ID CONSULT

Feds Should Help Bring Vaccines to U.S. Market

Vaccine shortages have become all too common in the United States, with no end in sight. In my view, the best solution would be for the federal government to step in and provide incentives to vaccine manufacturers to bring more products to the U.S. market.

The current situation with *Haemophilus influenzae* type b (Hib) vaccine is just the latest in a string of vaccine production problems that has been causing major headaches for physicians and patients over the past several years.

BY MICHAEL E. PICHICHERO, M.D.

As you know, on Dec. 13, 2007, Merck & Co. announced a voluntary recall of certain lots of both of its Hib conjugate vaccines, Pedvax-HIB (monovalent) and Comvax (combined Hib/hepatitis B), because of concerns about contamination. Merck does not anticipate resumption of distribution until the fourth quarter of 2008. Sanofi Pasteur, the other company that makes Hib vaccines that are licensed for the U.S. market (ActHIB and TriHIBit), won't be able to produce enough to cover all the remaining children for whom the vaccine is recommended. We've also seen recent supply problems with measles-mumps-rubella-varicella (MMRV) and hepatitis A vaccines.

In 2004 there were major shortages of influenza vaccine and of pneumococcal conjugate vaccine because of various production problems. And any pediatrician who was practicing in 2001-2002 will remember the nightmare when five different vaccines that protect against eight different diseases—diphtheria, tetanus, pertussis, measles, mumps, rubella, pneumococcus, and varicella—all fell into short supply simultaneously. There was no single reason for those shortages; rather, they were due to a combination of factors: manufacturing and compliance problems; vaccine manufacturers' leaving the market for business reasons; supply and demand issues; and the removal of thimerosal from vaccines, which led to a lower yield.

Each time a shortage occurs, we're handed yet another set of interim guidelines for prioritization that means more paperwork; more hassles for us, our staffs, and our patients; plus the ongoing concern that at some point these shortages will result in true resurgence of disease. That hasn't happened yet, but I worry that it's right around the corner—herd immunity can take us only so far.

The Centers for Disease Control and Prevention maintains a stockpile of routine pediatric vaccines, which is a good safety net in case of a disease outbreak or a short-term production problem. However, not all pediatric vaccines are included in the stockpile, and it contains only a 6-month supply. Some of the recent shortages have lasted longer than that. Moreover, that stockpile competes for government dollars with vaccines devoted to bioterrorism and pandemic flu vaccines.

Some of my colleagues have talked about stockpiling their own vaccines. I don't think that is a viable solution, given the short shelf life of vaccines and the high cost that would be involved. In my practice, vaccines now are the second most expensive item on my balance sheet—second only to my staff payroll. My rent comes in third.

Of course, this is primarily because the newer vaccines—Prevnar, Menactra, Gardasil, etc.—are still patent protected and cost around $80-$120 per dose. For an average pediatrician, even a short-term supply would end up totaling around $40,000-$50,000. Multiply that by the number of partners in a group practice, and you'd easily be up to a quarter of a million dollars' worth of vaccine in your refrigerators and freezers. It's not a long-term solution to the shortage problem.

I believe the real answer is to ensure an adequate number of products from an adequate number of manufacturers. In 1967 there were 26 licensed vaccine manufacturers in the United States. By 2005, only six U.S. manufacturers with licensed products remained. What's worse, for several vaccines—including inactivated polio virus, MMR, and pneumococcal conjugate vaccines—there is only one manufacturer (Pediatrics 2006;6:2269-75).

This isn't good news. Just as they do after mergers in the airline industry, consumers end up with fewer choices and higher prices. The consolidation we've seen in the vaccine industry—brought on by increased regulatory demands for licensure; the high risk involved in developing a product, and competition with products like Lipitor, which patients take for a lifetime and generate billion-dollar profits—is really the core of the problem. Vaccine companies must be given incentives to compete.

How? The National Institute of Allergy and Infectious Diseases (NIAID) maintains nine Vaccine Treatment and Evaluation Units (VTEUs) around the country. Funded by the National Institutes of Health, these centers have stepped in at various times to conduct phase I and phase II testing on vaccines when there was critical need, such as the 2005 influenza vaccine shortage.

