in the serum of patients with rheumatoid arthritis and other chronic inflammatory diseases. Rheumatoid factors may participate in the inflammatory process stimulated by immune complexes. DeMaria and colleagues demonstrated rheumatoid factor in 85% of 156 middle-ear fluids obtained from patients with otitis media with effusion; the factor was found in only 8% of the serum from the same patients.22 The investigators suggested that rheumatoid factor is produced in the middle ear and may participate in the pathogenesis of middle-ear effusion. These results were not corroborated by Bernstein; none of 21 middle-ear fluids tested showed positive results for rheumatoid factor.14

PRODUCTS OF IMMUNE REACTIONS

A variety of other substances that take part in immune reactions have been identified in the middle-ear effusions of patients with chronic otitis media with effusion.

A chemotactic factor for neutrophils and macrophage inhibition factor have been found in middle-ear effusion.23 Chemotactic substances alter the pattern of movement of neutrophils so that cells, which otherwise would migrate randomly, are directed to the vicinity of the chemotactic substance.

Histamine was identified in 104 of 131 middle-ear fluids of patients with otitis media with effusion at the time of tympanostomy tube placement. Berger and colleagues postulated that mast cells in the middle-ear mucosa were triggered to degranulate and release histamine by a product derived from activation of the complement system.24

IMMUNOLOGY OF ACUTE OTITIS MEDIA

Role of Serum Antibody

An immune response reflected in a rise in serum-specific antibody occurs in some children after AOM. The response depends on age (the youngest children are less likely to respond) and on the antigenic stimulus of the organism. The antibodies may be evident in middle-ear fluids and serum early in the course of the disease.30,31 The evidence from natural infection indicates that
serum antibody plays an important role in protecting the middle ear from bacterial infection. The infant is protected by passively transferred antibody from the mother; antibody concentrations to *S. pneumoniae* in cord blood correlate with development of pneumococcal otitis media in the first months of life.32 Passive or active immunization protects against AOM; the efficacy of enriched Ig for RSV and of the conjugate pneumococcal vaccine is presumed to be based on the presence of protective serum and local antibodies.

The studies of conjugate pneumococcal vaccines in Finland33 and the Czech Republic and Slovakia34 provide data about the immune response to the vaccine antigens and the role of concentrations of antibody in protection against serotype-specific AOM. In each study, there was a substantial immune response to each of the pneumococcal serotypes. Although the assays were performed in different laboratories the geometric mean concentrations after the initial series of three doses with the 7-valent conjugate pneumococcal vaccine used in the Finnish study were higher than the concentrations of antibody achieved with the 11-valent conjugate pneumococcal vaccine used in the Czech and Slovak study. Surprisingly, antibody concentrations were not directly correlated with protection (Table 2). As examples, following the initial immunization series in the Finnish study, there were relatively low concentrations of serotype 6B antibody but substantial protection against episodes of serotype 6B otitis media; in contrast, serotype 19F achieved high concentrations of antibody but was less protective. In the Czech and Slovak study, vaccine serotype 3 produced high concentrations of serum antibody but was not protective.34 The failure of correlation of serum antibody and protection against type-specific middle ear infection means that investigators need to look to other markers to determine surrogates for vaccine efficacy against pneumococcal AOM.

### Role of Breast Milk Antibody

Type-specific pneumococcal polysaccharide and C polysaccharide antibodies are present in human milk.35 Breast milk IgA antibodies were higher in women who were immunized with polysaccharide pneumococcal vaccine than in unimmunized women.36 There was no reduction in the nasopharyngeal carriage of *S. pneumoniae* and no decrease in the incidence of AOM in breast-fed infants whose mothers had antibodies to pneumococcal polysaccharides.35

### Otitis Media owing to *S. pneumoniae*

The number of infants who develop protective antibodies after pneumococcal otitis media is variable and depends on the age of the patient and the pneumococcal serotype. Infants respond to acute pneumococcal infection with low levels of serum antibody. Eighteen percent of Finnish children younger than 1 year, 48%

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**Table 2. TYPE-SPECIFIC IMMUNE RESPONSE AND PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY AGAINST ACUTE OTITIS MEDIA**

