Stefania Hartley

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antibiotics
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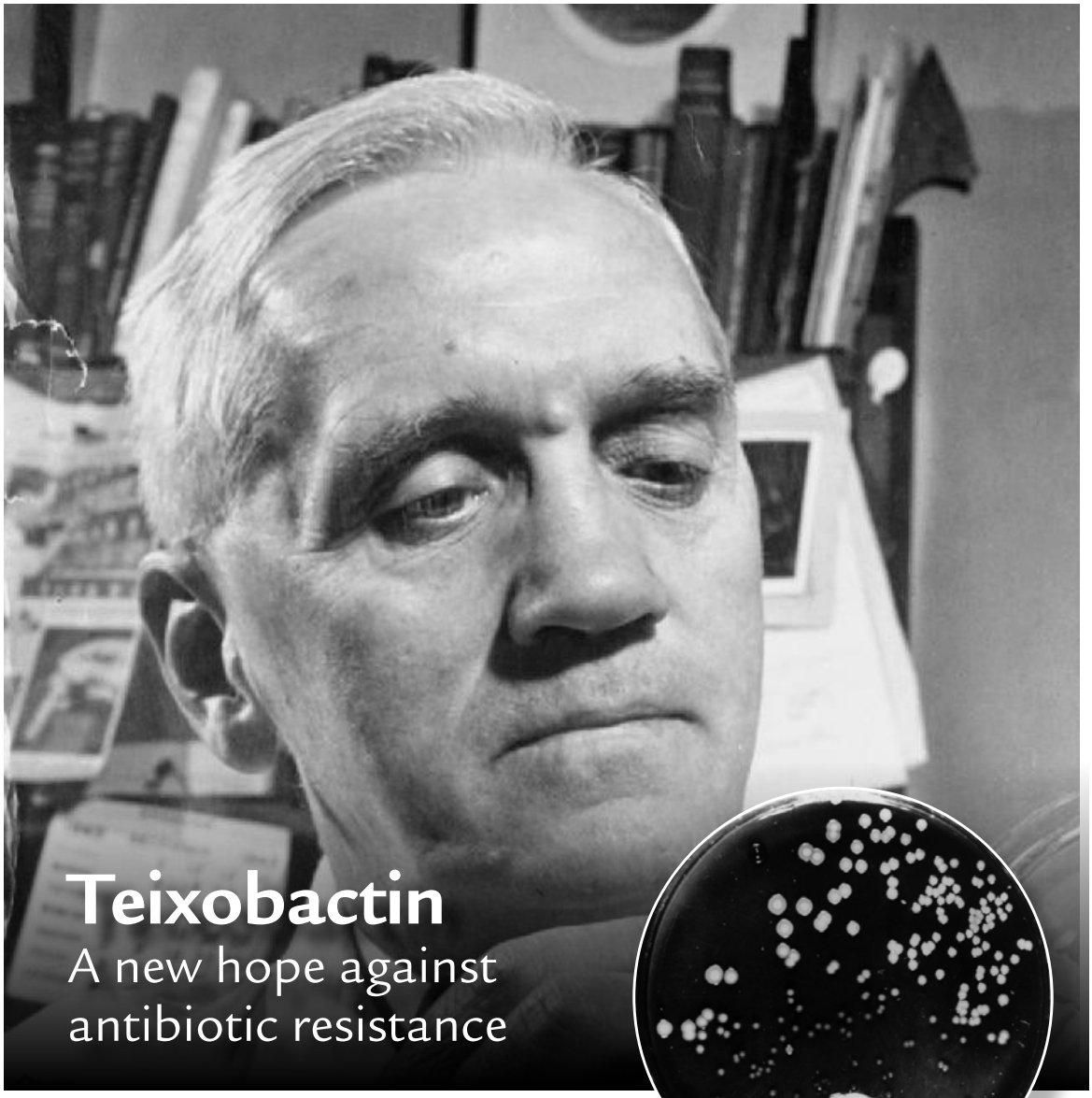


Alexander Fleming, discoverer of penicillin, at work in St Mary's Hospital in in 1942, together with the plate which he found in his lab on 3rd September 1928. Colonies of Staphylococcus *are growing normally at the top but in the centre they are severely affected by penicillin spreading out from the* Penicillium *mould at the bottom.*

Teixobactin
A new hope against antibiotic resistance

In the animation *The Incredibles*, the 'Omnidroid' – a robot which learns from the moves of its opponent – becomes more skilled after each fight. Imagine that your adversary is not an artificial intelligence but millions of unicellular organisms, and that they look set to win.

