



After the Fact | [The Fight Against Antibiotic Resistance](#)

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TRANSCRIPT

[Door clanks]

Dan LeDuc, host: We are in a fascinating room. We've climbed up the steps in St. Mary's Hospital, here in London, and are in Alexander Fleming's actual laboratory.

Kevin Brown, curator, the Alexander Fleming Laboratory Museum: Yes, this is where it all happened. Now you look at it, it's old fashioned, low tech, musty, a bit dusty, even.

Dan LeDuc: *[Chuckles]*

Kevin Brown: However, it's only somewhere like this penicillin could have been discovered. If there's no possibility of the contamination of a Petri dish by a spoor of mold—no penicillin.

Dan LeDuc: Right.

Kevin Brown: It wouldn't happen in a modern lab.

Dan LeDuc: Too clean.

Kevin Brown: At least it shouldn't.

Dan LeDuc: It's too clean. Amazing.

[Music]

Dan LeDuc: From The Pew Charitable Trusts, I'm Dan LeDuc and this is "After the Fact."

Here at London's St. Mary's Hospital is where Alexander Fleming discovered penicillin in 1928. Ninety years later it's worth pausing to remember what life was like nearly a century ago without antibiotics. Infections were frequently deadly and a host of medical procedures like joint replacement surgery weren't possible.



A lot has changed since then, of course. But one thing that hasn't is how bacteria work. They're always adjusting and finding ways to fight against new antibiotics. Ninety years after the discovery of penicillin, public health experts warn that we face a new age of superbugs—which leads us to our data point for this episode: two million. The Centers for Disease Control and Prevention report that two million Americans get a drug resistant infection each year and 23,000 of them die. In a moment, we'll learn more about today's fight against superbugs. But first a little history.

Fleming's lab is small, not much more than a workbench with room for two people, overlooking a big bay window. In this old city, the buildings outside haven't changed much, so museum curator Kevin Brown says the view of London is pretty much what Fleming saw, too.

Kevin Brown: This is the actual room in which Fleming discovered penicillin. It wasn't built as a lab, it was adapted. It's fairly small by modern standards.

Dan LeDuc: A couple of microscopes. The old-fashioned kind, where you have a mirror underneath so that the light reflects in.

Kevin Brown: Yes. Even by the standards of 1928, it was primitive.

Dan LeDuc: The discovery of penicillin, like so many scientific milestones, was by chance. Fleming had been writing a chapter for a medical textbook about some common bacteria. And he had prepared some culture plates, made his observations, and then went off on a six-week holiday, leaving the dirty Petri dishes sitting on the workbench. Then, on Monday, September 3, 1928, he came back to work. And when he looked at those old Petri dishes something caught his attention. "That's funny," he said.

Kevin Brown: He was a master of understatement. Now, what he saw was that one of the Petri dishes had become contaminated by a fungus. That fungus didn't interest him one little bit. Contamination like that happened all the time.

What interested Fleming wasn't what was there, it's what was not there. Close to the mold, there were no colonies of bacteria. They should have covered the whole plate. Close to the mold, there was what is now called a zone of inhibition.

Dan LeDuc: The fungus had introduced something that stopped the bacteria from growing. At first, Fleming called it "mold juice," but that wasn't very scientific so he decided to name it "penicillin," after the fungus that was classified then as *Penicillium Notatum*. It became a wonder drug, and by the 1940s and 1950s, it was in wide use. But Fleming knew he hadn't discovered a final cure with penicillin.



Kevin Brown: Fleming was warning, as early as 1943, of antibiotic resistance. He'd observed it. Other bacteriologists observed it. His attitude was that what you had was a very strong weapon against infection. So use it wisely. Don't use it on something trivial. And only use it when you know it will be effective.

[Music]

Dan LeDuc: With each new antibiotic developed since the discovery of penicillin, bacteria have adapted and antibiotic resistance has continued—and as our data point reminds us, two million Americans get sick from these drug-resistant infections each year. The race is on to create new drugs faster than the build up of resistance.

