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Drug-Defying Germs From India Speed Post-Antibiotic Era

By Jason Gale and Adi Narayan - May 7, 2012 4:00 PM GMT-0500
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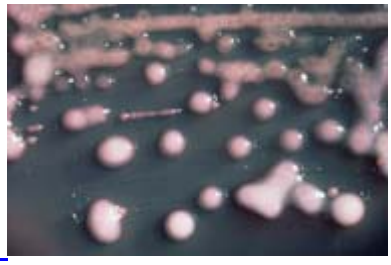
Lill-Karin Skaret, a 67-year-old grandmother from Namsos, Norway, was traveling to a lakeside vacation villa near India's port city of Kochi in March 2010 when her car collided with a truck. She was rushed to the Amrita Institute of Medical Sciences, her right leg broken and her artificial hip so damaged that replacing it required 12 hours of surgery.

Three weeks later and walking with the aid of crutches, Skaret was relieved to be home. Then her doctor gave her upsetting news. Mutant germs that most antibiotics can't kill had entered her bladder, probably from a contaminated hospital catheter in India. She risked a life-threatening infection if the bacteria invaded her bloodstream -- a waiting game over which she had limited control, Bloomberg Markets magazine reports in its June issue.

Enlarge image 

Klebsiella pneumoniae, the bacterium in which NDM-1 was first identified. Photograph: CDC

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May 8 (Bloomberg) -- India's overuse of antibiotics, coupled with the nation's poor sanitation, has led to a new type of superbug, mutated bacteria that even the most high-powered antibiotics can't kill. Scientists warn this superbug is spreading faster, further and in more alarming ways than any they've encountered. Bloomberg's Adi Narayan reports on the story featured in the June issue of Bloomberg Markets magazine. (Source: Bloomberg)

Enlarge image 

Karthikeyan K. Kumarasamy in Chennai worked with international doctors to identify the NDM-1 gene causing untreatable bacterial infections in India. Photographer: Anay Mann/Bloomberg Markets via Bloomberg

“I got a call from my doctor who told me they found this bug in me and I had to take precautions,” Skaret remembers. “I was very afraid.”

Skaret was lucky. Eventually, her body rid itself of the bacteria, and she escaped harm from a new type of superbug that scientists warn is spreading faster, further and in more alarming ways than any they’ve encountered. Researchers say the epicenter is India, where drugs created to fight disease have taken a perverse turn by making many ailments harder to treat.

India’s $12.4 billion pharmaceutical industry manufactures almost a third of the world’s antibiotics, and people use them so liberally that relatively benign and beneficial bacteria are becoming drug immune in a pool of resistance that thwarts even high-powered antibiotics, the so-called remedies of last resort.

Medical Tourism

Poor hygiene has spread resistant germs into India’s drains, sewers and drinking water, putting millions at risk of drug-defying infections. Antibiotic residues from drug manufacturing, livestock treatment and medical waste have entered water and sanitation systems, exacerbating the problem.

As the superbacteria take up residence in hospitals, they’re compromising patient care and tarnishing India’s image as a medical tourism destination.

“There isn’t anything you could take with you traveling that would be useful against these superbugs,” says Robert Moellering Jr., a professor of medical research at Harvard Medical School in Boston.

The germs -- and the gene that confers their heightened powers -- are jumping beyond India. More than 40 countries have discovered the genetically altered superbugs in blood, urine and other patient specimens. Canada, France, Italy, Kosovo and South Africa have found them in people with no travel links, suggesting the bugs have taken hold there.

Post-Antibiotic Era

Drug resistance of all sorts is bringing the planet closer to what the World Health Organization calls a post-antibiotic era.

“Things as common as strep throat or a child’s scratched knee could once again kill,” WHO Director-General Margaret Chan said at a March medical meeting in Copenhagen. “Hip replacements, organ transplants, cancer chemotherapy and care of preterm infants would become far more difficult or even too dangerous to undertake.”

Already, current varieties of resistant bacteria kill more than 25,000 people in Europe annually, the WHO said in March. The toll means at least 1.5 billion euros ($2 billion) in extra medical costs and productivity losses each year.

