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From the Division of Epidemiology (N.C.L.) and the Department of Medicine (M.B.), Stanford University School of Medicine, and the Center for Innovation in Global Health, Stanford University (M.B.) — both in Stanford, CA.

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1. Bendavid E, Avila P, Miller G. United States aid policy and induced abortion in sub-Saharan Africa. Bull World Health Organ 2011;89:873-880C.
2. Glasier A, Gülmezoglu AM, Schmid GP, Moreno CG, Van Look PF. Sexual and reproductive health: a matter of life and death. Lancet 2006;368:1595-607.
3. Jones KM. Evaluating the Mexico City policy: how US foreign policy affects fertility outcomes and child health in Ghana. Washington, DC: International Food Policy Research Institute, 2011 (http://www.ifpri.org/publication/evaluating-mexico-city-policy).
4. Bendavid E, Holmes CB, Bhattacharya J, Miller G. HIV development assistance and adult mortality in Africa. JAMA 2012;307:2060-7.
5. Lo NC, Lowe A, Bendavid E. Abstinence funding was not associated with reductions in HIV risk behavior in sub-Saharan Africa. Health Aff (Millwood) 2016;35:856-63.

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Ensuring Access to Injectable Generic Drugs — The Case of Intravesical BCG for Bladder Cancer

Benjamin J. Davies, M.D., Thomas J. Hwang, A.B., and Aaron S. Kesselheim, M.D., J.D., M.P.H.

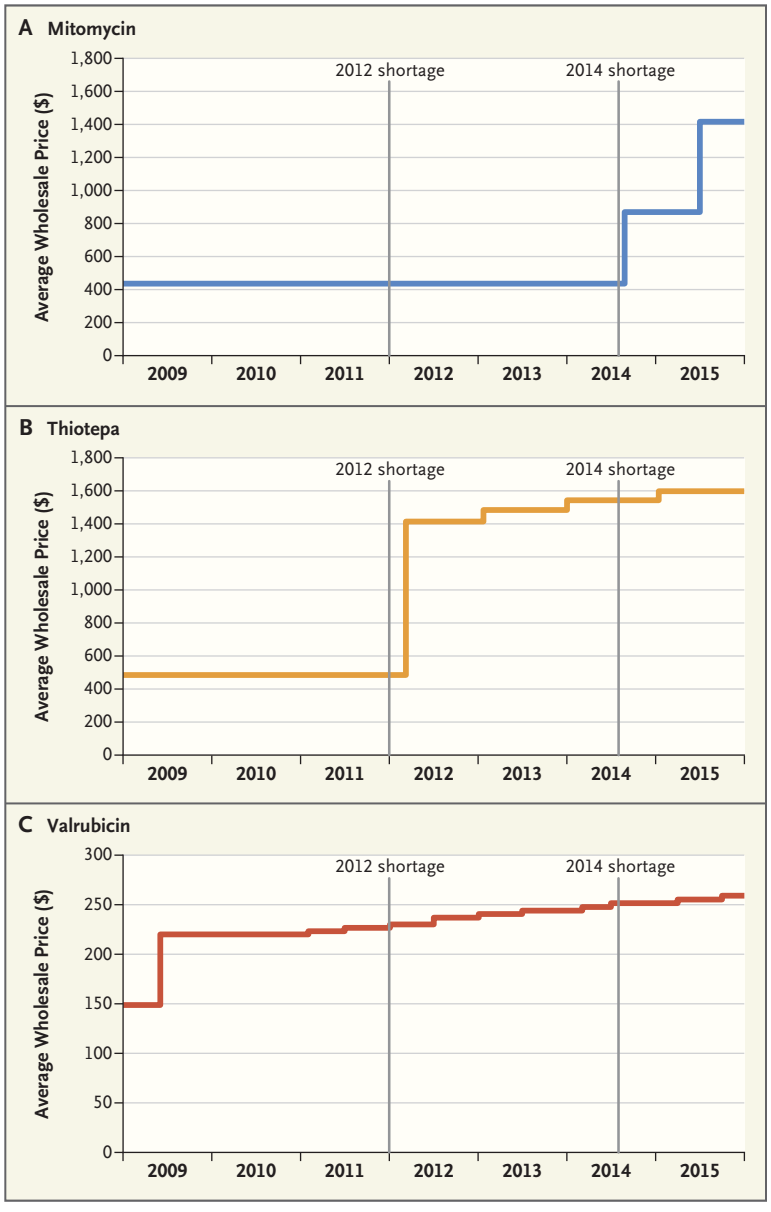
In November 2016, one of the two manufacturers of bacille Calmette–Guérin (BCG) informed health care providers that it planned to exit the market in mid-2017.[1] Intravesical immunotherapy with BCG is the standard of treatment for preventing recurrence and disease progression in high-risk patients with non–muscle-invasive bladder cancer, who account for a substantial minority of patients with newly diagnosed bladder cancer.[2] Yet the past few years have seen intermittent disruptions of the BCG supply. The most recent disruption occurred in 2014, after a plant was temporarily closed because of manufacturing quality issues. The November announcement raises the prospect of a sustained shortage or substantial price increase, even as National Comprehensive Cancer Network treatment guidelines recommend intravesical BCG over chemotherapy for these patients.