Now you've got the picture of the war between humans and pathogenic bacteria. Thankfully, things might have just started to turn in our favour.

The first antibiotic

On the morning of 3 September 1928, biologist Alexander Fleming returned to his lab from his summer holiday. He wasn't a particularly tidy person so it was no wonder that some of his bacterial cultures were contaminated with a mould. What was wonderful was that the bacteria did not grow around the mould. The mould was *Penicillium notatum*, from which Fleming isolated the first antibiotic, penicillin. Humanity now had a sure-fire weapon against bacterial diseases which, until then, had cost millions of lives and huge suffering.

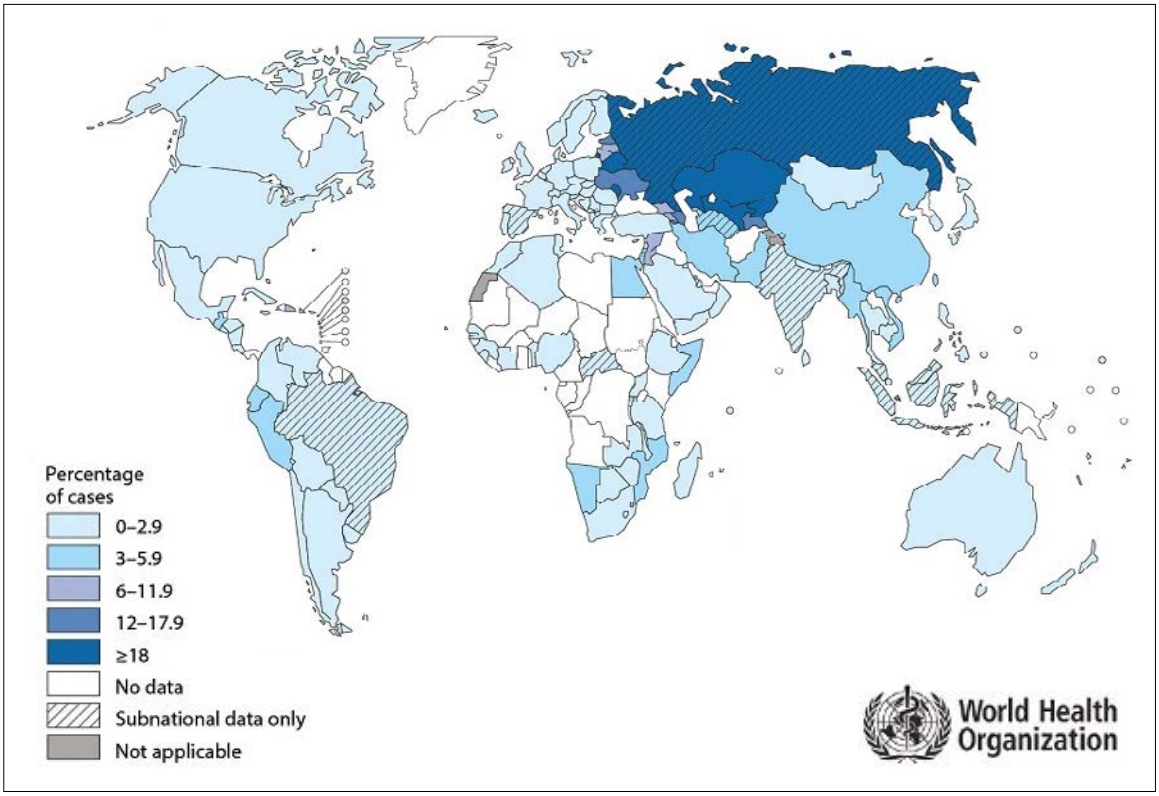
The major problem, at the beginning, was that of getting enough penicillin: it took 2000 litres of *Penicillium notatum* 'juice' to extract enough penicillin to treat one person.

