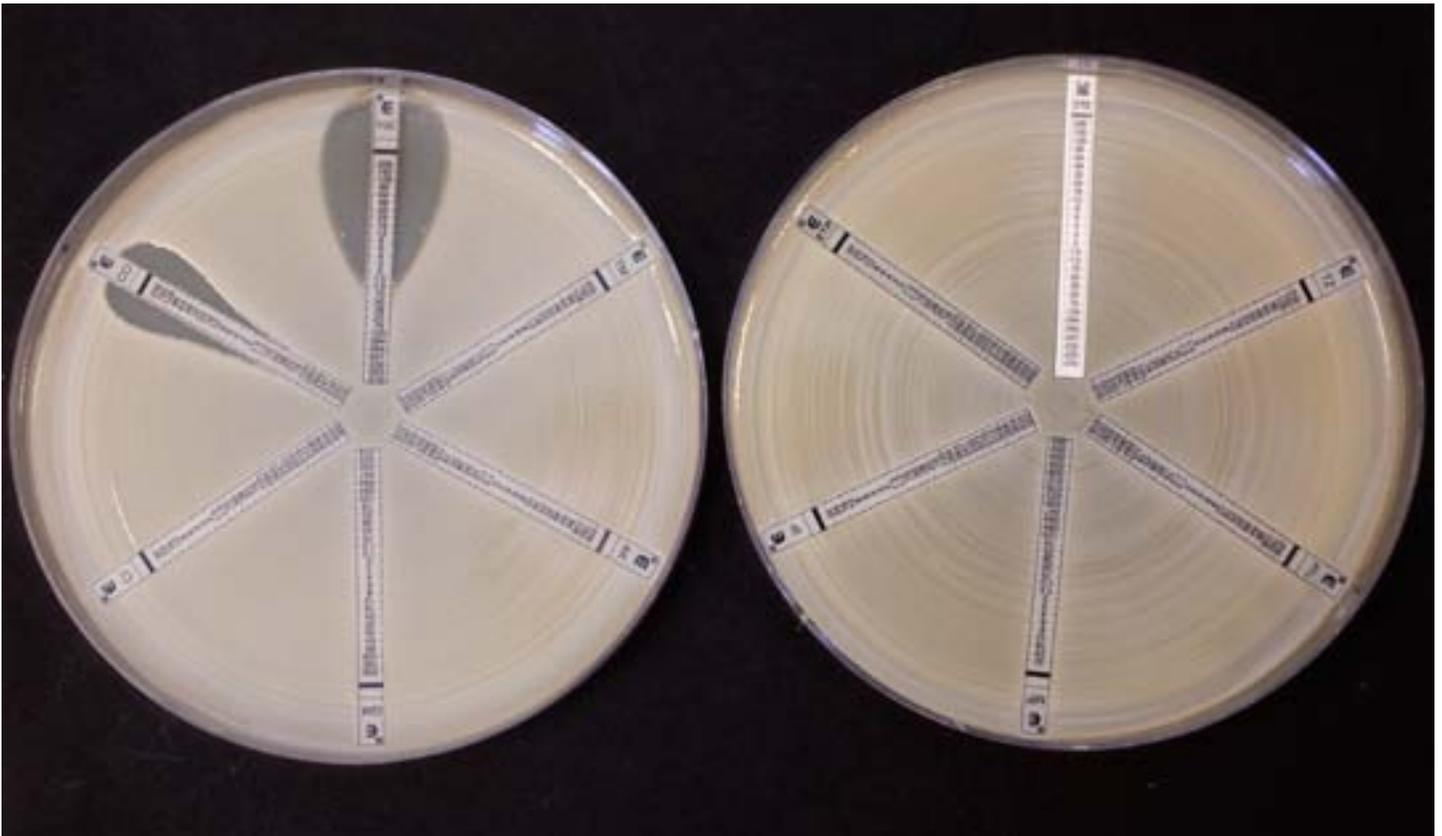


# WHEN THE DRUGS DON'T WORK

In the race between medicine and bacteria, the bugs are winning.  
Are we headed back to a pre-antibiotic age?



