

SAFE, SECURE AND CONTROLLED: MANAGING THE SUPPLY CHAIN OF ANTIMICROBIALS

**THE REVIEW ON
ANTIMICROBIAL RESISTANCE**

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INTRODUCTION

Antimicrobial drugs – such as those used to cure malaria, tuberculosis and a wide range of bacterial infections – are essential life-saving medicines. Used correctly, they deliver enormous benefits to the health of the public in all parts of the world. Timely access to affordable products of dependable quality is therefore essential in the treatment of infectious diseases.

Their use is not without its risks, however. As we have set out in an earlier paper, the more that antimicrobial medicines are used, the more microbes develop resistance to them. This is exacerbated by the fact we often use large volumes of these medicines inappropriately, when we do not need them. We have set out the case for why there needs to be a transformation in the way in which clinicians prescribe antimicrobials and how this should be led by a new generation of diagnostic technology.

However, shifting towards a paradigm of better and faster diagnosis can only represent part of the solution, as large quantities of antimicrobials are consumed without a formal prescription. Non-prescription use of antimicrobials is difficult to quantify systematically, and estimates across general populations are often patchy. However the available evidence indicates that it is more commonplace in – but by no means limited to – low and middle-income settings. Estimated rates of non-prescription antimicrobial use in parts of southern and eastern Europe, for instance, are between 20% and 30% of total consumption, rates that are as high as or higher than those seen in India, Mexico and Indonesia¹.

Many individuals buy antimicrobials and other drugs without a prescription either because they cannot access formal clinical advice, or because they decide to self-medicate as a matter of personal choice. Improvements in rapid diagnostics, along with incentives to encourage their use, may well have a greater role in improving the accuracy of non-prescription use in the medium-term. However, governments should also seek to reduce this kind of self-medication in the shorter term. This goal can be achieved by improving access to proper clinical advice and improving education and understanding of the personal and public risks of self-medicating (whilst recognising that in some settings, informal or over-the-counter access to antimicrobials may in practice be the only route to accessing urgent medications.)

But as well as changing individuals' demand for antimicrobials via informal routes, action by government and regulators is also needed to address the 'supply side'.

In this paper we outline two areas on which we think policymakers should focus to improve the way we consume antimicrobial and curb the rise of drug-resistant infection.

The first area is the sale of antimicrobial drugs on the internet without a prescription. The second is the problem of falsified and poor quality products. Regardless of how antimicrobials are accessed, doctors and patients need to be sure that the drugs that they use are what they say they are, and of good quality – something that, sadly, cannot always be taken for granted. Poor quality antimicrobials can represent a significant public health concern, as they deliver a sub-therapeutic dose of the active ingredient. This provides a pathogen with enough exposure to the drug to give a selective advantage to the drug-resistant microbes, but not enough of the drug to kill off the infection, encouraging drug-resistant microbes to develop and spread.

¹ Morgan D J, Okeke I N, Laxmanirayan R, Perencevich E N, Weisenberg S. Non-prescription antimicrobial use worldwide: a systematic review. *Lancet Infectious Diseases* 2011; 11: 692–701.

² Orizio G, Merla A, Schulz P J, Gelatti U, 2011, "Quality of online pharmacies and websites selling prescription drugs: A systematic review", *Journal of Medical Internet*

Research, 13(3): e74.

³ Nuffield Council on Bioethics, 2010, "Medical profiling and online medicine: the ethics of 'personalised healthcare' in a consumer age", ISBN: 978-1-904384-21-2.

⁴ Mainous III A G, Everett C J, Diaz V A, Heuston W H. Availability of antibiotics for purchase without a prescription on the internet. *Annals of Family Medicine* 2009; 7:

INTERNET SALES OF ANTIMICROBIALS

The sale of medicines over the internet is a common phenomenon, one that began in the 1990s² and is gaining increasing popularity with the growth of e-commerce and the steady march towards near-universal internet access. Online sales of medicines are convenient for patients who are unable to reach a pharmacy, either for reasons of mobility or simple convenience. Properly regulated online pharmacies, servicing legitimate prescriptions, are a thus natural and indeed welcome evolution of the pharmaceutical retail sector. However, there are nonetheless significant risks associated with the growth of online pharmaceutical sales, especially with respect to use of antimicrobials and the development of antimicrobial resistance (AMR).

