Ronald Saldarini (President, Wyeth-Lederle Vaccines & Pediatrics) discusses the factors that can hinder or encourage greater industrial investment in vaccine research and development. Saldarini argues that the commercial sector's commitment to vaccines has never been higher and that appropriate national and international policies on pricing and purchasing will ensure better implementation and continuing research.

For vaccines, the future is now

If industry were describing its role in vaccines of a decade ago, it would stress a good record as a reliable supplier of diphtheria-tetanus-pertussis, measles-mumps-rubella, and oral polio vaccines to children in the United States, but it could not boast a strong research program, especially compared to the overall investment in pharmaceutical research. Although the biggest obstacle to the development of new vaccines was the scientific challenge, vaccines were not a particularly attractive area for pharmaceutical company investment. Under the influence of substantial government purchases, prices were generally low and the total US pediatric market was limited to the annual birth cohort of about four million.

This poor climate for vaccine research worsened when, in the mid-1980s, industry faced sensational media coverage of the potential risks associated with vaccines and a subsequent wave of vaccine liability claims. Press attention to the injury cases undermined public confidence in immunization. Although parents and providers pressed for the development of safer vaccines to replace existing products, they did not have faith that the benefits of vaccines dramatically outweighed the risks and so did not advocate development of vaccines to protect against more diseases. The furor surrounding vaccine liability made the vaccine business—already only marginally attractive to corporations—even less appealing and the few companies that were in the market carefully evaluated their continued involvement in this area.

The US government sought to stabilize the liability situation and after considering a number of options, including the creation of a large stockpile of vaccines and a government role in manufacturing, Congress established a no-fault compensation system for children with vaccine-associated injuries. The system provided children and families compensation for their injuries, and although the system did not completely shield the industry from liability claims, it did significantly reduce the liability burden and improve the environment for research. Perhaps as important, the compensation program helped restore parents' confidence that the government was standing by the vaccines it recommended for routine use. As the government acted to resolve the vaccine liability crisis, scientists were making discoveries in molecular biology that created new possibilities for disease prevention through immunization. Opportunities in vaccine research then seemed almost unlimited.

RONALD J. SALDARINI

Vaccines of the late 1980s and early 1990s

The first indication of the importance of the biotechnology revolution was the introduction of the *Haemophilus influenza* type b conjugate (Hib) vaccine. By linking the protective Hib antigen to a protein that would be recognized by the immature immune system of young infants, researchers addressed the failure of young infants to respond to a Hib vaccine made through more traditional vaccine methods. Before the Hib conjugate vaccine, the Hib bacterium was the predominant cause of childhood meningitis and acquired mental retardation, as well as a major source of deafness and other neurological defects in children.

Although parents did not know what *Haemophilus* disease was, they did recognize and fear meningitis and the sequelae of Hib disease, and they and the US public health community enthusiastically accepted a Hib vaccine. This vaccine dramatically reduced the incidence of Hib disease because of high compliance with the immunization recommendation and the ability of the vaccine to provide herd immunity.

Since then, three more vaccines have been introduced to the childhood market in the US. Hepatitis B was initially administered only to adult populations at high risk of occupational or other exposure to the hepatitis B virus, but has been recommended for routine infant use since 1991. Acellular pertussis vaccine, which was first approved for use in toddlers and more recently for infants, was identified as the top vaccine development target when parental concerns about the whole cell pertussis vaccines threatened immunization compliance again, a result of sensational media coverage in the US and around the world. For fear of adverse events, parents refused to immunize with whole cell pertussis vaccines, and pertussis disease incidence rose slowly but steadily in the US and to epidemic proportions in Japan and the United Kingdom. The acellular pertussis vaccines have addressed parents' fears about the safety of pertussis immunization. Varicella vaccine, the most recent addition to the childhood vaccine schedule in the US, is beginning to demonstrate its value in reducing the most serious cases of chicken pox that result in hospitalization. The last ten years have been a period of transition between the time of crisis in the industry in the mid-1980s to an era of exploding opportunities.

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The vaccine pipeline

Upon FDA licensure, we will introduce a vaccine to prevent rotavirus, the most common cause of severe diarrhea among chil-

dren. This three-dose, oral vaccine, developed in the laboratory of Albert Kapikian of the National Institute for Allergy and Infectious Diseases (NIAID), has been tested in developed and developing countries and found to prevent around 80 percent of cases of severe rotavirus disease and 50 percent of all cases of rotavirus. The direct medical costs associated with rotavirus in the US are more than \$400 million annually, and the total societal costs are over one billion dollars annually. Less developed countries, where rotavirus is a major killer, stand to benefit even more.

