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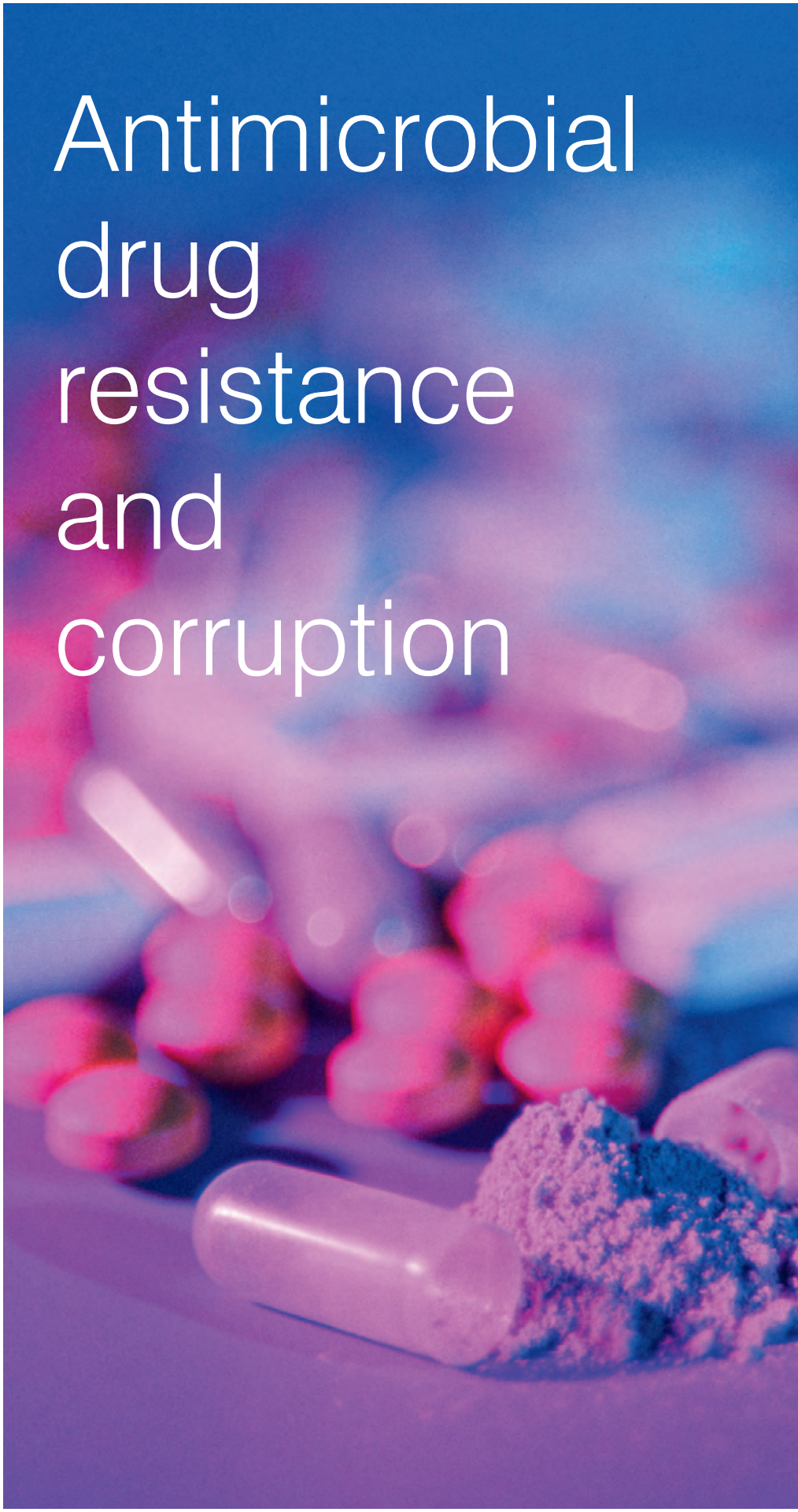
Antimicrobial drug resistance and corruption



Research recently conducted at the Australian National University by Dr Peter Collignon et al has shown there is a higher correlation between government corruption and antimicrobial drug resistance than there is between the incidence of drug usage and other commonly assumed factors.