REUTERS/SUZANNE PLUNKETT

BY KATE KELLAND AND BEN HIRSCHLER  
LONDON, MARCH 31

David Livermore is in a race against evolution. In his north London lab, he holds up an evil-smelling culture plate smeared with bacteria. This creamy-yellow growth is the enemy: a new strain of germs resistant to the most powerful antibiotics yet devised by humankind.

Out on the streets, Steve Owen is running

the same race -- physically pounding the pavements to draw attention to the problem of drug-resistant infections.

Owen's father Donald died four years ago of multiple organ failure in a British hospital. He had checked in for a knee operation. But what he got was methicillin-resistant *Staphylococcus aureus*, commonly known as MRSA, a so-called "superbug" that all the drugs his doctors prescribed couldn't beat.

After almost 18 months of severe pain, the infection got into his blood, overpowered his vital organs and killed him.

Owen and his wife Jules have pledged to run 12 big races in as many months, to raise funds for a charity that is working to fight MRSA. "It just shouldn't have happened," says Jules, as the pair nurse their own aching limbs after running a half-marathon. "It was his knee -- that's not something he should have died from."

## TODAY, ONLY TWO LARGE COMPANIES STILL HAVE STRONG ANTIBIOTIC R&D PROGRAMMES. IN 1990, THERE WERE NEARLY 20.



**RACING FOR HELP:** Steve Owen and his wife Jules after a run to support an MRSA awareness charity **REUTERS/HANDOUT**

Welcome to a world where the drugs don't work.

After Alexander Fleming's 1928 discovery of the first antibiotic, penicillin, we quickly came to assume we had the chemicals to beat bacteria. Sure, bugs evolve to develop resistance. But for decades scientists have managed to develop new medicines to stay at least one step ahead of an ever-mutating enemy.

Now, though, we may be running out of road. MRSA alone is estimated to kill around 19,000 people every year in the United States – far more than HIV and AIDS -- and a similar number in Europe. Other drug-resistant superbugs are spreading. Cases of often fatal "extensively drug resistant" tuberculosis have mushroomed over the past few years. A new wave of "super superbugs" with a mutation called NDM 1, which first emerged in India, has now turned up all over the world, from Britain to New Zealand.

NDM 1 is what's growing on the plates that Livermore holds in his gloved hands. "You can't win against evolution," says the scientist, who spends his days tracking the emergence of superbugs in a national reference laboratory at Britain's Health Protection Agency. "All you can seek to do is to stay a jump ahead."

That's not happening now for a number of reasons. For a start, antibiotics are everywhere, giving bacteria countless opportunities to

evolve escape routes. The drugs can be picked up, without prescription, for pennies in countries like Thailand, India and parts of Latin America. Even though their use is controlled in the west, the system encourages doctors to shoot the bugs first and ask questions later. Perhaps most worryingly, the world's top drug companies, faced with decreasing returns and ever more expensive and difficult science, have not only slowed their efforts to develop new antibiotics but have been quitting the field in droves.

Today, only two large companies – GlaxoSmithKline Plc and AstraZeneca Plc -- still have strong and active antibiotic research and development programmes, according to the Infectious Diseases Society of America. Back in 1990, there were nearly 20.

That could have a profound impact on how we treat our sick. "If some of the most potent multi-resistant strains that we see now accumulate, then modern medicine -- from transplants to cancer treatment and even quite straightforward gut surgery -- potentially becomes untenable," says Livermore. "You need the ability to treat infections in vulnerable patients. Lose that and a swathe of modern medicine becomes unstable."

Are we about to start going backwards, to a pre-antibiotic era in which things like hip replacements, chemotherapy and intensive care are simply impossible? It's a big enough fear for the World Health Organisation to devote this year's World Health Day on April 7 to antimicrobial resistance in a bid to safeguard these drugs for future generations.

