

An eye for the truth: On the trail of an international medical mystery

When John D. Bullock, M.D., M.P.H., M.Sc., FIDSA, FACE, paid a visit to a friend and colleague on an early March afternoon in 2006, he expected nothing more than some casual conversation in pleasant company. Instead, he found the first clues to a global medical mystery he would spend the next three years unraveling.

An ophthalmologist by training and former professor and chair of ophthalmology at the medical school, Bullock was visiting Ronald E. Warwar, M.D., who had taken over Bullock's private practice a few years before. When Warwar mentioned a patient with an unusual condition—a fungal corneal ulcer—Bullock's curiosity was piqued. Once he learned that Warwar actually had two patients newly diagnosed with the condition, Bullock knew the occurrences were no coincidence.

“That was an immediate alarm bell,” Bullock said. “In over 25 years of clinical practice, I had only seen one case, and yet here were two cases in the same practice within a week.”

His concern arose from more than decades of personal experience, however. In addition to earning a medical degree from Harvard University and a master's degree in microbiology and immunology from Wright State, Bullock returned to Harvard and received a master of public health (M.P.H.) degree in 2003, concentrating in quantitative methods

and epidemiology. He also completed additional course work at the London School of Hygiene and Tropical Medicine and became a Fellow of the Infectious Diseases Society of America (FIDSA) and the American College of Epidemiology (FACE).

This specialized training prepared him well for his current position teaching infectious disease epidemiology in the Wright State M.P.H. program as a clinical professor of community health and professor of mathematics and statistics. It also gave him the tools to recognize his colleague's cases as the first signs of a serious disease outbreak.

He did some quick calculations on the chances that two patients would independently develop such a rare condition in this short interval of time.

“The probability of that was in the tens of millions to one,” Bullock said. “Some brand new factor was in play.”

Sounding the alarm on a global outbreak

Bullock and Warwar followed up with some online research and discovered a report of nearly 40 similar cases a few weeks earlier, but half a world away in Singapore. The patients there had developed corneal ulcers caused by a specific type of fungus, *Fusarium*, and

nearly all had used the same type of contact lens solution: ReNu® by Bausch & Lomb.

Bullock immediately checked the cultures from Warwar's patients and inquired about the products they'd been using. On both counts, their cases were a perfect match. Each was suffering from *Fusarium* keratitis and had used the same solutions as the patients in Singapore. Bullock had uncovered evidence of a global outbreak.

“The next step was to contact the CDC (Centers for Disease Control and Prevention) and the FDA (Food and Drug Administration),” Bullock said.

His calls came in just two days after the organizations had received similar reports of three cases in New Jersey. Bullock's information confirmed the severity of the situation and led to the launch of a national investigation.



“It’s unusual to have *Fusarium*, in the northern climates,” he explained. The fungus is common in tropical settings like Singapore, or even parts of Florida, but “in the northern states in the winter... to see it in one state, you kind of scratch your head, but to see it in two states, then the CDC and the FDA realized something serious was going on.”

Refusing to accept the easy answers

When preliminary inquiries turned up additional cases in other states, the FDA notified Bausch & Lomb and launched an investigation of the company’s manufacturing plant in Greenville, South Carolina. The CDC began issuing updates on the outbreak in April 2006, and the company halted domestic shipments of ReNu with MoistureLoc™, the product associated with most of the cases, on the same day. A recall of products already shipped in the United States, and then worldwide, followed shortly after.

As updates on the outbreak, and its causes and containment, came out day by day, Bullock remained skeptical. He continued to gather his own information online, conducting a second-hand investigation based on documents from the company, the FDA, and the CDC, as well his own review of the scientific literature and other information sources. And he found himself reaching conclusions at odds with the official explanations.

“This solution was made in four factories around the world: in China, India, Italy, and South Carolina,” Bullock said. “However, cases of *Fusarium* were traced only to the South Carolina plant. Right away you know that something’s funny.”

Extensive testing had found no contamination in the U.S. facility or the

solution produced there, however. Also, patients in different locations were affected by different strains of the fungus, ruling out a single, central source. These findings led the company to conclude—and report—that at least part of the problem arose from improper use of its product. By failing to follow usage guidelines, customers in far-flung locations had compromised the product, rendering them vulnerable to distinct, local strains of the fungus. Bullock disagreed.

“In point of fact, no patient ever follows the instructions exactly right” when it comes to contact lens care, he said. “We call that noncompliance.”

In addition, both of Warwar’s patients happened to be experienced health care providers. If anything, they were more likely than the average consumer to use eye care products properly. To Bullock, blaming the patients just didn’t make sense.

If patient behavior, exposure to *Fusarium* (which is common worldwide, though it typically thrives in warmer climates), and the specific product were the same everywhere, he argued, one wouldn’t expect every case to be linked to shipments from a single location.

“You have the same noncompliant patients all over the world, the same fungus, and the same solution,” he said. “If that’s all it was, then wouldn’t you expect to trace cases to each of the four factories?”