<table>
<thead>
<tr>
<th>Serotype</th>
<th>7-Valent Vaccine*</th>
<th>11-Valent Vaccine†</th>
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<tr>
<td></td>
<td>Geometric Mean (μg/mL)</td>
<td>Vaccine Efficacy (%)</td>
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<tr>
<td>3</td>
<td>—</td>
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<tr>
<td>6B</td>
<td>2.0</td>
<td>84</td>
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<tr>
<td>14</td>
<td>6.3</td>
<td>69</td>
</tr>
<tr>
<td>19F</td>
<td>3.3</td>
<td>25</td>
</tr>
<tr>
<td>23F</td>
<td>25.0</td>
<td>59</td>
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*7-valent pneumococcal conjugate vaccine with CRM197.33
†1 month following initial three-dose series (average age 7 months).
†11-valent pneumococcal conjugate vaccine conjugate with protein D.34
of 1-year-olds, and 39% of children aged 2 to 7 years had a significant increase in type-specific antibody after pneumococcal otitis media. Types 3 and 18 induced the highest concentrations of antibody irrespective of age; types 4, 7, 8, and 9 were intermediate; and types 6, 19, and 23 were poor antigens, even in older children. Age-specific responses were also found in Alabama children who had AOM owing to S. pneumoniae; only 12% of children younger than 1 year had a significant rise in type-specific antibody in the convalescent serum, whereas 48% of the children 2 years or older responded. In contrast to the type specificity of the capsular polysaccharide, the cell wall (C) polysaccharide is common to all pneumococcal strains. After acute pneumococcal otitis media or immunization with the polysaccharide vaccine, children developed antibody to pneumococcal C polysaccharide, the species-specific cell wall antigen. However, the protective role of antibody to the C polysaccharide against subsequent infection is uncertain. Pneumolysin is a species-specific protein toxin produced intracellularly by pneumococci. Virolainen and colleagues demonstrated serum antibodies to pneumolysin in infants after pneumococcal otitis media but less frequently than antibodies to pooled capsular polysaccharides (27%). Antibodies to the protein antigen pneumolysin developed at an earlier age than did antibodies to the capsular polysaccharides. Because seroconversion is uncommon, the value of pneumolysin as a diagnostic test for pneumococcal infection is limited.

Nasopharyngeal antibodies were detected to pneumococcal capsular polysaccharides in children with AOM. Local production of IgA but not of IgM or IgG class antibody was detected in infants as young as 6 months. The role of mucosal antibody in decreasing carriage or protecting against subsequent infection is unknown. Clinical trials of the polysaccharide and conjugate pneumococcal vaccines have shed some light on the immunology of the middle ear and are discussed below and in Chapter 8.

Otitis Media owing to H. influenzae

The antigens of nontypeable H. influenzae are enclosed in an outer membrane of approximately 20 proteins and a lipo-oligosaccharide. Antibody to some of the outer membrane proteins is bactericidal. Specific serum and middle-ear fluid antibodies develop after episodes of AOM owing to nontypeable H. influenzae. Susceptibility to otitis media owing to H. influenzae correlates with absence of bactericidal antibody in acute serum samples. Recurrent episodes of AOM owing to various strains of nontypeable H. influenzae indicate a lack of cross-protection; an immune response to one strain does not protect against another and argues for multiple and different antigenic types. A majority of Alabama children aged 2 years or younger with H. influenzae infection had specific antibody in convalescent serum. Shurin and colleagues found a similar immune response in children aged 2 months to 12 years with AOM owing to nontypeable strains of H. influenzae; 11% of the children had homotypic antibody in the acute serum, but 78% had antibody in the convalescent specimen. Barenkamp and Bodor identified homotypic bactericidal antibody in convalescent serum samples of each of eight children with AOM owing to nontypeable H. influenzae; antibody was absent in the acute serum samples. Harabuchi and colleagues demonstrated the presence of nasopharyngeal SlgA antibodies reactive with the P6 outer membrane protein in colonized children. The results suggested that eliminating the organism from the nasopharynx was associated with a mucosal immune response.

Otitis Media owing to Moraxella catarrhalis

The antigens of M. catarrhalis are found in the outer membrane; eight proteins have been identified. Leinonen and colleagues identified an antibody rise to a pool of M. catarrhalis antigens in 50% of children with acute middle-ear infections owing to this organism. Faden and colleagues found antibody to homologous outer
membrane proteins in the middle ear and serum of patients with acute *M. catarrhalis* infections.\textsuperscript{49} The role of antibody in eliminating the organism from the middle ear or protecting it from subsequent infection is unknown.

**Recurrent Episodes of Acute Otitis Media**

Children with recurrent episodes of otitis media have new middle-ear infections owing to the same species that was responsible for the first episode. *S. pneumoniae* and nontypeable *H. influenzae* are the most common bacteria in recurrent infections, but the new episodes are rarely due to the same serotype that infected the child in a previous episode.

Austrian and colleagues found that in recurrent episodes of pneumococcal otitis media, approximately 1% of isolates of *S. pneumoniae* were of the same serotype responsible for a previous episode.\textsuperscript{50} Recurrent episodes of otitis media owing to nontypeable *H. influenzae* were also associated with new types. Using outer membrane protein gel analysis and biotyping, Barenkamp and colleagues determined that episodes of early recurrence of otitis media owing to nontypeable *H. influenzae* (less than 30 days after the initial *H. influenzae* infection) had first and second isolates that were identical.\textsuperscript{51} In contrast, children with late recurrences of nontypeable *H. influenzae* (more than 30 days after the initial infection) had disease owing to a different strain. These data suggest that infections owing to *S. pneumoniae* or nontypeable *H. influenzae* produce an immune response that protects the child against subsequent infection owing to the same type.

