INTRODUCTION

Vaccination is one of the most valuable and cost-effective strategies available to medicine in the battle to prevent and control infectious diseases. It is considered to be one of the ten greatest public health achievements of the 20th century (1). In the Americas, vaccination has brought about the eradication of smallpox in 1970 and of polio in 1991; the interruption of indigenous measles transmission in 2002; and the lowest numbers of reported cases of congenital rubella syndrome (CRS) and neonatal tetanus at the onset of the 21st century (1, 2).

Over the last four decades, important new and improved vaccines to prevent childhood diseases have been developed; more are in the pipeline. As the number of vaccine-preventable diseases increases, so does the number of injections a child must receive to be fully protected. In 1999, the Recommended Childhood Immunization Schedule in the United States included 10 different vaccines—hepatitis B (Hep B); diphtheria, pertussis, and tetanus (DPT); Haemophilus influenzae type b (Hib); injectable polio vaccine (IPV) or oral polio vaccine (OPV); measles, mumps, and rubella (MMR); and varicella—which required a minimum of 13 injections to immunize a child from birth to age 6 years (3). By 2005, the United States childhood immunization schedule (4) recommended the inclusion of two additional vaccines: the conjugated pneumococcal vaccine (PCV) and the influenza vaccine. At this juncture, OPV was replaced with IPV, and diph-
theria, tetanus, and whole-cell pertussis (DTwP) was replaced with diphtheria, tetanus, and acellular pertussis (DtaP). Thus, the current United States childhood vaccination schedule now requires between 18 and 21 separate injections before a child enters school and as many as 5 separate injections in a single doctor’s office visit. Most Latin American countries, on the other hand, follow a schedule that differs both in the number and the type of vaccines—10 vaccines, including BCG at birth; OPV, DTwP, Hib, and Hep B at 2, 4, and 6 months; and MMR at 12 months, require between 6 and 7 injections before school entry and as many as 2 separate injections during a single clinic visit (5).

Judging by recent vaccine coverage levels in the United States and the rest of the Region of the Americas, the number of injections required at this time does not appear to deter parents from vaccinating their children. There are two potential threats to the future of immunization programs, however. As new vaccines are introduced, requiring more injections, the acceptance threshold may begin to decline. Equally worrisome is the fact that, as specific diseases preventable by immunization are contained, the public’s perception of disease risk and vaccine benefit for a disease that is no longer common may negatively affect the acceptance of numerous injections. A way to reduce the number of injections without reducing the number of diseases for which a child receives protection is to use combination vaccines (6–9).

**COMBINATION VACCINES**

Combination vaccines contain multiple antigens combined into a single preparation by the manufacturer or by the health-care worker, providing protection against multiple diseases. DTP is an excellent example of a combination vaccine, which protects against diphtheria, tetanus, and pertussis. There also are combination vaccines that protect against multiple strains of an infection that cause the same disease (multivalent vaccines), such as the Sabin oral attenuated polio vaccine (OPV) and the injectable Salk inactivated polio vaccine (IPV), both of which protect against polio viruses 1, 2, and 3. And there are vaccines that protect against serotypes of the same organism, such as the currently licensed heptavalent conjugated pneumococcal vaccine (PNV), which protects against the seven serotypes of *Streptococcus pneumoniae*. Another example is the trivalent influenza vaccine, which is prepared yearly with three inactivated viruses, type A (H1N1), type A (H3N2), and type B.

The use of combination vaccines reduces the number of injections required to prevent specific diseases and, in so doing, reduces trauma and pain experienced by the recipient (9, 10). Other potential advantages or at-
tributes of combination vaccines are that they: a) improve the timeliness of vaccination coverage, b) reduce costs associated with stockpiling and administering separate vaccines, c) reduce costs associated with extra healthcare visits that result from delayed vaccinations, and d) facilitate the integration of new vaccines into the childhood immunization schedule. Although the price of a new combination vaccine usually exceeds the total price of separate vaccines for the same diseases, the extra expense should be considered against the direct and indirect costs of extra injections, delayed or missed vaccinations, and additional handling and storage (11, 12).