Several vaccine manufacturers are developing conjugate vaccines to protect against *Streptococcus pneumoniae*, a major cause of pneumonia, bacteremia, meningitis and otitis media in children. In the US, as many as half of all visits to pediatricians are attributed to ear infections, with as many as half of those infections caused by *S. pneumoniae*. Globally, *S. pneumoniae* is the primary cause of pneumonia in young infants. An effective pneumococcal vaccine may, therefore, dramatically change pediatric practice in the US and save millions of lives worldwide. Given the emergence of antibiotic-resistant strains of *S. pneumoniae*, now seen as an urgent public health problem, the development of a vaccine to prevent infection may be the only effective way to address the problem.

Whereas these and other new vaccines are to be welcomed, they have resulted in an embarrassment of riches and created concerns that the increase in the number of required injections may undermine compliance with immunization schedules. Therefore, industry is devoting substantial resources to the development of vaccines that combine several of the antigens currently being administered in order to reduce the number of injections required for complete immunization.

The development of these combination vaccines has, however, proved more problematic than anticipated. Hib and diphtheria-tetanus-acellular pertussis vaccines—identified as prime targets for combination because they are administered at the same intervals in the immunization schedule—have proved difficult to combine because of significant interference between the acellular pertussis and *Haemophilus* components of the vaccines. Although these difficulties may yet be overcome, they have shown that vaccine development is difficult and unpredictable. Nevertheless, industry is pushing ahead with plans to combine as many antigens as possible into single doses of vaccine. For example, we hope to combine *Streptococcus pneumoniae* vaccine with Hib and a new vaccine to protect against group C meningococcus. Such a combination would protect against most of the major bacterial infections that cause meningitis. Eventually, we hope to add vaccines against *Haemophilus influenzae* and *Moraxella catarrhalis*, organisms that along with *S. pneumoniae* account for most childhood otitis media. Our dream is to have a single vaccine that can largely eliminate both meningitis and ear infections.

Oral vaccines and intranasally administered vaccines present alternatives to the problem of multiple injections. Even better, maternal immunization can establish immunity in the fetus even before birth, thus preventing diseases which strike so early in infancy that traditional immunization is not practicable. Among the targets for maternal immunization are vaccines to protect against group B streptococcus and respiratory syncytial virus (RSV). The latter is a particularly promising vaccine from a public health perspective because RSV is the primary cause of lower respiratory tract illness in infants and young children.

Vaccines aimed at protecting adolescents from sexually

transmitted diseases are also being pursued. A particularly attractive target is human papilloma virus infection which is strongly associated with cervical cancer. Of course vaccines against sexually transmitted diseases could also be part of an adult immunization strategy. And despite reports that it has no interest, industry is in fact working hard on AIDS vaccines, not only with a role in identifying promising candidate vaccines but also bringing to the table years of experience in vaccine development. Among the AIDS vaccine strategies that industry is pursuing are DNA vaccines, subunit vaccines and combinations of vaccines of different designs. The challenge of developing an HIV vaccine is daunting (see Burton & Moore, page 495, and Heilman & Baltimore, page 532), but industry is dedicated to the task.

Industry and governments

Vaccines have long been regarded a public health priority by many governments. For years, the US government purchased approximately half of all the vaccines manufactured for the US market and provided for distribution of these vaccines to children in need. In 1993, the potential purchasing power of the federal government was greatly increased by the enactment of the Vaccines for Children (VFC) program, a new entitlement that provides vaccine free of charge to even greater numbers of children than had been historically served through federal programs.

At the time Congress was considering the VFC program, industry was apprehensive that the government's purchasing power would inhibit the ability of vaccine developers to continue strong research programs. However, certain safeguards were included in the legislation to address industry's concerns. In addition to providing for multiple contracts that allow more stability than the traditional "winner takes all" process, Congress made clear that decisions about which vaccines to purchase should be based on the scientific and public health expertise of the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC), rather than on budget or cost considerations. Moreover, although the price of vaccines under contract at the time of VFC enactment was capped, newly introduced vaccines are not subject to such limits. If honored, the promise of rapid uptake of new vaccines and reasonable pricing policies embodied in the VFC program will provide a significant stimulus to further vaccine research.

