Current and Future Use of Vaccines for Viral and Bacterial Respiratory Tract Infections

Martin G. Ottolini, MD

Address

Department of Pediatrics, F. Edward Hébert School of Medicine,
The Uniformed Services University of the Health Sciences,
4301 Jones Bridge Road, Bethesda, MD 20814-4799, USA.
E-mail: mottolini@usuhs.mil

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Viral and bacterial respiratory infections remain the number one cause of infectious disease-related deaths around the world. In the past, vaccines were often created by repeatedly passing laboratory cultures to develop attenuated strains or simply by inactivating live cultures of pathogens. A variety of new and innovative technologies are being applied to develop vaccines against the more elusive pathogens. A variety of protein conjugates have been used to greatly enhance the immunogenicity of *Haemophilus influenzae* type B vaccine, and are now being employed for new pneumococcal and meningococcal vaccines. Live attenuated vaccine strains of respiratory syncytial virus and influenza, which induce protective immunity through localized replication in the nasopharynx, may soon be available for routine use. Future innovations may include genetic vaccines that introduce DNA into host cells to produce specific protective antigens, along with a desired cytokine response to induce a protective immune response.

Introduction

The burden of respiratory disease

Respiratory infections remain the most common cause of infectious disease deaths around the world. The World Health Organization's (WHO) 1999 statistics estimate that acute respiratory infections, including those caused by *Streptococcus pneumoniae*, *Bordetella pertussis*, *Haemophilus influenzae* type B (Hib), influenza, and respiratory syncytial virus (RSV), lead to 3.5 million deaths each year, and tuberculosis directly accounts for another 1.5 million deaths annually [1,2]. Measles is responsible for another 900,000 deaths per year. In addition, tremendous morbidity occurs both in healthy individuals, as a result of the concurrent loss of economic productivity and expenditure

of health care dollars, and in high-risk populations that include the extremes of age and the growing numbers of patients living with permanent or periodically immunocompromised medical conditions.

Existing vaccine schedules

The middle of the twentieth century was marked by the development of highly effective vaccines against a variety of pathogens that in retrospect seemed to be "easy" targets. The 2000 Childhood Immunization Schedule [3], issued by the American Academy of Pediatrics, the Advisory Committee on Immunization Practices, and the American Academy of Family Physicians (updated regularly on the American Academy of Pediatrics website [www.aap.org]) recommends immunizations against several respiratory pathogens, including *Corynebacterium diphtheriae*, *B. pertussis*, Hib, measles, mumps, and rubella, as standard immunizations for healthy individuals. In addition, influenza and pneumococcal vaccines are recommended for adults 65 years of age and older, as well as for adults and children with chronic illness or other high-risk factors, though regular implementation of these vaccines has been sporadic [4-6]. Meningococcal vaccine is recommended for those over 2 years of age with anatomic or functional asplenia, or terminal complement deficiencies [7]. The WHO Expanded Programme on Immunizations also recommends bacille Calmette-Guérin (BCG) immunization against tuberculosis, although this is currently believed to be unnecessary in the United States where overall rates of infection are low [8]. Table 1 presents a brief summary of current vaccine recommendations.

While mass immunization against these pathogens has been one of the great medical success stories of the past century, some current immunizations, such as those against influenza, pneumococcal disease, and tuberculosis, have limited efficacy. Other pathogens such as RSV have no effective immunization strategies. The current expeditious expansion in our understanding of immunology and advances in molecular biology has led to an exciting array of simple and complex technologies to develop new and improved vaccines against several respiratory pathogens, particularly in previously difficult-to-immunize groups. This review highlights a variety of respiratory pathogens that