**Role of Antibody in Middle-Ear Effusions**

Specific antibody to homotypic strains is present in middle-ear effusions and serum after episodes of AOM. Type-specific IgG predominates in the middle-ear fluid; IgM- or IgA-specific antibodies are present in a small proportion of children with acute infections.\textsuperscript{12,44} In response to AOM owing to nontypeable *H. influenzae*, IgG titers increased in serum during a period of 2 months, whereas middle-ear fluid titers initially increased, then decreased, and disappeared at 3 months. Specific IgG antibody was present in both ears in bilateral and unilateral otitis media, although in lower titers in the unaffected ear.

Clearance of fluid from the middle ear in patients with AOM owing to *S. pneumoniae* and *H. influenzae* is significantly associated with the presence and concentration of specific antibody to the infecting strain in the middle-ear fluid at the time of diagnosis. Sloyer and colleagues associated clearance of effusion by the second visit (2 to 7 days after diagnosis) with specific antibody in the middle-ear effusion at the first visit that was directly associated with the concentration of specific antibody.\textsuperscript{52} Effusion owing to *H. influenzae* cleared rapidly in more children (45.3%) than did effusion owing to *S. pneumoniae* (13.6%), whether or not antibody was present. The source for the antibody in the effusion at presentation of AOM is uncertain; antibody may have developed after a previous infection, or it may have developed rapidly after a current infection, or it may indicate a delay of presentation until the specimen of middle-ear fluid was obtained. If present from a previous infection, type-specific antibody did not protect the patient from a recurrent episode of AOM but did reduce the duration of effusion.

**Polymorphonuclear Leukocyte Response**

Although recurrent AOM is a frequent early sign of children with significant defects in the white blood cell response to infection (see the section on children with defects of the immune system), there are patients who appear to be immunologically competent but have subtle changes in polymorphonuclear leukocyte response. Hill and colleagues identified a defective chemotactic response in selected patients with recurrent episodes of AOM and diarrhea.\textsuperscript{53} Ichimura identified defective neutrophil chemotaxis in 20 children who had had recurrent episodes of otitis media (four or more episodes during the
Role of Antibody in Middle-Ear Fluid

All of the major classes of Igs—IgA, IgG, IgM, IgD, and IgE—have been identified in the middle-ear fluids of patients with otitis media with effusion. SIgA, IgA, and IgG are synthesized by the mucosa of the middle ear; synthesis of other Igs in the middle ear is less certain. Both IgA and IgG are present in middle-ear effusions in concentrations higher than those found in simultaneously obtained serum, whereas IgM and IgE are present in effusions in concentrations equivalent to or lower than those found in serum. The highest concentrations of each of the major classes of immunoglobulins are present in mucoid effusions, the lowest are found in serous effusions, and intermediate values occur in leukocytic middle-ear effusions.

Immune Complexes

Some investigators suggest that chronic otitis media with effusion may be an immune complex disease. Antigen (microbial agents or allergens) may combine with antibody (locally produced or derived from serum) to form an immune complex, which activates the complement sequence through the classic or alternative pathway. Polymorphonuclear leukocytes and monocytes are attracted to the site. With the death of these cells, intracellular enzymes are released, producing local tissue damage and stimulating effusion. Maxim and colleagues identified immune complexes in middle-ear fluids by using the fluorescent Raji cell assay. Others have not been able to corroborate the results. If immune complexes do occur in middle-ear fluid, they may represent microbial antigen-antibody complexes as part of the normal process of elimination of infectious product through phagocytosis.

Children with Defects of the Immune System

Most children with recurrent episodes of AOM have no apparent systemic or local immune defect and do not suffer from infections at other sites. These children have normal serum concentrations of IgG, IgM, and IgA; normal systemic cell-mediated responses; and normal phagocytic and bactericidal capacity of neutrophils in peripheral blood. Available data about the immune system of the middle ear in children with recurrent otitis media with effusion indicate that most children with recurrent disease have the essential elements for immunologic resistance, including T- and B-cell responses that are fully operative, macrophages that are available for engulfing and ingesting antigenic material, and an appropriate antibody response by middle-ear mucosa.

