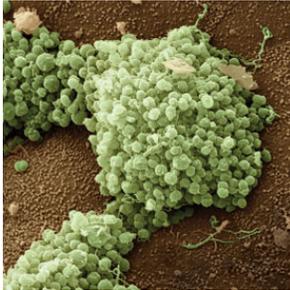


# Return of the Clap

Gonorrhea, once a minor illness, is developing resistance to the last category of drugs that still works against it and could become untreatable

By [Maryn McKenna](#) | May 4, 2012



Gonorrhea colony, as seen under a microscope Image: Juergen Berger/Photo Researchers, Inc.

Mark Pandori was worried. It was 2008, and he had just read the latest in a string of reports from Japan. The **articles all described patients infected with a particular strain of gonorrhea that was less susceptible than usual to an important class of antibiotics.** Pandori, director of the laboratory at the San Francisco Department of Public Health, knew that gonorrhea had become resistant to other antibiotics in past decades. Each time, the resistance seemed to arise in Asia and spread to California. He wondered if something new was heading across the Pacific.

The latest report from Japan described a test that could identify resistant strains of bacteria by isolating and amplifying the culprit gene. Pandori tried the procedure on 54 samples of gonorrhea bacteria collected that year from men in San Francisco. Five samples, or 9 percent, contained the altered gene. When he analyzed the bacteria in the lab, he found that they—like the Japanese strains—**possessed partial resistance to cephalosporins, the only antibiotics that still work reliably and inexpensively against gonorrhea.**

**Pandori and his research partner at the time, a health department epidemiologist named Pennan Barry,** were alarmed and baffled. No physicians in the state had reported any difficulties treating patients with gonorrhea. **Cephalosporin resistance had apparently infiltrated California without anyone noticing.** Perhaps it had started spreading across the country as well.

Last summer a surveillance network run by the **Centers for Disease Control** and Prevention confirmed their fears. Using a different test, the CDC demonstrated that up to 1.4 percent of 5,900 gonorrhea bacterial samples from around the U.S. had **diminished susceptibility to cephalosporins, meaning they would succumb only to unusually high doses.** A *New England Journal of Medicine* editorial published in February said the

occurrence of that partial resistance increased 17 times between 2006 and 2011. “The **threat of untreatable gonorrhea is emerging rapidly,**” the editorial warned.

That **threat is troubling for two reasons.** First, gonorrhea is abundant: it is the **second-most reported infectious disease in the U.S.,** with more than 600,000 new cases a year. Second, if **untreated, it can cause widespread organ damage, pelvic inflammatory disease and infertility.** Making matter worse, our current methods for tracking and controlling gonorrhea are actually contributing to the spread of resistant disease.

### **A Slow But Steady Spread**

Gonorrhea is the first of the major sexually transmitted diseases (STDs) to tiptoe to the threshold of untreatability. True, **chlamydia, which infects 426 of every 100,000 people in the country every year, is more common, and cases of syphilis, which doubled in incidence between 2000 and 2010, are growing faster.** But **syphilis infects only 4.5 of every 100,000 people, and neither chlamydia nor syphilis has developed significant resistance to antibiotics.**

**Gonorrhea, in contrast,** has been **developing defenses against drug treatment for decades.** The latest news from Japan and California is making the disease a priority for public health planners—a status it has not known *since before Alexander Fleming and the discovery of penicillin.* Once antibiotics became abundant and inexpensive, **gonorrhea and syphilis seemed like solved problems.**

Neither infection was vanquished, however. **Gonorrhea, in particular, held on by borrowing DNA from other bacteria to construct new microbiological defenses.** It steadily **gained resistance against entire classes of antibiotics: first the penicillins in the 1960s, then the tetracyclines in the 1980s, and Cipro and its chemical cousins, known as fluoroquinolones, in the 1990s.** By 2000 the *only class of drugs that could provide what public health strategies rely on—something that is inexpensive, delivered in a single dose and works well enough to obviate follow-up appointments—was the cephalosporins.*

### **Moving From East to West**

**Cephalosporin resistance** has been emerging in Japan, and moving east and west from there, for at least a decade. In 1999 physicians in Kitakyushu in southern Japan saw two men with gonorrheal infections that had not responded to the usual doses of cephalosporins or related drugs. Within two years more resistant cases emerged. A clinic in Hawaii treated a man with the standard dose of cefixime—a cephalosporin that comes in oral form—but he returned because his symptoms had not gone away. The man said he had had two sex partners who came from Japan, both women. One woman could not be found; the other woman and the man were cured only after receiving higher than usual doses of several different drugs.