Table 1. Routine immunization schedules for common respiratory pathogens

Immunization	Childhood immunization schedule (AAP/AAFP/ACIP)	Adult immunizations (ACIP)	Expanded Programme on Immunizations (WHO)
Diphtheria	Routine	Routine (every 10 y)	Routine childhood
Pertussis	Routine	Possible future recommendation?	Routine childhood
Measles	Routine	Born after 1956, with no history or serologic proof	Routine childhood
Mumps	Routine	Born after 1956, with no history or serologic proof	Routine childhood
Rubella	Routine	Nonpregnant postpubertal women without serologic proof	Routine childhood
<i>Haemophilus</i>	Routine		Select countries
Pneumococcus	High risk, >2 y	High risk, >65 y	
Meningococcus	High risk, >2 y	High risk	
Influenza	High risk, >6 mo	High risk, >65 y	
Bacille Calmette-Guérin	Rare with unavoidable continual exposure	Rare with unavoidable continual exposure	Routine childhood

AAP—American Academy of Family Physicians; AAP—American Academy of Pediatrics; ACIP—Advisory Committee on Immunization Practices; WHO—World Health Organization.

Table 2. Technical challenges and innovative solutions to immunizations

Challenges to immunization	Solution by existing or new technologies
Enhancing (Th2) immune response: formalin-inactivated RSV, leishmaniasis, schistosomiasis	Adjuvants such as MPL or QS-21, or addition of IL-12 to push a Th1 response; genetic immunization with sequences for antigens and immunoadjuvants (IL-12)
Vaccine disease: live RSV vaccines	Intranasal delivery of temperature-sensitive mutants (local replication only)
Vaccine disease: BCG in the immunocompromised individual	Genetically attenuated BCG, or bacterial autotrophs, die after limited replication
Incomplete protection: influenza	Local and systemic immunity via intranasal immunization
Reactogenicity: whole cell pertussis	Multiple subunit acellular vaccines
Newborn and infant immunologic immaturity: lack of response to polysaccharide antigens	Protein conjugation: strong Th1 response, immunogenic at an earlier age, improved amnestic response

BCG—bacille Calmette-Guérin; IL—interleukin; RSV—respiratory syncytial virus; Th—T-helper.

reflect the current diversity of vaccine approaches, ranging from simple existing vaccines that are primarily social challenges for global implementation, to new and highly effective technologies emerging in the immediate and more distant future.

Technical Challenges to the Development of Effective Vaccines

Our improved understanding of the host immune response has allowed us to focus our attention on the specific technical issues involved in development of effective vaccines for more challenging pathogens and in previously difficult to immunize hosts. Table 2 summarizes some of these challenges, the highlights of which will be discussed briefly in this section.

T-helper-1 versus T-helper-2 responses

Since the discovery of differential T-helper (Th) cell cytokine responses in the past decade, much attention has been focused on developing vaccine constructs that induce a

primary Th1-type response, as reflected by the production of interferon- γ , interleukin-2 and -12, and tumor necrosis factor- β , associated with a strong cell-mediated immune response [9••]. Although this may be an oversimplification, the Th1 response is generally believed to be associated with better initial priming of cellular memory, with earlier protection as well as a strong subsequent amnestic response, plus potentially fewer side effects. This may be best demonstrated by the highly effective improvement of the Hib polysaccharide (polyribosylribitol phosphate [PRP]) vaccine through conjugation to a variety of protein carriers. This technology induced a strong Th1 response to PRP and led to successful immunization of young infants, a technology now being used to develop the next generation of pneumococcal and meningococcal vaccines [10•]. Also, a variety of investigators evaluating experimental leishmanial, schistosomal, and respiratory syncytial viral vaccines in murine models have demonstrated that the use of interleukin-12 as an adjuvant can induce a predominantly Th1 or type 1 response, which appears to result in more protective and less inflammatory responses to sub-

sequent challenges in murine models of these infections [9••]. The observation that the Th1 pattern of cytokines predominates with some of the most successful current and experimental vaccines supports the current trend toward development of vaccines that shift to this pattern of cytokine responses [10•].

