[I AM A SCIENTIST]

Bugged by the malaria malaise

NTU don, who leads study on parasite's resistance to main killer drug, flags concerns

Feng Zengkun

The normal treatment for malaria has been failing in parts of South-east Asia, and the parasite's resistance to artemisinin, the main drug used to kill it, might be spreading, say experts.

Nanyang Technological University's Associate Professor Zbynek Bozdech led an international team of 31 scientists from 11 countries to find out why and how the parasite could be adapting to survive. Their findings were published in the scientific journal Science this month. He tells The Sunday Times why this development could wipe out the world's success in combating malaria.

Q: Artemisinin was introduced in the mid-1990s, and the standard treatment for malaria now is to give people a cocktail of drugs including it for three days, at one dose per day.

The first case of the parasite resisting artemisinin was detected in 2007 in Cambodia. But doctors say the drugs still work if the treatment is extended to six days. So why is this resistance a concern?

If you look around the whole world, in every case of malaria for 10 years, you gave people drugs for three days every day and the people were cured. It was always this way, never different.

All of a sudden, in 2007, in the province of Pailin in Cambodia, some patients still had the parasites on Day 3. That is a huge difference.

It is correct that in most of the cases, if you prolong the treatment to six days, most of the patients are cured again. But what this development is saying, is that something has changed. The parasites have changed genetically, and they can withstand the drug twice as long as they could before.

If the parasite changed once, it can change again, and even more so. And now that you have given the parasites more time to fight the drug – six days as opposed to three – there is an increased chance that they will evolve further. If this happens, which we should expect to happen, then artemisinin may not work at all someday. All nations' success that we have seen in the last 20 years will be wiped out.

Q: But can't we go back to using drugs that were used to combat malaria before artemisinin was invented?

Yes, indeed. In some cases this is being done. The most famous and long-used drug for malaria is quinine, which was invented some 300 years ago. That is still used for severe cases, but it is not a nice drug to take.

It has a lot of side-effects, and people feel sick. Its side-effects include muscle weakness, hearing problems, diarrhoea, kidney damage and even possibly severe bleeding.

It is also tough to go back to previous drugs, which the parasite may no longer be resistant to, because you would have to do very thorough clinical trials to make sure the drugs still work. Countries' ministries would have to recommend it, register it, and those are long processes. A lot of study and work would have to go into it, and the results are not guaranteed.

But artemisinin is typically used in combination with other drugs, so, right now, different partner drugs are being tested to see if there are more efficient combinations. That may yield a solution.

Q: A Myanmar health official has said the artemisinin resistance could be caused by fake or low-quality drugs dispensed at village shops. Can you explain?

If a drug is used in the prescribed way, there is enough of the drug to kill the pathogen quickly and efficiently. But if you use the drugs in sub-optimal doses, or use sub-optimal drugs or fake drugs, you don't have enough of the drug to kill the pathogen. Instead, you have enough of the drug so that the pathogen knows it is being targeted, and it changes to give it a way to deal with the drug. That applies pretty much to any drug resistance of any pathogen.

Q: To study how the parasite had evolved to resist artemisinin, your team studied about 1,000 malaria samples taken from patients in the Greater Mekong area, which includes Cambodia, Thailand, Vietnam, Laos and Myanmar. What did you find?

We have technologies called micro-arrays, which we can use to measure the activity of all of the genes in a genome at the same time.

We compared the gene activity of the parasites that were resistant to the drug, to those that were susceptible. We found that in the resistant parasites, all of the genes that are known to be involved in self-repairing were more active. That makes perfect sense, because the parasite is fighting against the damage caused by the drug.

We also observed another phenomenon that may be unique to this malaria parasite. Artemisinin has a very short half-life. When people take it, within 20 to 40 minutes, it goes into the blood and it reaches a very high concentration, but then very quickly it goes away. Literally in two to three hours, it is no longer in the blood, because the liver degrades it very quickly.

We found that the resistant parasite stalls its growth when it detects the drug – our speculation is that this makes it less susceptible to the drug. It is as if the parasites have noticed that they only need to stall for a short time, for the drug to disappear from the blood. Then they can recover and keep going.

Q: You and your team gave a presentation to the World Health Organisation in September about your findings. What were your recommendations and what is the next step in the research?

Right now, the resistance has been confirmed in a handful of countries in South-east Asia. The big question is, is it also happening in Africa, South America or other countries with malaria like some Middle Eastern countries? So, we recommended that if the countries' ministries of health or authorities decide to monitor this, they should be using a genetic test for a specific mutation in the parasite that is associated with the resistance.

We also need to find out how this mutated gene is linked to the resistance, whether it is responsible together with something else that we do not know yet. This mutation actually exists everywhere in the world, which is why we think it may not be the sole reason for the resistance. There are additional factors, and we do not know what they are.

zengkun@sph.com.sg

PHOTO: LESTER KOK

Associate Professor Zbynek Bozdech led an international team of 31 scientists from 11 countries to find out why normal treatment for malaria has been failing in parts of South-east Asia and how the parasite could be adapting to survive. Their findings were published in the scientific journal Science this month.

SINGAPORE A KEY WARRIOR IN THE FIGHT

Malaria has plagued people for more than 3,000 years, with scientists finding traces of it in the mummified bodies of Egyptian pharaohs.

King Tutankhamun, the boy pharaoh who died at age 19 in about 1324BC, for example, was likely killed by a severe bout of malaria combined with a degenerative bone condition.

The disease is caused by a parasite called Plasmodium, and is transmitted via the bites of infected mosquitoes.

Last year, there were about 198 million cases worldwide, according to the World Health Organisation (WHO).

Most cases and deaths occur in sub-Saharan Africa, but Asia, Latin America, the Middle East and some parts of Europe are also affected.

Singapore was declared malaria-free by the WHO in 1982, but the country remains vulnerable, due to the influx of travellers and the number of foreign workers arriving from malaria zones.

In 2009, there was a minor outbreak here, with 29 cases reported in three clusters.

Nanyang Technological University's (NTU) Associate Professor Zbynek Bozdech, who has been studying the parasite for more than a decade, does not expect to see the disease eradicated in his lifetime.

"I remember a presentation from one of the people at the forefront of the fight against polio. The (last few) per cent of cases took the most amount of effort," said the 47-year-old, whose wife is now in Mali working for an American non-governmental group to conduct public health surveys about Ebola.

Prof Bozdech came to Singapore from the United States in 2004, and is the associate chairman for research at NTU's School of Biological Sciences. He said the Republic has become a world-famous hub for malaria research, especially in the past few years.

Several laboratories here that work on the disease, at the National University of Singapore, Agency for Science, Technology and Research and other institutes, have created a research network called SingMalNet.

"We organise a big conference every four years, and also have regular meetings. In fact, we are in the final stages of registering our network with the Government as a society," Prof Bozdech said.

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