Re-educating superbugs could save lives, as Clare Wilson discovers

IT IS a superbug with quite a few tricks up its sleeve. Found pretty much everywhere, from soil and water to your skin and lungs, it thrives with oxygen and without. It can dine on diesel and tar. It is naturally resistant to many antibiotics and can rapidly evolve resistance to all the rest. And for its party piece, it can stand upright and walk. Step forward Pseudomonas aeruginosa.

What makes Pseudomonas and many other kinds of bacteria so deadly, though, is their ability to work together. Millions of them can join forces to form powerful armies that overwhelm our defences.

It is not surprising, then, that if you are ever unlucky enough to end up in intensive care, there is a chance Pseudomonas will kill you. In fact, the real mystery has been why it doesn’t kill more of us. Even though the bacterium infects just about everyone who remains on a ventilator for a long period, only 15 per cent ever get pneumonia.

Now we may have discovered why. It turns out that the armies of Pseudomonas are often greatly weakened by indiscipline in the ranks. They come to be dominated by cheaters and layabouts, who feast on the spoils of victory but ignore all orders to attack. These selfish bacteria multiply faster than the obedient ones, resulting in a less aggressive infection.

This discovery opens up the possibility of a radical new way to tackle superbug infections: deliberately encouraging the growth of cheater strains, perhaps by injecting them into people. Some think it is a crazy and dangerous idea. For others it is a bold approach that is sorely needed as antibiotic resistance grows.

Long seen as simple, solitary creatures, in the past few decades we have come to understand that bacteria are actually highly social. Large groups of bacteria can cooperate closely – and it is this ability to work together that makes some species so dangerous to us.

Many disease-causing bacteria have dual personalities. In small numbers they live independently and peaceably within us, 
The mystery is why superbug infections don’t kill more people

The infection is hard to fight as resistance develops whatever antibiotic is used, and the patients are too sick to cope with the drug’s side effects. "The first time you can treat with not too many problems, the second episode will be more difficult and the third will be a nightmare," says van Delden.

What has long baffled doctors is why Pseudomonas causes pneumonia in only 10 to 15 per cent of people on ventilators. "There are no risk factors that clinicians could identify on the patient’s side," says van Delden. "This suggests the bacteria are different."

As more and more papers were published on bacterial cheating, van Delden began to suspect that this could be the explanation. Perhaps people who didn't develop pneumonia had Pseudomonas infections weakened by cheaters.

The chance to test this idea arose when van Delden was involved in a trial of an existing antibiotic called azithromycin. Though poor at avoiding shooting themselves in the foot, the armys that overwhelm our defences" 

Diggle, a microbiologist at the University of Oxford who had done some of the early work on the antibiotic based on its quorum-sensing activity, and asked van Delden to test the drug. To show the drug was working through quorum quenching, repeated sputum samples were taken and the bacteria analysed to see if they had responded to quorum-sensing signals and turned virulent.

The trial ended abruptly when Abbott’s US patent application was rejected, but van Delden realised he could still make use of the drug with Angus Buckling, an evolutionary biologist at the University of Oxford who had done some of the early work on Pseudomonas cheating. “It was a fantastic opportunity,” says Buckling.

Sure enough, their team found that more than half of people infected with non-cheater strains produced pyocin-blocking compounds to avoid shooting themselves in the foot. Cheaters that ignore the signal to turn virulent, however, do not ready their defences, and thus are killed along with unrelated bacteria. So if we could find drugs that block pyocins, they should help cheating mutants to survive and take over populations, rendering the infection harmless.

Diggle’s group in Nottingham, meanwhile, is exploring the radical approach. In 2009 his team deliberately infected the wounds of mice with various strains of Pseudomonas. They found that those infected with cheater strains were twice as likely to survive as those infected with normal bacteria. Mice dosed with a 50-50 mix of cheaters and normal bacteria were also twice as likely to survive, which suggests giving cheaters to people already infected with normal strains might help save lives (Current Biology, vol 18, p 341).

Diggie hopes to try out this daring strategy in people with burns with severe Pseudomonas infections. He is in talks with regulatory agencies now and hopes that tests could be done. “I don’t think it’s as crazy as it seems,” he says. “It’s early days and there are huge regulatory hurdles to overcome, but there’s potential for it to work.”

Subversive superbugs

If it fulfills its promise, the approach could help clinicians turn the tables on some of the biggest battles in modern medicine. Staphylococcus aureus, another common cause of wound infections and pneumonia, is thought to be the explanation. In 2008, Richard Novick, a microbiologist at New York University, showed that cheats ignore quorum-sensing signals exist among S. aureus resistant to the antibiotic methicillin, better known as MRSA, a huge problem. In a study that has not yet been published, Novick’s colleague Bo Shopsin found that in people with pneumonia caused by S. aureus, the presence of cheaters made them more likely to survive.

Whether any of the strategies to exploit bacterial cheating will bear fruit remains to be seen. But these discoveries are changing the way researchers think. At first, mainstream microbiologists were doubtful about applying theories about social evolution to bacteria. "They are interested in the ‘how’ questions, we are interested in the ‘why,”’ says Diggle. “It was received with a bit of scepticism.”

Coevolution is not just leading to a wealth of new insights. For instance, Sarah Reece, a parasitologist at the University of Edinburgh, has found that the organism that causes malaria alters its reproductive strategy depending on how many of its fellows are cheaters. By studying how closely related they are (Nature, vol 453, p 609), “This could be a new opportunity to control these parasites,” says Reece.

It is even relevant to industry. Cheating among Lactococcus lactis has been found to save millions in cheese factories by allowing the fermentation process to proceed faster. It’s one thing to inject bacteria into a Stilton, quite another to stick them into a person. Yet it is no exaggeration to say that the rise of antibiotic resistance is one of the biggest threats to our health. If a time comes when people are dying because conventional antibiotics are no longer any use, injecting them with “cheatobiotics” might look a lot less crazy.  

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