PAST, PRESENT, AND FUTURE COMBINATION VACCINES

Combination vaccines have been available for more than half a century. The concept was put into practice in the United States in 1945, with the licensing and introduction of the trivalent influenza vaccine; a hexavalent pneumococcal polysaccharide vaccine followed in 1947. It wasn’t until the licensing of the combination vaccine that included diphtheria and tetanus toxoids and whole-cell pertussis (DTwP) in 1948, however, that combination vaccines had widespread acceptance in routine vaccination practices of infants and children. Seven years later, the trivalent inactivated polio virus vaccine (IPV) was licensed and introduced. Then came the oral polio vaccine (OPV) in 1962 and the measles-mumps-rubella vaccine (MMR) in 1971.

More recently, additional combination vaccines have been licensed and introduced into the immunization schedule of children in the United States, including: diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP); DTwP-Haemophilus influenzae type b (Hib) vaccine (DTwP-Hib); DTaP-Hib; Haemophilus influenzae type b conjugate vaccine-hepatitis B vaccine; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus vaccine; pneumococcal conjugate vaccine (which contains seven serotypes of Streptococcus pneumoniae conjugated); and the trivalent influenza vaccine (13–15). Combination vaccines recently introduced in Latin American countries include the DTwP-Hep B-Hib vaccine. This combination vaccine allowed Hep B and Hib vaccines to be introduced without adding new injections. Rubella and mumps vaccines also have been added to many country schedules by combining rubella and mumps antigens with the measles antigen (MR and MMR vaccines).

The great variety of available combination-vaccine options poses a challenge for the clinician who must keep current with new knowledge about the antigens in the combinations, let alone the commercial names. In the future, additional combination vaccines designed to protect against other diseases are likely to emerge. They will need to be tailored to regional needs wherever the prevalence and disease burden of known, emerging,
or reemerging diseases may justify their manufacture. It should be kept in mind, however, that although most of the technology and infrastructure needed to manufacture these products resides in industrialized countries, these combination vaccines may not necessarily be a priority in the country of origin. WHO recognizes that, other than the United States and Canada, there are three Western Hemisphere countries that are capable of producing vaccines: Brazil (through the Oswaldo Cruz Foundation and the Butantan Institute), Cuba (through its Center for Genetic Engineering and Biotechnology, known for its Spanish acronym, CIGB), and Mexico (through the Mexican Laboratories for Biologicals and Reagents, known for its Spanish acronym, BIRMEX). All three are attempting to satisfy local needs.

**IMMUNOGENICITY AND EFICACY OF COMBINATION VACCINES**

Combination vaccines differ from single-component vaccines in makeup and in how they are manufactured. Combining multiple antigens into one preparation requires the in vitro demonstration of chemical compatibility. In addition, clinical trials are needed to substantiate that there is no decrease in the safety of the combined vaccines or immunologic interference when different antigens and other components (such as adjuvants, stabilizers, and preservatives) are combined into one vaccine. Such interference could compromise the safety, immunogenicity, and efficacy of the combined vaccine. Chemical incompatibility or immunologic interference when different antigens are combined into one vaccine are difficult challenges to overcome. The carrier proteins of conjugate vaccines may suppress or increase the response of other preparations containing these. In a combination vaccine, the adjuvant should improve the response to at least one of the relevant antigen(s), without exerting a clinically significant detrimental effect on immune responses to any other antigen in the vaccine (16–18).

Because each combination vaccine is unique, existing guidelines often fail to provide sufficient information to overcome the inevitable problems encountered when developing and implementing potency tests. Another potential challenge in giving vaccines in combination is that it may not always be clear which component is responsible for a particular adverse event. Combination vaccines from different manufacturers may have different recommended dosage schedules, potentially increasing the confusion for the provider (19).

Since the licensing of the diphtheria, tetanus, whole-cell pertussis vaccine (DTwP) in 1948, its impact on childhood morbidity and mortality has
been undisputed. Inclusion of DTwP in childhood immunization programs continues to have wide acceptance in routine immunization programs of infants and children throughout the world. However, the nature of the pertussis antigens in DTP may influence the immunogenicity and effectiveness of the vaccine.

