THE LAST RESORT

Health officials are watching in horror as bacteria become resistant to powerful carbapenem antibiotics — one of the last drugs on the shelf.

BY MARYN MCKENNA

As a rule, high-ranking public-health officials try to avoid apocalyptic descriptors. So it was worrying to hear Thomas Frieden and Sally Davies warn of a coming health "nightmare" and a "catastrophic threat" within a few days of each other in March.

The agency heads were talking about the soaring increase in a little-known class of antibiotic-resistant bacteria: carbapenem-resistant Enterobacteriaceae (CREs). Davies, the United Kingdom's chief medical officer, described CREs as a risk as serious as terrorism (see *Nature* **495,** 141; 2013). "We have a very serious problem, and we need to sound an alarm," said Frieden, director of the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia.

Their dire phrasing was warranted. CREs cause bladder, lung and blood infections that can spiral into life-threatening septic shock. They evade the action of almost all antibiotics — including the carbapenems, which are considered drugs of last resort — and they kill up to half of all patients who contract them. In the United States, these bacteria have been found in 4% of all hospitals and 18% of those that offer long-term critical care. And an analysis carried out in the United Kingdom predicts that if antibiotics become ineffective, everyday operations such as hip replacements could end in death for as many as one in six[1].

The language used by Davies and Frieden was intended to break through the indifference with which the public usually greets news about antibiotic resistance. To close observers, however, it also had a tinge of exasperation. CREs were first identified almost 15 years ago, but did not become a public-health priority until recently, and medics may not have appreciated the threat that they posed. Looking back, say observers, there are lessons for researchers and health-care workers in how to protect patients, as well as those hospitals where CREs have not yet emerged.

"It is not too late to intervene and prevent these from becoming more common," says Alexander Kallen, a medical epidemiologist at the CDC. At the same time, he acknowledges that in many places, CREs are here for good.

Hindsight is key to the story of CREs, because it was hindsight that identified them in the first place. In 2000, researchers at the CDC were grinding through analyses for a surveillance programme known as Intensive Care Antimicrobial Resistance Epidemiology (ICARE) , which had been running for six years to monitor intensive-care units for unusual resistance factors. In the programme's backlog of biological samples, scientists identified one from the Enterobacteriaceae family, a group of gut-dwelling bacteria. This particular sample — of *Klebsiella pneumoniae*, a common cause of infection in intensive-care units — had been taken from a patient at a hospital in North Carolina in 1996 (ref. 2). It was weakly resistant to carbapenems, powerful broad-spectrum antibiotics developed in the 1980s.

Antibiotics have been falling to resistance for almost as long as people have been using them; Alexander Fleming, who discovered penicillin, warned about the possibility when he accepted his Nobel prize in 1945. Knowing this, doctors have used the most effective drugs sparingly: careful rationing of the powerful antibiotic vancomycin, for example, meant that bacteria took three decades to develop resistance to it. Prudent use, researchers thought, would keep the remaining last-resort drugs such as the carbapenems effective for decades.

The North Carolinan strain of *Klebsiella* turned that idea on its head. It produced an enzyme, dubbed KPC (for *Klebsiella pneumoniae* carbapenemase), that broke down carbapenems. What's more, the gene that encoded the enzyme sat on a plasmid, a piece of DNA that can move easily from one bacterium to another. Carbapenem resistance had arrived.

At first, however, microbiologists considered this CRE to be a lone case. Jean Patel, a microbiologist who is now deputy director of the CDC's office of antimicrobial resistance, says that CDC staff were reassured by the fact that the sample had been collected four years earlier and that testing of the remaining archives revealed no further instances of resistance. "It wasn't that there was a lack in interest in looking for these," Patel says.

