UK and China join forces to fight the next global pandemic

Through a joint initiative, the two nations are rallying scientists and policymakers in the war on 'superbugs' as we approach a future where traditional antibiotics no longer work

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In a laboratory at the University of Lincoln's school of pharmacy, novel drug designer Ishwar Singh holds a thin vial of clear liquid up to the light.

"It's not like any other antibiotic," Singh says. "That is why it's so interesting."

Inside the vial is a molecule that has the potential to save millions of lives.

After years of false starts — and a vital brainwave that challenged dogma in the field — Singh and his students have successfully synthesized teixobactin, a new class of antibiotic that kills bacteria that are resistant to conventional antibiotics — otherwise known as "superbugs".

Singh describes the moment he and his team first made the molecule as "quite satisfying", which is about as self-congratulatory as the modest chemist gets.

When pushed, he will admit that if the drug ever becomes commercially available, it could have major implications for humanity.

"A future where antibiotics are ineffective is a scary one," Singh says. "Even simple infections could be fatal, and antibiotics are essential to surgeries and courses of chemotherapy. The impact would be massive."

That worrying version of the future — as bleak as it is — is not a distant one. Presently, at least 700,000 people around the world die each year due to drug resistance, according to a review on antimicrobial resistance, or AMR, commissioned by the United Kingdom government.

If left unchecked, AMR could lead to 10 million deaths a year by 2050. That's more than the number of people that die from cancer each year and is on a par with the number of annual deaths during the worst outbreaks of the Black Death.

It's a scenario that the UK Chief Medical Officer Sally Davies calls the "post-antibiotic apocalypse". And this year through a joint initiative, the governments of the UK and China significantly ramped up joint efforts to ensure that day doesn't come.

'An unthinkable scenario'

In 2014, ex-UK prime minister David Cameron commissioned Jim O'Neill — the former Goldman Sachs chief economist who coined the term "BRICS" — to conduct a comprehensive study into AMR.

The review outlined the devastating impact that AMR may soon have on both world health and the global economy. He forecast that the cost in terms of lost production between now and 2050 could reach $100 trillion if no action is taken.

Agreeing the problem was too large for one government to solve, Cameron and President Xi Jinping established a $72-million Global AMR Innovation Fund, also called GAMRIF.

"If we fail to act, we are looking at an almost unthinkable scenario where antibiotics no longer work and we are cast back into the dark ages of medicine," said Cameron.

This year, the UK and China injected a further 47 million pounds ($62 million) into GAMRIF and the fight against superbugs.

Through the fund, both nations hope to raise $1 billion from public and private sources, which will be allocated to tackle a broad range of issues.

Reducing the inappropriate use of antibiotics in humans and animals is the tip of the spear in the battle against superbugs as this compounds the resistance problem. Studies have determined that one in five antibiotics is prescribed inappropriately in the UK, and in the United States the number is one in three.

The fund also aims to support projects involved in improved sanitation, rapid diagnosis, increased public awareness and the development of new forms of treatment.

"By operating together, the UK and China will represent a formidable force against one of the most dangerous global crises facing the modern world," said UK Health Minister Steve Brine.

In June, GAMRIF and the Canada-based International Development Research Center announced a global call for research proposals to reduce AMR in poultry, swine, and aquaculture animals. Overuse of antibiotics in livestock has led to several strains of drug-resistant bacteria that also infect humans.

> **"Many antibiotics are becoming useless, causing hundreds of thousands of deaths each year."**
> **Dong Changjiang,** microbiologist at the University of East Anglia

In May, GAMRIF and the Switzerland-based Foundation for Innovative New Diagnostics committed 5 million pounds to a three-year project focused on developing AMR surveillance programs in low- and middle-income countries.

In March, the UK health department committed 10 million pounds and the Chinese Ministry of Science and Technology put forward 60 million yuan ($8.8 million) to fund a collaborative competition encouraging researchers in the UK and China to develop solutions that address the threat of AMR.