"Modern medicine can't function without effective antibiotics," says Derek Butler, chairman of the MRSA Action UK charity for which the Owens are raising money. "If we lose these magic bullets, medicine will be set back over 80 years."

### RAT ON THE WARD

ONE ASPECT OF THE race against bugs has changed little since Fleming's time, or Florence Nightingale's before that. Hospital hygiene is the basic, unglamorous and underpaid work that forms the vital first-line of defence against pathogens. If it is done properly, it can ease the demand for drugs in the first place. Yet Steve Owen remembers his dad telling him he'd seen a rat running through his ward – a shock in a developed world hospital.

Bugs are no respecters of age. Donald

Owen was 82 when the treatment for his knee problems ended up killing him. Susan Fallon's daughter Sammie was just 17 when she was admitted with flu-like symptoms to another British hospital in April 2008. Pretty, petite -- at only five feet tall she was "like a little doll", her mother says -- Sammie dreamed of being a professional photographer. When her hospital blood tests came back with worrying results, doctors ordered more, including a bone marrow biopsy. That led to a diagnosis



**HUMAN TOLL:** From top, David Livermore, a scientist at Britain's Health Protection Agency, holds a culture with the NDM 1 mutation. Sammie Fallon died after she was infected following a bone marrow biopsy. Donald Owen, killed by a superbug after a knee operation **REUTERS/SUZANNE PLUNKETT/HANDOUTS**

## “WE HAVE MORE OR LESS A GAP OF FIVE YEARS WITHOUT RESEARCH INTO NEW ANTIBIOTICS.”

of a rare blood disorder which required chemotherapy. She also picked up a superbug. Just over a month later, before any treatment had a chance to work, Sammie was dead.

The experience left her mother bereft, angry and with a fear of hospitals and the people who work in them “I don’t know which one came in without washing their hands and gave this bug to Sammie,” she says. “But if I went into hospital now I’d be saying ‘Wash your hands before you come near me’ -- I’d be really vigilant.”

In developed nations, a big push to improve hospital hygiene is starting to keep MRSA in check. At the same time, cheap international travel is breaking down the geographical barriers to infection. Medical progress is accelerating in places like India, China and Brazil, but often more swiftly than basic infection control in hospitals, Livermore says. “It’s sexier to say you can do a kidney transplant, but it’s not so sexy that infection control nurses go around and berate people for not washing their hands. And yet it may well be that the infection control nurse would save more lives than the renal surgeon.”

The fact that the latest superbug -- NDM 1 stands for New Delhi metallo-beta-lactamase, an enzyme that gives bacteria multidrug resistance -- first emerged in India comes as little surprise to many microbiologists. Use of antibiotics is rampant and unregulated in a country with appalling sanitation, high rates of diarrhoeal disease and overcrowding -- creating ideal conditions for resistance to develop. A week-long course of antibiotics can cost as little as 30 or 40 U.S. cents from one of the thousands of chemist shops that all too often dispense poor advice along with their non-prescription drugs.

On top of this, even in the developed world, the antibiotics used today are “broad” products, whose blunderbuss approach can kill a wide range of bugs but also trigger knock-on problems. One reason for this is that for the first 48 hours, patients are effectively treated blind while lab staff go through the process of growing a culture sample to see just which microbe is to blame. In particular, Clostridium difficile infection has become a significant problem in hospitals because such broad-spectrum antibiotics damage gut flora, which creates an environment for it to flourish.