Back in Washington, we sat down with Allan Coukell, who heads up Pew's health programs, to talk about this need for more drug innovation.

We've just been listening to a story about Alexander Fleming and the development of penicillin. It's probably worth reminding people, that was less than a century ago. I mean, there are people alive today who remember the days without antibiotics. But the new thing we're starting to talk about beyond all of that is resistance to antibiotics. First of all, tell us what that actually means and what the problem is.

Allan Coukell, senior director, health programs, The Pew Charitable Trusts: Yeah, so bacteria are much older than we are—billions of years old. And they've engaged in chemical warfare for as long as they've been around. And so they're really good at defending themselves. And so, when we start using antibiotics, which are mostly natural molecules that kill the bacterial cells, bacteria are really good at picking up genes that let them live in the presence of those antibiotics. And they're also really good at passing those genes around, which means almost as soon as you develop a new antibiotic the bacteria will start becoming resistant to them.

Any time we use an antibiotic we are helping to create resistance, which doesn't matter. That's sort of the price you pay if you're using an antibiotic to treat an infection. What we have to be really sure we're doing is not using antibiotics when we don't need them.

And it turns out that about 30 percent of the time, those antibiotics that adults take for a cold or whatever are unnecessary—probably more than that.

Dan LeDuc: And it's leading to a serious problem. What are the numbers?

[00:02:05.42] ALLAN: Yeah. So the numbers are surprising, and I think there's a tendency of people and policymakers to think, "This is a problem, and if we don't do something



someday we'll have this problem.” But the CDC actually has produced numbers that show that about two million Americans a year get a resistant infection.

And of those, 23,000 die from that resistant infection. So that's not people who die with a resistant infection. That's actually the *cause*. And those are pretty conservative estimates that the CDC has generated. So if you think about it, that's the equivalent of a jet plane crashing every week.

But even more worrisome is how fast new resistant strains can emerge. So I'll give you an example. So there's a bacteria called CRE, which has a long acronym. But somebody called it at one stage the nightmare bacteria, and that name sort of stuck. So the CRE, this nightmare bacteria, shows up in the U.S.—the first time in North Carolina in 2001. So it's in one state. The next couple of years there are outbreaks in New York City. And then it starts to march across the country like a plague of locusts.

So by 2016, it's in 48 states. Now, this year, it's in all 50 states. And that is a bug that can really, until recently, only be treated with one drug—and a pretty old, kind of toxic drug. And so as that bacteria starts to develop resistance to that drug, all of a sudden you have potentially an untreatable infection. And that's happening now. So that's going to march across the country, too.

Dan LeDuc: Why is it happening now? Why didn't it happen decades ago, or was it we didn't know it?

Allan Coukell: Well, it was happening, actually. And resistance to penicillin was around actually before penicillin was widely available. Because the bacteria sort of do this innately.

Dan LeDuc: Fleming, in fact, sort of predicted this would happen.

Allan Coukell: In his Nobel lecture, Fleming said “If we don't use these drugs wisely, resistance will emerge.” And it did. But for the first 60 years of the antibiotic era, scientists and pharmaceutical companies produced a lot of new antibiotics. And so we were always able to stay ahead of the resistance.

But for decades, it didn't matter much. Because we came out with different penicillins, and then we came out with cephalosporins, and then we came out with erythromycin and tetracycline, and all of these new classes of antibiotics that people know about. And the reason we have all those and the reason we use them, is because penicillin stopped working. So from 1945 to the mid '80s we had lots and lots of new antibiotics. And then the pipeline sort of went dry.



Dan LeDuc: Why?

Allan Coukell: It's a great question. I think there were a few things that happened. One is pharmaceutical companies—it just didn't seem like that exciting or dynamic an area to be in. It was thought to be kind of a solved problem.

Dan LeDuc: Wow. Even though, of course, all this development was happening because of a continual problem.

Allan Coukell: Yup. So that's one thing. It's also true that companies in the mid '80s, a number of companies—and to their immense credit, they've actually published on their experience—spent a lot of money, millions or tens of millions of dollars, pursuing scientific strategies that just failed. They were using some new high throughput screening, and gene targeted strategies, and so on. And they just didn't produce anything.