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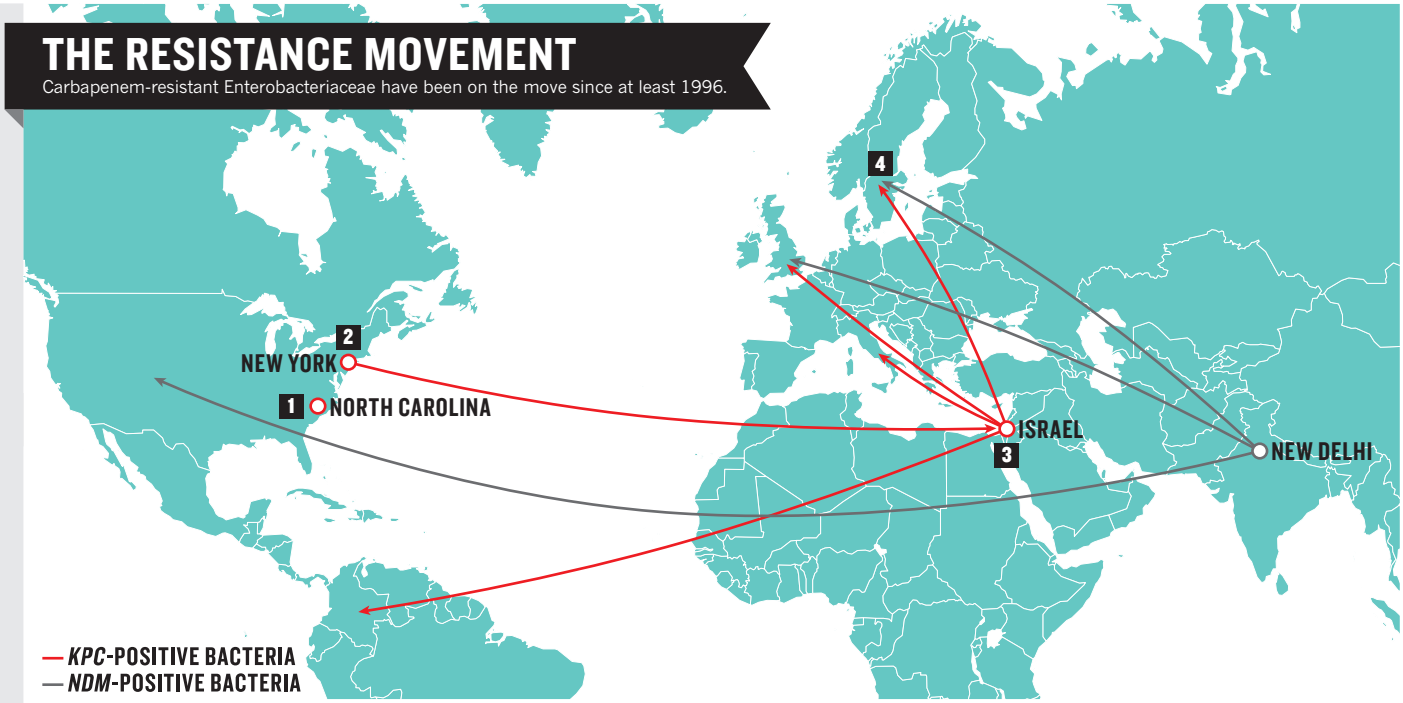

1 **2000:** Analysis of a 1996 sample from a North Carolinan hospital finds infectious *Klebsiella pneumoniae* carrying a gene called *KPC* that confers resistance to carbapenems.

2 **2003:** *KPC*-positive bacteria are found spreading rapidly through hospitals across New York City. By 2007, 21% of *Klebsiella* in the city carry the resistance gene.

3 **2005:** *KPC*-positive bacteria make their way from New York to several other countries, including Israel. From Israel, the bacteria travel to Italy, Colombia, the United Kingdom and Sweden.

4 **2008:** Doctors in Sweden find a new carbapenem-resistance gene, *NDM*. Traced back to India, *NDM*-positive bacteria have moved quickly.

Instead, the attitude at the time was, "We have a system for identifying these and it's working, and if more occur we'll hear about it".

But the CDC's surveillance programme was limited: it tracked only 41 hospitals out of some 6,000 and its analyses lagged far behind sample collection. So when carbapenem resistance emerged again, years passed before anyone noticed.

A DIRE TREND

The State University of New York (SUNY) Downstate Medical Center in Brooklyn draws patients from some of the poorest neighbourhoods in New York City, so it tends to be a place where dire health trends surface. It was not part of the CDC's ICARE programme, but physicians there conduct their own bacterial surveillance to scan for emerging infectious threats. In 2003, a review of results from the centre's microbiology lab and some collaborating ones at nearby hospitals picked up something that city physicians had never seen before. Over the previous six years, a handful of patients spread across seven institutions had been diagnosed with *Klebsiella* infections that were partially resistant to carbapenems. "These had been infrequent and they were flying under the radar," says John Quale, a medical researcher at Downstate. "And at about the time we picked them up, they just exploded."