### MEET THE FAMILY

ANTIBIOTIC-RESISTANT bugs like MRSA and C. difficile tend to be picked up by patients in

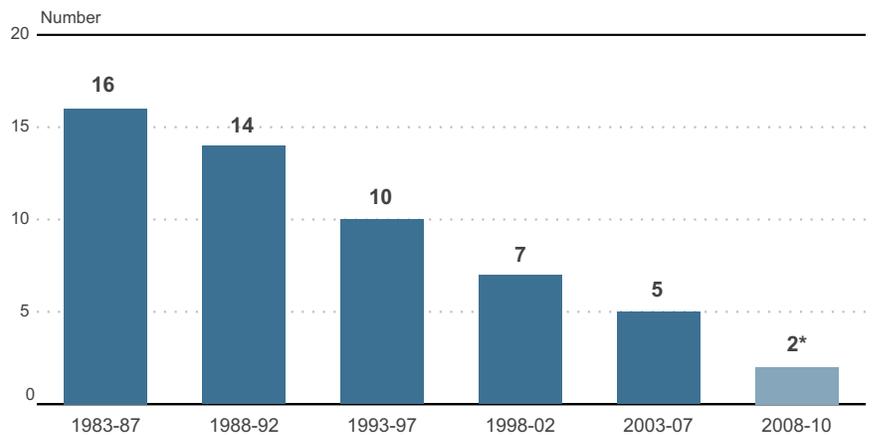
hospitals, but the risks are far broader than a hospital stay. Take the story of the 100 or so Swedes who went travelling to different parts of the world and were tracked by scientists to see what bugs they brought home. Of the eight who went to India, seven -- that’s 88 percent -- came back with bacteria in their guts that were resistant to a whole class of antibiotics called cephalosporins. Not one of the people in the study had been in a doctor’s clinic or hospital while they were there -- indicating the superbugs they picked up were freely circulating in the community.

What makes the NDM 1 enzyme so dangerous is not only its ability to outflank

carbapenems, the most powerful class of antibiotic drugs, but also the company it keeps -- in tough bacteria already resistant to many other antibiotics. Despite being identified only three years ago, it has already been detected in a wide variety of bugs, including many familiar pathogens such as Escherichia coli, or E. coli. In contrast to so-called Gram-positive bacteria, like MRSA, these microscopic enemies are Gram-negative, meaning they have tougher outer membranes which block out many antibiotics, and an unnerving ability to pump out others, making them much harder to take on and beat.

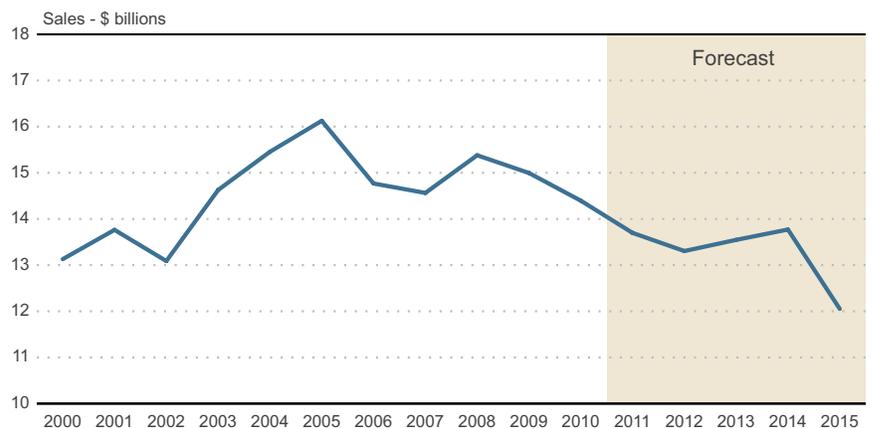
Cases of bacteria producing NDM 1 have

### Antibiotic approvals by FDA



Source: Infectious Diseases Society of America \*Partial-year period only  
Reuters graphic/Scott Barber, Ben Hirschler

### Global antibiotics sales



Source: Thomson Reuters Pharma  
Reuters graphic/Scott Barber, Ben Hirschler

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now been found and documented in two dozen countries from North America to Europe to New Zealand to China to Kenya.