“If this latest bug becomes entrenched in our hospitals, there is really nothing we can turn to,” says Donald E. Low, head of Ontario’s public health lab in Toronto. “Its potential is to be probably greater than any other organism.”

Promiscuous Plasmids

The new superbugs are multiplying so successfully because of a gene dubbed NDM-1. That’s short for New Delhi metallo-beta- lactamase-1, a reference to the city where a Swedish man was hospitalized in 2007 with an infection that resisted standard antibiotic treatments.

The superbugs are proving to be not only wily but also highly sexed. The NDM-1 gene is carried on mobile loops of DNA called plasmids that transfer easily among and across many types of bacteria through a form of microbial mating. This means that unlike previous germ-altering genes, NDM-1 can infiltrate dozens of bacterial species. Intestine-dwelling E. coli, the most common bacterium that people encounter, soil-inhabiting microbes and water-loving cholera bugs can all be fortified by the gene.

What’s worse, germs empowered by NDM-1 can muster as many as nine other ways to destroy the world’s most potent antibiotics.

Untreatable Killers

NDM-1 is changing common bugs that drugs once easily defeated into untreatable killers, says Timothy Walsh, a professor of medical microbiology at Cardiff University in Wales. Or as in Skaret’s case, the gene is creating silent stowaways poised to attack if they find a weakness -- or that can pass harmlessly when the body’s conventional microbes win out.

Cancer patients whose chemotherapy inadvertently ulcerates their gastrointestinal tract are especially vulnerable, says Lindsay Grayson, director of infectious diseases and microbiology at Melbourne’s Austin Hospital.

“These bugs go straight into their bloodstream,” Grayson says. Newborns, transplant recipients and people with compromised immune systems are at higher risk, he says.

Six infants died in a small hospital in Bijnor in northern India from April 2009 to August 2010 after NDM-1-containing bacteria resisted all commonly used antibiotics.

India Vulnerable

India is susceptible because it has many sick people to begin with. The country accounts for more than a quarter of the world's pneumonia cases. It has the most tuberculosis patients globally and Asia's highest incidence of cholera.

Most of India's 5,000-plus drugmakers produce low-cost generic antibiotics, letting users and doctors switch around to find ones that work. While that's happening, the germs the antibiotics are targeting accumulate genes for evading each drug. That enables the bugs to survive and proliferate whenever they encounter an antibiotic they've already adapted to.

India's inadequate sanitation increases the scope of antibacterial resistance. More than half of the nation's 1.2 billion residents defecate in the open, and 23 percent of city dwellers have no toilets, according to a 2012 report by the WHO and Unicef.

Uncovered sewers and overflowing drains in even such modern cities as New Delhi spread resistant germs through feces, tainting food and water and covering surfaces in what Dartmouth Medical School researcher Elmer Pfefferkorn describes as a fecal veneer.

Tap Water

Germs with the NDM-1 gene existed in 51 of 171 open drains along the capital's streets and in two of 50 samples of public tap water, Walsh found in 2010.

Abdul Ghafur, an infectious diseases doctor in Chennai, southern India's largest city, sees patients every week who suffer from multidrug-resistant infections. He and others who used to successfully combat infections with such common antibiotics as amoxicillin now must use more-expensive ones that target a broader range of germs but typically cause greater side effects. Some infections don't respond to any treatment, evading all antibiotics, he says.

That's bad news because the more frequently the NDM-1 gene is inserted into different bacteria, the more likely it will enter virulent forms of E. coli, sparking outbreaks that may be impossible to subdue, says David Livermore, who heads antibiotic resistance monitoring at the U.K.'s Health Protection Agency in London.

Black Death

The gene may even spread to the microbial cause of bubonic plague, the medieval scourge known as Black Death that still persists in pockets of the globe.

"It's a matter of time and chance," says Mark Toleman, a molecular geneticist at Cardiff University. Plasmids carrying the NDM-1 gene can easily be inserted into the genetic material of Yersinia pestis, the cause of plague, making the infection harder to treat, Toleman says.

"There is a tsunami that's going to happen in the next year or two when antibiotic resistance explodes," says Ghafur, 40, seated at a polished wooden table in a consulting room in Chennai as patients fill 20 metal chairs in the waiting area, forcing others into the corridor. "We need wartime measures to deal with this now."