Neonatal immunization

Because of the residual presence of maternal antibody in newborns along with the developmental immaturity of the young immune system and the unacceptability of such simple side effects as fever (which often requires an extensive clinical and laboratory evaluation during the first 2 months of life), immunization strategies in this high-risk group are problematic. Despite these formidable challenges, Fischer *et al.* [11] noted in a recent review that evidence from animal studies as well as the success of neonatal hepatitis B immunization suggest that certain vaccines can stimulate the appropriate T-cell cytokine response to ensure appropriate B-cell responses.

Genetic immunization strategies

Advances in molecular biology have made it theoretically possible to simultaneously induce a vaccine recipient to produce a desired immunogen, as well as modulate the immune response to that antigen. Current genetic vaccines under investigation use direct intramuscular or intradermal inoculation of DNA, usually inserted in a bacterial plasmid with a promoter gene via syringe or gene gun (plasmids are attached to gold particles to enhance intracellular activity) [12••]. Host cells then manufacture the desired products. Vaccine DNA is usually designed to code for either specific antigens and/or expression of cytokines to induce or enhance specific immune responses (*ie*, to act as immunoadjuvants).

Past, Current, and Future Vaccines

Haemophilus influenzae type B

Disease background and past efforts

Clinicians who cared for pediatric patients prior to the late 1980s need no reminders of the devastating impact of Hib disease (which was quoted in one major pediatric textbook from that time as being responsible for an estimated 20,000 yearly cases of invasive disease [half meningitis]), the vast majority of which occurred in children less than 2 years of age [13]. In the mid-1980s, a polysaccharide vaccine using the capsular polysaccharide from Hib (PRP) was licensed in the United States. As a polysaccharide vaccine alone, it induced a T-cell-independent (Th2) response that was a poor stimulator of immunologic memory (with no booster response) and a poor immunogen in children younger than 2 years of age [10•]. No impact was seen on the highest risk age groups between 6 to 18 months of age, and overall rates of invasive *H. influenzae* disease did not clearly decline until the introduction of conjugated vaccines beginning in late 1987 [14,15].

Current and future vaccines

During the late 1980s, several vaccine formulations that conjugated PRP to a variety of proteins, including diphtheria toxoid, *Neisseria meningitidis* outer membrane protein (OMP), tetanus toxoid, and a mutant diphtheria toxin (CRM197) to induce a Th1 response, were phased into pediatric use [10•,14,15]. None of the four major preparations led to significant adverse reactions [14]. By 1993, all but the PRP-D formulation were approved for use beginning at 2 months of age. PRP-D was the only preparation which, after a three-dose primary immunization series at 2, 4, and 6 months of age, did not lead to initial anti-PRP antibody levels greater than the 1.0 µg/mL level believed to be predictive of long-term protection [14,15]. As a result it has only been licensed for use as a “booster” immunization after the first year of life where it has proven highly immunogenic [14]. By the early 1990s, the rate of invasive disease dropped over 90% and has all but disappeared in the United States in the late 1990s, a development likely explained by the discovery that nasopharyngeal carriage was greatly diminished in immunized children [10•,14,15].

Haemophilus influenzae type B vaccines offer no protection against nontypeable strains of *Haemophilus* that lack the PRP-containing capsule of Hib, which though less invasive, are still responsible for a wide spectrum of respiratory infections. Due to the significant differences among nontypeable strains, research has focused on the identification of antigens common to most isolates that may offer broad protection in a vaccine. In recent years several outer membrane proteins have been identified that are present in most nontypeable *H. influenzae* strains, and have demonstrated some protection when used as mucosal (via gut and pulmonary lavage) vaccines in a rat model [16]. These protein antigens will require significant further study prior to testing of a potential human vaccine.

Another challenge has been in the development of multivalent combination formulations to coadminister *Haemophilus* vaccine with other pediatric immunizations. Concern was recently raised when it was discovered that coadministration of an acellular pertussis-diphtheria-tetanus trivalent vaccine with PRP-tetanus toxoid resulted in generation of five- to 10-fold less levels of antibodies to PRP (compared to administration with diphtheria, tetanus, and pertussis [DTP] possessing whole cell pertussis vaccine), though fortunately this does not appear to be clinically relevant, since no impairment of antibody function or immunologic memory have been detected [17].