So far this year, further funds have been committed to: A project in Argentina focused on AMR in agriculture; the development of a new antibiotic for drug-resistant gonorrhea; and 20 million pounds went to the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, a project in the US that supports research on the most dangerous drug-resistant bacteria.

The drugs don't work

Antibiotics revolutionized medicine in the 20th century. Penicillin alone is thought to have saved more than 200 million lives since it was first used to treat infection in 1942.

Most conventional forms of antibiotics, including penicillin and methicillin, attack bacteria by inhibiting the formation of cell walls, or by interrupting vital processes such as protein synthesis.

Some bacteria develop resistance to antibiotics through genetic mutations that alter areas or processes targeted by medication.

Over time, these genes proliferate, creating entire strains of antibiotic resistant bacteria, such as Methicillin-resistant Staphylococcus aureus, or MRSA. A study conducted last year by the London School of Hygiene and Tropical Medicine suggests MRSA is widespread in the UK. Over the course of a 12-month period, 173 separate infection clusters were identified in the east of England alone.

Earlier this year, an outbreak of MRSA in a hospital in Dublin, Ireland, led to the infection of six infants and the deaths of two babies that had been born premature.

Victoria Wareham, a senior staff nurse at St Thomas' Hospital in London, says that a few years ago she would treat a child for a drug resistant infection on average once a week. Today, she said it is not uncommon for three or four children to be admitted in a week.

"For some cases, like MRSA, the course of treatment can take weeks," Wareham said. "We try to make the bed space as homely as possible, but with these kids the toys they can play with and the linen we use is really restricted."

The problem of AMR is compounded by the fact that new strains keep arising. Last year, a previously unknown drug-resistant strain of pneumonia killed five people at a hospital in Zhejiang, China.

Professor Ishwar Singh is hopeful that teixobactin could be used to treat superbug infections.
ANGUS MCNEICE / CHINA DAILY

The search for a cure

There are 48 registered new antibiotics that have the potential to combat drug resistance, according to a database compiled by the Pew Charitable Trust, a US-based public policy body.

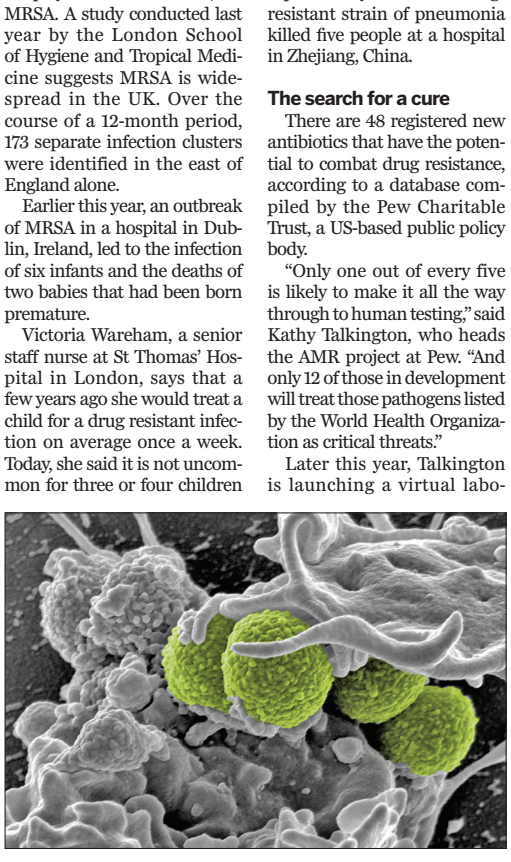
"Only one out of every five is likely to make it all the way through to human testing," said Kathy Talkington, who heads the AMR project at Pew. "And only 12 of those in development will treat those pathogens listed by the World Health Organization as critical threats."

Later this year, Talkington is launching a virtual laboratory of drug development data, so scientists will be able to seek out patterns in terms of what drugs are most effective against superbugs.

"Our hope is that it makes everything readily available so that people don't repeat the same research," Talkington said. "We simply don't have time for those repetitions."

Some of the most promising recent work in the development of the next generation of treatments is currently underway in the UK and China.