Children with congenital or acquired immunodeficiency may have defects of phagocyte function or humoral systems. Respiratory tract infections, including otitis media, are associated with...
with defects of chemotaxis, phagocytosis (neutropenia or intrinsic cellular defects), or killing (chronic granulomatous disease); problems with the humoral system include deficiency of circulating antibody (hypogammaglobulinemia or agammaglobulinemia), mucosal antibody (IgA deficiency), and complement. Multiple infections in the same system (respiratory tract, urinary tract, or central nervous system) suggest a local anatomic or physiologic defect. The majority of children with recurrent episodes of otitis media as the sole form of recurrent infectious disease probably have an underlying defect that is not immunologically mediated—for example, eustachian tube dysfunction. A few children have recurrent respiratory infections, including recurrent otitis media and pyogenic infections in other systems, as part of an immunodeficiency syndrome.63–65 Multiple serious pyogenic skin infections (furunculosis, subcutaneous abscess, or cellulitis), accompanied by pneumonia or recurrent otitis media, raise the suspicion of neutropenia, defective chemotaxis, or problems with phagocytosis. A pattern of subcutaneous abscesses or furunculosis, accompanied by abscess formation in lymph nodes, liver, or lung, and recurrent AOM suggests chronic granulomatous disease. Meningitis, osteomyelitis, septic arthritis with recurrent AOM, or pneumonia raises concern for a deficiency of antibody or C3. Protracted diarrhea, when it is accompanied by recurrent episodes of otitis media, sinusitis, or pneumonia, suggests IgA deficiency (although many children with deficiencies of IgA are otherwise normal without undue susceptibility to infection). Children with selective IgG2 or IgG3 subclass deficiency had recurrent sinopulmonary infections and otitis media (more than six episodes per year).66 The bacterial pathogens of AOM in children with primary immunodeficiencies are likely to be the same as those in normal hosts, including S. pneumoniae, H. influenzae, and M. catarrhalis, but also Staphylococcus aureus.67

Patients with defects in splenic function are susceptible to overwhelming infection owing to encapsulated organisms such as S. pneumoniae and H. influenzae type b. Such patients, including those with congenital or acquired asplenia and those with sickle cell disease, have not been identified as groups with unusual susceptibility to infections at local sites, such as the skin and soft tissues or middle ear.

Human immunodeficiency virus (HIV), the organism responsible for acquired immunodeficiency syndrome (AIDS), is highly tropic for T lymphocytes. Children with AIDS have abnormalities of T-cell, B-cell, and complement functions and phagocytosis. The children are susceptible to local and systemic pyogenic infections, and otitis media is only one of the many bacterial diseases that may occur. In a study of Boston children observed from infancy, otitis media was as frequent in infants aged 2 years or younger with AIDS as in infants who were initially HIV positive because of maternal antibody and seroreverted to normal.68 However, after the age of 2 years, the children with AIDS continued to have recurrent episodes of AOM, whereas the children who were now seronegative had the expected lower age-specific incidence. The prevalence of S. pneumoniae, H. influenzae, and group A streptococcus isolated from middle-ear fluids of children with acute otitis media was similar in HIV-infected and normal children.69 HIV-infected children younger than 2 years were able to respond to a 5-valent pneumococcal conjugate vaccine, suggesting that the vaccine may be useful for reducing both local and invasive pneumococcal disease in HIV-infected infants.70

Children with recurrent and severe AOM may have subtle immune deficits that are elicited only by indirect techniques, such as response to infection and immunization. Prellner and colleagues demonstrated that throughout the first 3 years of life, children with recurrent AOM had lower IgG antibody concentrations than those of age-matched healthy children to pneumococcus types 6A and 19F, but not against type 3.71 The antibody response to rubella vaccine was significantly lower in children with recurrent otitis media, but the response to diphtheria and tetanus toxoids was similar to that in children without
experience with recurrent AOM. Similarly, Yamanaka and Faden noted that otitis-prone children had poor responses to the outer membrane protein P6 of nontypeable H. influenzae; otitis-prone children observed longitudinally had lower concentrations of antibody to P6 than did normal children. Pelton and colleagues identified an impaired response to Haemophilus capsular polysaccharide protein conjugate vaccine in children with recurrent otitis media. These data suggest that some children who have recurrent middle-ear infections are immunologically different from children without recurrent ear infections and may benefit from the use of bacterial polysaccharide Ig. The evaluation of a child with recurrent AOM for possible immune deficiencies was reviewed by Adamkiewicz and Quie.

ROLE OF ALLERGY IN OTITIS MEDIA WITH EFFUSION

The role of allergy as an etiologic factor in otitis media with effusion is uncertain. The role of allergy and eustachian tube function is discussed in Chapter 3. Few critical studies of appropriate design are available to clarify the relationship of allergy and otitis media with effusion. Available studies are often biased (enrollees include children referred for allergy evaluation) and do not include appropriate control patients. The association of reaginic antibody with IgE, however, provides a specific measure for precise definition of allergy and has already provided some significant information about the primary or secondary role of allergy in otitis media with effusion. Mogi and Suzuki summarized current information about the evidence for IgE-mediated allergic reactions in the pathogenesis of otitis media with effusion.