The risks of online sales

There is at present very limited evidence to quantify the contribution of online sales of antibiotics to increasing levels of AMR. It is also the case that, at least in terms of its impact on drug resistance, an inappropriate act of self-medication is no worse than an unnecessary prescription from a legitimate source. However, there can be no doubt that it has the potential to have a significant impact³, and that the emergence of unregulated and unscrupulous online retailers presents a novel regulatory challenge. Demonstrating the potential scale of the problem, a study carried out in 2009 showed that a variety of antibiotics were available online including penicillins, macrolides, fluoroquinolones and cephalosporins, identifying 136 unique vendors who would ship them to the US without a prescription⁴.

Online sales of antibiotics occur either with prescriptions or without and may be legal or illegal depending on the regulations governing these kinds of sales within countries. In many developed countries, including the UK and US, sales of antibiotics from regulated online pharmacies with prescriptions is legal and common. And, in most countries, the sale of antibiotics from unverified sources and without prescriptions is illegal. However, the global nature of e-commerce means that online pharmacies are liable to fall into gaps between conventional national regulatory jurisdictions. Online vendors of antibiotics can often bypass domestic regulation – in countries where it is in place – by allowing customers to purchase antibiotics from sites based in countries where regulations are not as strict or poorly enforced. Websites can take advantage of lax regulatory regimes in their ‘home’ countries and gaps in customs checks in the countries to

which they ship. Many such online vendors will sell quantities that exceed single courses, or have shipping times of a week or more – meaning that their services are far more suited to irresponsible self-medication and ‘stockpiling’ than fulfilling immediate needs for an acute infection^{5,6}.

The risks associated with the internet sales of antimicrobials go beyond the problems of excessive consumption.

By their very nature, illegal internet pharmacies that take advantage of regulatory gaps or blind spots will often be operating beyond normal arrangements for oversight of the quality of the products on sale. This increases the risk that the drugs sold by spurious websites could be falsified or poor quality – an issue that is discussed in more detail below. For instance, a fake version of the antiviral drug Tamiflu was available on fraudulent internet pharmacy sites within weeks of the 2009 H1N1 pandemic being declared by the World Health Organization⁷. And even where online vendors sell antimicrobials ‘by prescription’ there may be no mechanism to verify the authenticity and accuracy of a script. There are particular vulnerabilities where online ‘consultation portals’ could potentially be gamed, simply by making up symptoms in order to guarantee a prescription or by mistaking symptoms. This behaviour remains difficult to measure.

The need for better regulation

The availability of antibiotics on such websites therefore represents an international problem, and requires global solutions from pharmaceutical regulators, customs authorities, and internet companies. Currently, there are significant gaps in the international regulations and enforcement that govern the movement of antibiotics and other medicines from one country to another.

While developed regions such as the US and Europe have regulations governing the online sale of antibiotics with prescription, many others do not. A concerted international effort is therefore needed to make substantial progress in this area and to control access to antimicrobials, to ensure that consistent standards are met for internet sales. The internationally coordinated action, led by INTERPOL in 2015 and targeting illegal online pharmacies was a notable success story. Operation Pangea VIII, with 115 countries participating, targeted criminal networks responsible for the sale of falsified medicines via illegal online pharmacies. The operation resulted in the seizure of 81 million USD worth of potentially dangerous

431–435.

⁵ Drlica K S, Perlin D S. *Antibiotic Resistance: Understanding and Responding to an Emerging Crisis*. Pearson Education Inc. 2011.

⁶ Mainous et al 2009

⁷ Redpath S. Trade in illegal medicine hits pharmaceutical sector. World Finance [online], April 20 2012. Available from <http://bit.ly/1kByA2s> [Accessed November 2015]

⁸ INTERPOL, ‘INTERPOL-coordinated operation strikes at organized crime with seizure of 20 million illicit medicines’, Available from: <http://www.interpol.int/News-and-media/News/2015/N2015-082> [Accessed November 2015]

medicines, 156 arrests across the world and the shutdown of two internet domain names that sold these drugs. This operation represented the largest ever internet-based operation and involved multiple international agencies from government agencies, to private sector companies such as Google, MasterCard, Visa and PayPal⁸. This demonstrates the importance of organisations from across the world coming together to address this issue.