In September, Richard Kao Yi-tsun, a microbiologist at Hong Kong University, revealed he had successfully used a compound called NP16 to inhibit the production of a pigment in MRSA. The pigment, called staphyloxanthin, helps MRSA weather attacks from the immune system, and the body can naturally clear infection more easily in its absence.



MRSA bacteria (green) interacting with human white blood cells.
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASE

A protein in bacteria cell walls that future drugs may target.
THE UNIVERSITY OF EAST ANGLIA

Martha Clokie at the University of Leicester has had some success using viruses called phages to kill E. Coli bacteria, suggesting that viral therapy could be used as an alternative to antibiotics to treat infection.

Dong Changjiang, a microbiologist from Hubei province, currently working at the University of East Anglia, studies the structure of the outer membrane of so-called "gram-negative bacteria" which include MRSA and E.Coli. Gram-negative bacteria are particularly resistant to antibiotics due to an impermeable lipid-based outer membrane.

Dong used intense X-Rays to map the structure of the outer membrane and identified pathways through which the cell sends "building block" proteins to construct the membrane. Dong discovered that molecules can be used to block these pathways, rendering the bacteria defenseless.

He says he is currently collaborating with drug designers who might be able to develop medications that exploit what Dong calls bacteria's "Achilles heel".

"Many antibiotics are becoming useless, causing hundreds of thousands of deaths each year," Dong said. "Superbug numbers are increasing at an unexpected rate. We want to change that."

One of the most encouraging AMR projects underway in Britain is at the University of Lincoln where Ishwar Singh and his team have developed synthetic teixobactin.

In 2015, scientists in the US discovered teixobactin in soil-dwelling bacteria. These bacteria use the molecule — made up of 11 amino acids — as a kind of chemical weapon to kill other bacteria. Unlike other naturally occurring antibiotic substances such as penicillin, teixobactin targets lipids in a bacteria's cell walls, instead of proteins.

And crucially, teixobactin works on multiple targets, one of which is coded for by what geneticists call "highly conserved" genes. This means that mutations to these genes are likely to be lethal to the bacteria, so the chances of bacteria developing resistance to teixobactin is very low.

Immediately after its discovery teixobactin was shown to be effective against several drug-resistant strains of bacteria, including MRSA. However, it proved challenging to synthesize in the lab.

To get a drug to market, it has to be simple and cost-effective to manufacture, and teixobactin is a complex molecule. One of its amino acids — the 11 building blocks that make up the molecule — is rare and not commercially available. It is positively charged and takes 30 hours and multiple steps to introduce during the synthetization process.

After years of experimentation, Singh and his team reached a breakthrough after "trying something that shouldn't have worked".

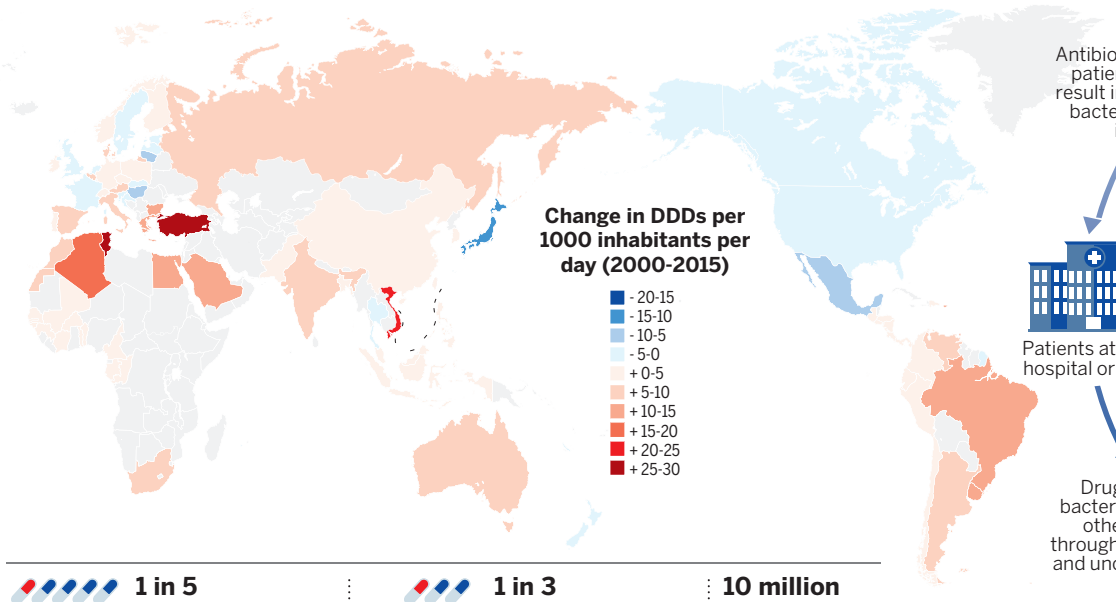
They replaced the problem amino acid with a different, commercially available amino acid that had no charge. Conventional wisdom said the revised teixobactin analogue should have fallen apart, but incredibly it held together. And it was also more potent, killing off superbugs in test-tubes more efficiently than its naturally occurring cousin.