Bordetella pertussis

Disease background and past efforts

Pertussis (whooping cough) still is a major contributor to global mortality leading to greater than 350,000 annual deaths [1]. Extensive vaccine use in the United States has shifted the population at risk to include a combination of partially or unimmunized infants, plus a growing population of adults with waning vaccine immunity [18]. From the time of introduction of killed whole cell pertussis

vaccine in the late 1940s through the 1970s, the reported annual incidence of pertussis dropped by 99%, though widespread debate continues regarding the exact efficacy of the whole cell vaccine [19••]. Despite this success, concerns rose about the common significant side effects of the vaccine, which included local pain and swelling, systemic fever, anorexia, vomiting, and behavioral changes, along with the poorly substantiated claims of permanent neurologic sequelae, which led to a groundswell of negative publicity [18,19••]. As a result, intense efforts were undertaken to develop subunit or acellular pertussis vaccines to replace the whole cell preparations [19••].

Current and future vaccines

International efforts to develop an acellular pertussis vaccine focused on purified pertussis antigens that led to protective antibody responses in animal models [18]. Four licensed diphtheria-tetanus-acellular pertussis (DTaP) vaccines are currently available in the United States, containing in order one to four of the following subunits: pertussis toxoid (PT), filamentous hemagglutinin (FHA), an outer membrane protein (pertactin), and a fimbriae protein (fimbriae-2) [19••]. Though in general side effects are less than observed with whole cell preparations, this may be at the expense of efficacy. A complex and heated ongoing debate continues regarding the efficacy (the calculation of which is also a point of contention) and suitability of these products. One recent review suggests that efficacy, as defined by the most demanding assessment (against pertussis with ≥ 7 days of cough) of the four component vaccine, was 58%, while that of the single toxoid component vaccine was only 16% [19••]. Careful long-term monitoring of the protection offered by widespread use of these products will be necessary to judge the appropriateness of their use in the future.

A second issue that will need to be decided in the near future is the role of pertussis immunization in adults. While it is known that pertussis occurs in adolescents and adults, the specific epidemiology in these age groups has been poorly studied. Preliminary results suggest a favorable safety profile in use of these vaccines in otherwise healthy adults [20]. It is possible that acellular vaccine may be used in high-risk groups, such as those routinely exposed to young children, as well as more extensive incorporation into routine adult immunization schedules.

Measles vaccine: a potential target for global eradication

Disease background and past efforts

In an experience similar to the one observed with RSV (a related paramyxovirus), initial attempts in the 1960s to immunize children with a simple formalin-inactivated killed measles vaccine offered only brief protection and led to a more severe "atypical measles" illness in those who were subsequently infected with wild virus [21]. The first live attenuated measles vaccine, the Edmonston B strain, was associated with a high incidence of rash and fever,

which resulted in the practice of coadministration of immunoglobulin with this vaccine [22].

Current and future vaccines

The current measles vaccines have been further attenuated from the original strains, and only occasionally result in a mild fever or rash [22]. Subacute sclerosing panencephalitis (SSPE), a chronic degenerative central nervous system disease due to a persisting infection with a measles-related virus, was at one time thought to be related to live vaccine use. The decline of SSPE after widespread use of measles vaccine [22] supports the current belief that this disease was most likely a sequelae of natural measles infection. Overall, live attenuated measles virus leads to a strong serologic response in at least 95% of recipients [22]. Despite this, in the late 1980s sustained transmission was observed in highly immunized populations of young adults, leading to the decision in the United States to administer a second dose in childhood.