Antibacterial drugs (commonly known as antibiotics) have been used for more than 60 years to cure infections, whether or not their use was appropriate in individual cases. However, as early as 1945, Alexander Fleming in his Nobel Prize speech warned that bacteria would become resistant to these treatments. Today we are seeing his prediction come true, and the world is now faced with the consequences of a long-term overdependence on the use of these drugs.

Antibiotics are actually a subset of a broader range of antimicrobial drugs. The commonly used term 'antibiotic resistance' refers specifically to the resistance to antibiotics that occurs in bacteria that cause infections. 'Antimicrobial' is a broader term, encompassing drugs used to treat infections caused by other microbes as well, such as parasites (eg, malaria), viruses (eg, influenza) and fungi (eg, *Candida*).

Antimicrobial resistance - a worldwide health problem

The World Health Organization (WHO) defines antimicrobial resistance as "resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it".

"Resistant microorganisms (including bacteria, fungi, viruses and parasites) are able to withstand attack by antimicrobial drugs, such as antibacterial drugs (eg, antibiotics), antifungals, antivirals and antimalarials, so that standard treatments become ineffective and infections persist, increasing the risk of spread to others.

"The evolution of resistant strains is a natural phenomenon that occurs when microorganisms replicate themselves erroneously or when resistant traits are exchanged between them. The use and misuse of antimicrobial drugs accelerates the

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emergence of drug-resistant strains. Poor infection control practices, inadequate sanitary conditions and inappropriate food handling encourage the further spread of antimicrobial resistance."[1]

It is also important to remember that it is not only antimicrobial drug use in humans that is increasing the problem. The use of antibiotics in animal husbandry and veterinary medicine is also impacting the growth of antimicrobial resistance. Since the 1960s, antibiotics have been used extensively in food animals as a means to reduce morbidity and increase farm yields. It has been claimed by some[2] that in the US in 2013 some 80% of antibiotic drugs sold were used on animals. Antibiotic contamination in wastewater, particularly from the pharmaceutical industry, has also in the past been linked to the increase in antimicrobial-resistant organisms in the environment.

In its *Antimicrobial Resistance Global Report on Surveillance* released in 2014[3], WHO raised the alarm at the extent of the problem:

"Some estimates of the economic effects of AMR have been attempted, and the findings are disturbing. For example, the yearly cost to the US health system alone has been estimated at US $21 to $34 billion dollars, accompanied by more than 8 million additional days in hospital. Because AMR has effects far beyond the health sector, it was projected, nearly 10 years ago, to cause a fall in real gross domestic product (GDP) of 0.4% to 1.6%, which translates into many billions of today's dollars globally."

In 2014, the UK government commissioned a report on the future effects of antimicrobial resistance. The resulting report published in December and titled *Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations*[4] predicts that antimicrobial resistance will kill 300 million people worldwide by 2050 and cost the global economy US$100 trillion if action is not taken to ease dependence on antibiotic medication.

"The damaging effects of antimicrobial resistance (AMR) are already manifesting themselves across the world. Antimicrobial-resistant infections currently claim at least 50,000 lives each year across Europe and the US alone, with many hundreds of thousands more dying in other areas of the world…But reliable estimates of the true burden are scarce."[4]

Antimicrobial resistance variation by country

Antimicrobial resistance has been observed to vary greatly from country to country. Factors that may contribute to this variation may include the relative wealth (GDP) of a country, the level of health expenditure, the quality of available health services and environmental factors - not least of which is the quality of sanitation and related services. However, these types of factors alone do not appear to adequately explain the actual variation found.

