cine. Several broadly neutralizing mAbs targeting the highly conserved stem portion of the hemagglutinin protein of influenza A have had promising results in preclinical studies against a range of influenza subtypes and were well tolerated in early-stage clinical trials.[5] These agents have therapeutic potential and may also interrupt transmission if administered to uninfected persons who are in proximity to index cases. Transmission studies in ferrets demonstrated that administration of one such antibody, MEDI8852, to uninfected ferrets can protect them from airborne transmission of the H1N1pdm09 virus.[5]

Although mAbs have potential for use in responding to EIDs, pragmatic concerns must be addressed — notably cost. Targeted development and deployment of antibodies with high potency (requiring less material per dose) will help reduce the cost, as will improvements in manufacturing. Administration of mAbs, particularly those requiring cold storage and intravenous infusion, may also be challenging in some outbreak settings. In the future, the EID field may turn increasingly to high-affinity antibodies, allowing subcutaneous dosing, or novel delivery platforms such as nucleic acid and vectored constructs, minimizing the need for intravenous administration. Finally, EID pathogens probably vary in their vulnerability to mAbs, and particularly to neutralizing antibodies. Yet the knowledge gained in advancing the field of mAbs for EIDs will enable the development of other countermeasures, including vaccines, and increasingly specific diagnostics.

An audio interview with Dr. Fauci is available at NEJM.org

Despite the challenges, mAbs are positioned to play a larger role in future public health responses involving the diagnosis, prevention, and treatment of EIDs, and the lessons learned will most likely apply to infectious diseases in general. If we are to fully realize mAbs' promise in EIDs, leaders in preparedness and response will have to assign them a high priority in research and development agendas.

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Saline Shortages — Many Causes, No Simple Solution

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Severe and long-standing prescription-drug shortages have become a major threat to public health and patient safety.[1] Despite increased awareness and mitigation strategies, the United States has experienced shortages of many lifesaving drugs and other supplies essential to patient care. There was already a shortage of saline solution, for example, when Hurricane Maria devastated Puerto Rico, home to a key saline manufacturer, causing the problem to reach critical levels.[2]

Saline is an inexpensive product — it's simply salt water — but proper manufacturing practices are required to keep it sterile, pyrogen-free, and free from particulate matter. Production demands are challenging, since very large quantities are needed: more than 40 million bags per month. Saline is required for virtually all hospitalized patients, whether as a component of a medication infusion or as a hydration, resuscitation, or irrigation fluid.[2] Unfortunately, shortages of saline have become commonplace in recent years (see table).

Most drug shortages occur with older, generic, injectable medications that are produced by a small number of suppliers — typically three or fewer. The United States gets its saline from just three companies: Baxter International, B. Braun Medical, and ICU Medical. Most shortages are caused by a quality or production problem at the manufacturing facility — causes that apply to the current saline shortage as well.[2,3] In ad-

History of Saline Shortages in the United States.*

Product	Date Shortage Began	Date Shortage Resolved	Reason for Shortage
0.9% Sodium chloride, small-volume bags	5/24/2007	7/25/2008	Supply unable to meet demand
0.9% Sodium chloride, large-volume bags	1/28/2013	Not yet resolved	Manufacturing delays
0.9% Sodium chloride for irrigation	8/12/2014	9/25/2015	Manufacturing problems
0.9% Sodium chloride for irrigation	11/9/2016	Not yet resolved	Manufacturing delays
0.9% Sodium chloride, small-volume bags	8/25/2017	Not yet resolved	Manufacturing delays due to Hurricane Maria

* The reasons for shortages are as determined by the University of Utah Drug Information Service. Drug-shortage information is available at www.ashp.org/shortages.

dition, when one supplier experiences a shortage, other suppliers often have insufficient manufacturing capacity to make up the difference. Drug manufacturers are not required to have redundancy in their facilities or even a business contingency plan in case of a disaster, no matter how essential or lifesaving the medication they are producing.[1]

The shortage of small-volume saline bags (250 ml or less) became dire almost immediately after Baxter's Puerto Rico manufacturing plant was hit by Hurricane Maria.[2] Baxter supplies approximately 50% of U.S. hospitals with this product, which is used as a diluent to deliver a variety of parenteral medications. Despite this tremendous need, Baxter has no redundancy in manufacturing capacity for small-volume saline bags. The other two saline suppliers have not been able to increase their production enough to make up for the shortage.[2,3] In fact, saline produced by B. Braun was already in short supply before the hurricane, as the company worked to correct manufacturing-quality problems.[3]