The lack of either prolonged shedding or latent infectious disease as well as the absence of a natural reservoir outside of humans theoretically makes measles an attractive target for global eradication. Epidemiologic surveillance in 1998 reported a record low 100 cases of measles in the United States, with the majority of cases having proven or suspected links to importation, indicating that measles appears to have been eliminated in the United States as an indigenous disease [23]. An intensive international effort is under way to first globally control and then eliminate measles [24]. Substantial progress has been made in the Americas, although portions of Africa, the Eastern Mediterranean, and Southeast Asia have required increased attention. These regions have been impacted negatively by regional political instability, reminding us that immunization strategies require social and political support for effective implementation.

Streptococcus pneumoniae

Disease background and past efforts

Now that *H. influenzae* has been effectively controlled, *S. pneumoniae* reigns as one of the most significant invasive bacterial pathogens in children and adults. In addition to the general global impact previously discussed, in the United States pneumococci are responsible for an estimated 3000 cases of meningitis, 50,000 cases of bacteremia, 500,000 cases of pneumonia, and several million cases of otitis media annually in children, and estimated to be responsible for approximately 100,000 admissions and 40,000 deaths annually in adults [25]. Additionally, steadily increasing rates of penicillin, cephalosporin, and macrolide resistance in *S. pneumoniae* have made antimicrobial therapy more difficult and less efficacious against many of the clinical diseases caused by this pathogen.

Current and future vaccines

The current pneumococcal vaccine contains purified capsular polysaccharides to the 23 most common serotypes

causing invasive disease (out of approximately 90), including nearly all strains that cause meningitis. As a pure polysaccharide vaccine, it is ineffective in children younger than 2 years of age and is not recommended for healthy adolescents or young adults. It is recommended for populations at increased risk for invasive disease, including those with functional or anatomic asplenia, humoral immunodeficiencies, neoplasms, chronic renal disease, recent organ transplantation, and disorders involving disruption of the meninges. In these high-risk populations the vaccine has demonstrated an approximately 57% efficacy [5]. It has also been recommended for adults over 65 years of age, in whom its efficacy has been estimated at 75% [5].

The tremendous success of the Hib vaccines has led to conjugation of pneumococcal capsular polysaccharides to the same array of protein conjugates, including diphtheria and tetanus toxoids, CRM₁₉₇, and *Neisseria meningitidis* OMP, which are used to shift towards a T-cell–dependent response [10•]. A greater challenge with pneumococcus is that unlike the single serotype of invasive Hib, approximately 90 serotypes of pneumococcus have been identified. Fortunately, a relatively small number account for the majority of invasive diseases, particularly meningitis. Current projections plan initial implementation of seven serotype (heptavalent) vaccines in the United States, including 85% of US invasive pathogens; nine serotype vaccines in Europe; and 11-serotype vaccines for global applications [25]. It is likely that the array of serotypes included in vaccines will need to be modified based on current regional patterns of invasive disease.

The vaccine closest to licensure in the United States is Wyeth-Lederle's (West Henrietta, NY) heptavalent vaccine, which contains polysaccharides to serotypes 4, 6B, 9V, 14, 19F, 23F and oligosaccharides of 18C, conjugated to CRM₁₉₇ [26]. This vaccine, along with other seven-, nine-, and 11-serotype vaccine preparations, are in active clinical testing, with all preparations appearing to be safe and immunogenic and leading to dramatic rises in highly avid and strongly opsonophagocytic antibody [26–28].

Preliminary results from the Northern California Kaiser Permanente Efficacy Trial using CRM₁₉₇ (pneumococcal vaccine), one of the largest efficacy trials, demonstrate no cases of invasive pneumococcal disease caused by vaccine serotypes in half of over 37,000 infants who were fully immunized with the pneumococcal vaccine versus 37 cases in control infants immunized with meningococcus type C CRM₁₉₇ conjugate vaccine [29•]. Additional benefits include a 20% efficacy against severe otitis media resulting in tympanostomy tube placement as well as a greater than 60% efficacy against serious pneumonia with consolidation. Although the goal of these vaccines is to protect immunized individuals, one study using the Merck (West Point, PA) heptavalent pneumococcus-OMP conjugate indicates that one or two doses may subsequently reduce nasopharyngeal carriage of both antibiotic-sensitive and resistant vaccine strains for at least 1 year in immunized

infants [30]. This could reduce disease in the population overall in a manner similar to the reductions seen in *Haemophilus* disease. Further testing of these vaccines is being pursued vigorously in other regions of the world as well as in specific high-risk groups.