Research on the effect of corruption

Research recently published in Australia has highlighted the effect that government corruption and poor governance appears to have on the incidence of antimicrobial resistance. In a March 2015 paper by Australian National University (ANU) researchers titled *Antimicrobial Resistance: The Major Contribution of Poor Governance and Corruption to This Growing Problem*[5], the authors report that they found evidence to "support the hypothesis that poor governance and corruption contributes to antibiotic resistance and correlate better than antibiotic usage volumes with resistance rates".

The authors (Peter Collignon, Prema-chandra Athukorala, Sanjaya Senanayake and Fahad Khan) performed a multivariate analysis of the variation of antibiotic resistance in Europe in terms of human antibiotic usage, private healthcare expenditure, tertiary education, per capita GDP and quality of governance. The model used seven common human infections and covered 28 European countries for the period 1998-2010.

"The general perception of antibiotic resistance is that it is almost entirely related to the amounts of antibiotics used, not only in the broad sense of comparative usage by different countries but also in individuals. However, the available empirical evidence suggests that these two variables are not

perfectly correlated at national levels and across countries. We believe that other factors are as important, or even more important, to account for the variations in resistance observed between regions and countries. In particular, we wished to look at the contribution of corruption."[5]

Europe was chosen for the estimation because it was the only region where data was available for all parameters in the study across multiple countries. The countries covered are Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

The research also covered 25 pathogen/antibiotic combinations grouped into seven classes, namely:

- *Streptococcus pneumonia* resistance to penicillins and macrolides
- *Staphyloccocs aureus* resistance to methicillin and rifampicin
- *Pseudomonas aeruginosa* resistance to amikacin, aminoglycosides, carbapenems, ceftazidime, fluoroquinolones and piperacillin/tazobactam
- *Klebsiella pneumonia* resistance to cephaolosporins, aminoglycosides, carbapenems and fluoroquinolones
- *E. coli* resistance to cephaolosporins, aminoglycosides, aminopenicillins, carbapenems and fluoroquinolones
- *Enterococcus faecium* resistance to aminopenicillins, gentamicin and vancomycin
- *Enterococcus faecalis* resistance to aminopenicillins, gentamicin and vancomycin

Governance found to play a crucial role

The simplest of estimations, based on variations in antibiotic usage, showed that only 28% of the total antibiotic resistance variation in Europe could be attributed to usage patterns alone. When this was extended to include time-dependent effects, such as global shocks, it increased to only 33% that could be explained by usage.

Surprisingly, the income level of a country appeared to have no effect on resistance rates, nor did gross tertiary education enrolments. So in general, the wealth and relative educational advancement of a country was not a factor.

The rankings of countries by government control of corruption, however, yield a significantly different result. The data used was from the *International Country Risk Guide* published by the Political Risk Services Group, and when

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correlated with the other data, 63% of the antibiotic resistance variation was now explained. This would indicate that government corruption is a greater factor in explaining antimicrobial resistance than usage variation, and overall was by far the greatest socioeconomic factor.

Interestingly, when the data was compared on a year-on-year basis, it showed that the level of corruption in past years did not appear to influence outcomes in later years. In other words, the fact that corruption was higher in the past had no bearing on present levels of antimicrobial resistance - reduction in corruption resulted in a reduction in the level of resistant pathogens.

Governance factors

The results of the report indicate factors affecting antimicrobial resistance that are not expected in the common perception of most people. The authors of the ANU research have suggested that when the quality of governance is poorer it is less likely there will be effective controls over the use of antibiotics, not only in people, but also in food animals and the agricultural sector generally.

Where antibiotic use is not effectively controlled, it is suggested that there will be not only an increase in the development of resistant bacteria, but the spread of these bacteria will also be easier. Poorer control and law enforcement in relation to food and water safety would also help to increase the spread of drug-resistant bacteria.

How corruption affects the health sector

Corruption occurs to varying degrees in all countries, creating financial, economic and social costs, but it is especially damaging in poorer countries because of its effects, not only on pubic health, but also on development in general.

