

VACCINES IN THE NEW MILLENNIUM

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Disability and death from infectious diseases can be prevented through vaccination, which is regarded as one of the most cost-effective interventions within the public health armamentarium. In the last 200 years, since the time of Edward Jenner, vaccination has been able to control eleven major diseases, at least in many parts of the world. These major diseases are: smallpox, diphtheria, tetanus, yellow fever, pertussis, poliomyelitis, measles, mumps, rubella, hepatitis B, and *Haemophilus influenzae* type B. As we move into the new millennium, new vaccines offer exciting possibilities for both the prevention and treatment of infectious and noninfectious diseases.

Vaccines of the Future

The introduction of vaccines for newly preventable diseases poses a challenge for their incorporation into an already complex immunization system. However, the following innovations are likely to have an important impact in the next few years.

Combination Vaccines

The current childhood vaccination schedule requires a minimum of 13 separate injections to immunize a child from birth to the age of six years. Combination vaccines merge into a single product antigen that prevents different diseases and/or protects against multiple strains of infectious agents causing the same disease. Thus, they increase coverage, decrease the number of injections in each clinic visit, and help to contain costs. There have been some successful vaccine combinations, such as diphtheria/tetanus/whole-cell pertussis (DTwP), measles-mumps-rubella (MMR) vaccine, and trivalent inactivated polio vaccine (IPV). New combinations in recent years are listed in Table 1. In the future, more combination vaccines are likely to emerge to protect against other diseases, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, hepatitis A and varicella.¹⁻³

Pneumococcal Conjugate Vaccines

In *Streptococcus pneumoniae*, the pneumococcus is the foremost cause of bacterial respiratory tract disease. In children, it is the most common cause of acute otitis media and sinusitis. In addition, the pneumococcus is clearly an important cause of pneumonia at all ages. Moreover, it can invade the bloodstream, and is responsible for more than

90% of cases of bacteremia in febrile children under the age of two years.⁴ Once in the bloodstream, the pneumococcus may cross the blood-brain barrier and cause meningitis. The current 23-valent polysaccharide pneumococcal vaccine has been shown to be ineffective in children under the age of two years.⁵ In addition, resistance of the pneumococcus to penicillin, cephalosporins and other antibiotics has become a serious problem.^{4,5} These factors prompted investigations that have culminated in the development of conjugated polysaccharide-protein vaccines. Covalent coupling of polysaccharide antigen to a carrier protein can improve the immunogenic response in young children. These new vaccines are similar in design to the already licensed *Haemophilus influenzae* type b conjugate vaccine.

Several conjugate pneumococcal vaccines are currently in development. More recently, a heptavalent preparation including serotypes 4, 6B, 9V, 14, 18C, 19F, 23F (PCV7) was deployed in two large prospective trials. The vaccine has been 90% effective in preventing pneumococcal bacteremia and meningitis in approximately 19,000 children who received the vaccine.⁶ The US Food and Drug Administration approved PCV7 (Premvar) in February 2000, and in June 2000 the American Academy of Pediatrics (AAP) recommended the use of this vaccine concurrently with other recommended childhood vaccines at 2, 4, 6 and 12 to 15 months (Table 2).⁷ Future implementation of routine immunization with the new conjugate pneumococcal vaccine could lead to significant reductions in the burden of pneumococcal disease in children and adults.

Live-Attenuated Influenza Vaccine

Vaccination with inactivated virus has been the mainstay of prevention of influenza for the last 40 years and provides around 70%-80% protection when there is a good match between the vaccine and circulating strains.⁸ Live-attenuated, cold-adapted intranasal vaccines are currently under development. This vaccine delivers a larger dose of immunogen to bronchus-associated lymphoid tissue than inactivating vaccine, offering the advantage of a broader immunologic response.⁸ In addition to their convenient route of administration (nasal spray) and high patient acceptability, live cold-adapted vaccines stimulate local mucosal immunity, thereby providing the

strongest possible line of defense against influenza. In a recent multicenter, placebo-controlled trial in children, the overall protective efficacy of these vaccines was 93% (influenza A, 95%; influenza B, 91%).⁹

