Shortages of Antibiotics, Antivirals, and Vaccines Threaten the Public Health

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(See the article by Strausbaugh et al. on pages 1495–501.)

In this issue of Clinical Infectious Diseases, Strausbaugh et al. [1] present the results of 2 surveys of the Emerging Infections Network (EIN) performed in 1999 and 2000 regarding shortages of certain antibiotics. The EIN is a group of nearly 800 infectious disease physicians from all regions of the country, representing individual, group, and academic practices. They are supported by a contract from the Centers for Disease Control and Prevention (CDC), with the purpose of acting as a sentinel for new and emerging infectious disease problems. Members communicate regularly through the Internet, and in 1999, many noted problems in the availability of antibiotics in their practices. As a result, a formal survey of the entire EIN membership was conducted in 1999 and again in 2000. Responses rates (~65%) were excellent, and although the methods of the survey certainly can be challenged, the results testify to a general problem in availability of such classic drugs as penicillin, gentamicin, and many others, including meropenem and ticarcillin-clavulanate. In 1999, ~60% of respondents experienced at least occasional unavailability of penicillin G, and 30%–40% experienced unavailability of meropenem or gentamicin, respectively. There were some regional differences in shortages, and the shortages seemed to diminish in 2000. In general, patient care was not affected seriously, because in most instances alternative drugs were available, but some patients did receive less-than-optimal care. There were concerns that the shortages may have increased pressure for selection of resistant bacteria, because the alternative drugs used to treat patients had broader spectrums than did the intended antibiotics.

This problem is unexpected and alarming. The instinctive question is, if we can produce new immunosuppressive drugs and pay for transplants, prosthetic devices, and numerous other new drugs and innovations, why do we have shortages of antibiotics needed to treat ordinary infections?

Unfortunately, shortages of antibiotics are not the only problem; recently there also have been shortages of certain vaccines, antiparasitic drugs, and other biological agents that are sometimes essential for the treatment of infectious diseases. Shortages of ganciclovir were noted by the EIN surveys.

There are currently shortages of tetanus vaccine in many areas. Shortages of influenza vaccine caused much concern in 2000 and were the cause of a recent investigation and report by the United States General Accounting Office (GAO-01-624, May 2001). The GAO report on the influenza vaccine shortage is instructive, citing 2 main causes of the delay in getting the vaccine to the public in a timely manner. The first problem was relatively trivial—it consisted of temporary delays experienced by 2 of 4 manufacturers in growing 1 of the 3 influenza strains used in the 2000 vaccine. The other problem was more serious: 2 of the 4 manufacturers were cited by the Food and Drug Administration (FDA) for problems in good manufacturing practices, which resulted either in delays while manufacturing facilities were improved or, for one manufacturer, in abandonment of production of the influenza vaccine altogether.

The evidence from the EIN surveys prompted the Infectious Disease Society of America (IDSA) to organize a meeting, which was held in Washington, DC, on 3 October 2000, to discuss the possible causes and remedies of the antibiotic shortage problem. In attendance were senior representatives from the FDA, CDC, pharmaceutical manufacturers, the EIN, IDSA, a national pharmacists’ group, and practicing physician communities. Discussions were frank but collegial. Testi-
mony was given to the generalized nature of shortages, involving additional categories of antimicrobials that were not covered in the EIN survey, in particular antiparasitic drugs. Although the CDC is organizing stockpiles of certain drugs in anticipation of possible biological attacks on the population, the stockpiles are inadequate to address the current situation. The shortages do not currently pose a major and immediate threat to patient care in general, but they are a worrisome and continuing problem.

Considerable discussion related to possible reasons for the shortages. All the answers were not forthcoming from such a short meeting, but certain factors were obvious. The manufacturing of antibiotics involves a few plants or, in some cases, a single plant that provide(s) either the active pharmaceutical ingredient used in subsequent manufacture or the finished product. When such a plant is cited for problems regarding the maintenance of good manufacturing practices during an FDA inspection, or when a firm discovers manufacturing problems as part of its own quality control or quality assurance activities, a slowdown or sudden total unavailability of the final product may ensue. On occasion, the FDA has shifted the focus of inspections, which has resulted in the discovery of problems in the manufacturing of drugs that have been marketed for years. This may increase costs of manufacturing the drug, which in our extremely cost-conscious health care environment may cause serious problems for the manufacturer.

It is the responsibility of the FDA to ensure that drugs and biological agents that are given to humans are safe and effective, and, therefore, manufacturers must be aware of and take the necessary steps to comply with these regulations. The FDA is aware of the importance of maintaining the availability of products used to treat serious illness, particularly in the absence of adequate alternatives, and it works proactively with manufacturers to resolve problems. For products used to treat serious diseases when adequate alternatives are not available, the FDA will often use enforcement discretion when attempting to resolve the problem. Despite this flexibility, and despite good intentions among all parties involved, shortages can and obviously do occur. There are procedures that should enable the FDA to move rapidly when a product is deemed to be medically necessary, although in the case of penicillin G, some at the meeting thought the FDA took too long to make this determination. The FDA maintains a Web site to list current shortages, including information on product availability. The site also includes instructions on how to report shortages.

All the problems with shortages are not the result of regulatory actions by the FDA that affect pharmaceutical manufacturing activities. Availability of raw materials and many other factors may be critically important. In addition, in a free-market economy, there are incentives to produce new drugs rather than old generic drugs, because selling the new drugs is more profitable. Some may decry this situation, but it is wise to remember that profits are essential to the ability of industry to bring important new drugs to market. Creation of new drugs is expensive, and without profit, the industry would not have the means to tackle risky and important new ventures, such as an HIV vaccine, to cite only one example. These issues are complex and were not discussed at the meeting, but they may be part of the explanation for the exasperating circumstance that penicillin and some other drugs and vaccines have almost become orphan products. Regardless of explanations, shortages exist, patient health is sometimes compromised by the shortages, and we need to do something to resolve these unfortunate problems.

How can the problems of shortages of antibiotics and vaccines and other antimicrobials be solved? The meeting discussants suggested several first steps. These included the establishment of a working group that will continue to meet to discuss the problems, including representatives of government, industry, and health care practitioners. Vulnerabilities in the current system of production, government regulation, industry compliance, and distribution need to be identified. Better surveillance systems need to be developed that will anticipate, detect, and monitor shortages. Lists of medically essential drugs need to be developed, for which it is particularly important to avoid shortages. All participants agreed with these goals. It may become necessary to develop new incentives to produce drugs that are threatened with becoming de facto orphan drugs, including especially older and inexpensive generic drugs, such as penicillin G, that remain essential to practice.

Discussion of these problems was an important first step, but there is a long way to go. The membership of the IDSA may take some pride in the growing national leadership role of the IDSA. The real challenge may be to sustain the energy required to develop solutions. Progress will require effective partnerships with industry and government, including the FDA and the CDC in particular. One may hope that recognition of these problems will lead to new opportunities to improve treatment and prevent infectious diseases in this country.

Reference