The saline shortage had actually begun in 2014, affecting large- as well as small-volume products.[4] Large-volume saline products (>500 ml) are typically used as maintenance or resuscitation fluids or for irrigation. Although some shortages of large-volume saline solutions are attributable to problems at manufacturing facilities, increased demand for intravenous fluids due to a severe influenza season has also contributed to the current short supply.[2]

Saline shortages can affect patient care in various ways. Medication errors and adverse drug events can result when medications that are typically administered as short infusions are given by intravenous push or when providers choose less familiar but more readily available products as substitutes. Increased ad hoc compounding of drugs may result in dilution errors or microbial contamination.[3,4]

Fixing the problem is difficult and requires a multifaceted approach entailing both focusing on current shortages and working to prevent future ones. Neither Congress nor the Food and Drug Administration (FDA) can force any manufacturer to produce a medication, no matter how lifesaving the product or how critical the need. Incentives such as accelerated approval for another product or tax relief for funding facility repairs may help reduce shortages, yet these incentives may have the unintended consequence of precipitating more shortages if companies value the incentives more than current profits. Alternatively, moving forward, the Department of Homeland Security could mandate that saline be considered part of the essential infrastructure, which would require the relevant companies to develop business continuity plans, although implementing manufacturing redundancies would be costly and require significant time.

The FDA's Good Manufacturing Practice rules require a minimum level of quality, yet shortages continue to occur because of poor conditions at manufacturing facilities. It is costly and time consuming to bring facilities up to standard, and the process of doing so can interrupt the supply chain. Since drug companies are not required to disclose the identity or location of the manufacturer that produces a drug,[1] a complete list of medications affected by Hurricane Maria is available only to the FDA and not to clinicians who need to plan for patient care. Woodcock and Wosinska have argued that poor quality is due to a lack of transparency regarding which company actually makes a product, because without such transparency clinicians cannot purchase drugs and supplies on the basis of quality.[1]

Changing the transparency re-

quirements and mandating manufacturing redundancies may not change the course of the current saline shortage, but they are important actions for preventing future shortages. In response to the current shortage, the FDA has recently approved saline products from two additional manufacturers; however, there is a lag time between approval and the arrival of these products on the market. The newly approved products may also cost more than the currently available ones, since most organizations purchase their saline in a bundle that also includes tubing, pumps, and other accessories.

Importation of products can help in some cases. In response to the current saline shortage, the FDA has permitted manufacturers to import saline from their facilities in other countries, such as Brazil.[2] Importation is usually a temporary measure, because the FDA generally cannot find a company with sufficient foreign supplies to share with the U.S. market without creating a shortage in the country providing the import. When it comes to saline, logistics make it impractical to import products for long periods: saline is heavy and bulky, making air transport costly and shipment periods lengthy. The FDA has also permitted extension of product expiration dates when that can be done safely. And Baxter's facility in Puerto Rico is expected to be functioning again in the near future, which will help to ameliorate the current shortage.[2]

In the meantime, the saline shortage has required clinicians to use a number of work-arounds that consume valuable resources and increase health care costs.[3,4] Supplies may need to be reserved for the sickest patients, and providers require an ethical framework for rationing products,[4] while pharmacy staff closely monitor inventory. Some medications now have to be administered as direct injections over several minutes, which increases the time nurses must spend with each patient. Some institutions have switched to syringe pumps or use Buretrol (Baxter) infusion devices (which hold small quantities of fluids) to deliver medications. Hospitals are also using more expensive premixed products and are changing the concentration of some medications so they can be mixed in larger volumes, when small-volume bags are unavailable. Making such changes requires substantial informatics resources, because the ordering platform in the electronic health record must be altered.[4,5] To conserve large-volume saline bags, oral hydration is recommended when possible (see Patiño et al., pages 1475–1477). For patients who cannot take oral fluids or who require aggressive resuscitation, alternative crystalloid solutions may be considered. During shortages of large-volume saline irrigation solution, sterile water or even tap water may be substituted when appropriate.[4]

The current shortage of saline solutions demonstrates the profound effects that drug shortages can have on patient care. It is anticipated that the situation will improve in the United States in the coming weeks to months, although hospitals will continue to face shortages of other basic products. In the meantime, a multifaceted approach will be needed to ensure that patients safely get the medications they need.

Disclosure forms provided by the authors are available at NEJM.org.

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