And then right around that time the FDA—which sets the standards for the clinical studies of the drugs—really looked at the way clinical trials for antibiotics were being done and realized there were some scientific problems, and basically said “We need a higher standard of clinical trials.” And that made it that much harder—perfectly good scientific reasons for doing that—but it made it that much harder to study the drugs and bring them to market.

And, combine all of that with the fact that the market for an antibiotic is just not that big. When you get a new antibiotic, you don't get nearly the revenue you get for an exciting new drug for multiple sclerosis, or cancer, or whatever. And so sort of all of those things combined to have companies kind of exit the field.

Dan LeDuc: When was the last sort of significant antibiotic put on the market?

Allan Coukell: Well, we are having a couple of drugs a year come to market. And in the last few years, there has been some exciting innovation and some new classes of antibiotics coming, but not enough.

Dan LeDuc: How do we spark that sort of creativity in the pharmaceutical research world?

Allan Coukell: Well, there are a number of things that need to happen and can happen. One thing that is happening, which is beneficial, is the government is supporting early stage development. So that's helpful.



There are people working on other kinds of economic incentives to increase their reward one way or another when the drug comes to market. The FDA has created some new pathways to get those to market. But there's still this kind of fundamental problem of not being able to find new chemical structures.

And this is a place actually that Pew has been focusing on. A few years ago we brought together a big group of scientists from industry and academia. And we published a report outlining a number of major areas. And now we're actually tackling the first one of those, which is "How do you get molecules, drugs, into bacterial cells?"

So, you can divide the common bacteria that we see in hospitals into two categories. One they call gram positives. And they have a cell wall, and it's kind of hard to get the drug past that cell wall. Another kind, which is really the big problem we see now in the really scary area of resistance, are called gram negatives. And they have a double cell wall.

So, you can think of these bacteria as sort of medieval castles, and the drugs are like soldiers trying to storm the castle. And in the case of these gram negatives, you have to get through one wall. And then the defenders are in there kicking you back out again before you breach that second wall.

Dan LeDuc: What more can be done on the economic side, then, to start making this more attractive to private industry where a lot of this innovation is going to come from?

Allan Coukell: So one is sort of de-risking the investment by helping to defray some of those research costs. There are various ideas out there about how you might do it. But all essentially intending to increase the revenue that you get from an antibiotic when you come to market, either through a prize, or a tax incentive, or some kind of voucher that you can sell to another company.

Dan LeDuc: And the thing to remember—this is not just a U.S. problem. The antibiotic issue is a global one.

Allan Coukell: It is absolutely a global issue. And the U.S. government has created a strategy for the U.S. government that calls on every agency that touches this issue to have an action plan and move forward. But we've also seen a lot of leadership from the U.K. government, the Germans, the Swedes, Mexico. So, there is a lot happening at the international level. There are certainly countries that do much better than we do at reducing antibiotic use.

Dan LeDuc: Can we feel some sense of optimism here?



Allan Coukell: It would be nice to end on an optimistic note, wouldn't it?

Dan LeDuc: *[Laughs]* But only if it's true.

[00:25:51.32] ALLAN: There are good things happening. There is awareness. But if we sort of think of the two halves of the equation: how do we stop using antibiotics when we don't absolutely need to, and how do we make sure that there are new antibiotics—and we should also say new diagnostics to help diagnose infections—to help us not use them when we don't need them? How do we make sure that we have a robust innovation pipeline? And on both sides of that equation, good things are happening. We have a lot of progress still to go.

Dan LeDuc: Allan Coukell, thanks so much.

Allan Coukell: Great to talk with you.

[Music]

Dan LeDuc: To learn more—and see an infographic all about antibiotic-resistant bacteria—visit us at pewtrusts.org/afterthefact.

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Our thanks to St. Mary's Hospital and the Alexander Fleming Laboratory Museum for all their hospitality during our time in London.

For The Pew Charitable Trusts, I'm Dan LeDuc and this is "After the Fact."