The EU and the US have taken steps to ensure proper registration and regulation of online pharmacies. For instance the UK requires all online pharmacies to sell only against a prescription, to be registered with the Medicines and Healthcare products Regulatory Agency (MHRA), and to display a logo that is common across the EU⁹.

Ultimately, however, achieving improvements in the sale of antimicrobials over the internet will also need a change in behaviour by the public, who need to be informed of the risks that are involved in buying antibiotics online without prescription and from illicit pharmacies. While there are steps being taken in the right direction, more needs to be done.

COUNTERFEITS AND SUBSTANDARD ANTIMICROBIAL DRUGS

From a biological perspective, one of the most effective ways of encouraging the development of drug-resistant infections is to expose pathogens to sub-therapeutic doses of an antimicrobial. In simple terms, this provides a pathogen with enough exposure to the drug to give a selective advantage to the drug-resistant microbes, but not enough of the drug to kill off the infection, and thus stop the emergent resistance in its tracks.

Exposure to sub-therapeutic doses can happen in several ways. This could be for innocent or inadvertent reasons, such as a patient deciding not to complete the course of antibiotics as they start to feel better, or the dose they are given being calculated inaccurately – both important problems in their own rights. But another, less innocent and less well-examined source of under-dosing has also emerged: poor quality medications.

The nature of the problem

Poor quality antimicrobials can manifest themselves in a number of forms:

- i. Drugs produced by legitimate, registered manufacturers that are manufactured to appropriate standards, but are degraded by inappropriate handling once they enter the market;
- ii. Drugs produced by registered manufacturers, but below acceptable quality standards – the result of either inadvertent (i.e. negligent), egregious (i.e. grossly negligent) or intentional deviation from good manufacturing practice (GMP).
- iii. Drugs produced by unregistered and unregulated manufacturers, below acceptable quality standards.

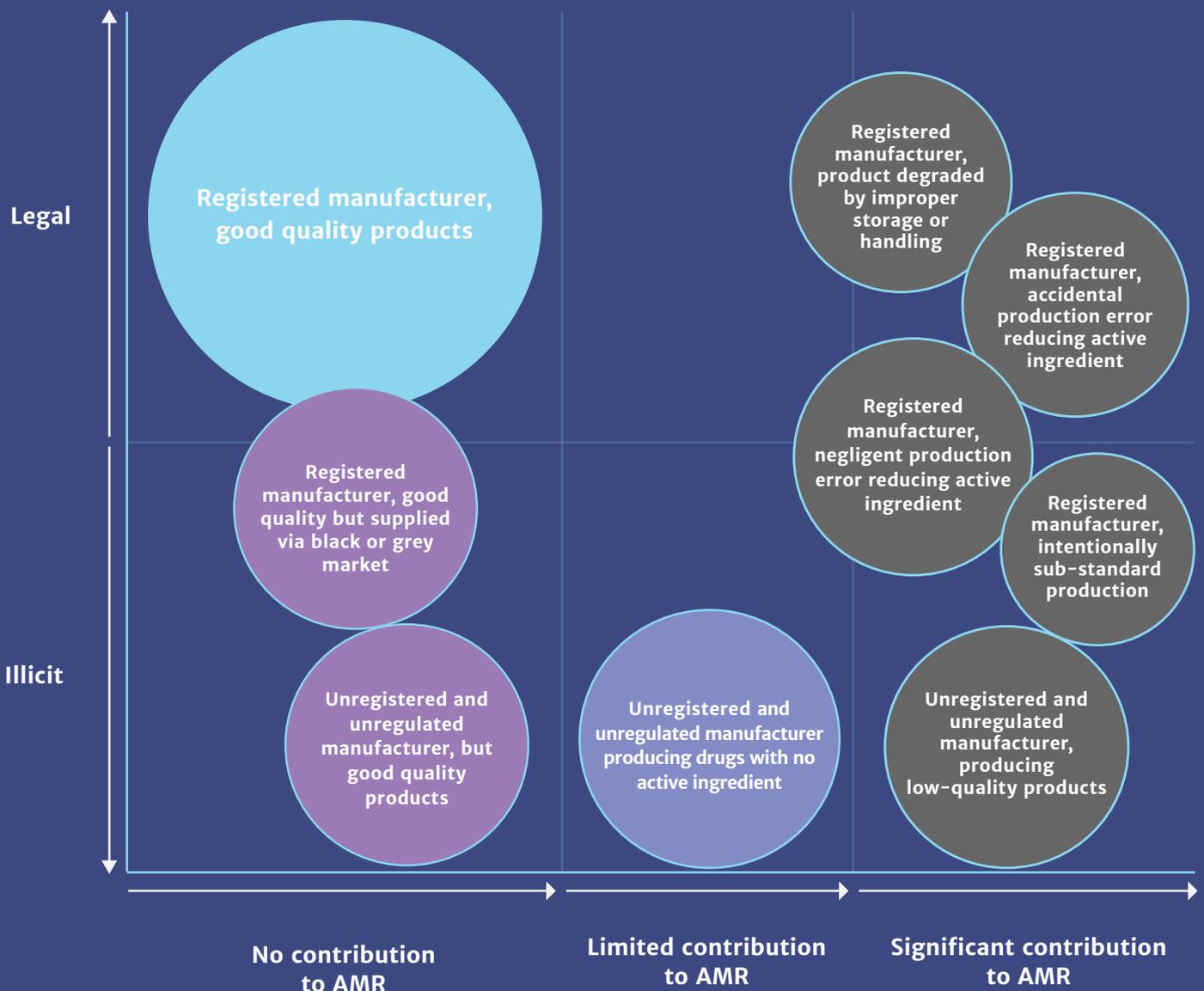
Fraudulent practice will often be central to the problem – including where drugs in the third category are sold as counterfeits of trademarked products – but these problems of illicit supply and sub-standard medicines are not one and the same.