On a macroeconomic level, corruption limits economic growth: private organisations see corruption as adding risk to their investment decisions, and while particular multinational corporations might gain by bribing an official to win a contract or tax break, evidence suggests that corruption generally reduces the overall level of investment.[6] As a result, the lower economic growth means that less government revenue is available for investment, including investment in the health sector.

Choices in how to invest revenue are also affected by government corruption, since such governments are more likely to invest in infrastructure-intensive activities such as transport and the military, where there is a greater potential to extract bribes. Within the health sector, the construction of hospitals and purchase of medical equipment, while in themselves beneficial, can be prioritised over primary health care and health education for the same reason.

Corruption directly operating in the health sector also has a negative effect on access to, and quality of, patient care. It tends to drain resources from health budgets so that less funding is available to pay salaries and fund operations and education, leading to lower quality of care and reduced service availability and use - as well as poor diagnosis and the ineffective or inadequate prescription of medication, including the overprescription of common antimicrobial treatments.

The avoidance of the regulation of drugs is also common in jurisdictions without adequate governance. The dilution of medicines and the use of counterfeit drugs has been increasing - unregulated medicines that are of subtherapeutic value can contribute to the development of drug-

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resistant organisms and increase the threat of pandemic disease spread.

Another problem - well recognised in developed countries - has also been the unethical promotion of drugs and conflicts of interest for medical practitioners. In her January 2009 article *Drug Companies & Doctors: A Story of Corruption*[7], Marcia Angell, former editor-in-chief of *The New England Journal of Medicine*, wrote that pharmaceutical companies spend about $54 billion each year on drug marketing, including industry-sponsored education, drug information publications, and gifts and hospitality targeted at doctors. These activities, along with many other questionable consulting and education activities, help to influence decision-making and can lead to non-rational prescribing.

Example: Tuberculosis in India

The incidence of tuberculosis in India averages around two million cases per annum and poses a significant public health risk for the rest of the world. While India has been working hard to reduce the incidence of TB, in recent years there has been a rise in the incidence of multidrug-resistant tuberculosis (MDR-TB). According to the *Wall Street Journal* (19 June 2012)[8], "India's slow response to years of medical warnings now threatens to turn the country into an incubator for a mutant strain of tuberculosis that is proving resistant to all known treatments, raising alarms of a new global health hazard.

"In most of the country, India pays only for standard TB treatment, which medical authorities say is useless against the antibiotic-resistant strains. In fact, experts said, antibiotics that don't kill the disease provide favorable conditions for mutation of new, stronger strains."

India is well known for endemic public and private sector corruption. In 2012, India ranked 94 out of 176 countries in the Corruption Perception Index of Transparency International. Other recent surveys also reveal that, globally, corruption has worsened in the last two years, according to a survey conducted by Ernst & Young in India in 2013[9].

The availability of free diagnosis and treatment of MDR-TB has only occurred in recent years and in some locations, such as Mumbai, these services have been delayed. There is also an issue of the poor quality of TB and MDR-TB laboratory diagnosis in the private sector. The use of serology to diagnose TB, commonly used in India, is known to misdiagnose and has been recommended against by WHO and other expert groups.

There is also a lack of information about patients diagnosed with TB and MDR-TB in the private sector, since the public health sector is not informed, and the quality of the private care is not supervised.

Anti-TB drugs are also available without prescription and there is, therefore, subsequent widespread irrational and irresponsible use of them, further expanding the development of drug-resistant strains.

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Conclusion

Research recently conducted at ANU, while not accounting for all factors, has nevertheless shown that government corruption and poor governance is significant in raising the incidence of the development of antimicrobial drug-resistant strains of infection. The research has shown that the effect of corruption is significantly larger than the actual use of antimicrobial drugs in explaining variations in drug resistance between countries.

While medical research will continue to find ways to alleviate the effects of past medicine use, changes and improvements to the way governments manage corruption, not only in the health sector, but across all aspects of society, will help achieve better public health outcomes.

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