Mycobacterium tuberculosis

Disease background and past efforts

Since the time of Koch, the prevention of tuberculosis remains a widely sought but enigmatic goal. The Advisory Council for the Elimination of Tuberculosis recently recommended that a "concerted and sustained national effort" to develop a new vaccine be made, including collaboration using private and public funds as well as partnership among the National Institutes of Health, the Food and Drug Administration, and the Centers for Disease Control and Prevention (CDC) [31]. Vaccine development is further challenged by the need for more rapid and accurate diagnostics of both latent and active disease, determination of the immunologic and genetic markers related to disease protection and progression, lack of ideal animal models, difficulties in performing efficacy studies, and a still poor understanding of the exact nature of the immune response to natural tuberculosis infection [31,32].

Current and future vaccines

Many countries immunize infants with BCG, a strain of *Mycobacterium bovis* that was attenuated through 13 years of serial passages in the laboratory until it apparently lost its virulence [8,32]. BCG is not used in the United States where overall rates of infection are low, where protection against disseminated disease in a small number of individuals would be offset by the difficulty in interpretation of tuberculosis skin testing for years after BCG, and the small risk of disseminated BCG disease (particularly in immunocompromised vaccinees) [8]. Though over a billion doses have been given globally in the three quarters of a century since its introduction, debate still exists regarding its efficacy, an issue further clouded by the evolution and use of several different offspring BCG vaccine strains since the 1920s [32]. Two large meta-analyses indicated that BCG was approximately 80% effective in preventing tuberculous meningitis and miliary tuberculosis in young children, although efficacy in older children and adults was uncertain [8,33].

Several potential new tuberculosis vaccines are under investigation and extensively discussed in a recent review [32]. The simplest technology might be to improve on the safety and infectivity of the BCG strain, enhancing its immunogenicity by adding either antigenic or cytokine genes that would enhance the appropriate T-cell response to the vaccine [32]. Also, some of the benign rapid-growing saprophytic mycobacteria, as well as bacterial autotrophs (ie, mutant mycobacteria that will die after limited replication) [32], are an attractive option for immunocompromised patients, where BCG or more potent attenuated live bacterial vaccines may potentially disseminate.

Tuberculosis is also one of the pathogens for which the use of DNA vaccines in mouse models appears potentially encouraging. In two recent studies, multiple (three to four) injections of three different plasmids coding for mycobacterial antigens each alone proved effective in leading to a degree of protection against *Mycobacterium tuberculosis* challenge that equaled BCG vaccine [34,35]. Recently developed "gene gun" technology may introduce intracellular vaccine plasmids more efficiently by attaching them to gold particles administered by a handheld helium-powered gun, although preliminary experience with this delivery route suggests that it alone may not stimulate a predominantly cellular response, indicating the need for adding genes to act as immunoadjuvants [12••].

Respiratory Syncytial Virus

Disease background and past efforts

In the wake of the highly successful inactivated polio vaccine, an attempt was made in the early 1960s to immunize infants against RSV using a similar simple formalin-inactivated vaccine. Unfortunately, immunized infants were incompletely protected, and on subsequent natural infection developed a higher incidence of pneumonia and hospitalization, with some mortality [36]. The exact nature of this "enhancing" immune response has been a source of investigation for over 30 years, with explanations that have included an imbalanced humoral response with excessive nonneutralizing antibody and more recently an excessively inflammatory Th2 immune response [37••]. This trial has haunted subsequent vaccine development, especially in light of some similar enhancement seen after immunization with a purified preparation of RSV's purified F surface glycoprotein [38].