In the clinical development of the DTwP-HB-Hib vaccine, studies were conducted in several countries to evaluate how incorporating Hib into a DTwP-HB tetravalent vaccine might improve protection and kinetics. This pentavalent vaccine proved to be highly immunogenic for all vaccine antigens and no interference was demonstrated for any of the antigens, including PRP/Hib. A very important, albeit unexpected, finding was that the kinetics response for the anti-HBs component was significantly improved in some combination vaccines (9, 20). The anti-HBs response reached a 95% seroprotection level (≥10mIU/ml) after the second dose of the DTwP-HB and DTwP-HB-Hib vaccines. In contrast, when DTwP and HB were given separately, the seroprotection response level for the anti-HBs component after the second dose of both vaccines was only 66%. The tetravalent DTwP-HB vaccine mixed with Hib also induced protective antibody titers against diphtheria, tetanus, and *H. influenzae*, as well as high anti-pertussis titers. A study conducted in five Latin American countries and involving 400 subjects confirmed the immunogenicity and reactogenicity profile of the DTwP-HB-Hib pentavalent vaccine established earlier. In this study, the immunogenicity for the individual components of the pentavalent vaccine was 100% for tetanus, *Bordetella pertussis*, hepatitis B, and PRP (poly-ribitol-phosphate, the capsular polysaccharide of Hib) type b/Hib and 98% for diphtheria. Seroprotection levels and geometric mean titers (GMTs) were comparable with the group receiving separate injections of DTwP-HB + PRP-TT (20, 21).

The difficulty in interpreting the clinical significance of antibody interference with combination vaccines is highlighted by the experience of combinations containing acellular pertussis (aP) vaccines (22). Two trials in Europe found a significant difference in post-immunization levels of diphtheria antitoxin, depending on whether any pertussis antigens were present in the vaccine and what the nature of the antigens was (23). The addition of an efficacious whole-cell pertussis (wP) component to the diphtheria and tetanus vaccine increased the geometrical mean titer of diphtheria antitoxin in the recipients. The addition of aP or a poorly efficacious whole-cell pertussis vaccine produced lower geometrical mean titers of diphtheria, compared to diphtheria titers in tetanus vaccine. In a few children, the concentrations reached were considered non-protective, confirming the well known “adjuvant” effect of efficacious whole-cell pertussis vaccines.
Combinations of Hib vaccines with DTwP vaccines were generally not associated with significant diminutions in immunogenicity to the Hib or DTP components. When Hib vaccines were combined instead with some DTaP vaccines, however, significantly lower geometrical mean concentrations of anti-Hib capsular polysaccharide IgG were observed (24). The extent of this reduction is not the same for all DTaP-Hib combinations. DTaP-Hib combinations containing five-component acellular pertussis appear to show little, if any, such reduction (25–28). Most importantly, the clinical significance of the lower antibody concentrations remains unclear. Recently the United Kingdom has reported a rise in Hib cases in fully immunized children who received a DTaP-Hib preparation (29). While this observation clearly suggests that there may be clinical significance to these antibody differences, other factors, such as the accelerated three-dose regimen used in the country, may have also contributed to the observed rise in Hib cases as well.

Responding to a recent rise in the incidence of *H. influenzae* type b disease in the United Kingdom, researchers conducted a study to assess Hib antibody concentration and avidity before and after the administration of an Hib booster. The rise in incidence was temporarily linked to the use of diphtheria-tetanus-acellular pertussis combination vaccine (DTaP-Hib) during 1999–2002. Between 1999 and 2002, the United Kingdom used aP combination vaccine because of a shortage of whole-cell combination vaccine. Their data suggest that DTaP can interfere with normal antibody avidity maturation that occurs after priming with Hib vaccine, and may explain the increased incidence of *H. influenzae* type b after 1999 (30).

Dagan et al. (31) reported that infants who were given a diphtheria-tetanus-pertussis-polio-Hib vaccine in which the Hib component was conjugated to tetanus, simultaneously with a pneumococcal vaccine also conjugated to tetanus toxoid, had lower Hib PRP antibody concentrations than infants who had received pneumococcal vaccine conjugated to diphtheria toxoid. Furthermore, children who had received higher doses of pneumococcal tetanus conjugate had poorer responses.