An allergic response to environmental antigens may be responsible for AOM or otitis media with effusion in some children. Evidence of a role for allergy in recurrent otitis media with effusion in some children was presented by Siegel and Bernstein:

1. Many patients with recurrent otitis media with effusion have concomitant allergic respiratory disease.
2. A history of one or more major allergic illnesses in parents is usually present.
3. Nasal or peripheral eosinophils are often present in increased numbers.
4. Skin test responses to allergens or radioallergosorbent test results are positive in many patients.
5. Elevated IgE levels in middle-ear effusions and in serum of some children have been identified.
6. Mast cells (some that are degranulating) are found frequently throughout the middle-ear mucosa.
7. An elimination diet led to improvement in serous otitis media in infants identified as having food allergy by means of skin prick testing, specific IgE tests, and food challenge.

Evidence that allergy plays only a minor role in AOM or otitis media with effusion and only in selected patients or selected episodes was summarized by Bernstein:

1. In unselected series of cases of otitis media with effusion, less than one-third of patients are atopic. Allergic airway disease was not a predisposing factor for Arizona Indian children with recurrent otitis media. These children are likely to have other factors responsible for the susceptibility to middle-ear infection.
2. The seasonal incidence of otitis media with effusion (winter to spring) is contrary to the season when grasses, trees, and pollens cause acute nasal allergy (late spring and early fall).
3. Most studies indicate an absence of eosinophils and an absence or only small numbers of IgE-producing cells in middle-ear fluids and middle-ear mucosa.
4. A failure to improve with aggressive allergic treatment, including hyposensitization and use of antihistamines in spite of improvement in nasal symptoms, is seen in most patients.
In summary, many patients may be allergic and many children have recurrent AOM and otitis media with effusion, but there is no substantive evidence correlating allergy with the two conditions as the major pathogenetic mechanism in most children. It is likely, however, that the allergic response plays a role in some children with otitis media with effusion or in some episodes of otitis media with effusion. The presence of specific IgE on mast cells in middle-ear mucosa could result in release of mediators of inflammation, with the mucosa functioning as a shock organ similar to respiratory mucosa in other areas. Alternatively, the allergic reaction might be a predisposing factor producing congestion of the mucosa of the nose and eustachian tube, leading to obstruction of the tube with retention of fluid in the middle ear.

**VACCINES AND IMMUNOGLOBULINS TO PREVENT OTITIS MEDIA**

If type-specific serum antibody is correlated with protection from homotypic infection, bacterial vaccines may be an effective mode of prevention of type-specific otitis media. The pneumococcal conjugate vaccine has been very effective in reducing the incidence of invasive disease in infants but has been only modestly successful in reducing the incidence of AOM (see discussion below and Chapter 8). The conjugate polysaccharide vaccine for *H. influenzae* type b has been successful in reducing the incidence of invasive disease in infants but has been only modestly successful in reducing the incidence of AOM (see discussion below and Chapter 8). The conjugate polysaccharide vaccine for *H. influenzae* type b has been successful in reducing the incidence of invasive disease owing to this organism in immunized infants, but it is of limited interest in preventing AOM because the type b organisms cause only about 2% of AOM. A vaccine for nontypeable *H. influenzae* is not available, but current investigations are focusing on the use of outer membrane antigens for development of a vaccine (see the section on nontypeable *H. influenzae* vaccines). The apparent increase in *M. catarrhalis* as a pathogen for AOM suggests that this organism may also need to be included in an “otitis media vaccine.” Influenza virus vaccines and vaccines and IgGs to protect against infection owing to RSV have been effective in reducing the number of episodes of AOM in infants and will need to be included in the overall immunization strategy to reduce otitis media.

Data about the use of IgGs to prevent AOM are also presented in this section. The proceedings of a symposium on otitis media vaccines were published in 1989.82

In addition to immunization of the infant, protection during the first months of life can be provided by passively transferred antibody from the mother. Tetanus toxoid immunization of the mother has been successful in developing countries for prevention of almost all neonatal tetanus deaths. Immunization with respiratory vaccines would provide passively transferred antibody that could protect from AOM during the first months of life until the infant is able to respond to active immunization. Salazar and colleagues found that low cord blood IgG antibodies predicted early-onset AOM in Minnesota infants.32 Shahid and colleagues immunized healthy pregnant women in Bangladesh with pneumococcal polysaccharide vaccine and found antibody concentrations of 6.8 and 7.5 μg/mL to types 6B and 19F in cord blood.36 The median half-life of the passively transferred antibody was about 35 days.

Vaccines and immunoglobulins to prevent otitis media are discussed further in chapter 8.