Limits on access to BCG mean that providers must use potentially less efficacious alternatives, current patients may have to discontinue or temporarily halt therapy, and new patients may need to undergo cystectomy. Similar concerns about potential harms to patients during shortages have arisen in other areas of oncology. One study revealed that drug substitutions due to shortages were associated with higher relapse rates among pediatric patients whose lymphoma might otherwise have been cured.[2]

Beyond leading to inferior outcomes, alternative treatment agents can be expensive, adding to the substantial financial burden of cancer care. Recent media coverage has focused on rapid price increases for certain generic drugs, but little is known about drug-price changes during supply disruptions. To assess the effect of a BCG shortage on treatment costs, we compared the listed average wholesale prices (AWPs) for mitomycin, the primary alternative to BCG for high-grade bladder cancer, and for the third-line treatment agents valrubicin and thiotepa, before and after the BCG shortages that began in 2012 and 2014.

We found that the list prices for mitomycin increased dramatically during the BCG shortage beginning in 2014, and prices for third-line agents increased modestly (see graphs). After BCG supply disruptions were reported in August 2014, the listed AWP for mitomycin increased on August 26, 2014, from $436.80 to $869.59 for the 40-mg dose and from $67.20 to $165.60 for the 5-mg dose — increases of 99% and 146%, respectively. Although actual drug costs can differ from the AWP, Medicare data show that these price changes were passed on to patients and were likely to translate into higher costs for payers and taxpayers. Between 2012 and 2015, annual spending by Medicare Part B on mitomycin increased from $4.3 million to $15.8 million. Since beneficiaries are responsible for 20% of Part B drug payments in coinsurance, out-of-pocket costs for mitomycin (substituted for BCG) for a patient covered by Medicare would have increased from approximately $49 per year in 2012 to $155 in 2015.[3]

Yet even with price increases, the number of manufacturers producing these second- and third-



Trends in Chemotherapy Prices after BCG Shortages.

Data for mitomycin, thiotepa, and valrubicin are average wholesale prices before and after BCG supply disruptions reported first in 2012 (continuing until 2014) and then again in 2014 (continuing until 2015). All three drugs are approved for the treatment of bladder cancer. We excluded gemcitabine, which may be used off-label for patients with BCG-refractory cancers but is not indicated for non–muscle-invasive bladder cancer and is not included in National Comprehensive Cancer Network treatment guidelines. Price data are from the Red Book (Truven Health Analytics).

line therapies has been unstable; in fact, since 2012, simultaneous shortages of mitomycin and thiotepa have been reported. Similar trends have been reported with regard to other generic drugs. For example, after quality-control issues forced a manufacturer of glycopyrrolate — an injectable agent commonly used before surgery to reduce secretions — to suspend production, the remaining manufacturer increased the listed AWP of its product by 855% ($1.44 to $13.75 per 0.2-mg-per-milliliter dose). The list price remained at this new level even after both manufacturers restored production capacity.

In the past, public outcry has prompted executive and legislative action targeting drug shortages. In 2012, Congress passed the Food and Drug Administration (FDA) Safety and Innovation Act, which required public reporting of shortages and directed the FDA to expedite the availability of alternative products. Although the number of new drug shortages has declined somewhat since 2012, the number of ongoing shortages has exceeded 250 in every year since 2012, and 291 active national shortages were reported in 2015.[4] In addition, the duration of these shortages appears to have increased over time.[5] Shortages of important generic drugs remain unacceptably frequent, which suggests that policy efforts to date have not been sufficient in preventing supply disruptions.