At that time, the NIAID worked closely with the Food and Drug Administration to conduct a clinical trial of GlaxoSmithKline's Fluarix—which was already available in Europe—to rapidly demonstrate sufficient safety and immunogenicity for the FDA to approve it in less than a year, in time for that year's influenza season. "The Fluarix study is an excellent example of what government and industry can accomplish in a short time frame, when faced with a serious public health need," NIH Director Elias A. Zerhouni said at the time.

The VTEUs played a role in testing acellular pertussis vaccines in the late 1980s, when pressure from activist groups led to congressional demands for a safer alternative to whole-cell pertussis vaccines, and again in the 1990s, when the United States initiated the transition from oral to inactivated poliovirus vaccines. In each case, the FDA has been in the loop to ensure that adequate testing takes place. And importantly, the government also has promised to purchase a certain number of vaccine doses from the companies, thereby further ensuring economic feasibility.

Thus far the VTEUs have been brought into use on a case-by-case basis. I think their use should become a routine mechanism in shortage situations. For example, GlaxoSmithKline (GSK) currently has another Hib vaccine on the market in Europe called Hiberix. It's virtually identical to Sanofi Pasteur's ACTHib, yet it is not licensed in the United States. Why? My guess is that GSK has determined that the large investment it would take to satisfy FDA's stringent safety and immunogenicity requirements wouldn't be worthwhile simply to bring a third Hib vaccine to market.

In the interest of public health, I believe the FDA should ask the VTEUs to conduct those studies in order to bring Hiberix here to help alleviate our current Hib vaccine shortage. The same goes for an MMRV vaccine that GSK also makes for the European market. Both are "mature" vaccines that can't command the kind of prices that the newer vaccines like Prevnar and Menactra can. I believe these are cases where the government must step in and help. We should not have to rely on a single source for these products. It's unsafe for the public. ■

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Influenza Burden Found to Be Greater in Asthmatic Children

BY ELIZABETH MECHCATIE
Senior Writer

The influenza-related hospitalization rates of young children with asthma were four times greater than those of children without asthma, and outpatient visits attributable to influenza were about twice as likely among those with asthma, according to Dr. E. Kathryn Miller and her associates.

The results are similar to those of retrospective studies that found that the rate of influenza-attributable outpatient visits for children with asthma and other medical conditions was higher than among healthy children, the investigators noted. But they added that their study may be the first to use prospective, laboratory-confirmed surveillance over several years to estimate rates of influenza-attributable visits for these two groups of children in outpatient settings (Pediatrics 2008;121:1-8).

The investigators conducted a prospective study that included children aged 6-59 months. Patients were either hospitalized between 2000 and 2004 or presented to clinics or emergency departments with acute respiratory illnesses (ARIs) or fever during two flu seasons between 2002 and 2004. In both the hospital and outpatient settings, throat and nasal swabs were obtained and tested for influenza, said Dr. Miller of the department of pediatrics at Vanderbilt University in Nashville, Tenn.

Of the 1,468 children hospitalized, 81 (6%) had lab-confirmed influenza; about one-quarter of these 81 children had asthma. Among children aged 6-23 months, the average annual rate of hospitalizations attributable to influenza was 2.8 cases/1,000 children with asthma, compared with 0.6 cases/1,000 children among healthy children, a significant difference. But the difference was not significant among those children aged 24-59 months: 0.6 cases/1,000 children among those with asthma, vs. 0.2 cases/1,000 children among the healthy children.

Among the 1,432 children enrolled in the outpatient settings, influenza was confirmed in 249 patients (17%); 15% had asthma. Among the children aged 6-23 months with asthma, the average annual rate of outpatient visits attributable to influenza was 316/1,000 children, compared with 152/1,000 children among healthy children. Among those children aged 24-59 months, the rates were 188 cases/1,000 children with asthma, vs. 102 cases/1,000 healthy children in 2003-2004. Both differences were statistically significant.

The authors speculated that possible explanations for the higher rates of inpatient and outpatient visits among children with asthma included their greater susceptibility to influenza and the greater likelihood they will have a more severe influenza-related illness.

They also may be more likely to seek medical help for a fever or ARI and may be more likely to be hospitalized because of concerns about their risk of asthma exacerbations, the investigators noted.

Vaccination rates were low in both groups: About 27% of those children with asthma had been vaccinated, and 12%-15% of the children without asthma had been vaccinated, according to parent reports. ■