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Is pollution driving antibiotic resistance?

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Pollution from sewage sludge, animal slurry, disinfectants and fabric softeners may be linked to the rise in bacteria resistant to the most powerful antibiotics, says William Gaze.

Everyone will be familiar with newspaper headlines describing the latest reports of hospital infections caused by superbugs - such as Methicillin-resistant *Staphylococcus aureus* known as MRSA. The media often blame over-prescription of antibiotics and poor hygiene standards, but these are just two of the reasons why bacteria now resist many antibiotics.

We have been investigating antibiotic resistance genes in bacteria living in soils, and how pollution may influence the way resistance evolves.

Bacteria have existed on Earth for at least three billion years. In this time they have evolved complex strategies to adapt to different habitats and compete with other bacteria for every available niche. One strategy involves attacking rivals with chemical weapons - which we call antibiotics. Logically, any bacterium attacking a competitor needs to protect itself and its species from its own antibiotics.

Antibiotics and other chemicals that could drive antibiotic resistance enter rivers and soils in many ways.

Resistance genes have also evolved in bacteria which do not produce antibiotics, but compete with those that do. Resistance is often provided by a protein produced by a single gene. The gene is small and self-contained, making it easy to move through a gene pool from bacterium to bacterium. This ease of movement is significant because of the clever ways bacteria use to swap genes.

We are taught that bacteria are primitive asexual organisms that reproduce by simple division, and that sex - responsible for genetic exchange and variation - evolved only in higher organisms. But bacteria exchange genetic material on a huge scale, not only from parent to offspring - vertically - but horizontally to other individuals of the same generation. This horizontal gene transfer can be between unrelated bacteria and can

be assisted by viruses or even by passing bacteria latching on to strands of naked DNA lying around in soil or water.

One strategy involves attacking rivals with chemical weapons - antibiotics.

Horizontal gene transfer has the power to drive the spread of resistance genes when bacteria are faced with antibiotics, disinfectants or other pollutants in waste from towns, cities and agriculture.

Antibiotics and other chemicals that could drive antibiotic resistance enter rivers and soils in many ways. Industry uses large volumes of detergents and disinfectants - including quaternary ammonium compounds (QACs) - known together as biocides. Nearly all domestic cleaning products and shampoos also contain QACs. They wash out in large volumes with the waste water from factories and homes. QAC resistance genes are significant because they are often located with antibiotic resistance genes on the same piece of DNA, so exposure to one will co-select for the other.

Reed bed treatment system used to remediate mill effluent.

Farmers spread millions of tonnes of sewage sludge and animal slurry on UK land every year. Sewage sludge contains antibiotics, resistant bacteria and biocides. In addition, animal slurry harbours veterinary antibiotics. All this eventually flows or seeps into the soil and water.

Finding out how these pollutants affect bacteria in soil is exceptionally difficult. Between 90 and 99 per cent of bacteria won't grow in the lab. So microbiologists now take a sample of soil or water and use techniques similar to human DNA fingerprinting to study DNA from the whole sample. From this they can work out what is living in a sample and what genes different bacteria carry.

This takes us back to this idea of horizontal gene transfer. Genes that give resistance to antibiotics and biocides can be situated on the same mobile genetic element - DNA that can easily pass from one bacterium to another in the same generation - known as an integron. These integrons were so named because they can integrate mobile genes into bacterial DNA, allowing bacteria to deploy a wide range of different resistance genes depending on the selective pressure. If a doctor changes antibiotic treatment of a patient because of resistance, the integron can cut out a gene and integrate a new one giving resistance to the new antibiotic treatment.

The gene is small and self-contained, making it easy to move through a gene pool.

Because integrons carry resistance to both biocides and antibiotics, pollution containing biocides will naturally favour bacteria which can defend themselves by deploying genes conferring biocide resistance. It seems this may have the knock-on effect of co-selecting for antibiotic resistance.

Using molecular techniques to analyse bacteria in soils, we compared the number of integrons and genetic diversity of resistance genes in polluted samples with those from control agricultural soils. Polluted samples had a significantly higher number of integrons. We also found new genes - similar to known antibiotic resistance genes - were more numerous in polluted samples than in unpolluted control soils.

William Gaze sampling effluent from textile mill.

It appears that certain methods of waste disposal such as sludge and slurry application introduce genetic elements known to carry antibiotic resistance genes into agricultural soil. Further research is needed to study survival of bacteria carrying these elements in soil contaminated with waste, and the risk of transmission to people through meat and vegetables in the same way as food poisoning bacteria such as *E. coli* and *Salmonellae*.

The number of bacteria on Earth has been estimated by scientists from the University of Georgia as five million trillion trillion - if each bacterium were a penny, the stack would reach a trillion light years. Because this huge number of bacteria can freely exchange genes that have evolved over billions of years it is not too surprising that new genes giving resistance to clinical antibiotics appear soon after an antibiotic is introduced. But what is surprising is that it is not just antibiotics driving resistance - pollutants and waste disposal practices may also be contributing to this process.

Dr Will Gaze is a researcher at the University of Warwick.

Research was carried out by a team of scientists at Warwick and Birmingham University led by Professor Liz Wellington, Dr Will Gaze and Professor Peter Hawkey.

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