Do our medicines boost pathogens?

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This is a typical village in the Siraha district, Nepal, where leishmaniasis is endemic. Credit: © ITG

Scientists of the Institute of Tropical Medicine (ITG) discovered a parasite that not only had developed resistance against a common medicine, but at the same time had become better in withstanding the human immune system. With some exaggeration: medical practice helped in developing a superbug. For it appears the battle against the drug also armed the bug better against its host. "To our knowledge it is the first time such a doubly armed organism appears in nature", says researcher Manu Vanaerschot, who obtained a PhD for his detective work at ITG and Antwerp University. "It certainly makes you think."

Vanaerschot studies the *Leishmania* parasite, a unicellular organism that has amazed scientists before. *Leishmania* is an expert in adaptation to different environments, and the only known organism in nature

disregarding a basic rule of biology: that chromosomes ought to come in pairs. (The latter was also discovered by ITG-scientists recently.)

The parasite causes Leishmaniasis, one of the most important parasitic diseases after malaria. It hits some two million people, in 88 countries – including European ones – and yearly kills fifty thousand of them. The parasite is transmitted by the bite of a sand fly. The combined resistance against a medicine and the human immune system emerged in *Leishmania* donovani, the species causing the deadly form of the disease.

On the Indian subcontinent, where most cases occur, the disease was treated for decades with antimony compounds. As was to be expected, the parasite adapted to the constant drug pressure, and evolved into a form resisting the antimonials. In 2006 the treatment was switched to another medicine, because two patients out of three did not respond to the treatment. The antimonials closely work together with the human immune system to kill the parasite. This probably has given *Leishmania* donovani the opportunity to arm itself against both. It not only became resistant against the drug, but also resists better to the macrophages of its host. Macrophages are important cells of our immune system.

There is no absolute proof yet (among other things, because one obviously cannot experiment on humans) but everything suggests that resistant *Leishmania* not only survive better in humans – have a higher "fitness" – but also are better at making people ill – have a higher "virulence" – than their non-resistant counterparts.

Superbug?

It is the first time that science finds an organism that always benefits from its resistance. Normally resistance is only useful when a pathogen is bombarded by drugs; the rest of the time it is detrimental to the organism.

Resistant organisms are a real problem to medicine. More and more pathogens become resistant to our drugs and antibiotics – to a large extend because you and I use them too lavishly and improperly. For several microbes, the arsenal of available drugs and antibiotics has so diminished that people may die again from pneumonia, or even from ulcerating wounds.

Luckily for us, resistance helps pathogens only in a drug-filled environment. In the open field their resistance is a disadvantage to them, because they have to invest energy and resources into a property with no use there. Just like a suit of armour is quite useful on the battle field, but a real nuisance the rest of the time.

So the propagation of resistant organisms is substantially slowed down because they are at a disadvantage outside of sick rooms. But this rule, too, is violated by *Leishmania*: even in absence of the drug, the resistant parasite survives better, instead of worse, and it is more virulent than a non-resistant parasite.

Did our medicines create a superbug? A legitimate question, and the phenomenon has to be investigated, but this sole case doesn't imply we better stop developing new medicines (as a matter of fact, the antimony-resistant *Leishmania* are still susceptible to a more recent drug, miltefosine). On the contrary, we should develop more new drugs, to give new answers to the adaptive strategies of pathogens, and we should protect those drugs, for instance by using them in combination therapies. In this never-ending arms race we should use our drugs wisely, to minimise the chances for pathogens to develop resistance.

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