Rapid international travel allowed the resistance mutation to hopscotch the globe. **Sweden found its first case of the less susceptible strain in 2002. By 2005 it was in England. In 2010 Norway identified its first cases, in men who had had sex with women**

while traveling in the Philippines and Spain. That same year a Swedish man who contracted gonorrhea after having sex with a woman in Japan could not be cured until he received four times the standard dose of ceftriaxone, an injectable cephalosporin that doctors used because oral cefixime no longer worked. “We may now be reaching the ceftriaxone [doses] for which complete bacterial eradication ... will be impossible,” warned the physicians who treated him in a February 2011 report.

Last July Japanese researchers announced at a meeting in Canada that they had found a gonorrhea strain in a Kyoto sex worker that was “highly resistant” to both ceftriaxone “and most other antimicrobials tested.” The infection was finally controlled with intravenous antibiotics, but experts say that was a one-time fix, impractical for most clinics. In March other researchers announced a similar case in France.

“We can’t go back to older antibiotics,” says Peter Leone, who is board chair of the National Coalition of STD Directors and medical director of North Carolina’s STD prevention program. “Once resistance emerges in gonorrhea, it is there for good. Cephalosporins are all we have left.”

### **Uncertain What Comes Next**

Efforts to control STDs may have inadvertently accelerated the spread of resistance. For years standard practice has been to quickly identify an infection, dole out the appropriate treatment and then move on to the next patient. If symptoms return, the assumption has been that the patient was reinfected. Experts now say that such patients may in fact have harbored resistant bacteria that were never killed in the first place—bacteria that the patients possibly spread to others.

Physicians would not have recognized that they were dealing with increasingly resistant bacteria, because the rapid tests most commonly used to diagnose sexual infections cannot identify resistant organisms. Instead the tests look for a DNA segment that is unique to gonorrhea, destroying the bacteria in the process. *Identifying resistance requires intact living bacteria that researchers can grow in a lab dish and expose to antibiotics to see which drugs work or do not.*

Routinely testing patients for resistant strains with the culture tests instead of rapid tests would be costly and time-consuming. But in the February *New England Journal* editorial, lead author Gail Bolan, director of the CDC’s division of STD prevention, argues that it is necessary. She also recommends retesting patients after treatment to make sure the infection is gone.

Doctors who treat sexually transmitted infections say that although such changes are sensible, they are not easy. Collecting bacterial samples for analysis requires supplies that most offices do not keep on hand, says Melanie Thompson, executive director of the AIDS Research Consortium of Atlanta, which also does STD testing. “A health care provider who suspected a resistant case would have to recognize it,” she explains, “contact the CDC or state health department to report it, go about getting the materials and then get the patient back in to give a sample.”

Barry, who helped to reveal that cephalosporins are becoming unreliable and now works for the California Department of Public Health, says the **news of burgeoning resistance has not reached either patients or most frontline physicians.** “We need to make clinicians aware of the problem and to **make patients aware that it is not normal for symptoms to come back,**” he says.

**For any infectious disease, the ultimate control strategy is vaccination,** but so far attempts to create a vaccine against gonorrhea have failed. Meanwhile, although infectious *disease experts strongly encourage research into new antibiotics for gonorrhea, only one clinical trial is under way, and it is investigating combinations of older drugs, not new compounds.* Some older drugs, such as azithromycin, have already started losing effectiveness against gonorrhea bacteria.

All these efforts—to educate physicians and patients, to track resistant strains and to develop new treatments—must be carefully targeted and well coordinated with one another. If not, truly untreatable gonorrhea, and its expensive, destructive consequences, could be the worldwide result.