Finally, a phase 2 randomized controlled trial conducted in two United Kingdom centers examined the immunogenicity and safety of two vaccines. It compared a combination 9-valent pneumococcal-group C meningococcal conjugate candidate vaccine (Pnc9-MenC) with a monovalent group C meningococcal conjugate vaccine (MenC) administered in addition to routine immunizations (diphtheria and tetanus toxoids and whole-cell pertussis [DTwP], *Haemophilus influenzae* type b [Hib] polyribosylribitol phosphate-tetanus toxoid protein conjugate, and oral polio vaccine) in infants aged 7 to 11 weeks. The results revealed that although the Pnc9-MenC vaccine administered to infants at ages 2, 3, and 4 months was safe
and immunogenic for all contained pneumococcal serotypes, it demonstrated reduced group C meningococcal immunogenicity compared with the MenC vaccine. The immunogenicity of concomitantly administered Hib and DTwP vaccines also was diminished for group C meningococcus antigen. The authors conclude that the Pnc9-MenC vaccine as tested may not be a suitable replacement for individual MenC or pneumococcal glycoconjugate vaccines. More importantly, this study is unique in that it also evaluated the concomitant administration of seven vaccines, including three separate combination vaccines—DTwP, trivalent OPV, and Pnc9-MenC—underscoring the importance of assessing the immunogenicity of all co-administered vaccine antigens in prelicensure trials (32).

In many cases, combination vaccines may give a lower but still protective immune response as compared to separate vaccines. Some vaccine efficacy studies have generated antibody levels that correlate with protection from disease. These “immunologic correlates” of protection are important because they allow us to assess the clinical significance of any immunologic interference.

**REACTOGENICITY AND SAFETY OF COMBINATION VACCINES**

There is substantial evidence that combining vaccines into one product does not increase the overall rate of clinically significant, temporally associated adverse events. With some combinations, such as DTaP, the rates are sometimes lower than when the component vaccines are given separately (9, 15, 18). An important exception has been DTwP, the first combination vaccine licensed.

There have been long-standing concerns about the relative safety of the whole-cell pertussis component of this vaccine. The reactogenicity, temporally associated with the wP component of the DTwP vaccine, including redness and swelling at the site of injection, agitation, febrile seizures and hypotonic-hypo-responsive episodes, high fever, persistent crying, and a fear of rare, but serious, acute or chronic neurological events, led several countries to discontinue its inclusion in routine immunization programs and prompted the development of a new generation of pertussis vaccines, the acellular (aP) vaccines. It is important to mention that despite thorough investigations, the link suspected between wP vaccines and rare cases of permanent neurological damage has not been confirmed (9, 35, 36). Schmitt et al. compared antibody responses in children receiving DTaP-HBV-IPV-Hib as one injection with children receiving the same antigens but with the Hib given at a different site. No difference was found in adverse events temporally associated with the different regimens (34).
In 1998, a paper published in the *Lancet* was interpreted by anti-vaccine groups as showing a link between measles, mumps, and rubella vaccine and developmental disorder and bowel disease (35), even though the authors said they had not proved such a link. Subsequent research has failed to find evidence for this link (35, 36). The suggested mechanism behind the hypothesis was that combining antigens produced an unpredictable response. Some parents are concerned that multiple antigens may overload the infant’s immune system. A recent review set in context the antigenic load from vaccines in comparison with that from the environment and emphasized the capacity of the immune system to respond effectively to numerous simultaneous antigens (37). The tetravalent DTwP-HB vaccine mixed with Hib also induced protective antibody titers against diphtheria, tetanus, and *H. influenzae* and high anti-pertussis titers. Results involving 400 subjects did not reveal an increase in the reactogenicity with the addition of hepatitis B antigen to DTwP or the mixing of Hib with the DTwP-HB combination as compared to DTwP alone (20, 21).

The preservative thimerosal plays a role in the heat inactivation of bacteria in the production of whole-cell pertussis vaccines and is present in DTwP and DTwP-Hib products. It is not present in some of the acellular pertussis products available such as DTaP and DTaP-Hib. A recent study has shown that the amount of mercury in the blood of children receiving thimerosal-containing vaccines is well below that potentially associated with any toxic effect, even when administered at 2 months of age (38).