R.K. Srivastava, India's former director general of health services, says the government is giving top priority to antimicrobial resistance, including increasing surveillance of hospitals' antibiotics use.

Name Shame

At the same time, it's trying to preserve the country's health-tourism industry. Bristling that foreigners coined a name that singles out their capital to describe an emerging health nightmare, officials say the world is picking on India for troubles that impede all developing nations.

When Indian researchers joined international teams studying the NDM-1 gene, the government questioned the data and methods of the scientists, among them Chennai microbiologist Karthikeyan K. Kumarasamy.

"These bacteria were present globally," says Nirmal K. Ganguly, a former director general of the Indian Council of Medical Research and one of 13 members of a government task force created in September 2010 to respond to the NDM-1 threat.

"When you are blamed, the only reaction is that you put your back to the wall and fight."

Ulterior Motive?

S.S. Ahluwalia, a former deputy opposition leader in the upper house of India's parliament and a member of the Bharatiya Janata Party, says Western rivals want to muscle in on the medical tourism industry. Josef Woodman, founder of the guidebook "Patients Beyond Borders," values the industry globally at $54 billion a year.

"These reports are meant to destabilize India's emergence as a health destination," says Ahluwalia, whose term ended in April.

About 850,000 medical tourists traveled to India in 2010 for treatments from lifesaving cancer operations to cosmetic surgeries, generating $872 million in revenue, according to the Associated Chambers of Commerce and Industry of India, or Assocham. The number of foreign patients is predicted to almost quadruple by 2015, the trade body says.

Manish Kakkar, a doctor researching infectious diseases at the New Delhi-based Public Health Foundation of India and a task force member, says the government has its priorities wrong.

"We have been in a phase of denial," he says. "Rather than responding to the situation scientifically, we've completely diverted attention, saying that it's attacking our medical tourism."

'That's What's Scary'

Kakkar and others worry about NDM-1 because unlike germs such as VRE, short for the vancomycin-resistant enterococci bug that can cause infection around a patient's surgical incision, NDM-1 is spreading beyond hospitals.

Two travelers from the Netherlands picked up an NDM-1 bug in their bowels after visiting India in 2009 although they hadn't received medical care there, says Maurine Leverstein-van Hall, a clinical microbiologist at the University Medical Center in the Dutch city of Utrecht.

"That's what's scary," she says. "It's not just surgery or being near a hospital. In some way, you get it through the food chain or through the water."

For now, it's impossible to tell how common NDM-1 infections are or how often the mutant germs kill because testing and surveillance are inadequate in developing countries, says Keith Klugman, the William H. Foege chair of global health at Emory University's Rollins School of Public Health in Atlanta.

'Perfect Breeding Ground'

Cardiff's Walsh estimates 100 million Indians carry germs that harbor the NDM-1 gene, based on an extrapolation of studies in New Delhi and from neighboring Pakistan.

"It's not measured, and that's the problem," says Klugman, who pinpoints India as the epicenter.

India's jammed cities, poor sanitation and abundant antibiotics produce an ideal incubator, Harvard's Moellering says.

"You have almost no control over the prescription of antibiotics," says Moellering, who has studied drug resistance for four decades. "You have horrible sanitation problems in many parts of the country. You have incredible poverty, and you have crowding. When you put those four things together, it's the perfect breeding ground for multidrug-resistant bacteria."

Antibiotics even pollute India's rivers, streams and soil. The bacteria that thrive in these places do so because they've developed resistance to the drugs they encounter. People or animals who ingest the water or soil may become colonized by the resistant germs.

Mining Cipro

Until the government built a pipeline to a modern sewage plant in 2010, the Patancheru Enviro Tech Ltd. treatment facility on some days released the equivalent of 45,000 daily doses of ciprofloxacin into the Isakavagu stream outside Hyderabad in southern India, Swedish researchers reported in 2007. The plant treated wastewater from drug-making factories.

Residue from ciprofloxacin, a mainstay treatment for E. coli infections, was so prevalent in river sediment downstream that lead researcher Joakim Larsson of the University of Gothenburg jokes, "Had ciprofloxacin been a little bit more expensive, we could probably mine it from the ground."