Livermore's work shows only two or three remaining antibiotics can kill these bugs -- one is toxic, so doctors use it only in extreme cases; the second can't be used to treat urinary tract infections, one of the most common infections caused by E.coli; and the third is not available in many countries and is anyway susceptible to easily developed resistance. What's more, no new drugs in the pipeline active against NDM 1-producing bacteria have yet reached even the Phase II stage of the three-step process of clinical trials needed for regulatory approval. That means any new drug to tackle NDM 1 is at least five or six years away.

Even more alarmingly, NDM 1 is no lone threat -- it comes as part of a family. Similar enzymes in the same class, known as carbapenemases, have been detected worldwide. Just this month, the Eurosurveillance journal of the European

new patients every year. Until now largely a disease of the marginalised and poor, it's the sort of infection that mutates and could start killing more widely, regardless of its victims' wealth or home country.

"We're dealing here with a public health emergency of global proportion. If we don't do anything we're just going to see more and more," Raviglione says.

You might think all that adds up to a great business opportunity for the pharmaceuticals industry. But in the past 40 years only two new classes of antibiotics have won marketing approval, while the total number of antibacterial agents approved for sale has dived. Why are the drugs firms so quiet?

### CINDERELLA BUSINESS

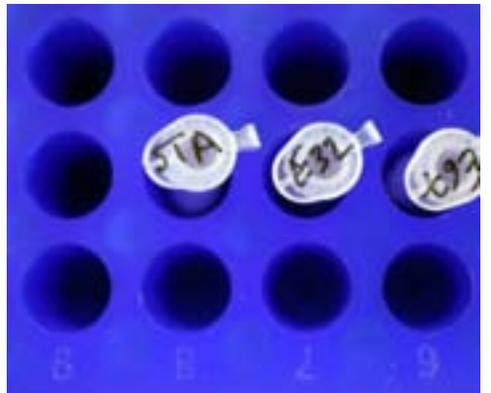
THE EUROPEAN MEDICINES Agency is easy to miss among the imposing towers of London's Canary Wharf financial district. Yet alongside the U.S. Food and Drug Administration (FDA) in Washington, it is a pivotal gatekeeper to the west's flow of new

than in antibiotics.

"We have more or less a gap of five years without research into new antibiotics," Lonngren complained. "It's an issue where commercial consideration doesn't really match the public health need." He went on to warn that, while it was not the job of regulators to tell commercial companies where to invest, they might in future need to advise politicians and the public at large about such research deficiencies.

Across the Atlantic, FDA Commissioner Margaret Hamburg shares his concerns. "We need new and better drugs ... and we need them now. Yet the R&D pipeline is distressingly low," she said in a speech to the National Press Club in Washington in October.

It wasn't always like this. For many years, making antibiotics was a bread-and-butter activity for the drugs industry. Today it has shrunk to a neglected Cinderella business -- complacent about past successes and reflecting the skewed economics that can drive pharmaceutical development.



**DWINDLING R&D:** Test tubes filled with samples of bacteria to be tested at the Health Protection Agency in London, March 2011.  
REUTERS/SUZANNE PLUNKETT

Centre for Diseases Prevention and Control reported that four separate cases of a related strain had been found in Switzerland between May 2009 and November 2010. Three had come from Italy, one from Greece.

That suggests that NDM 1 and its kin are not, in fact, the ultimate "super superbugs" but rather just the tip of the iceberg. The WHO's Mario Raviglione, who is fronting its antimicrobial campaign, is particularly worried about "superbug" forms of tuberculosis -- a disease that earned the nickname of "white plague" during Victorian times in Britain because sufferers' skin tone turned so pale.

TB already kills around 5,000 people a day and cases of multidrug resistant TB are spreading fast, with about 440,000

drugs. Last December, outgoing Executive Director Thomas Lonngren sent invitations to a conference looking back on the watchdog's past decade of achievements, and the great and the good of the pharmaceuticals world turned out en masse.

If they had expected a celebration, they were misguided. Lonngren, a softly spoken Swedish pharmacist, berated the industry for its pitiful record of innovation, arguing that out of the estimated \$85 billion spent globally each year on drug research and development, about \$60 billion was effectively wasted on dead-end projects. Worse, he said, drug manufacturers were failing to put their research dollars into key areas of unmet medical need.