**Pneumococcal Polysaccharide Vaccines**

Although there are 90 antigenically separable types, relatively few serotypes are responsible for most infections. A 14-type pneumococcal polysaccharide vaccine was licensed for use in the United States in 1978 and was replaced by a 23-valent vaccine licensed in 1983. The vaccine contains purified polysaccharide antigens of types associated with otitis media in children. Each pneumococcal-type polysaccharide antigen produces an independent antibody response. In older children (older than 2 years) and adults, antibody develops in about 2 weeks. In general, children younger than 2 years exhibit unsatisfactory serologic responses to most pneumococcal polysaccharides; in contrast, type 3 evokes a significant antibody response in infants as young as 6 months.83 Clinical trials of the pneumococ-
cal polysaccharide vaccine failed to decrease the number of episodes of AOM.83–87

**Pneumococcal Polysaccharide Conjugate Vaccines**

Polysaccharide antigens are processed as non–T lymphocyte–dependent antigens, and the immune system of infants younger than 2 years does not respond adequately to such antigens with a strong, durable response that could be boosted with subsequent administration. Protein antigens are processed by T lymphocytes, and young infants can mount an adequate antibody response. The conjugate *H. influenzae* type b vaccine linked saccharides to a protein carrier that could be processed by T lymphocytes, resulting in a protective antibody response and immunologic memory in infants as young as 2 months. The success of the *H. influenzae* conjugate vaccine in eliciting protective antibody in infants as young as 2 months led to the use of similar technologies to develop a serotype-specific conjugate pneumococcal vaccine. For the *Haemophilus* vaccines, capsular polysaccharides were combined with proteins that included diphtheria toxoid, tetanus toxoid, a diphtheria mutant toxin protein (CRM 197), and an outer membrane protein of meningococcus group B. The same protein has been used to prepare conjugate pneumococcal vaccine.

A 7-valent conjugate pneumococcal vaccine employing CRM 197 as the protein carrier (PCV 7, Prevnar, Wyeth Vaccines, Philadelphia, PA) was introduced in 2000 and recommended in the United States for universal immunization in a four-dose schedule (2, 4, 6, and 12 months of age). The vaccine combined pneumococcal serotypes 4, 6B, 9V, 18C, 19F, and 23F. The vaccine is immunogenic in children as young as 2 months of age.88 Serum titers considered to be protective against invasive disease were achieved after doses administered at ages 2, 4, and 6 months but waned during the following 6 months, requiring a booster between the ages of 12 and 15 months. By December 2005, 80 million doses of the vaccine had been distributed in the United States (P. Paradiso, personal communication, December 2005).

Two clinical trials, one in northern California and the second in Finland, established the efficacy of PCV for prevention of pneumococcal AOM.33,88,89 The vaccine reduced the number of episodes of otitis media by 7% in California and 6% in Finland. Efficacy in the California trial was based on clinical diagnoses of AOM, whereas the Finnish study provided data about microbiology efficacy since all children had tympanocenteses after completing the initial vaccine series at 7 months of age.33 The reduction in the number of pneumococcal episodes in immunized children was 57% against vaccine serotype otitis, a 51% decrease against episodes attributed to serotypes that are cross-reactive with those in the vaccine, an increase of 33% in the number of episodes owing to all other pneumococcal serotypes, and an increase of 11% of episodes owing to nontypeable *H. influenzae*. The increase in episodes of pneumococcal AOM owing to serotypes not in the vaccine may have been anticipated from the results of studies that show a shift in nasopharyngeal carriage in immunized children to non-vaccine serotypes.

The immunogenicity of the vaccine was demonstrated in the northern California and Finnish trials. In both trials, there was a substantial immune response to each serotype measured after the initial series at 7 months and following the booster dose of vaccine at 12 months. However, serum antibody concentrations were not directly correlated with vaccine efficacy (see Table 2 and the section above on the role of antibody in middle ear effusions and serum). These results indicate that pneumococcal type–specific serum antibody concentrations are a surrogate for protection against invasive pneumococcal disease but not for protection against AOM.

An 11-valent conjugate pneumococcal vaccine prepared by combining pneumococcal capsular polysaccharides with protein D of *AOM* provided protection against AOM owing to vaccine serotypes and to nontypeable *H. influen-
zae and was evaluated in the Czech Republic and Slovakia. Vaccine efficacy was shown for episodes of AOM owing to pneumococcal vaccine serotypes (52.6%) and for vaccine-related cross-reactive pneumococcal serotypes (65.5%). In contrast to the PCV 7 study in Finland in which there was an increase in episodes of AOM owing to nonvaccine serotypes, the 11-valent vaccine did not alter the number of episodes caused by nonvaccine serotypes. Similar to the results of PCV 7, antibody concentrations were not correlated with protective efficacy (see Table 2).

**Pneumococcal C Polysaccharide Vaccines**

The ideal vaccine to protect against pneumococcal infection would include an antigen common to all types of pneumococci. The C polysaccharide is a cell wall component common to all known types of pneumococci. Unfortunately, antibodies against the C polysaccharide do not protect against infection in humans. Henrichsen and Sorensen suggested that the C polysaccharide lacks immunogenicity because the capsular polysaccharides of growing pneumococci conceal the cell wall and prevent binding of anti–C polysaccharide antibodies to the bacterial cells. The anti–C polysaccharide antibodies do bind to nonencapsulated or only partly encapsulated pneumococci and promote phagocytosis of such bacterial cells. Koskela demonstrated serum antibodies to pneumococcal C polysaccharide in children after acute pneumococcal otitis media or vaccination with polysaccharide vaccine. Henrichsen and Sorensen demonstrated anti–C polysaccharide Ig in nasopharyngeal secretions of children with recurrent otitis media. The role of antibody response to the C polysaccharide is controversial; protection against subsequent infection is unproven, and Henrichsen and Sorensen suggested that prompt production of these antibodies may lead to immune complex formation and continuous local inflammation before the infant is capable of mounting protective type-specific antibodies to combat the infection.