India's antibiotics overload is forcing doctors to rely on ever-more-powerful drugs. Many now turn to a class called penicillin-based carbapenems to treat ailments as routine as urinary tract infections, says Grayson, who was editor-in-chief of medical text "Kucer's The Use of Antibiotics" (Hodder Arnold/ASM Press, 2010).

'Antibiotic Stewardship'

NDM-1 has rendered even carbapenems useless, sometimes leaving no way to fight infections. Two drugs potentially capable of treating NDM-1 bacteria have toxic side effects in some patients that include an increased risk of death.

“It’s an example of why we need to have good surveillance and why we need to have good antibiotic stewardship,” says Thomas R. Frieden, director of the U.S. Centers for Disease Control and Prevention in Atlanta. “We are looking at the specter of untreatable illness.”

Drugmakers have been slow to respond with new medicines. Most abandoned antibiotic discovery during the past decade, says Karen Bush, a microbiologist at Indiana University in Bloomington. She led teams that developed five bacteria-fighting drugs beginning in the 1970s in laboratories that are now part of AstraZeneca Plc (AZN), Bristol-Myers Squibb Co. (BMY), Johnson & Johnson and Pfizer Inc. (PFE)

Companies instead pursued hypertension and high-cholesterol drugs that patients take for a lifetime rather than a few weeks, she says.

International Uproar

Kumarasamy, the Chennai microbiologist, says he thought he was doing his country a favor when he helped track down the cause of unexplained deaths inside India. Instead, he sparked an international uproar over NDM-1.

Beginning in June 2000, Kumarasamy, now 36, studied bacteria and went from hospital to hospital in Chennai to collect specimens. He says he witnessed a steady increase in difficult-to-treat infections. Patients were dying, and doctors couldn’t identify what type of resistant germs killed them, he says.

“No matter how skilled or intelligent the doctor is, they are helpless when it comes to these infections,” he says over lunch of rice and curry in a noisy Chennai food court. He didn’t keep a tally of the deaths.

Kumarasamy, who received a Bachelor of Science degree from Navarasam Arts & Science College in Tamil Nadu state in 1997, says he began isolating bacteria from the blood, sputum, pus and urine of patients and freezing the samples. He quit his lab job in 2007 to study resistant germs for a doctorate in microbiology at the University of Madras. He’s winding up his thesis on carbapenem-resistant bacteria.

Festering Bedsores

Kumarasamy’s curiosity spiked in 2008 when he realized he was dealing with something totally new. He reached out to Walsh, whose Cardiff lab was at the forefront of international antibiotic resistance research.

Around that time, Walsh was studying the case of a diabetic stroke patient of Indian origin. The man had festering bedsores and had been transferred from New Delhi to his home in Sweden for treatment. When bacteria cultured from his urine and feces evaded more than a dozen drugs, including last-resort carbapenems, Christian G. Giske, a clinical microbiologist at Stockholm’s Karolinska University Hospital, sent the samples to Walsh’s lab.

Stockholm Hotel

In a hotel room in the Swedish capital, Walsh and Giske named the gene that made the bacteria immune to virtually all these antibiotics New Delhi metallo-beta-lactamase-1.

Beta-lactams are a class of antibiotics that includes penicillins, cephalosporins and carbapenems. Beta-lactamase is an enzyme that destroys those drugs. Metallo-beta-lactamases are so named because they contain zinc and destroy carbapenems, the most powerful beta-lactams.

Kumarasamy, suspecting something similar in his own specimens, asked Walsh to share the DNA sequence of this new bacterial gene. Walsh did -- and Kumarasamy got a match.

Kumarasamy began visiting Chennai hospitals anew to look for drug-resistant specimens. He also got samples from researchers in India's northern Haryana state.

When his collection was added to those Walsh and his colleagues were studying, the researchers discovered the same NDM-1 gene from four countries: India, Pakistan, Bangladesh and the U.K. For most of the British patients, the link was recent travel to India or neighboring Pakistan.

In Kumarasamy's samples from inside India, many cases emerged in people who hadn't recently been hospitalized. That suggested the bacteria were spreading in the community.

'Unsung Hero'

"He is India's unsung hero," Walsh says.