In the first category, products will be manufactured to proper standards, and will be of high quality when they leave the factory. However, their quality – and thus the dose of the labelled active pharmaceutical ingredient (API) – will subsequently be degraded by inappropriate storage or handling. This is likely to be a greater problem in non-temperate climates and areas where management of the pharmaceutical supply chain is weaker, resulting in medicines being stored at higher temperatures than intended or in packaging that does not offer adequate protection against degradation (open bottles, for instance, rather than sealed blister packs.)

Medicines in the second category are produced by properly registered suppliers, but are sub-standard when they leave the factory. This can be the result of inadvertent errors in the manufacturing process, although clearly it is desirable to have quality control regulatory oversight measures in place to ensure that such deviations in quality are spotted. More concerning, though, are instances of gross negligence and chronic under-investment in quality control, and evidence of ‘tiered production’ by registered (but unscrupulous) producers, whereby as a cost-saving measure products destined for markets where regulatory checks are known to be lax are intentionally produced to sub-optimal levels of quality.

⁹ UK Government, ‘Register for the EU common logo’, Available from: <https://www.gov.uk/guidance/register-for-the-eu-common-logo>, [Accessed November 2015]

HOW SUB-STANDARD ANTIMICROBIALS CONTRIBUTE TO DRUG RESISTANCE



Finally, the third category is formed of manufacturers operating without appropriate registration and oversight from regulatory authorities, allowing them to produce products of low (or at least indeterminate) quality. Although medicines produced in this setting may not necessarily be poor quality, production that takes place beyond regulatory oversight should always be a source of significant concern, with a very high likelihood of the products reaching market from this source being low quality, or outright dangerous.

All three categories of poor quality antimicrobials are of concern. They are all likely exacerbate the development and spread of drug resistance, as they result in the patient receiving a dose of the API that is below what they or their doctor expects. This can happen either because there is not enough API in the product, or because it is poorly formulated.

Most dangerous for drug resistance are products where the level of API delivered is just enough to kill susceptible microbes, handing the greatest selective advantage to the resistant ones in an infected patient. Products with very low API levels (or none altogether) will result in treatment failure, but this actually presents less of a problem in terms of catalysing the development of resistance. Poor quality antimicrobials can also induce physician behaviour that is at odds to good stewardship practice: unless susceptibility tests are available, a doctor may confuse failure of a poor-quality medicine with drug-resistance, and respond by switching to second-line treatment options which are not in fact necessary.

The link to resistance

The relationship between sub-therapeutic dosing and the development of resistance is acknowledged to be difficult to quantify. Although there are some limited *in vivo* and *in vitro* studies that attempt to model the relationship, clinical studies are generally few and far between. More common are mathematical models of the dosing-resistance relationship, which show clearly the highest risk of resistance as lying in a so-called 'mutant selection window' between an API dose so low to have no impact whatsoever, and an adequately high therapeutic dose that kills both susceptible and resistant microbes.