Respiratory syncytial virus remains a major seasonal cause of infant hospital admissions in developed countries, is increasingly found in the elderly and in immunocompromised patients of all ages [39], and causes over 300,000 deaths annually in the developing world [1]. The natural immune response to RSV is brief and incomplete, as was dramatically demonstrated in a study that sequentially challenged 15 adults with the same RSV viral isolate on 2, 4, 8, 14, 20, and 26 months after initial natural RSV infection [40]. Thirty percent of adults were still susceptible to reinfection after the third challenge, and even after the seventh RSV challenge, 26 months after initial infection, at least 30% became infected. Thus, any potential RSV vaccine would have to overcome a naturally poor immune response.

One of the most promising to date includes the use of "temperature-sensitive" mutants (ie, RSV isolates initially selected and later engineered to survive only in the nasopharynx of vaccine recipients), thus inducing a protective immune response without the risk of lower respiratory disease. Although early isolates proved either too virulent or too attenuated, the latest vaccines appear sufficiently immunogenic yet maintained their temperature-sensitive

stability through clinical testing, even after replication in children without preexisting antibody [41]. Unfortunately, these isolates led to an excessive amount of upper respiratory symptoms in children as young as 6 months of age, whereas a subsequent generation of attenuated vaccine caused an unacceptable degree of nasal congestion in 1- to 2-month-old infants [41,42]. Other vaccines under investigation include a variety of RSV surface glycoprotein preparations (F, G, or chimeric combinations of both), some with adjuvants such as QS-21 to induce a shift to a Th1 response, glycoprotein expression vectors such as recombinant vaccinia, and DNA vaccines [37••,43].

Influenza Virus

Disease background and current vaccines

The CDC estimates that at least 110,000 influenza-related hospitalizations occur yearly, although rates obviously fluctuate widely [44]. One frequently understated fact is that current influenza vaccines are safe, inexpensive, and immunogenic, with an estimated efficacy of 70% to 90% for healthy children and adults [44,45]. Current preparations include inactivated whole virus, subvirion (split) virus, and purified-surface-antigen preparations [44,45]. All current preparations are trivalent, containing three relevant serotypes chosen annually based on the strains circulating at the end of the previous season. In recent years vaccines have consisted of the most recent H3N2 isolate, a circulating H1N1 (which accounts for a small percentage of disease since the late 1970s), and a B isolate. These vaccines are a "bargain" by today's standards, with late 1999 commercial costs ranging from \$2.80 to \$6.60 (US) per dose based on preparations and single- versus multiple-dose packaging [46].

Many argue that the greatest public health challenge is not in vaccine efficacy but in underutilization of effective existing vaccines. Although currently recommended for a variety of adults and children with chronic cardiac or pulmonary disease, diabetes, metabolic or renal disease, children on aspirin therapy, healthy adults over 65 years of age, and health care workers and home contacts of these patients [4,45], one recent study suggests that group-based immunization of school-age children could save upwards of \$35 (US) per vaccinated child, primarily in the reduction of indirect costs of associated family member illness and missed time from work [47]. Although significant progress has been made in the past decade, with immunization rates for individuals over 65 years of age increasing from 33% in 1989 to 65.5% in 1997, adults who have missed receiving immunization still give as their primary reason that they "did not know the shot was needed" [44].

Future Vaccines

A potentially more immunogenic and easy-to-administer intranasal influenza vaccine has gone through extensive clinical testing and may soon be available. This vaccine

Table 3. Currently used and potential future respiratory viral and bacterial vaccines