**EXTRA DOSES AND INTERCHANGEABILITY OF COMBINATION VACCINE ANTIGENS**

The Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP) recommend that, in order to minimize the number of injections children receive, licensed combination vaccines may be used whenever any components of the combination are indicated and other components of the vaccine are not contraindicated (4, 7, 13). Since immunization providers might not have vaccines available that contain only those antigens indicated by a child’s immunization history, it is not necessary to stock all available types or brand-name products; rather, sufficient types of combination and monovalent vaccines needed to vaccinate children against all diseases for which vaccines are recommended should be stocked. Alternatively, the indicated vaccines might be available, but the provider nevertheless might prefer to use a combination vaccine to reduce the required number of injections. When patients have already received the recommended vaccinations for some of the components in a combina-
tion vaccine, administering the extra antigen(s) in the combination is often permissible if doing so will reduce the number of injections required (4, 9).

In general, since the safety, immunogenicity, and efficacy of unlicensed combinations are unknown, products that are not specifically approved for mixing should not be mixed in the same syringe.

INTERCHANGEABILITY

In the case of the immunization series for an individual patient, certain vaccines from different manufacturers that protect against the same disease may be administered interchangeably in sequential doses (e.g. HepB and Hib). Combination products with similar component antigens produced by the same manufacturer (such as DTaP, DTaP-Hib, or other DTaP-combination vaccines that contain similar acellular pertussis antigens from the same manufacturer) may be used interchangeably (9).

WHICH COMBINATION VACCINES ARE APPROPRIATE FOR WHICH COUNTRY? EPIDEMIOLOGIC AND ECONOMIC CONSIDERATIONS

ACIP, AAP, and AAFP recommendations on combination vaccines for childhood immunization extend beyond the United States borders. These recommendations exert a strong influence in the private practice of pediatricians, family practitioners, and other physicians who attend children around the world.

In most developing countries, immunization is carried out as a national-level program under the responsibility of the Ministry of Health. Immunization policy is driven largely by the burden of disease to be prevented by the combination vaccine in question, the public health resources available, and WHO recommendations. In the Americas, PAHO’s Technical Advisory Group (TAG) on vaccine-preventable diseases has played and continues to play a pivotal, proactive role. Thus, while specific combination vaccines such as IPV and DTaP, PNV, and trivalent influenza vaccines are now the standard of care for children in the United States, OPV and DTwP are still recommended by both WHO and PAHO. In the case of the hepatavalent conjugated PNV, which is a well accepted priority in most countries, both cost and supply issues have precluded its introduction into developing countries thus far. Acellular pertussis vaccines are generally better tolerated than whole-cell products. However, the difference between the two products is predominantly in the rate of mild adverse events, which do not have an impact on health as severe as that from whooping
cough or Hib infection, both of which can be life threatening. Because of these factors, the tetravalent DTwP-Hib and the pentavalent DTwP-HepB-Hib combinations continue to be recommended by PAHO’s Technical Advisory Group on vaccine-preventable diseases as the preferred vaccine for the primary series at 2, 3, and 4 months (9). This recommendation is also supported by the recent experience in the United Kingdom (30) (see Box 1).

Many, but not all, of the new combination vaccines have been found to be safe and protective in clinical trials in developing countries under controlled conditions; however, evidence from post-marketing surveillance is often needed in order to evaluate whether the vaccine will perform equally well under field conditions once introduced into a program and sustainability can be assured (39, 40).

There are other circumstances in which the introduction of a combination vaccine into the routine schedule poses dilemmas. This is the case with combination vaccines that contain Hep B vaccine as a component, which are being introduced in countries with high seroprevalence of antibodies against hepatitis B core antigen (anti-HBC). Some experts have con-
cerns about what to do about the birth dose (the birth dose is the standard of care in the United States, as recommended by ACIP, AAP, and AAFP (4)). Since most other countries in the Region are using combination vaccines containing Hep B vaccine, a routine birth dose not only adds to the direct costs because of the need for single-dose vials, but also makes it programmatically difficult to introduce in countries with significant rural populations or marginalized urban populations. Both WHO and PAHO have established priorities for hepatitis B immunization strategies in order of importance: routine infant vaccination; prevention of perinatal HBV transmission from mother to offspring; and catch-up vaccination for older age groups. Hepatitis B seroprevalence was investigated in over 12,000 subjects in six Latin American countries or regions of countries: Argentina, Brazil’s Amazon region, Chile, the Dominican Republic, Mexico, and Venezuela. Each study population was stratified according to age, gender, and socioeconomic status. Antibodies against hepatitis B core antigen (anti-HBc) were measured in order to determine hepatitis B infection. The highest overall seroprevalence was found in the Dominican Republic (21.4%), followed by Brazil (7.9%), Venezuela (3.2%), Argentina (2.1%), Mexico (1.4%), and Chile (0.6%). In all the countries, an increase in seroprevalence was found among persons aged 16 years and older, suggesting sexual transmission as the major route of infection. In addition, comparatively high seroprevalence levels were seen at an early age in the Dominican Republic and Brazil, implicating a vertical route of transmission (41).