The University of Madras initially thought so, too. It feted Kumarasamy after he became the youngest scholar from the 155-year-old institution to have research appear in any publication of the British medical journal "The Lancet." His August 2010 paper, in "The Lancet Infectious Diseases," became that publication's most-read article that year.

The mood soured a few days later. Officials at India's Ministry of Health & Family Welfare balked at the gene's name, which threatened medical tourism's public image.

"There was a lot of stress and tension, and I could not sleep properly for two months," says Kumarasamy, who says he developed gastric reflux and heartburn.

The next month, authorities at the ministry grilled the eight Indian contributors to the "Lancet" report, including lead author Kumarasamy, according to two co-authors who declined to be identified because their employers don't permit them to speak to the media.

'Batten Down the Hatches'

Officials questioned their data and chastised them for sending specimens overseas without approval, saying the researchers had violated a 13-year-old regulation, according to two in the group.

The Indian Council of Medical Research says it requires researchers to submit detailed proposals to send any bacterial collections abroad. The process may take at least four months.

“The regulations were already in place,” says Sandhya Visweswariah, a professor at the Indian Institute of Science in Bangalore.

The researchers countered that the rules were nebulous and were rarely enforced.

“It is suppression of scientific freedom,” Walsh says of the government behavior. “They just try to batten down the hatches and make everything very, very difficult and pretend nothing has happened.”

Front-Page News

After front-page stories on the superbug appeared in Indian newspapers, the government formed an antibiotic resistance task force. It recommended in April 2011 that antibiotic use be tracked in the country’s 100,000 hospitals to find excessive prescribing. The group advised making it harder to get antibiotics without a prescription by requiring pharmacists to keep records for two years to aid audits and inspections.

Current rules make a prescription mandatory, but regulations are rarely enforced and it’s easy to get potent antibiotics, even intravenous ones, without a doctor’s assent. The group advised enacting rules allowing drug inspectors to immediately cancel the license of pharmacists dispensing unprescribed antibiotics.

Task force member Ganguly says tracking antibiotic use will be difficult.

“How do you regulate 1.2 billion people with so much diversity?” he asks.

Dying Babies

While Kumarasamy was documenting NDM-1 in Chennai hospitals, pediatrician Vipin Vashishtha was discovering how deadly the gene can be.

In June 2010, new father Sanjeev Thakran, 28, rushed his half-hour-old son in a car through monsoon-soaked streets to Vashishtha’s Mangla Children’s Hospital in Bijnor. His wife, Lalita, had delivered baby Tapas in a maternity hospital across town three weeks early, and the infant was laboring for air.

Nurses in green scrubs warmed the 4-pound (1.8-kilogram) newborn in a dome-covered crib and fed him milk and medicines through a nasal tube. About 2 feet away, a frail-looking baby was connected to a ventilator, Sanjeev Thakran says.

Vashishtha, seated on a leather swivel chair in his consulting room, recalls thinking that Tapas might need only a few days of intensive care. Instead, the baby spent weeks in and out of the unit. Blood sometimes trickled from his nose and shriveling umbilicus, according to medical records.

Even though he was being treated with a carbapenem, the most powerful class of antibiotic, bacteria raged inside his tiny lungs and bloodstream, eventually attacking membranes covering his brain and spinal cord.

Incurable Scourge

Other infants in the eight-crib neonatal intensive care unit were suffering, too. Vashishtha, 48, had tried several antibiotics without success. When carbapenems didn't work, he says, he felt helpless because he knew he was dealing with a potentially incurable scourge.

Tapas died 11 weeks after he was admitted. Lab results identified the culprit a month later: NDM-1. The gene was in bacteria known as Klebsiella pneumoniae. The germ exists in people's gastrointestinal tract and can cause pneumonia and urinary-tract infections in hospital patients.

The lab also found two soil-borne species that normally cause trivial infections but that were suddenly becoming killers.

Tapas was one of 14 infants at the hospital who were infected with NDM-1-containing bacteria over the course of 17 months. Six of the babies died. Among the eight survivors, half developed meningitis, arthritis or water on the brain, Vashishtha wrote to an Indian medical journal in February 2011.

