The events of September 11, 2001 have focused unprecedented attention on the availability of antimicrobial agents and vaccines. The potential need for large amounts of specific antimicrobials was highlighted by the subsequent use of anthrax as an instrument of terror and the depletion of stocks of ciprofloxacin HCl (Cipro, Bayer), the preferred agent for prophylaxis in patients exposed to anthrax. The increased demand for ciprofloxacin led to geographic shortages of this agent and a threat to patient care in general. Fortunately, that episode appears to have been limited in scope and duration. The effects, however, emphasize the vulnerabilities of the health care system to the finite supplies of specific antimicrobials. A more sustained absence of antimicrobials has been shown to adversely affect health care on a far wider scale.

SCOPE

The unavailability of drug products has become an all-too-frequent occurrence over the past decade. Shortages can be temporary and affect only a segment of the industry or geographic area, or they can be global in scope and result in the absence of certain agents in the marketplace. Difficulty anywhere along the supply chain, from raw material to inventory management practices of end-users, can result in a disruption of product availability. Temporary disruptions in availability or local supplies should be distinguished from true shortages; because these temporary disruptions usually result from unique circumstances, they will not be covered extensively in this review.

According to the Food and Drug Administration (FDA), a shortage is defined when:

- The total supply of all versions of the approved product available at the market level will not meet the current demand.
- A registered alternative manufacturer will not meet the current and/or projected demands for the potentially medically necessary use(s) at the user level.

The FDA works actively with pharmaceutical manufacturers to identify and correct circumstances that can lead to shortages. Despite these precautions, shortages still occur.

Penicillin G was the first antibiotic affected by a shortage, beginning late in the summer of 1999. A recall of products by Marsam Pharmaceuticals, a subsidiary of Schein Pharmaceuticals, was linked to regulatory concerns, expressed by the FDA, concerning the production facility in which penicillin G was manufactured. As a result of those concerns, the availability of meropenem (Meronem or Merrem, AstraZeneca) and cefazolin (Ancef or Kezol, Braun Medical Inc), both of which were also produced at that facility, was also decreased. The shortage of penicillin G was further aggravated by the absence of alternative producers of this generic antibiotic.

As a result of these shortages, the Infectious Diseases Society of America (IDSA) Emerging Infections Network (EIN), in November 1999, organized a survey of its members across the country concerning the availability of antimicrobial agents. This was followed by a second survey in August 2000, the results of which have recently been published. In that report, in which 67% of the members responded, 77% reported a lack of penicillin G. In addition, respondents reported shortages of gentamicin (50%), meropenem (38%), ticarcillin with or without clavulanate (24%), cefazolin (20%), and nafcillin/oxacillin (13%). Although respondents to the second survey indicated improvement in the availability of most agents, penicillin G remained in short supply. During 2001, piperacillin-tazobactam (Zosyn, Wyeth) experienced similar shortages. Antibiotics have not been the only agents affected. Delays in production and distribution resulted in decreased availability of influenza vaccine in 2000 and 2001, and tetanus vaccine in 2001.

In the case of tetanus vaccine, the decision of one manufacturer, Wyeth-Ayerst, to discontinue production of all products containing tetanus toxoid (Td, for adults and children seven years of age or older; diphtheria and tetanus toxoids adsorbed, DT, for children six years of age or younger; and diphtheria and tetanus toxoids with acellular pertussis vaccine, DTap, for...
CONSEQUENCES

The clinical impact of these shortages cannot be underestimated. According to the EIN survey, the lack of specific antimicrobial agents led to an alteration of therapy by 82% of the respondents. The survey identified sepsis, streptococcal and enterococcal endocarditis, pneumococcal meningitis, group B streptococcal infections, and neurosyphilis as those indications most likely to require alterations of therapy. For some indications, the absence of specific antimicrobials removes the only adequately studied therapy. Penicillin G remains the drug of choice for the treatment of syphilis and is essential for the treatment of neurologic and congenital disease associated with that infection. The adequacy of alternative regimens remains to be validated.

Changes in clinical outcomes are not the only consequences of decreased antimicrobial availability. Alternative therapies might place a patient at risk of reduced response rates, but might also increase the risk of drug toxicity. The absence of meropenem resulted in a shift of prescribing to imipenem, which has the potential for an increased risk of seizures. Absence of a particular vaccine can lead to inadequate levels of immunity, both in the individual and in the population at large. The recent absence of intravenous ganciclovir has shifted the burden of therapy to the more toxic alternatives of foscarne and cidofovir.

Because therapy with a preferred agent might not be available, the use of alternative agents might entail antimicrobials with broader spectrums or different mechanisms of action. This could increase the likelihood of the emergence and spread of resistance among other pathogens. Decreased availability of ticarcillin with or without clavulanate and piperacillin-tazobactam might result in greater dependence on cephalosporin antibiotics and subsequent increases in antibiotic pressure increasing the risks of colonization and disease with Clostridium difficile, vancomycin-resistant enterococci (VRE), and resistant gram-negative organisms. Lastly, the absence of older, generic drugs can shift the burden of therapy to newer, more costly agents.

