

Indeed, if we don't take action against multidrug resistance now, we might soon be thrown back to a 19th century situation in which basic infections, for instance those contracted in the course of routine surgical procedures, would be lethal in a majority of cases – not to mention the inability to administer some of our most efficacious cancer treatments (Prof. Dame Sally Davies, BBC interview 11 March 2013). Whereas bacterial drug resistance genes in DNA extracted from 30,000 year old permafrost sediments in Canada show that drug resistance is certainly not just a recent evolutionary trend, the increasing spread of multidrug resistant strains that are able to withstand complex antibiotic cocktails is novel and highly concerning.

One major factor driving the increasing emergence of these multi-resistant organisms is certainly the excessive application of antibiotics in medicine and farming. It has played a major role in the adaptation of multidrug-resistant bacterial strains to the continuous exposure to antibiotics in these environments. The rapid emergence of multidrug resistant bacterial strains also represents a serious ethical issue for the global community. An ineffective treatment does not just affect the patient, but has wider implications for the population. Interestingly, the evolution of drug resistance is the result of simultaneous over-consumption or incorrect use (e.g. failure to finish the full course) of antibiotics by wealthy nations and under-consumption by developing countries.

In the latter, dangerous strains are rarely treated correctly due to the lack of medicines and treatment, and are therefore never fully eradicated. The same pathogenic strains can then be further selected for hyper-multidrug resistance in an environment like a patient's intestine exposed to multiple antibiotics in a typical Western hospital. This interconnectivity means that health, especially in the context of MDR and infectious diseases, should be treated as a global public health concern, not just a national one (Selgelid, 2007).

Health involves 'externalities' affecting third parties: when microbes develop resistance in one patient because of over- or under-consumption of medication, this more dangerous malady poses an increased risk to others (Selgelid, 2007). Compounding this, many international pharmaceutical companies have abandoned the development of new antibiotics. The rapid global spread of antibiotic resistance, which has significantly reduced the time span during which antibiotics are effective, together with the low prices of antibiotics have made return of investment problematic for many companies. As a result, the antibiotic pipelines dried up decades ago.

Even though new attempts to develop antibiotics and blocking agents of multidrug resistance have restarted recently, real progress is difficult due to a lack in our detailed understanding of the mechanisms by which drug resistance develops. Basic research on the evolution, spread and mechanisms of MDR is needed, more than ever, in order to overcome these roadblocks in a development process aimed at launching sustainable drugs on the market. This research can reveal surprising new insights that might become important therapeutically in the future.

One of the major known mechanisms that leads to multidrug resistance is based on the presence of drug efflux pumps in (pathogenic) bacteria. These molecular structures (proteins), embedded in the plasma membrane of the bacterial cell, recognise and expel a vast range of antibiotics from the cell before these drugs can do significant harm inside the pathogen (Neuberger and van Veen, 2015). Hence, multidrug efflux pumps allow pathogenic bacterial strains to cope with high amounts of the most complex cocktails of antibiotics.

How do multidrug transporters recognise so many different drugs? Can they be inhibited such that existing drugs can still be used in the treatment of diseases? Can new drugs be developed to bypass these multidrug transporters? My research in Dr. Hendrik W. van Veen's lab at the Department of Pharmacology (University of Cambridge) is aimed at providing answers to these questions.

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