TABLE 1. *New combination vaccines.*

Vaccine
DTwP-IPV
DTwP-IPV-HIB
DTaP-IPV
DTaP-IPV-HIB
DTwP-HBV
DTaP-HBV
MMR-V
HBV-HAV
HBV-HIB
DTwP=diphtheria-tetanus-whole cell pertussis; DtaP=diphtheria-tetanus-acellular pertussis; IPV=inactivated poliovirus vaccines; HIB= <i>Haemophilus influenzae</i> type b; MMR-V=measles-mumps-rubella-varicella; HBV=hepatitis B virus; HAV=hepatitis A virus.

TABLE 2. *Recommended schedule of doses for heptavalent pneumococcal conjugate vaccine (PCV7), including primary series and catch-up immunizations in previously unvaccinated children.*

Age at first dose	Primary series	Booster dose*
2-6 months	3 doses, 6-8 weeks apart	1 dose at 12-15 months of age
7-11 months	2 doses, 6-8 weeks apart	1 dose at 12-15 months of age
12-23 months	2 doses, 6-8 weeks apart	
≥24 months	1 dose	

*Booster doses to be given at least 6 to 8 weeks after the final dose of the primary series.

TABLE 3. *Future targets for DNA vaccines.*

Virus	Bacteria	Parasite
Herpes simplex virus	Chlamydia	Leishmania
Human immunodeficiency virus	Tuberculosis	Malaria
Hepatitis C virus		
Human papillomaviruses		

TABLE 4. *Sources of vaccine information.*

Publications	Web Sites
Report of the Committee on Infectious Diseases. AAP (Red Book) published every 3 years	Questions and answers about vaccine safety (www.cdc.gov/nip/news/vacsafe/htm)
Report of the ACIP CDC publication in MMWR periodically.	The vaccine page, vaccine news and database (http://vaccines.com/aboutus.htm)
Health information for international travel (published yearly)	CDC travel information (http://www.cdc.gov/travel/travel/html)
Physicians desk reference and official vaccine package circulars	

AAP=American Academy of Pediatrics; ACIP=Advisory Committee on Immunization Practice; MMWR=Morbidity and Mortality Weekly Report.

DNA Vaccine

A DNA vaccine contains a piece of circular DNA including a promoter, gene segment and termination signal. This provides a plate form for producing a specific antigen. These vaccines can either be used for direct

vaccination or as tools to identify antigens which will elicit a protective immune response. Although the biological events following intramuscular infections of DNA vaccines are not fully understood, it is thought that the antigen encoded in the DNA is expressed in the cytoplasm of the muscle cell (via RNA and protein production), and presented to the endogenous MHC class 1 receptors, and also secreted from the cell.^{10,11} In many respects, the outcome of this form of immunization mimics the action of live-attenuated or recombinant virus vaccine. Because of their unique ability to elicit cellular responses, current targets for DNA vaccines include viruses, bacteria and parasites (Table 3).

Conclusion

The future of vaccines is particularly exciting, with the developments in DNA vaccines, conjugate vaccines and the availability of combination vaccines. The latter will play an important role in future childhood immunization strategies. Ongoing clinical trials using accelerated schedules of combination vaccines are in progress and may provide greater protection for children against infectious diseases. Research to develop and evaluate alternative means of antigen delivery by the mucosal¹² and cutaneous routes¹³ would allow new and existing vaccines to be administered less painfully and more safely than with needles and syringes.

Sources of Information on Immunization

Clinicians should utilize the scientific literature and other sources for data or answers to specific questions encountered in practice (Table 4). On the Internet, there are also informative websites by the Centers for Disease Control and Prevention (Table 4). These Internet resources allow health care providers to improve vaccine education for their patients and themselves.

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