DISCUSSION

The factors responsible for a shortage of an antimicrobial product are diverse (Table 1). These factors can be present singly or act in concert to produce a situation in which availability is decreased. Difficulties in acquiring raw materials can affect drug availability even when multiple manufacturers are present to produce the finished product. Raw materials might only be available from a single source. Many of the basic building blocks can only be found in underdeveloped areas of the world, in areas undergoing conflict, and areas that have been affected by natural disasters or changed climatic conditions. Even if the materials are available, problems with collection, quality, and transportation might serve to inhibit eventual drug production.

Manufacturing difficulties have been the most frequent reason for the shortage of injectable agents. In the case of penicillin G, regulatory concerns in response to an FDA enforcement action concerning noncompliance with current Good Manufacturing Practices (cGMPs) led to the recall by the major supplier of penicillin G of finished product vials in the U.S. Although it is the responsibility of the FDA to ensure that antimicrobial agents are both safe and effective, the increasing demand for product safety must be reconciled with the potential effects of limiting manufacturing capabilities. Supplies of oral procaine and benzathine preparations produced by other manufacturers were not affected; however, an alternative supplier (Biochemie GmbH, Kundl, Austria) had to be identified to fill the void.

Voluntary recalls can similarly affect drug availability, especially if a lone manufacturer’s product dominates the market. Voluntary recalls might only affect specific lots and therefore be of limited consequence, or they can involve safety or labeling concerns, resulting in a much wider effect upon the end users.

Market forces bear heavily on both manufacturers and distributors of antimicrobial agents. The entry of generic products onto the market can result in the discontinuation of production of the parent compounds. Decisions by health care organizations to create “preferred products” or even exclusive formulations can greatly affect the profitability of

Table 1 Factors That Can Influence Pharmaceutical Availability

- Shortage of raw materials/natural disasters
- Manufacturing difficulties
- Voluntary recalls
- Market shifts/increased demand
- Industry consolidation
- Manufacturer production decisions
- Distribution and inventory
agents, forcing corporate decisions regarding continuing production. Shortages are not only the result of “negative” market forces, however. Increased demand might also contribute to a shortage if production and supply cannot keep pace. Demand for caspofungin, a new antifungal agent from Merck, is a recent example of this phenomenon.

In a free-market economy, corporate decisions to discontinue the manufacture of less profitable antimicrobials and vaccines in favor of more profitable agents is a stark reality. The costs of raw materials, the need for modernization of manufacturing processes and facilities, the expiration of patents and falling demand for older agents all contribute to decreased reimbursement to the manufacturer. For the influenza vaccine, the discontinuation of production by one manufacturer and decreased yields of one vaccine component [influenza A (H3N2)] were two factors that led to the delayed delivery of vaccine during the 2000–2001 influenza season. The adjustment of manufacturing and vaccine delivery schedules has required a shift in the prioritization of vaccine delivery down to the level of the individual practitioner.

When a manufacturer decides to curtail production, the FDA is responsible for the performance of a “medical necessity” evaluation. If the absence of the medically necessary product is determined to increase the public risk, other manufacturers are encouraged to produce the agent.

When a manufacturer decides to curtail production, the FDA is responsible for the performance of a “medical necessity” evaluation. If the absence of the medically necessary product is determined to increase the public risk, other manufacturers are encouraged to produce the agent. These industry consolidations can further compromise availability, however, by limiting the manufacturing alternatives. Manufacturers of antimicrobials that have indications for a limited patient population might find incentives through the federal Orphan Drugs Program.

For many agents, especially those that are no longer under patent and that are therefore less profitable, there might be only a single manufacturer. The decision to suspend production of tetanus toxoid-containing products by Wyeth Lederle (Pearl River, New York) left Aventis Pasteur (Swiftwater, Pennsylvania) as the sole distributor of tetanus and diphtheria toxoids (Td) and tetanus toxoid (TT) in the U.S.7

Lastly, antimicrobial agent distribution systems can contribute to an agent’s decreased availability. Restricted distribution methods, exclusive or preferred suppliers, or end-users who enter into manufacturer agreements can result in shortages for others. The potential for profit has led secondary and non-traditional suppliers to enter the marketplace, often with the ability to purchase large quantities of compounds. This can effectively reduce the supply and subsequently allow for secondary markets to inflate prices. Distributors and end-users also have precipitated shortages by adoption of “just-in-time” inventory procedures. By only stocking supplies adequate for the current demand, any disruption in distribution or change in demand can result in a shortage.

A number of steps have already been taken to improve product availability. Representatives of government, and industry, and health care practitioners, have established working groups to identify vulnerabilities in the acquisition, manufacturing, distribution, and reimbursement of medically necessary agents. Increased evaluation of antimicrobial products as “medically necessary” or particularly vulnerable has begun. Surveillance systems to monitor and report agents that are experiencing difficulty have been established by the FDA. Health care organizations have recognized the need to assess inventory practices, distribution and contracting alliances, and to improve communication and coordinate actions to lessen the impact of future shortages.

These actions must be considered to be only a beginning. It will require the coordinated cooperation of everyone involved, including the patient as consumer, to ensure that necessary pharmaceutical agents remain safe, effective, and available.

REFERENCES

Coming Next Month:
A Hospital Pharmacy Perspective on Drug Shortages by Noreen H. Chan Tompkins, PharmD, Allegheny General Hospital, Pittsburgh, Pennsylvania.