The infections were very serious. In one Brooklyn hospital outbreak, 9 out of 19 patients died. In another, two infections blossomed into more than 30 in just six months, despite stringent infection-control measures. And the organism spread around the city — from Harlem Hospital at the north end of Manhattan to Mount Sinai Hospital on the Upper East Side, and then to Saint Vincent's in Greenwich Village in the south, where one patient died of a *Klebsiella* infection despite doctors throwing every drug they could at it.

One of the reasons why the resistant strains spread so rapidly was that they were difficult to detect. Most clinical microbiology labs no longer painstakingly culture bacteria over days to determine which drugs they are susceptible to: instead, automated systems, which expose bacteria to graduated dilutions of drugs, can give a result in hours. But these tests, Quale and his collaborators realized, were giving misleading results and were causing physicians to give patients doses or drugs that would not work. And because the infections were not eliminated, the resistant strain could be passed on. By 2007, 21% of all *Klebsiella* bacteria in New York City carried the carbapenem-resistance plasmid, compared with an average of 5% across the rest of the United States[3].

Such a rapid dissemination hinted that CREs were travelling from person to person rather than arising independently in each location. This made sense. Many Enterobacteriaceae, including *Klebsiella*, reside in the intestines and can easily be carried by an asymptomatic patient. If patients develop diarrhoea, as often happens after the administration of drugs during intensive care, the infectious bacteria can spread far, contaminating equipment or the hands of care-givers inside the hospital and out. So it was easy to imagine how CREs might ride the subway from Brooklyn to Manhattan. But it took a few years, and a much larger outbreak, to illustrate just how far CREs had travelled (see 'The resistance movement').

RAPID SPREAD

In late 2005, one patient at Tel Aviv's Sourasky Medical Center was diagnosed with a KPC-positive infection that was closely related to a New York strain. Within months, CRE infections stormed through the hospital, and then through Israel's small, tight-knit health-care system. By March 2007, there were 1,275 cases nationwide[4]. They were turning up across a network of hospitals, nursing homes, dialysis clinics and rehab centres.

Israel has a shortage of acute-care beds, explains Mitchell Schwaber, an infection-control physician who was on the Sourasky faculty when the KPC epidemic began. "Whenever a patient can be discharged, especially from internal medicine, they are — which creates a lot of movement from acute-care facilities to long-term care facilities, and then back to either the same hospital or a different one."

In response, the Israeli Ministry of Health created a national task force on CREs, headed by Schwaber. It demanded daily national-surveillance reports by e-mail, and instituted strict isolation precautions, including

dedicated wards, equipment and nurses. The new rules were backed up by surprise inspections and mandatory lab analyses to ascertain where new infections were coming from.

By mid-2008, Israel had reversed its soaring trend of resistant *Klebsiella*. But control came too late to prevent the pathogen from emigrating: patients, physicians and nurses had brought bacteria carrying the KPC enzyme to Italy, Colombia, the United Kingdom and beyond.

ALARM CALL

In January 2008, a urine culture performed on a sample from a 59-year-old man hospitalized in Sweden identified a *K. pneumoniae* strain that was resistant to multiple drugs, including carbapenems[5]. But rather than using KPC, the bacterium dismantled the antibiotics with a different enzyme, a metallo-β-lactamase. Within three years, more cases involving bacteria carrying this enzyme were identified in the United Kingdom and in the United States. These provoked immediate alarm: they were even more resistant to carbapenems than the KPC-carrying *Klebsiella* bacteria, and included other Enterobacteriaceae such as *Escherichia coli*.

Initially, most individuals carrying bacteria with the new resistance factor had some link to clinics in India, through medical tourism or health care needed while abroad. In accordance with taxonomic conventions, doctors named the new enzyme New Delhi metallo-β-lactamase (NDM), after the place where the initial Swedish patient was thought to have picked it up. The name proved unexpectedly controversial: Indian media and the Indian parliament denounced the acronym for stigmatizing India's medical-tourism industry. Further work by the team that first identified NDM only increased the outrage when it established that bacteria carrying the enzyme were present in sewage and municipal water in south Asia[6] (see *Nature* http://doi.org/dgcs33; 2011).