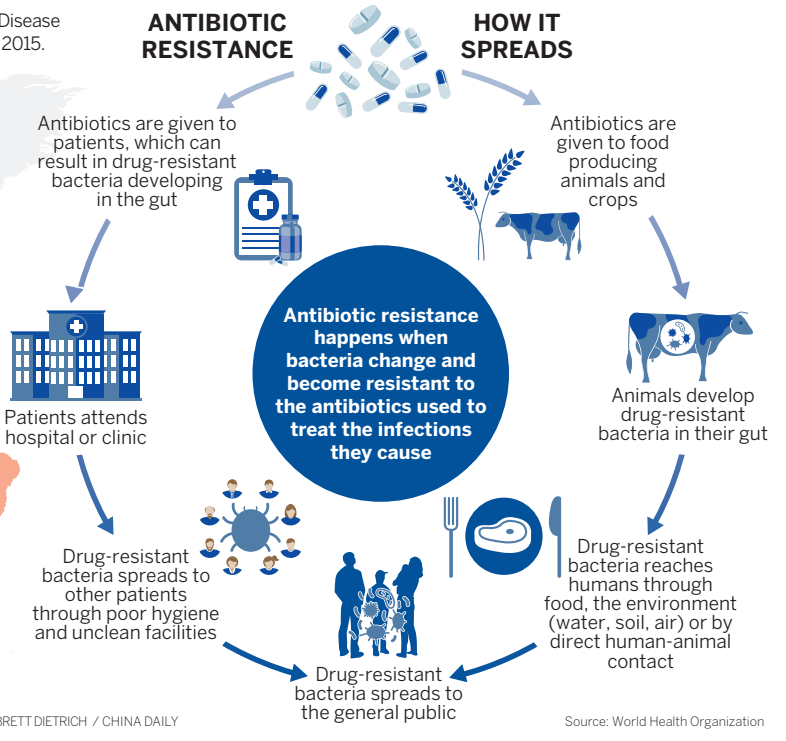
In March, Singh achieved another "quantum leap" in the drug's development. He sent the man-made teixobactin to the Singapore Eye Research Institute where researchers successfully used it to treat bacterial infection in mice.

Singh and his team are now working to further simplify the process of making the molecule. He is hopeful the new antibiotic will reach human testing in the next six to 10 years.

"I think it will be used as a last line of defense when conventional antibiotics fail to address issues," Singh said. "We are not finished yet, but we are excited."

Reduction of the use of antibiotics is essential to combating drug resistance. But data published in March 2018 by the Center for Disease Dynamics, Economics & Policy in Washington shows that global doses of antibiotics increased by 64 percent between 2000 and 2015.





1 in 5
antibiotics are prescribed inappropriately in the UK
Source: Public Health England

1 in 3
antibiotics are prescribed inappropriately in the US
Source: Center for Disease Control

10 million
annual deaths due to drug resistance by 2050
Source: the AMR Review

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Source: World Health Organization