Turning up the heat

When the FDA released a report on its investigation of the South Carolina manufacturing plant, Bullock pored over it for some hint of potential problems with the solution produced there. Eventually, he found it: the company had failed to regulate the storage and transport temperatures of the solution.

“The bottle says to ‘store at room temperature,’” Bullock said, which implied that failing to do so might have harmful consequences. Possibly due to the absence of contamination at the plant and the diverse *Fusarium* strains involved in the epidemic, however, the FDA did not consider the temperature regulation problems overly serious.

Unconvinced, Bullock conducted further research and turned up a guidance document issued by the FDA in 1997, which cautioned that increasing the storage temperature by only 10 degrees Celsius would cut the shelf life of contact lens solutions in half. Furthermore, the impact of rising temperatures was exponential: storing the solution at 30 degrees above room temperature would reduce the shelf life by more than 85 percent.

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Bullock wondered if temperatures in Greenville in the summer might reach dangerous levels inside non-climate controlled warehouses, delivery trucks, or overseas cargo containers. As an easy, initial test, he placed a thermometer inside his own car and left it sitting in the sun on a typical Ohio summer day. When he returned after several hours, the outside temperature was 91 degrees Fahrenheit. Inside the car, it was 166.

Surprised and encouraged by his findings, Bullock did additional research and found an earlier study of a solution used to treat glaucoma, which degraded when exposed to high temperatures. He also looked up data from the National Oceanic and Atmospheric Administration on summer

temperatures in Greenville, and additional documents on storage and shipping temperatures in the region.

“Now we have a puzzle,” Bullock said, “and we have two pieces. We have a company that has been officially cited by the FDA for inadequate storage and transport temperatures. We have actual data showing how hot things can get inside cars, warehouses, trucks, and cardboard containers, where the temperatures can be enormous.”

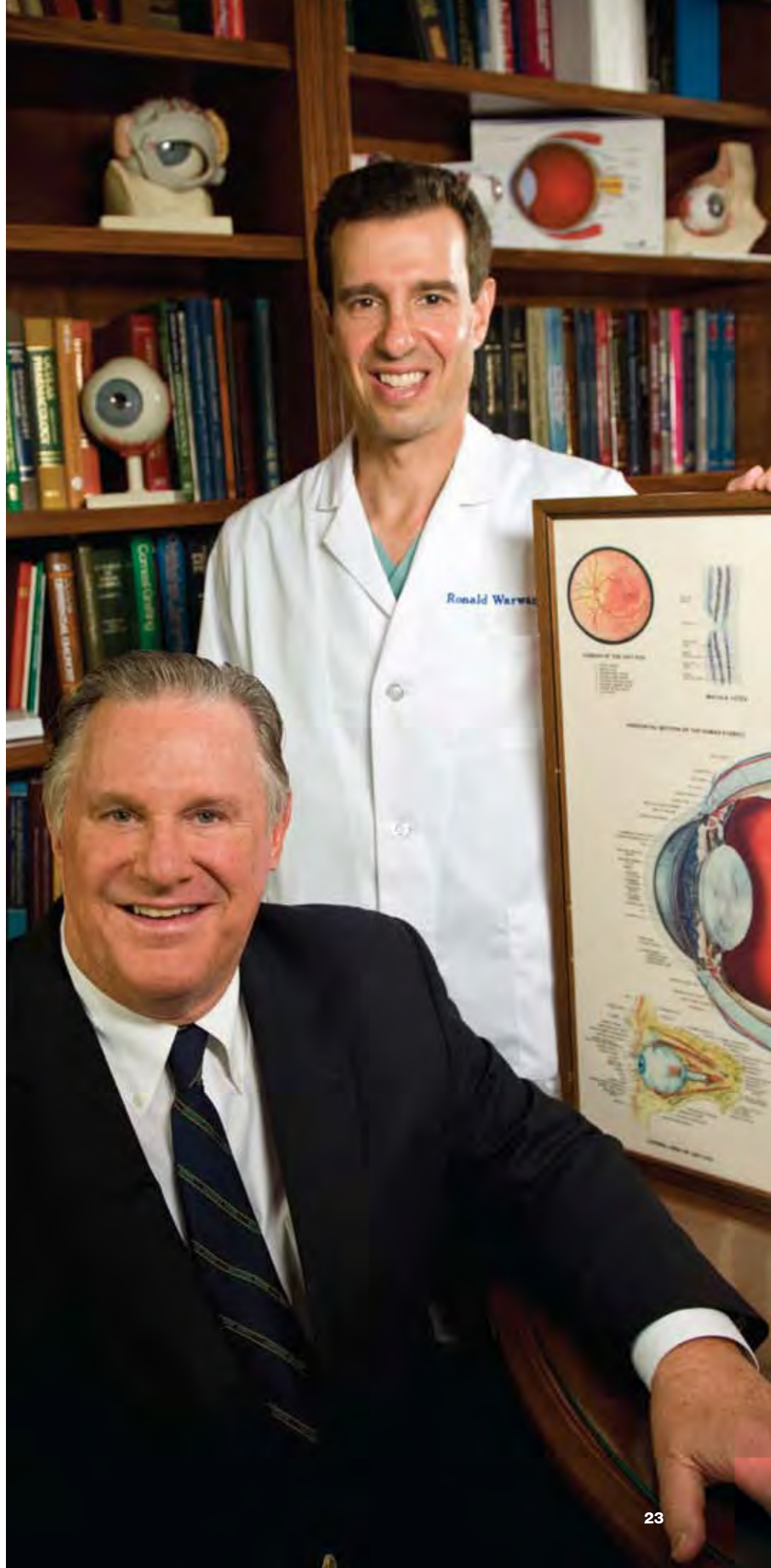
The next step, he said, was to try to create the same conditions in a laboratory setting to see how the solution might be affected.