Nowhere was the shortfall more glaring

Martin Mackay, a Scottish microbiologist who has worked for many of the world's top drugmakers and now heads up research at AstraZeneca, is better-placed than most to see the big picture. Back in the late 1970s he was a researcher at Beecham Pharmaceuticals -- now part of GlaxoSmithKline -- when many in the industry were checking off the fight against bacteria in the "Job Done" column. After all, doctors had a wide choice of effective treatments and all the drug companies needed to do was go out and sell them, and let the accounts department tot up the profits.

"Back then, there was a school of thought that said we had cracked the problem of bacterial diseases," Mackay says. "It looked a pretty good picture."



**POOR RETURNS:** The problem for Big Pharma is that antibiotics tend to cure people. REUTERS/SIMON NEWMAN

### THE SUMS DON'T WORK

TODAY, IT'S VERY HARD to make the commercial sums work. The drugs industry has seen dwindling returns on all its R&D in recent years, resulting in a wave of high-profile laboratory closures -- cost-cutting measures that have been cheered by the stock market. The payback on antibiotics has been even more dismal than in other diseases.

There are two main reasons for this. First and foremost antibiotics, when they work, tend to cure people. Patients take small quantities for several days, a few weeks at most. That's not a very attractive revenue flow. By contrast, a patient on a cholesterol-lowering heart medicine will keep using the pills, and contributing to drug industry profits, for the rest of his or her life. Second, even if a new antibiotic is approved for sale, its use is likely to be reserved for serious infections -- once again, minimising the sales opportunity.

*"IF YOU'RE IN THE BUSINESS OF ANTIBACTERIALS, I THINK YOU HAVE TO ACCEPT THAT IS THE WAY IT IS."*

To cap it all, most existing antibiotics have been around for decades and are widely available as cheap generics, setting a very low bar for prices.

"If you are in the business of antibacterials, I think you just have to accept that is the way it is," says Mackay. "Will it be as profitable as a really great cardiovascular drug? Probably not."

So it should be no surprise that while the global market for all prescription drugs grew by more than 40 percent over the last five years, the value of sales of antibiotics shrank to \$14.4 billion in 2010 from \$16.1 billion in 2005. That figure is projected to fall to \$12.0 billion in 2015 as some former blockbusters

lose patent protection, according to consensus analyst forecasts compiled by Thomson Reuters Pharma.

Faced with such economic hurdles -- not to mention the daunting scientific difficulties of outwitting fast-mutating superbugs -- a long list of big drug companies have decided to end their antibiotic research, including Roche Holding AG, Bristol-Myers Squibb Co and Eli Lilly & Co.

AstraZeneca and GlaxoSmithKline -- and to a lesser extent Novartis AG, Merck & Co Inc and Pfizer Inc -- remain in the antibiotic space. But scientists like Livermore fear work in drug company labs is being disrupted by the upheaval now sweeping the industry, following a wave of mergers and acquisitions. That's diverting attention from the job at hand: battling the microscopic pathogens that are threatening the practice of modern medicine.

### BARRIERS TO ENTRY

BUT THE BUCK DOESN'T stop with Big Pharma. Despite urgings from officials at the FDA and its European equivalent for drug companies to do more, many in the industry believe that regulators are actually a large part of the problem.

David Shlaes, a 30-year industry veteran who now works as a consultant, has particularly harsh words for the FDA, accusing it of a "lurch into Neverland as far as antibiotics are concerned" in an open letter to U.S. Secretary of Health and Human Services Kathleen Sebelius in February.

The problem, as critics like Shlaes see it, is the increasingly onerous nature of clinical trials demanded by officialdom before an antibiotic can be approved for sale. Regulators have grown much more cautious about clearing new drugs in recent years: the situation is especially sensitive in the case of antibiotics, following a scandal over Sanofi-Aventis SA's Ketek, which was approved in 2004 but subsequently linked to a risk of liver damage.