The 'spreading scourge' of antibiotic resistance

Far from being in limited supply, antibiotics are now widely available. Today's issue is a much more pernicious one. Already in 1945, in his Nobel Prize acceptance speech, Fleming had warned against the dangers of bacteria developing resistance to the penicillin. Now – seventy years later – the World Health Organisation (WHO) describes antibiotic resistance as a 'spreading scourge'.

On 30 April 2014, WHO released the first ever global report on antimicrobial resistance, including data from 114 countries. With high levels of bacterial resistance in all regions of the world and a patchy system of monitoring, the report warns of the danger of entering a post-antibiotic era, where microbial infections can again kill.

The situation is made worse by the fact that the speed with which we are discovering new antibiotics is no match for that at which bacterial resistance is spreading. No new classes of antibiotics have entered the market in the last thirty years.



Map showing the percentage of new cases of tuberculosis which are multiple-drug resistant (WHO 2014)

Soil bacteria

For drug companies, antibiotic development is a risky business: bacterial resistance gives antibiotics a limited and unpredictable shelf life. For the same reason, new antibiotics are not widely prescribed. Instead, they are treated as 'drugs of last resort' and used only for cases which are resistant to 'first line' drugs. In addition, the bacterial cell wall makes it difficult for antibiotics to penetrate into the bacterial cell. Synthetic antibiotics have proven much less successful in doing this than natural ones. However, only about 1% of the bacteria that live in soil (the source of most antibiotics) can be cultivated in a lab. By the 1960s, all the cultivable soil bacteria had been fully utilised. The challenge, until now, has been to unlock the secrets of the remaining 99%.

This is what scientists have just achieved, thanks to the diffusion chamber and the iChip, a new device that has made it possible to isolate 10 000 soil bacterial strains and grow them in their own environment.

The diffusion chamber sandwiches bacterial samples between sheets of a material with pores. These pores allow nutrients in and waste out, but trap the bacteria. The chamber is placed in a sample of the natural environment in the lab. This approach allowed thousands more bacteria to be cultured than had ever been achieved in the past.

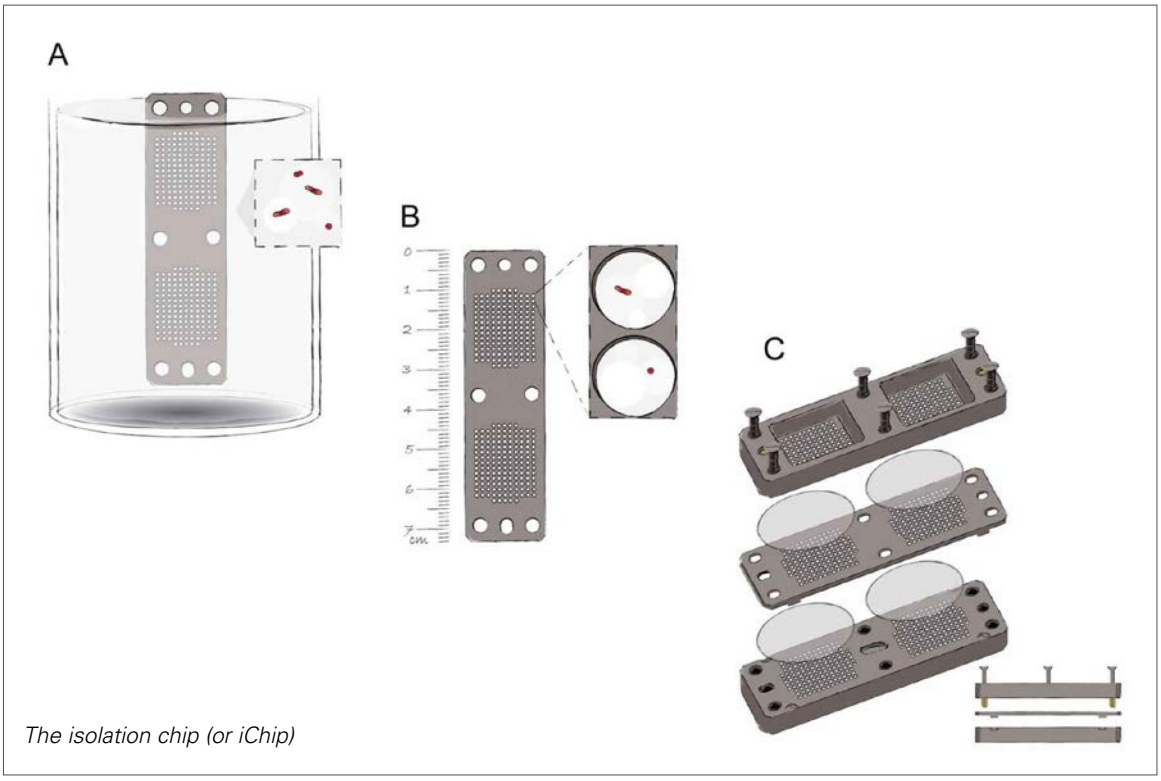
Then came the iChip, a piece of hard plastic with 192 wells in each of two arrays. A scientist just dips it into a sample of the mixed bacteria, thus