Thus, with the exception of the Dominican Republic and Brazil’s Amazon region, it usually has proved to be easiest when the three doses of hepatitis B vaccine are incorporated into the routine childhood vaccination schedule and given at the same time as the three doses of DTP, at 2, 4, and 6 months, respectively (9, 41). This schedule does not prevent perinatal hepatitis B virus infections, because it does not include a dose of hepatitis B vaccine at birth; however, this schedule does prevent infections acquired during early childhood, which account for most of the disease burden related to hepatitis B virus in countries of high disease endemicity. Over several years, as the child population gradually becomes protected against HBV infections acquired later in life, the prevalence of chronic HBV infection will decline. This process can be further accelerated by initiating an adolescent immunization campaign with a two-dose schedule where there is a documented increase in seroprevalence due to sexual transmission.

LESSONS FROM THE AMERICAS

In addition to the advantages of reducing the number of injections, combination vaccines have contributed significantly towards the harmoniza-
tion of immunization schedules of countries in the Americas. In 1992, WHO proposed including hepatitis B (HB) vaccine in countries where hepatitis B was endemic (carrier rates of 8% or greater) by 1995 and in all countries irrespective of prevalence by 1997. In 1991, the United States Advisory Committee on Immunization Practices (ACIP) recommended that both HB and Hib be included (as separate injections) into the routine universal immunization schedule for infants in that country. In 1996, WHO recommended that countries consider the use of combined DTP-HB vaccine when it became commercially available. In 1997, PAHO’s Directing Council urged its Member States to strengthen surveillance in preparation for the introduction of new vaccines (such as *Haemophilus influenzae* type b, hepatitis B, and measles-mumps-rubella) to accurately determine disease burden and develop an appropriate vaccination strategy. In 1998, several countries in the Region introduced MMR to supplant the measles vaccine, thus increasing the number of vaccines in the Expanded Program on Immunization (EPI) from six to eight vaccines without changing the immunization schedule. By 2002, more than 90% of the Region’s children were receiving MMR, and the countries of the Americas were documenting a significant drop in the number of registered cases of congenital rubella syndrome (CRS) (Figure 1) (8).

Although *Haemophilus influenzae* type b conjugate vaccine has been available and in use in the United States and Canada since 1987, it wasn’t until 1994 that Uruguay, which had a meningitis surveillance program in place, decided to include Hib vaccine in its regular immunization program. Two years later, based on a robust surveillance system and the ex-

**FIGURE 1.** Annual reported rubella cases, Region of the Americas, 1982–2005.

*Data for 2005 up to week 41.*

*Source: Pan American Health Organization/Ministries of Health.*
The impact of Hib vaccine on invasive disease in both countries was impressive (Figure 2). As the figure shows, within one year of its introduction, the incidence of invasive disease due to *Haemophilus influenzae* type b in both countries plummeted (10).