**Nontypeable Haemophilus influenzae Vaccines**

The novel 11-valent conjugate pneumococcal vaccine used in the Czech Republic and Slovakia includes 11 different polysaccharide serotypes each conjugated to a recombinant nonlipidated form of protein D as the carrier protein. Protein D is a lipoprotein of *H. influenzae* and has produced protection against nontypeable *H. influenzae* otitis media in rat and chinchilla models. In the clinical trial described above in the section on conjugate pneumococcal vaccines, the vaccine conjugated with protein D was effective against episodes of AOM caused by nontypeable *H. influenzae* (35.3% efficacy). These results are the first demonstration of a vaccine effective in clinical trials against AOM owing to nontypeable *H. influenzae*.

Other investigations of antigens of nontypeable *H. influenzae* that elicit protective antibodies against middle-ear infections include outer membrane proteins, pili or fimbriae surface proteins, and oligosaccharides. Twenty outer membrane proteins, with seven predominant proteins, have been identified among strains of nontypeable *H. influenzae*. Children have recurrent infections with reinfection by different strains rather than persistence of the same strain. Thus, the available data suggest that there is no cross-protection and that multiple infections with nontypeable *H. influenzae* occur with different antigenic determinants. The goal of identifying an antigen common to nontypeable strains of *H. influenzae* that will elicit protective antibody and could be incorporated into an otitis media vaccine remains elusive.

Studies by Murphy and colleagues have identified a number of outer membrane proteins that are immunogenic in infants. Current studies are directed to determination of the variety of outer membrane proteins of *H. influenzae* and the antigen characterization of selected proteins that compose large proportions of the outer membrane, including P6 and P2. The failure of infants with AOM owing to nontypeable *H. influenzae* to mount an antibody
response to P6 raises doubts about its efficacy as a vaccine candidate.73

Blocking attachment of the organism to receptors on respiratory mucosa would be another approach to prevention of infection owing to H. influenzae. High-molecular-weight proteins and pili or fimbriae play roles in attachment. St. Geme and colleagues identified high-molecular-weight proteins of nontypeable H. influenzae that mediated attachment to human epithelial cells.97 Their findings suggest potential vaccine candidates that would elicit antibodies to prevent attachment. Brinton and colleagues studied the roles of pili as vaccine candidates for nontypeable H. influenzae.98 Pili are filamentous appendages on the bacterial cell surface that may be responsible for adhesion of the bacteria to mucosal cells and may be a virulence factor for some pathogens. A family of pili have been identified, as occur on the surface of nontypeable H. influenzae. Antibodies directed against the pili may protect against disease that is pilus specific. Sirakova and colleagues found antigenic heterogeneity among pili of nontypeable strains of H. influenzae, indicating the need to include multiple antigens in an effective vaccine.99

Lipo-oligosaccharides are present in the outer membrane of nontypeable H. influenzae. Patrick and colleagues used monoclonal antibodies to characterize the antigenic properties of lipo-oligosaccharides and identified common lipo-oligosaccharide antigens among nontypeable and type b strains, but diversity existed among the lipo-oligosaccharide antigens of nontypeable strains.100

**M. catarrhalis Vaccines**

M. catarrhalis has been isolated from the middle-ear fluids of approximately 10% of children with AOM, but data are sparse about the role of antibody in protection against subsequent infection. Efforts to develop a vaccine with use of surface antigens of the organism are in progress.101 Eight outer membrane proteins have been identified.102 In addition, Murphy is investigating the potential value of lipo-oligosaccharides and fimbriae as antigens for vaccines.101 Because M. catarrhalis has surface fimbriae, antibodies to fimbriae could block attachment of the organism to respiratory mucosa.

**Viral Vaccines**

Viral infection is the likely antecedent of many episodes of AOM. Effective vaccines for the major respiratory viral infections could prevent many episodes of AOM. In anticipation of epidemic influenzal disease, influenza A vaccine administered to Finnish infants attending day care reduced the incidence of upper respiratory tract infections, including AOM.103 Influenza A vaccine reduced the incidence of AOM in 6- to 30-month-old North Carolina children in day care during the influenza season.104 A 3-valent live attenuated intranasal influenza vaccine administered as a nasal spray was effective in reducing the incidence of type-specific influenzal disease and febrile otitis media.105

The ease of administration should enhance the acceptability of influenza virus vaccines, which in the past required one or two parenteral administrations for efficacy. Other viral vaccines that might limit the incidence of acute episodes of otitis media are in various investigational phases, including vaccines for RSVs and adenoviruses.

