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A risky business

By Dr. Anthony S. Fauci

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The events leading to the current influenza vaccine shortage dramatically illustrate the fragility of our nation's vaccine enterprise, particularly with regard to the familiar and effective "flu shots" that have helped protect our nation's health for decades. An expected 46 million to 48 million doses of influenza vaccine designated for distribution in the United States this flu season — about half of this year's planned supply — unexpectedly became unavailable when the license of a single vaccine production facility in Liverpool, England, was suspended for three months.

This unfortunate situation has evolved from our dependence on just two vaccine manufacturers for production of the classic injectable influenza vaccine, and from an antiquated and inflexible system for manufacturing the vaccine that has changed little over the past half century.

We did not choose to limit ourselves to only two suppliers of the injectable influenza vaccine. As recently as the 1970s, two dozen pharmaceutical companies were licensed to sell vaccines in the United States. But many companies have bowed out of the vaccine business, and of the six remaining major manufacturers, only two are licensed to supply injectable influenza vaccine in this country. A third company recently introduced an effective nasal influenza vaccine licensed for use in healthy children and adults ages 5 to 49 years, but not in infants, the elderly or individuals with weakened immune systems, the groups most vulnerable to the complications of influenza infection.

Why are so few companies involved in the production of influenza vaccines? The reasons are complex but boil down to two realities: Vaccine manufacturing is a risky business, and companies have few incentives to enter or remain in the field.

Vaccines belong to a group of medical products called "biologics," which are created or isolated from a variety of natural sources — human, animal or microbial. The manufacture of biologics is less predictable than the synthesis of chemical compounds used to formulate most drugs. This unpredictability not only can affect the amount of vaccine available in any given year, but also makes their production less attractive to industry unless a strong return on investment can be expected.

Unfortunately, companies must also confront the challenges posed by vaccine pricing. Our culture tends to undervalue immunization and other preventive measures compared with drugs to treat medical conditions. A year's supply of a widely used and effective cholesterol-lowering drug can cost $1,600 per year and can provide enormous benefits in terms of preventing cardiovascular disease. But an influenza vaccine, which also can prevent a potentially deadly disease for an entire year, costs only $7 to $10.

Thus, vaccines have proven much less lucrative for their manufacturers than other pharmaceuticals. Today, companies face the choice of producing a vaccine, which generally will have a low profit margin and which customers may use only a few times in a lifetime, or investing their resources in developing a potential blockbuster drug that a person may use every day.

An additional disincentive for companies is the fact that consumer interest in influenza vaccine can

ebb and flow from year to year, leading to a frequent mismatch between supply and demand. Eighty-seven million doses of influenza vaccine were made for the 2003-2004 influenza season but only 83 million doses were used, even though there was a perceived vaccine shortage. In the previous season, 12 million doses of vaccine had to be thrown away, all at a loss for the vaccine manufacturers.

Repairing the vaccine enterprise will require strong collaborations between government, industry and academia. Government has an important role to play in providing incentives for companies to enter — and stay in — the vaccine business. This might be accomplished with regulatory relief, guaranteed purchases of unsold supplies, the addressing of liability concerns and other mechanisms to bolster the economics of the vaccine industry. Several bills have been proposed in the Senate and House that call for such measures to ensure an adequate influenza vaccine supply for the future.

In addition, government and academic researchers can help by developing new technologies and sharing them with industry to make the systems used in vaccine development more flexible, more predictable and better able to adapt to unexpected changes in the demand for vaccines and the resulting need for "surge capacity" in production. It currently takes several weeks to months to identify and isolate the strain of virus needed for the vaccine for the upcoming influenza season, and to provide a seed virus for a pilot lot to start production. It can take several more months to grow and harvest the virus, a painstaking process that involves injecting influenza viruses into millions of chicken eggs and then waiting for sufficient quantities to grow.

Newer techniques such as "reverse genetics," developed by National Institutes of Health (NIH)-funded researchers, allow us to rapidly construct the virus needed to make the vaccine against a particular strain of influenza, and to make this process more predictable. Cell-culture methods also are being developed that may allow us to grow the virus with greater flexibility and dependability than is currently possible with the egg-based system. Other efforts are focused on developing vaccines against constant molecular regions of the influenza virus so that we would no longer have to change vaccine composition from year to year.

Together, such innovations may eventually allow us to respond more rapidly and efficiently to new and evolving influenza strains. Such a system is important not only for the yearly influenza epidemics that typically kill more than 36,000 people and hospitalize 200,000 in the United States but also will be critical as we face the threat of a possible influenza pandemic, with the potential to kill millions of people throughout the world.

The current influenza vaccine shortage is a wake-up call that we ignore at our peril. Now, we must strengthen our current influenza-vaccine development and production system with technical innovation, new incentives to industry, and stressing at every opportunity the value of vaccines as safe, cost-effective tools of public health.

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