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The controversy obscured NDM's real significance: not only had another resistance mechanism emerged, but CREs were now flourishing beyond hospital walls.

Researchers were still struggling to pin down exactly how NDM was spreading. In the second half of 2012, staff at the University of Colorado Hospital in Aurora discovered that their institution had unknowingly hosted eight patients with NDM-positive *Klebsiella* bacteria, the largest cluster in the United States so far. The first three cases, all in patients with pneumonia, were found during a routine review of clinical specimens. When the hospital escalated its search, it also identified five asymptomatic carriers.

"There was no obvious pattern," recalls Michelle Barron, the hospital's infection-control physician. "These patients had been in the hospital a long time. They had been on multiple units. There was no single piece of equipment that had been used on all of them."

Even when the CDC sequenced the bacterial genomes from all eight patients, the data could not explain how the bacterium had spread. Barron hypothesizes that, at some point, the hospital harboured a "ghost patient" — someone who escaped detection despite the surveillance dragnet. She is still looking for that person: the hospital is attempting to call back and sample all 1,700 patients who were treated during the crucial period.

The episode ended well. The five carriers never fell ill, the three who were ill recovered, and once the hospital became aware of the cluster no further spread occurred. They might not be so lucky next time.

Fresh threats are on the way. Researchers have spotted other carbapenem-resistance factors moving around the globe; one has already appeared in the United States, and others are clustered in southern Europe and South America. Because each is genetically different, they are likely to present new challenges to detection. Infectious-disease specialists say that they have learned major lessons from CREs. Drug-resistant bacteria can emerge and spread much faster than patchy public-health surveillance systems and outdated laboratory-detection methods can pick them up, and what seems like adequate infection control cannot always contain their spread.

Some countries are trying to take those lessons on board. Hospitals in Israel now practise 'active surveillance', meaning that if a new patient has been to any other health-care institution in the past six months they are checked for CREs. And anyone who tests positive for such bacteria is flagged as a carrier in national-health records, which are accessible to hospitals, nursing homes and community physicians. France and the United Kingdom follow similar rules, but unfortunately many countries do not. Earlier this month, the European Centre for Disease Prevention and Control in Stockholm published a candid self-assessment by 39 European countries of their CRE burden and ability to counter these organisms[7]. Only 21 said they have achieved the kind of national coordination that allowed Israel to contain its epidemic.

The United States operates a patchwork of surveillance systems. The CDC looks for CREs through three separate data networks, but none of these covers the entire country. At least nine states have made reporting CRE cases to their health departments mandatory. The CDC has also created a robust tool kit of best practices for health departments and hospitals, such as restricting staff assignments and equipment use in hospitals, and identifying infections in the long-term care facilities that feed patients into hospitals. These measures helped institutions in Illinois and Florida to shut down outbreaks in 2008 and 2009.

LIMITED OPTIONS

Meanwhile, lab-detection methods have improved; the CDC's use of whole-genome sequencing to solve the Colorado episode was the first time that the agency deployed that technology to tackle a hospital outbreak. And public-health departments' ability to identify threats has been bolstered by boluses of federal money after the 2001 World Trade Center attack and subsequent anthrax attacks, and in the 2009 stimulus package. But these investments might be rolled back during the current federal budget sequester.

Physicians who treat patients unlucky enough to be caught up in these outbreaks have no better medicines than they did when CREs first emerged. Some organisms respond to two drugs, tigecycline and colistin (also known as polymyxin E). Neither works in every patient, and colistin is notorious for damaging the kidneys. Physicians find themselves caught between using bad drugs or using no drugs at all.

It seems unlikely that new drugs will become available soon. Perversely, the rapid advance of resistance and the consequent need to use these drugs sparingly has convinced pharmaceutical companies that antibiotics are not worth the investment.

That means, say infectious-disease experts, that their best tools for defending patients remain those that depend on the performance of health personnel: handwashing, the use of gloves and gowns, and aggressive environmental cleaning. Yet even research that could improve best practices has been short-changed, says Eli Perencevich, an infectious-diseases physician and epidemiologist at the University of Iowa in Iowa City who studies how resistant bacteria move around hospitals. "We haven't invested in research in how to optimize even standard infection-control practices. We just blame the health-care workers when they go wrong." ■ SEE EDITORIAL P.379

Maryn McKenna *is an independent journalist in Atlanta, Georgia.*

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