Delivering vaccines to the world's children

US industry considers itself a partner in the international effort to prevent disease through immunization, and it is committed to ensuring that its vaccines reach those who could benefit most from them. Rotavirus vaccine and pneumococcal vaccine, the next two vaccines out of the pipeline, may have greater benefits in the developing world than in the developed world, and industry wants to maximize the use of those vaccines. If new vaccines are to be made available to children in developing countries as well as those in developed countries, new relationships and partnerships between the developed and developing world must be forged, and developed countries must take a leadership role in guaranteeing that the world's children have access to life-saving vaccines.

Among the issues that must be addressed before new vaccines can be made widely available in the developing world are the means of collaboration to ensure adequate manufacturing ca-

capacity. In addition, cooperative clinical work in the sometimes vastly different circumstances of developing countries must be encouraged in order to answer concerns about the efficacy of vaccines in those countries and to avoid delays in implementing widespread immunization. Importantly, government and other purchasing interests in the United States and other developed countries must accept the concept of tiered pricing in which higher prices in industrial countries effectively subsidize lower prices in less developed nations. In the past, companies have been criticized for differential pricing of vaccines, but the potential for immunization is to be realized around the world, the policy of differential pricing must be not only condoned, it must be encouraged (see Batson, page 487).

Today we are on the verge of worldwide eradication of polio, an achievement that has been made possible through a number of public-private partnerships that include UNICEF, the World Health Organization, Rotary International, private vaccine companies and governments around the world. Similar collab-

orations must be developed for other disease control efforts if we are to meet the challenges associated with making new vaccines a part of routine immunization across the world.

The future of vaccines

The prospects for vaccines have never been brighter. Once regarded as a backwater of the pharmaceutical industry, vaccines now command the attention of the investment community as one of the most promising targets of research opportunity. The Wall Street Journal ran a headline earlier this year "The Vaccine Business Gets A Shot in the Arm". If the promise of vaccines is to be fully realized, however, success will be measured not just in returns on investment but in lives saved around the world.

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Amie Batson (formerly with the WHO's Global Programme for Vaccines and Immunization and currently a World Bank Health Specialist) explains the relationship between public sector agencies and industry—each at the mercy of the other's strategic policies and both able to benefit from collaboration. Batson explores how a greater understanding and collaboration can lead to better strategies to assure global vaccine supply.

Win-win interactions between the public and private sectors

Over the past decade there has been a resurgence of interest in vaccines from

both the public and private sectors. The public health potential of these cost-effective, efficient, easily deliverable medicines is enormous and growing. The market potential, long viewed as stagnant, has been re-vitalized by the development of new patentable vaccines and is now attracting tremendous corporate attention.

As both the public and private sectors look with increasing interest at vaccines, they are discovering that their efforts are inextricably linked, with the actions of one having significant impact on the risks, costs and goals of the other. Rather than an adversarial relationship, the players are finding, somewhat to their surprise, that open dialogue and tailored strategies can be mutually advantageous. Understanding their different strengths, weaknesses and motivations is enabling both sectors to discover new forms of cooperation that are ultimately to their own benefit.

A number of lead agencies involved in immunization have described their organizational objective as being to identify public health priorities and direct, support, and improve immunization programs accordingly. The strengths and weaknesses of the public sector's support of immunization lie in its very diversity, being comprised of a vast array of organizations, each with its own mandate and often different strategic and operational approaches.

AMIE BATSON

The Children's Vaccine Initiative (CVI)

works to provide a forum for all partners in immunization from governments to agencies to industry to develop a common vision and workplan to achieve the shared objectives. The policy makers like the Global Programme for Vaccines and Immunization (GPV) at the World Health Organization and United Nations Children's Fund (UNICEF) determine the specifications and use of new products, provide information which affects demand, raise funds, set minimum guidelines to assure safety and efficacy and monitor progress. Bilateral and multilateral donors provide critical financial and, at

times, technical support to governments. A host of non-governmental organizations (NGO's) provide important human and financial support to specific projects or regions. Agencies and NGO's often house another important function, the centralized purchasing function. Purchasing is one of the commercial links between the public sector and industry and represents a strategic tool for consolidating demand and employing different procurement strategies to minimize transaction costs and maximize the public sector's negotiating power.

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Fig. 1 Global coverage of traditional vaccines 1982–96. (WHO/EPI)

Despite their diversity, these groups have repeatedly emphasized in public health forums the importance of ensuring that priority new vaccines, generally defined as cost-effective vaccines that have a large health impact and are practical to deliver, are