**Immunoglobulins**

Specific serum antibody is correlated with protection from homotypic infection, and prevention of disease may be achieved (albeit for limited duration) by administration of Igs. Because infants who have recurrent episodes of AOM usually have fewer episodes as they become older, it is possible that a program of passive immunization might be effective in early infancy.

Diamant and colleagues showed that patients with recurrent episodes of AOM associated with hypogammaglobulinemia or agammaglobulinemia benefitted from frequent administration of gammaglobulin.106 Children aged 1 to 7 years
were enrolled after the first visit to the Ear, Nose, and Throat Department in Halmstad, Sweden. Children born on an odd date were given gammaglobulin at their first visit and then once a month for 6 months. Children born on an even date received no gammaglobulin. Of the 113 children treated, 10 had one or more episodes of AOM during the months of administration of the gammaglobulin; of 118 untreated children, 25 had one or more episodes of the disease during the same period. The protective effect of the gammaglobulin persisted during the 8 months after administration ended; 25 episodes occurred in the treated group and 53 in the untreated group. In the untreated group, some patients had up to five episodes, whereas no patient in the treated group had more than two bouts of AOM.

Use of intravenous Ig to prevent recurrent episodes of AOM indicated a lack of efficacy of pooled human Ig but efficacy of a bacterial polysaccharide immunoglobulin (BPIG). Jorgensen and colleagues noted no benefit from intramuscular administration of human pooled Ig every 3 weeks for 6 months to otitis-prone children (three or more episodes in the previous year). Kalm and colleagues evaluated the efficacy of Ig infusions administered at 3- to 4-week intervals to children with recurrent AOM (defined as six or more episodes of acute infection during the preceding 12 months); there was no difference in the number of episodes of AOM in the children who received the Ig or in the control subjects during a 7-month period of observation. Use of BPIG for prophylaxis of acute otitis media was investigated by Shurin and colleagues. An Ig was prepared from subjects who had recently been immunized with 14-valent pneumococcal vaccine. Children with previous episodes of AOM were enrolled in the first 24 months of life and randomized to a double-blind, placebo-controlled trial using the intramuscularly administered hyper-Ig preparation. Significantly fewer episodes of AOM caused by the pneumococcus occurred in the group that received the globulin (Table 3) during the 120-day observation period. The authors noted that colonization was not reduced in the vaccinated group; thus, the effect of the Ig was directed to protection of the middle ear from infection. The results also indicated that circulating antibody was effective in preventing AOM without stimulation of specific local immunity. Because systemic administration of polysaccharide vaccines may stimulate both systemic and local antibody responses, use of the Ig for protection suggests that systemic antibody alone is protective against middle-ear infection.

An intravenously administered RSV-enriched hyper-Ig given monthly was effective in reducing the incidence of RSV respiratory infections and the overall incidence of AOM. The difficulty of monthly intravenous infusions, concerns about interference with the immune response to live attenuated vaccines, and an unexpected increase in adverse events in children with cyanotic heart disease undergoing surgery have limited use of the hyper-Ig. The RSV-specific hyperimmune globulin has been replaced by a humanized monoclonal antibody directed against a surface protein (the F glycoprotein of RSV).

Reduction of Colonization by Vaccines

Because colonization of the nasopharynx may be the point of initiation of and the reservoir for infection of the middle ear, the ability of a vaccine or Ig to reduce nasopharyngeal carriage may be important in reducing the incidence of otitis media. Although not significant for AOM, the conjugate H. influenzae type b vaccine was effective in reducing implantation and carriage of

<table>
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<tr>
<th>Bacteria</th>
<th>Episodes Per Patient, n (%)</th>
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<tr>
<td><strong>Bacterial polysaccharide immunoglobulin (BPIG)</strong></td>
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</tr>
<tr>
<td>Streptococcus pneumoniae</td>
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<td></td>
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<td>21 (55)</td>
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Adapted from Shurin PA et al. BPIG = bacterial polysaccharide immunoglobulin. *Isolates from the middle ear during the 120-day study period. **Bacterial polysaccharide immunoglobulin.
type b organisms. The 14-valent pneumococcal polysaccharide vaccine failed to reduce carriage in healthy children. In contrast to the polysaccharide vaccines, the conjugate pneumococcal vaccines decrease the incidence of naso-pharyngeal carriage due to serotypes in the vaccine but increases nasopharyngeal carriage due to non-vaccine serotypes. The replacement of pneumococcal vaccine serotypes with non-vaccine serotypes in the naso-pharynx has been accompanied by an increase in non-antibiotic susceptibility among the colonizing strains due to non-vaccine serotypes. Because carriage is important in both the pathogenesis and communicability of respiratory infections, this outcome will be closely monitored as each immunizing product is developed.

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