Race against time to develop new antibiotics

The second part of a series of three news features on antimicrobial resistance looks at how the antibiotics pipeline is drying up while resistance to existing drugs is increasing. Theresa Braine reports.

Within a few days of scraping his leg in a scooter accident in 2009, nine-year-old Brock Wade was in hospital fighting for his life with a methicillin-resistant *Staphylococcus aureus* (MRSA) infection. Once the infection – caused by one of the bacteria most often resistant to antibiotics – had been diagnosed, doctors put him on five different antibiotics. "After a month in the hospital, and against all odds, Brock recovered and was well enough to come home," says his mother Rhonda Bailey-Wade on the web site of the Infectious Diseases Society of America (IDSA).

Scenarios such as this IDSA case study are increasingly being played out all over the world. But not all the thousands of patients that contract drug-resistant bacterial infections every year are as lucky as Brock. And the problem looks set to get worse. While infectious agents are becoming more and more resistant to the medicines that are currently in use, not enough drugs are being developed to combat them.

"MRSA continues to be a major cause of community-acquired antibiotic resistant infections," says Dr Brad Spellberg, one of the authors of the 2004 IDSA report *Bad bugs, no drugs*. "However, because companies in the late 1980s and early 1990s recognized the threat of MRSA, starting in 2000 we did get new MRSA drugs. Right now, we have reasonable antibiotics to treat MRSA. As resistance catches up with them, in the future we will have problems again."

Courtesy of Infectious Diseases Society of America

Young Brock Wade spent a month in hospital fighting an antibiotic-resistant infection.

WHO/Chadin Tephaval

Checking vials of biological samples at Thailand's National Institute of Health in Bangkok.

There are many reasons. One is scientific. "The low-hanging fruit has been picked," says Spellberg. "But the concept that we've exhausted the pantry is ridiculous. Now we have to dig deeper, think harder and more cleverly."

Another reason is commercial. Antibiotics, in particular, have a poor return on investment because they are taken for a short period of time and cure their target disease. In contrast, drugs that treat chronic illness, such as high blood pressure, are taken daily for the rest of a patient's life. "Companies have figured out that they make a lot more money selling the latter drugs than they do selling antibiotics," Spellberg says, highlighting the lack of incentive for companies to develop antibiotics.

That's why many companies have stopped developing antibiotics altogether. Only five major pharmaceutical companies – albeit five of the biggest – GlaxoSmithKline, Novartis, AstraZeneca, Merck and Pfizer, still had active antibacterial discovery programmes in 2008, according to an article published in the journal *Clinical Infectious Diseases* in January 2009.

Adding to the grim picture, a comprehensive study of antibiotic development, covering innovative, small firms, as well as pharma giants, found in 2008 that only 15 antibiotics of 167 under development had a new mechanism of action with the potential to meet the challenge of multidrug resistance. Most of those were in the early phases of development, according to the study entitled *The bacterial challenge: time to react*.

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> *Brad Spellberg*

But there is hope. "Given that the antibiotics we have available today were discovered as growth byproducts of bacteria that we can culture, and that we've cultured less than 1% of the bacteria on our planet, there are many potential solutions out there," Spellberg says.

A variety of biological solutions have yet to be fully explored, such as phage

therapy and the potential use of the lytic enzymes found in mucus and saliva to kill pathogens (as described by researchers in an article published in October 2010 in the Institute of Physics' journal *Physical Biology*).

Another example is that of researchers at GlaxoSmithKline who recently described a novel class of antibacterial agents that target type IIA topoisomerases. The article was published in *Nature* in August 2010. "This investigational compound class has activity against a broad spectrum of Gram-positive and Gram-negative bacteria," says Dr Mick Gwyn, the study's lead author and a researcher in antibacterial drug discovery at GlaxoSmithKline.

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>
> *Richard Bergström*

Antimicrobial resistance is the inevitable consequence of prescribing antibiotics. "Whatever infections we treat, the bacteria that are part of our normal flora are always exposed to these antibiotics," says Dr Hajo Grundmann, chair of infectious diseases and epidemiology at the University of Groningen and head of the Department of Bacteriology at the National Institute of Public Health in the Netherlands. "Simply by surviving the onslaught of antibiotics, they are developing more clever ways to overcome the most sophisticated and advanced antibiotics."

There are no global data on the number of cases, including fatal ones, of resistant bacterial infections. According to the 2008 study, every year at least 25 000 patients in the European Union alone die from an infection caused by multidrug-resistant bacteria and estimated additional health-care costs and productivity losses are at least 1.5 billion Euros.

Some of the most resistant infections are caused by Gram-negative *Acinetobacter*, and by certain strains of *Klebsiella* and *Pseudomonas* species, according to Spellberg. These bacteria cause a variety of illnesses ranging from hospital-acquired pneumonia, bloodstream infections, urinary tract infections from catheters, abdominal infections and even meningitis in people who have had head and spine procedures, for example, epidurals during labour.

"Anywhere in the body can be hit by these bugs. And the issue is that without effective antibiotics the death rate is much higher," says Spellberg.

The outbreak of resistant strains of *Escherichia coli* (*E. coli*) – a common cause of food poisoning – carrying a gene called NDM1 (New Delhi metallo-β-lactamase) in India in 2010, which spread to other countries, is a case in point. Until recently such completely resistant bacteria have only been found in hospitals, Spellberg says, but "now we're starting to see virtually or totally pan-resistant bacteria spilling into the community".

The solution may lie not only in scientific discovery but also in the economic incentives for developing drugs. "I think that Congress understands that this is now a market failure and that economic incentives are needed to correct the market failure," he says.

Public–private partnerships could provide one solution, according to a May 2010 commentary in the *British Medical Journal*, such as the GlaxoSmithKline research partnerships with the Wellcome Trust and with the United States Defence Threat Reduction Agency.

Referring to "the twin challenges of conserving the effectiveness of existing antibacterial drugs and developing new ones", authors of the *British Medical Journal* article Anthony So, Melissa Furlong and Andreas Heddini of Swedish-based nongovernmental organization, ReAct, write that "delinking research and development costs from drug pricing and the return that drug companies receive on investment could correct misaligned economic incentives".

This delinking of research costs and drug pricing is something that industry may be prepared to accept, according to Richard Bergström, director-general of LIF, the trade association for the research-based pharmaceutical industry in Sweden.

"Incentives that separate the financial return from the use of a product are the only way to change this behaviour," said Bergström at a conference held at Uppsala University in September 2010. "Intelligent pull incentives, such as advance commitments and prizes, provide financial rewards to the developer that are not based on the volume of use of the novel antibiotic. With the right set-up, pharma companies will have no incentive to drive use. Maybe they will not do any promotion at all. Use would be agreed with public policy-makers, purchasers and national health systems."

WHO/Chadin Tephaval

A laboratory technician at Thailand's National Institute of Health in Bangkok.

Bergström called for a "global compact" similar to the one used for the United Nations programme for good governance and sustainable development enshrined in Millennium Development Goal 7. This agreement "could focus on the agreed and gradual introduction – and responsible marketing and use of – new agents".

"A global compact would require that not only industry but also governments, physicians and pharmacists join forces to preserve the new medicines that our children and grandchildren need," said Bergström. "No single tool will solve the problem. What is really needed is a collection of incentives that address the multiple obstacles to success."

This year the World Health Organization is devoting World Health Day on 7 April to raising awareness around the issue of antimicrobial resistance. More information is available at: http://www.who.int/world-health-day ■