The need for new solutions is particularly acute for shortages of generic injectable drugs, which often have few suppliers. Paradoxically, manufacturers face few negative consequences during shortfalls, but if supply outpaces demand, they are financially penalized as they accumulate unsold and rapidly depreciating inventory. To better align incentives, companies that consistently maintain drug production without quality-control problems could be rewarded by the FDA with priority review of future generic-drug applications.

The FDA could also exercise

its discretion to permit importation of BCG licensed abroad, if available, as it does for other generic drugs that are in short supply in the United States. For example, in response to a shortage of a topical treatment for cutaneous lesions in patients with AIDS-related Kaposi's sarcoma, in January 2017, the FDA allowed the sale of a generic product already approved for use in Europe. Furthermore, direct investment in domestic manufacturing capacity can help address generic-drug shortages. The federal government could offer tax credits or preferential lending to offset the cost of upgrading aging generic-drug production plants and to encourage the development of new manufacturing capacity by competitors, particularly for products that are prone to shortages. Such a strategy would recognize such drugs as a vital public resource and could be part of a broader national investment in infrastructure.

Finally, payment reforms could further stabilize the market for generic injectable agents. A proposed revision of Medicare Part B reimbursement, which would pay prescribers a flat fee instead of the current average sales price plus 6%, could have increased the profitability of generics (although finalization of this rule appears unlikely in the current political climate). For other public goods with high fixed costs, such as utilities and roads, federal and municipal governments typically enter into long-term contracts and can offer subsidies to ensure redundant capacity, as they do in certain electricity markets. Federal purchasers could jointly procure a minimum quantity of generic injectable drugs, with the possibility of contract extensions for participating manufacturers if performance-based indicators tied to quality and supply reliability are maintained.

Several of these proposals would involve greater baseline expenditures by the federal government on generic prescription drugs. However, these outlays would be balanced by avoidance of the substantial financial and health costs borne by patients and payers during drug shortages. The experience with BCG highlights the vulnerability of the U.S. drug supply and suggests that disruptions in the production of an important generic drug can have a cascading effect, including price increases and shortages of alternative chemotherapeutic agents. Drug shortages and drug prices remain urgent public health crises in need of resolution.

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From the Department of Urology, University of Pittsburgh and Hillman Cancer Center, Pittsburgh (B.J.D.); and the Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (T.J.H., A.S.K.).

1. Davies B. Sanofi shuts down bladder cancer drug production: inevitable drug shortage to harm patients. Forbes. November 17, 2016 (http://www.forbes.com/sites/benjamindavies/2016/11/17/sanofi-shuts-down-bladder-cancer-drug-production-inevitable-drug-shortage-to-harm-patients).
2. Metzger ML, Billett A, Link MP. The impact of drug shortages on children with cancer — the example of mechlorethamine. N Engl J Med 2012;367:2461-3.
3. Centers for Medicare and Medicaid Services. CMS drug spending: Medicare drug spending dashboard. 2015 (https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/).
4. Government Accountability Office. Drug shortages: certain factors are strongly associated with this persistent public health challenge. July 7, 2016 (http://www.gao.gov/products/GAO-16-595).
5. Chen SI, Fox ER, Hall MK, et al. Despite federal legislation, shortages of drugs used in acute care settings remain persistent and prolonged. Health Aff (Millwood) 2016;35:798-804.

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Lessons from Standing Rock — Of Water, Racism, and Solidarity

David Goldberg, M.D.

"I heard you were in Standing Rock." So began a visit with Mr. Y., and we leaned in toward one another.

In the past, I'd felt off balance with Mr. Y., who often seemed to push me away. "Why can't you just fix this?" he asked, referring to his diabetes. Mr. Y. is a traditional Navajo, or Diné. In the Diné culture, medicine men and medicine women sense and name the source of their patients' disharmony in the world — perhaps a lightning strike, an accidental offense to nature, or contact with the spirit world. Ceremony restores harmony and balance, often over several days and nights. The medicine man or medicine woman guides the patient's clan and