Antibiotic resistance

Because of their quick life cycle and their high numbers, bacteria undergo evolution by natural selection very quickly. Thus, resistance against an antibiotic can spread quickly within a population:

- By chance, a mutation occurs in the DNA of a bacterium. The mutation allows it to survive and multiply, even in the presence of the antibiotic.
- The rest of the bacteria – without the favourable mutation – are decimated by the antibiotic.
- The mutated bacterium does not need to compete for resources and can multiply undisturbed.
- In the end, most of the bacteria in that population will be carrying the mutated DNA.

Bacteria are able to transfer their genes vertically (to their clones) and also horizontally to other bacteria of the same species or of other species, in a process called conjugation, during which one bacterium transfers a copy of a ring of DNA called a plasmid to another bacterium.



The isolation chip (or iChip)

trapping (on average) a single cell in each well. The whole is sealed in diffusion membranes and placed in a larger sample of the natural environment. This has allowed isolation of many species of bacteria new to science.

An iChip used for picking up marine sediment in the search for new antibiotics

Teixobactin

The bacterial extracts have been screened for the ability to inhibit the growth of *Staphylococcus aureus*. This has led to the discovery of a new compound with a chemical scaffold unlike that of any of the existing antibiotics. 'Teixobactin' (this is the name given to the new compound, from the Greek: *teixos* = wall) has not only proven successful against a number of pathogens (like *Mycobacterium tuberculosis, Clostridium difficile, Bacillus anthracis*), including those which are resistant to other antibiotics, but it has done so in a completely new way. It binds to two lipids which are the precursors of the bacterial cell wall's peptidoglycan and teichoic acid.

This is great news on the bacterial resistance front: whereas proteins are coded for by stretches of DNA – which may mutate – lipids are synthesized by the cell from organic precursors, which are unlikely to change.

The chances of bacterial resistance are reduced also by the fact that teixobactin affects Gram-positive bacteria but is produced by a Gram-negative bacterium, provisionally named *Eleftheria terrae*. Surrounded by an impermeable outer membrane and lacking teichoic acid, *Eleftheria terrae* is unaffected by teixobactin, and does not possess any specific mechanism to inactivate teixobactin (which could potentially be passed horizontally to other bacteria – see Box *Antibiotic resistance* below). It is not surprising, then, that lab trials did not show the development of strains of *Staphylococcus aureus* or *Mycobacterium tuberculosis* resistant to teixobactin, even when a low dose of the antibiotic was used.

There are good reasons to be optimistic about the future. Still, we'll need to make a tactical and disciplined use of our new weapon if we want to win against our own 'omnidroid'.

Stefania Hartley is a science teacher living in Singapore.

What you can do

As recommended by the World Health Organisation:

- Use antibiotics only when prescribed.
- Complete the full treatment course, even if you feel better.
- Never share antibiotics or use leftovers.

Find out more about microbial resistance: *www.who.int/mediacentre/factsheets/fs194/en/*