Pathogen	Current vaccines	Future vaccines
Diphtheria	Toxoid	
Pertussis	Acellular: proteins and toxoids	
Measles	Attenuated virus	
Mumps	Attenuated virus	
Rubella	Attenuated virus	
<i>Haemophilus</i>	Protein conjugated to PRP: PRP-OMP (meningococcus protein); PRP-tetanus toxoid; PRP-diphtheria toxoid; PRP-CRM ₁₉₇ (HbOC) (PRP-mutant diphtheria toxin)	
Pneumococcus	23-Valent pneumococcal polysaccharides	Protein conjugated to pneumococcus; pneumococcus-OMP (meningococcus protein); pneumococcus-tetanus toxoid; pneumococcus-diphtheria toxoid; pneumococcus RP-CRM ₁₉₇ (HbOC) (pneumococcus-mutant diphtheria toxin)
Meningococcus	A, C, Y, W-135 polysaccharides	Protein conjugate vaccines (still difficult for serotype B)
Tuberculosis	BCG (attenuated <i>Mycobacterium bovis</i>)	Improved BCG; benign saprophytic mycobacteria; limited replicating "autotrophs;" DNA vaccines; subunits?
Influenza	Whole virus (killed); "split" or subvirion; purified antigens	Cold-adapted, attenuated mutants; intranasal inactivated split virus
Respiratory syncytial virus	None (past failed formalin-inactivated virus)	Temperature-sensitive mutants; surface glycoproteins (F,G, or chimerics of both); subunits with novel adjuvants; vaccinia expression vectors

BCG—bacille Calmette-Guérin; HbOC—oligosaccharide-CRM₁₉₇ conjugate *Haemophilus influenzae* b vaccine; OMP—outer membrane protein; PRP—polyribosylribitol phosphate.

derives from a parent strain of cold-adapted, attenuated influenza developed by Maassab [48] in Ann Arbor in the 1960s that best replicates in the nose and thus stimulates local and systemic immunity without allowing lower respiratory infection. Several clinical trials in the past 15 years have shown that multivalent cold-adapted vaccines can be rapidly produced, containing desired reassortant strains. A double-blind randomized controlled trial comparing cold-adapted and inactivated influenza A vaccines (containing current H1N1 and H3N2 A serotypes) in 5210 healthy children and adults found that although serum hemagglutination inhibiting antibody titers rose higher in patients receiving inactivated vaccine, overall protection against subsequent influenza A infection was similar with both vaccines [49]. Significantly more complaints of sore throat, coryza, headache, and myalgia were noted in the live cold-adapted vaccine group.

A more recent study compared intranasal spray of cold-adapted trivalent (H1N1, H3N2, and B strains) influenza vaccine in one or two doses with placebo in children 15 to 71 months of age [50]. The intranasal vaccine proved to be highly protective, with an overall efficacy of 93% against all influenza (89% for one dose and 94% for two doses) and efficacies of 95% and 91%, respectively, against the H3N2 and B strains that circulated during that influenza season. Again, a small percentage of vaccine recipients

suffered from rhinorrhea, nasal congestion, or low-grade fever on day 2 after intranasal inoculation. Measurement of serum responses demonstrated that children who were initially seronegative were more likely to demonstrate four-fold increases in systemic HAI antibody titers. This did not correlate with vaccine efficacy as the high rates of efficacy were present in children of all ages, including the older ones with preexisting antibody. A commercial vaccine may be licensed in the near future based on these trials. Other influenza vaccines are being explored. Using an administration route similar to that of the attenuated vaccines, good protection rates have been seen with intranasal aerosol-containing inactivated split virus products [51].

Progress With Other Pathogens

Several pressing questions and challenges remain in the development of vaccines for other respiratory pathogens. Attempts are underway to apply the highly successful protein conjugate technology to development of meningococcal vaccines, though the B-serotype remains an enigmatic challenge. Group A streptococcal vaccines present a challenge of both multiple serotypes as well as approaching a pathogen for which significant immunologic and toxin-mediated complications exist [52]. Little progress has been made against "atypical pathogens" such as

mycoplasma and chlamydia. Several current vaccines may be improved by evolving technologies, as summarized in Table 3, and more convenient combination preparations are being investigated. In summary, although innovative technologies are leading to exciting new vaccines against respiratory pathogens, many difficult challenges remain, and one must recall that the history of vaccine development is full of "surprises." There will be sufficient challenge for scientists well into the twenty-first century.

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- Of importance
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