Pinning down the real problem

Bullock and Warwar worked with B. Laurel Elder, Ph.D., associate professor of pathology and internal medicine, and William I. Northern, M.S., of CompuNet Clinical Laboratories, during the next phase of their investigation. They maintained samples of several contact lens solutions, including both recalled and currently available products by Bausch & Lomb, at a constant temperature of 140 degrees Fahrenheit for four weeks. They then added each solution to a broth containing *Fusarium*.

“We then looked at the difference between the high-temperature storage versus room temperature storage,” Bullock said. “And the biggest difference that we found was with this Bausch & Lomb solution.”

Bullock (seated) and Warwar wanted to know the real story behind local cases of keratitis linked to a worldwide outbreak. Their persistence led to an elaborate research project, multiple papers and presentations, and an explanation that earned media coverage around the globe.



Based on these initial results, Bullock, Warwar, and Elder followed up with a broader and more specific study. In addition to the two strains of *Fusarium* available locally, they tested two provided by Stanford University and seven, obtained from the CDC, collected from patients involved in the original U.S. outbreak. Using the same approach, Bullock and his colleagues tested all 11 *Fusarium* isolates and four contact lens solutions, using multiple assays for each combination. As in the pilot study, the ReNu with MoistureLoc solution stored

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at high temperature fared the worst. It allowed fungal growth nearly 80 percent of the time, while the same solution stored at room temperature developed fungus in only 32 percent of the tests.

“After all this work, we found exactly the same conclusion as we had in our initial pilot study,” Bullock said. “But now we had the evidence in spades, and it was absolutely irrefutable.”

He and Warwar presented their results at the 2008 annual meeting of the American Ophthalmological Society. Their findings created quite a stir, and the American Medical Association published a report of their study in the November 2008 issue of the *Archives of Ophthalmology*. Once the journal article appeared, global media coverage quickly followed.

“There were articles from India, from England, literally from all over the world describing our paper,” Bullock said.

He attributes the widespread interest to the same impulse that led him to conduct the research: a desire for answers. Two years after the outbreak and initial investigations into its sources, no one had pinpointed an exact cause. A number of researchers at various institutions had conducted studies, but Bullock believes they were asking the wrong questions.

“All the people who looked at it were trying to model a noncompliant scenario,” he said, searching for patient behaviors that might have played a role.

A few studies identified conditions that could conceivably lead to the creation of biofilms that would permit the fungus to persist, but once again, the same issue should have affected solutions from all four manufacturing plants equally.

Learning from the past; protecting the future

In May 2009, Bullock again presented a paper at the annual meeting of the American Ophthalmological Society. Based on his statistical studies and reviews of documents from the FDA and other sources, he performed a detailed root cause analysis of the outbreak. The paper outlines his findings and includes recommendations to help prevent future epidemics.

In addition to publishing the current paper, Bullock, Warwar, and Elder hope to conduct follow-up studies to explore the causes of the keratitis outbreak in still finer detail, possibly at the level of individual chemical interactions. With the implicated product no longer available and the broader contributing factors identified, some would consider this work complete, but Bullock and Warwar insist on going further.

The first reason for his continued interest is strictly personal, Bullock admits. His scientific hero is John Snow, M.D., the British physician and pioneer in the fields of epidemiology and public health, whose work famously halted a cholera outbreak in London in the 1850s. Like Snow, Bullock feels driven to apply his expertise to address puzzling public health issues. Bullock’s work has been included in scientific publications more than 200 times, and his investigations have led to multiple product recalls and requirements for new warning labels.

“I’ve always been attracted to rare cases,” Bullock said. With the keratitis outbreak, he continued, “I thought, ‘I’m an ophthalmologist, I’m a microbiologist, and I’m an epidemiologist, and I should be able to figure this out.’ I saw this as a challenge... It’s a great intellectual mystery.”

Still more importantly, he wants to be sure this particular problem won’t arise again. The outbreak ultimately affected more than 150 people on multiple continents, leaving many with incurable eye conditions, including blindness. For Bullock, addressing any preventable risk of a similar outbreak is imperative.

“One of the tenets of public health is that you find out. You get these answers,” Bullock said. “You don’t want to deal just with the original epidemic. You want to do the after-analysis, and that’s part of downstream prevention.”

“It’s important for the future to find the complete answer to this,” he added, “so that some other set of circumstances doesn’t lead to the same thing.” **VS**