By 1996, the U.S., Canada, Uruguay, and Chile were applying Hib vaccine, benefiting 4.5 million infants, representing 30% of all newborns in the Americas Region but only 3.4% of all newborns in Latin America. In 1999, with the availability of a new vaccine formulation (DTP-HepB-Hib), Mexico and Brazil joined the PAHO Revolving Fund and, due to large-volume purchases helped reduce the price of Hib—the price of the vaccine had ranged from US$ 4.00 to US$ 8.50 when purchased directly from the manufacturers, and dropped to a record low of $3.50 (including DTwP and Hep B). By participating in the revolving fund, these two countries were able to introduce both Hib and Hep B without changing their immunization schedules. The lowered prices had an important impact on the prices of the monovalent Hib and DTP-Hib due to competition, which allowed other countries in the Region to incorporate Hib into their regular immunization program. By 2000, it was estimated that 15,889,000 infants, 92% of all newborns in the Region and 89% of all newborns in Latin America, had received Hib and hepatitis B vaccines (Figure 3). Since then, many countries in the Americas have introduced combination vaccines that contain Hib, Hep B, or both, such as in the DTwP-HB-Hib pentavalent vaccine (10).
COST ISSUES

One of the leading deterrents for introducing new vaccines has been their price. New combination vaccines are expected to cost more than traditional childhood vaccines. Thus, before introducing a new combination vaccine, or any vaccine for that matter, it is important to conduct economic evaluations looking at the actual vaccine and operating costs in the context of the country’s public health expenditure. Equally important is being able to guarantee the sustainability of the vaccine in the program once introduced, which often is determined more by guaranteed supply than cost issues (11, 42).

The introduction of combination vaccines in Mexico between 1956 and 2004 (Box 2) has had remarkable effects, as evidenced by recent developments. When Mexico adopted WHO’s EPI, the immunization schedule consisted of six vaccines—two combination vaccines, IPV (which was later supplanted by OPV), BCG, DTP, and measles. The schedule remained unchanged for 25 years until 1998, when MMR supplanted the measles monovalent vaccine. Successful field trials with DTP-HepB-Hib carried out in Mexico and other countries in the Region permitted this combination vaccine to be introduced in place of DTwP in 1999 (21). Combination vaccines also have been introduced into the adolescent immu-
nization schedule: the tetanus booster was supplanted by Td, and MR was added to the adolescent schedule in an effort to eliminate neonatal tetanus, protect against diphtheria, and accelerate the containment of wild measles and the elimination of congenital rubella syndrome. Concerned about the impending influenza pandemic, Mexico’s National Immunization Council (CONAVA) introduced the trivalent influenza vaccine in 2004 as part of the national immunization program for infants between 6 and 23 months.

Over an eight-year period (1997–2004), with the introduction of combination vaccines, Mexico’s immunization schedule almost doubled, increasing from six to 11 vaccines. Because combination vaccines were incorporated into the existing schedule, the number of injections did not change. During the same period, the vaccine cost increased significantly, from a low of US$ 1.40 for the complete EPI schedule to US$ 13.50 when measles was supplanted by MMR and DTwP by DTP-HepB-Hib. The reasons behind the success of Hib vaccine introduction in the Region can be attributed to the existence of strong EPI programs in the countries together with strong leadership at PAHO’s central and country levels.

REMAINING CHALLENGES

The future of combination vaccines in the 21st century will play an important role in future childhood immunization strategies. Combination vaccines present unique challenges and opportunities for manufacturing and
product development. Vaccine development should focus on generating strong, broad-based immunity to several antigens from a number of pathogens using combination methodologies to the extent possible. The advances in molecular biology and genetic engineering will play an important role in developing new combination vaccines, including DNA vaccines and conjugate vaccines. Alternative means of multiple antigen delivery by the mucosal and cutaneous routes are also being explored (45).

Achieving optimal safety and effectiveness for all vaccines is a top priority, particularly because vaccines are administered to healthy children. The pre-licensing evaluation of combination vaccines composed of previously licensed components or of novel antigens will require well-designed and well-coordinated multinational prospective clinical trials with realistic sample sizes and appropriate control groups. The major task ahead for anticipating the introduction of existing or new combination vaccines requires the joint participation of several government ministries, investigators, private and public vaccine manufacturers, international and local regulatory agencies, international agencies, and the public at large. The success of these public health strategies will depend on the extent to which countries place a value on the benefit of vaccines, and accordingly make vaccines available to their populations and guarantee their sustainability once introduced. It is important to underscore that there is a difference between vaccines being cheap and being affordable (11, 45, 46). Lessons learned from the Americas demonstrate that through political will, combined with innovative financing and consolidated purchasing strategies, new combination vaccines can be introduced and used in immunization programs by countries, regardless of their income level.

References