The result is a belt-and-braces approach to testing new antibiotics that means experimental

antibacterial drugs need more and much larger late-stage clinical studies, throwing up what senior Pfizer research executive Rod MacKenzie says is now the principal obstacle to antibiotic development for the handful of big players still left in the game.

"That's of course where the large bulk of our costs are -- in the late stage of development -- and so that really makes life very difficult," he says.

The pushback isn't just coming from the industry: Livermore is also convinced society needs to adjust its risk dial and make it easier for new antibiotics to win approval if it wants to secure a flow of future drugs. "As a result of seeking the perfect we risk squeezing out the good," he says. "It would introduce more risks -- but the biggest risk, looking forward, is that we are simply not going to get enough new antibiotics."

### "PUSH-ME, PULL-YOU"

EXPERTS FROM SCIENCE and industry meet often in conferences to ponder the problem. One such get-together in a swanky hotel in central London this month had the catchy title "Superbugs and Superdrugs". Unfortunately, the bacteria right now are proving a lot more "super" than the medicines, the delegates agreed, and many pharmaceutical industry investors are losing their appetite for the fight.

Fixing the system, experts argue, will require a mixture of "push" and "pull" incentives -- "push" measures to lower the cost of developing new antibiotics, and "pull" factors to increase the commercial rewards for successful products.

Adjusting the "pull" side of the equation may be the most controversial, since it effectively means offering a form of subsidy to drug companies. But the Infectious Diseases Society of America, which has called for a global commitment to develop 10 new antibiotics by 2020, believes stronger financial incentives are vital. Options include tax breaks, patent extensions or government commitments to buy future drugs. Some academics have also proposed more complex systems that would offer rewards based on how long a new product is on the market before resistance develops. The risk for taxpayers, of course, is that companies end up "gaming" any new reward system -- to the advantage of their shareholders but not necessarily society.

Ultimately, we may simply have to accept that antibiotics should no longer be cheap. Rather, they would become premium-priced products along the lines of targeted cancer therapies, which can cost tens of thousands of dollars a year for each patient. It would be

a radical change, and price out many in the developing world, but a high price would, at least, have the advantage of deterring over-use and helping to fund research, particularly in more narrowly targeted drugs.

Changing the business model could also open the door to new approaches to treatment. There's certainly plenty of room for improvement, since the current diagnosis of bacterial infection by growing cultures hasn't changed fundamentally in decades. In the future, scientists hope rapid point-of-care diagnostic tests will allow them to identify their adversaries within hours, making treatment decisions quicker and allowing drug companies to conduct small, focused clinical trials targeting a narrow population group.

All promising ideas, but not much is happening yet. The WHO is working on a six-point plan to target health authorities, doctors

and patients. Its main message: superbugs are not just a problem for the old and the sick -- this affects everyone.

Runner Steve Owen is the first to admit he finds the realities of what we face difficult to grasp. He knows that he lost his father because levels of hygiene in the hospital were too low. But why is the pace of drug development so slow? Why can't we do more to fix the problems that killed his dad?

"I've always thought that science would advance and keep up pace with the bugs, not that the bugs would get ahead of the expertise of the scientists," he says. "It's frightening."

*(Editing by Sara Ledwith and Simon Robinson)*

**BARRIER NURSE:** A patient with MRSA is pictured through the window of a security door at the Unfallkrankenhaus Berlin (UKB) hospital in February 2008  
REUTERS/FABRIZIO BENSCH



**COVER PHOTO:** Two plates coated with an antibiotic-resistant bacteria called *Klebsiella pneumoniae* with NDM 1 are exposed to various antibiotics at the Health Protection Agency in north London, March 2011. The clear areas show the bug was only sensitive to the antibiotics tigecycline (manufactured by Pfizer under the trade name Tygacil) and colistin. **REUTERS/ SUZANNE PLUNKETT**

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