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STAMPING OUT DRUG RESISTANCE

Staying ahead in the fight against tuberculosis

The discovery of new antibiotics — no matter the stage of development — tends to make headlines these days. But very few end up crossing the finish line. The level of interest in this branch of drugs reflects the seriousness of the threat posed by the growing number of drug- and multidrug-resistant bacteria, or superbugs.

In Singapore, the most commonly known superbug is methicillin-resistant *Staphylococcus aureus* (better known by its acronym MRSA). But there is another, for now less common, superbug that deserves our attention: Multidrug-resistant tuberculosis (MDR-TB). This grabbed headlines recently when six people contracted MDR-TB in a HDB block in Ang Mo Kio.

In 2014, an estimated 480,000 people developed MDR-TB worldwide. At the same time, one third of the world's population carry dormant TB bacteria in their lungs. While most of them do not go on to develop active TB, those with compromised immune systems, such as people living with HIV or transplant patients, and people with diabetes, have a higher risk of developing the disease. In fact, 15 per cent of TB cases worldwide are attributable to diabetes.

Mycobacterium tuberculosis, in its modern form, has co-existed with



humans for more than 15,000 years. Before the advent of antibiotics in the 20th century, TB patients were sent to sanatoria, the more effective of which were in the mountains, to recover. Like humans, *Mycobacterium tuberculosis* requires oxygen to cause disease. The lower level of oxygen found at high altitudes inhibits the growth of the bacteria, enabling patients' immune systems to fight back.

A lifelong effective TB vaccine is elusive and the longer we rely on just one new drug to combat this disease, the greater a public health threat we are likely to face. PHOTO: REUTERS

In the 1940s, the first effective antibiotic against TB was discovered — streptomycin. But within years, some TB bacteria developed resistance.

Over the next decades, a concerted effort, which saw key studies carried out in Singapore and Hong Kong, resulted in today's "modern short-course" treatment regimens — six to nine months of combination therapy — that have been unchanged since the 1980s.

While a cocktail of antibiotics reduces the chance of emergence of multi-drug resistance, the long treatment time is far from ideal because of side effects and non-compliance.

As Assoc Prof Hsu Li Yang wrote in TODAY recently, without community support, defaulting on treatment is not uncommon.

In addition to non-compliance, misuse of these drugs in some countries has contributed to increased rates of resistance. Outside of Singapore, Asian countries such as India, Thailand and Indonesia report MDR-TB rates of up to 30 per cent.

Our challenge is to develop more effective new drugs that can eliminate the bacteria faster, reduce the risk of resistance, and are less toxic to the rest of the body. To tackle these elusive goals, the world has joined forces to identify strategic goals, areas of need and experimental antibiotics with the greatest potential.

NEW CLASSES OF ANTIBIOTICS EMERGING

Since 2000, governments, international health authorities and large philanthropic foundations have set up new initiatives, such as the TB Alliance, Global Fund and, more recently, Global Drug-resistant TB Initiative. Singapore is one of the world's top TB research funders through its strategic SPRINT-TB programme that oversees more than 30 bench-to-bedside projects.

And efforts are bearing fruit. In 2012, the first new TB drug in 50

years, bedaquiline, received fast-tracked approval for the treatment of MDR-TB. Studies are underway to evaluate new combinations of existing drugs and bedaquiline, including a large-scale study in Bangladesh. If successful, this could dramatically shorten treatment time for MDR-TB, which currently takes between 18 to 24 months.

But just as it offers new hope, we again face the risk of greater resistance. Barely three years after it was first approved, a patient treated successfully with bedaquiline relapsed with bedaquiline-resistant TB. To break this vicious cycle, we need to find complementary antibiotics that can work with bedaquiline to deliver a new short-course treatment regimen.

Fortunately, new classes of antibiotics are emerging. One promising candidate is Q203, which is just about to complete its first human clinical trial phase I study in the United States.

Developed in 2013 by my team, it works on the same principle as bedaquiline, by preventing the bacteria from generating energy. Much like the low-oxygen air at sanatoria, Q203 prevents the tuberculosis bacilli from using oxygen, thereby "asphyxiating" them. Since bedaquiline and Q203 share many properties, they may represent the cornerstone of an entirely new drug regimen to treat MDR-TB in the future. Work on Q203 continues at the Lee Kong Chian School of Medicine in Nanyang Technological University and is supported by the National Medical Research Council.

We are in a high-stakes race against TB. Of the 9.6 million new TB cases in 2014, 58 per cent were in the South-east Asian and western Pacific regions. While much lower than the number of cases in 1990, we are at risk, of losing ground to more extreme forms of MDR-TB. Over the last nine years alone, laboratories around the world have seen a steady increase in the number of "extensively drug-resistant" TB cases, which means that the most effective first- or second-line antibiotics do not work anymore.

There is no single silver bullet cure for TB, a lifelong effective vaccine is elusive and the longer we rely on just one new drug to combat this disease, the greater a public health threat we are likely to face. The hope is to develop a standardised, affordable and non-toxic drug combination made of highly efficient antibiotics to curb the evolution of MDR-TB.

We are making progress, thanks to a united global effort to deliver next-generation TB treatments. But even in Singapore, where MDR-TB transmission is extremely rare, it can and does happen.

The recent outbreak of MDR-TB highlights that we need to reaffirm our commitment to this global compact — whether as scientists, clinicians, patients or policymakers — to play our part to stamp out drug resistance.

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