'Horrific Period'

"It was the most horrific period," Vashishtha says as he fixes his eyes on the playpen where he amuses children in his office. "I was losing neonates at regular intervals. I suspected we were dealing with something quite different, something quite new."

Vashishtha says he has improved infection control, walling off part of the ICU for contagious, complicated cases.

He can't, however, control what happens outside his hospital. Sewage from nearby homes flows in an open drain along one wall of the two-story building.

Bijnor, like other small cities in Uttar Pradesh, lacks a modern underground drainage system. During the rainy season, it's impossible not to wade through sewage water, the doctor says.

'Wash Hands Properly'

So far, Vashishtha has prevented more NDM-1 deaths. He fumigates his wards every four weeks and applies fresh paint every three months. He keeps hand-sanitizing liquid in his office, along the corridors and next to every bed in intensive care. Nurses must wash their hands with running water and soap and scrub with an antimicrobial sanitizer before handling patients.

"The first and foremost step to avoiding hospital-acquired infection is to wash hands properly," he says.

India's major hospitals are marshaling tactics from common cleanliness to computerized databases to outsmart resistant bacteria and prevent more tragedies.

Artemis Health Institute, a private, 300-bed specialty hospital in Gurgaon, southwest of New Delhi, employs an infection-control officer who collects data every month on the hospital's four most troublesome bacteria to review patterns of drug resistance. The officer, Namita Jaggi, also serves as national secretary of a Buenos Aires-based group that collates infection information worldwide.

'Infection Surveillance 24/7'

About 3 miles (4.8 kilometers) away, cardiac surgeon Naresh Trehan's medical complex, Medanta-The Medicity, requires patients transferring from other hospitals to be screened for resistant bacteria. This procedure, routine in some Nordic countries, isn't standard in India.

Medanta has a strict hand-washing policy and a 40-member team to monitor infections, says Trehan, 65, who trained in cardiac surgery at New York University and worked at Bellevue Hospital in Manhattan before returning to India in 1988.

"We have a very senior person whose sole responsibility is to keep the whole hospital under infection surveillance 24/7," he says.

Livermore at the U.K.'s Health Protection Agency says these efforts may not be enough in a country where 626 million people defecate in the open and that treats only 30 percent of the 10.1 billion gallons of sewage generated each day. Even the most modern hospitals can't exist as islands of cleanliness, he says.

"How does the hospital -- however good its surgeons and physicians -- isolate itself when its patients, staff and food all come from outside, where they are exposed to this soup of resistance?" he asks.

'Hope for the Future'

Bush, the antibiotics researcher, has been investigating novel ways to fight bacteria since 1977. She says combinations of existing drugs, including an experimental compound from AstraZeneca in late-stage patient studies, may neutralize some carbapenem-destroying enzymes.

Should these mixtures pan out, they may help the superdrugs regain at least some of their potency, potentially extending their usefulness for a decade or more, she says.

A drug candidate from Basel, Switzerland-based Basilea Pharmaceutica AG (BSLN) in early-stage trials shows some promise against NDM-1, she says.

"What's frustrating is to see that companies refused to address the issue until the last few years," Bush says. "There are still some that are trying, and that's the hope for the future."

'Very Cautious'

Drugs that could once again tackle the world's most resistant germs would be a relief for people worldwide, Norway's Skaret among them. She spent more than six months fearing a microbial time bomb until she learned that the NDM-1 supergerms had passed from her system.

Even though she escaped physical harm, Skaret says, NDM-1 made her feel isolated. She says therapists, concerned about their own exposure, refused to help her with rehabilitation to recover from the car accident. Neighbors who delivered food were careful not to get too close.

“When they heard about it, they were very cautious,” she says.

If Walsh’s projection is accurate, 100 million Indians may be carrying the NDM-1 gene unwittingly and doing little to contain its spread. The number of countries reporting NDM-1 will continue to grow as more bacteria pick up the gene and people transport it around the globe.

To prevent a worldwide catastrophe, microbiologists Kumarasamy and Walsh -- along with scores of scientists and doctors inside and outside India -- are sounding an alarm.

“Combine sophisticated medicine, poor sanitation and heavy antibiotic usage, and you have a rocket fuel to drive the accumulation of resistance,” Livermore says. “That surely is what India has created.”

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