The development of resistance is not the only threat to health that poor quality antimicrobials present, however. At a personal level, a patient taking a poor quality medicine will be unwell for longer (or may not recover at all); while from a public health perspective, poor quality versions of drugs for treatments

like malaria or HIV will offer fewer benefits in terms of these medications' crucial role in limiting the spread of infection.

The scale of the problem

Overall, there is considerable uncertainty over the scale of the problem of poor quality antimicrobials, as monitoring of the problem is presently difficult and extremely patchy as a result. Where studies have looked for evidence of the problem, though, they have often found it.

Within the various classes of antimicrobials, by far the greatest analysis and scrutiny has been in respect of antimalarials, spurred by concerns about the rapid emergence of resistance to artemisinin-based treatments in South East Asia. Such studies have often found evidence of falsified and poor quality antimalarials on sale across this region, and in Africa. These have occasionally found exceptionally high instances of falsified and poor quality antimalarials – more than 90% in Cambodia in 2003, for instance – although they also provide indications that increasing attention on the problem in recent years has begun to have an impact in reducing the penetration of poor quality products into these markets. Systematic studies of the problem beyond malaria – to include, for instance, antibiotics – and beyond low-income settings are extremely limited, though.

Accurately assessing the scale of the problem can in itself be problematic. Studies frequently rely on random point-of-sale surveys, essentially using 'mystery shoppers' to survey the products on sale in a representative sample of outlets. These are time-consuming and logistically difficult, however – meaning that they often only enable a snapshot of markets in a relatively limited area, rather than a representative picture across an entire country or region. Many studies may also not be systematic in their sampling, adding to the difficulties associated with using multiple surveys to derive an accurate picture of the overall problem.

In high and middle-income countries, there may be a greater dependence on systems of pharmacovigilance to spot issues of fake and poor quality medicines – i.e. mechanisms allowing clinicians to report concerns and adverse reactions to national regulatory authorities. However, these are liable to overstate the problem of toxicity in non-authentic products – which will yield the most obvious side-effects and adverse reactions – whilst under-estimating problems of poor quality, where treatment failure may go unnoticed or otherwise fail to ring alarm bells.

Adding to these difficulties, the assessment and definition of the problems of poor quality medicines can also be complex. The most accurate means of testing the active ingredients of a product are inevitably lab-based – meaning that they are resource intensive, and their availability is likely to be limited in lower-income settings. Although necessarily imperfect, field-based mechanisms of testing are available in varying forms. User-friendly, handheld ‘point and shoot’ spectrometer devices, for instance, can test products quickly, relatively accurately, and without opening or destroying a sample, but their widespread use is usually limited to border control agencies and wholesalers, rather than truly front-line users and clinicians. Instead, in these settings there will often be a greater reliance on simple, interpretative tests such as basic colorimetric ones that test for a given level of a given active ingredient. These are cheap – costing a matter of pennies – and easy to use, but inevitably this comes at the expense of a degree of accuracy (including via problems of human error), and they will often involve destruction of the sample.

Addressing the problem

Although there is clear and persuasive evidence of the role that poor quality medicines can play in driving the development of drug resistance, too many gaps remain in our understanding of both the relationship clinically, and the penetration of all classes of poor quality antimicrobials to markets around the world.

As well as closing the gap in the understanding of the science through the efforts of academia, concerted efforts are needed to improve national and global monitoring and mitigation of poor quality antimicrobials. This need not be unduly burdensome, and in large part can be seen as an important element of effective national systems of pharmaceutical regulation and pharmacovigilance. Having the mechanisms in place to rapidly spot and respond to deviation from manufacturing best practice by antimicrobial producers is key to preventing sub-standard products from legitimate sources reaching market.

Meanwhile, poor quality products need to be weeded out by more concerted efforts both from governments and from NGOs operating on the front lines in less developed countries – although this will require the development of and access to the necessary testing equipment and infrastructure. A model for surveillance of drug quality already exists along similar lines, in the form of the systems in place today to monitor supplies and assure the quality of malaria drugs – providing a model upon which broader surveillance systems could be built.

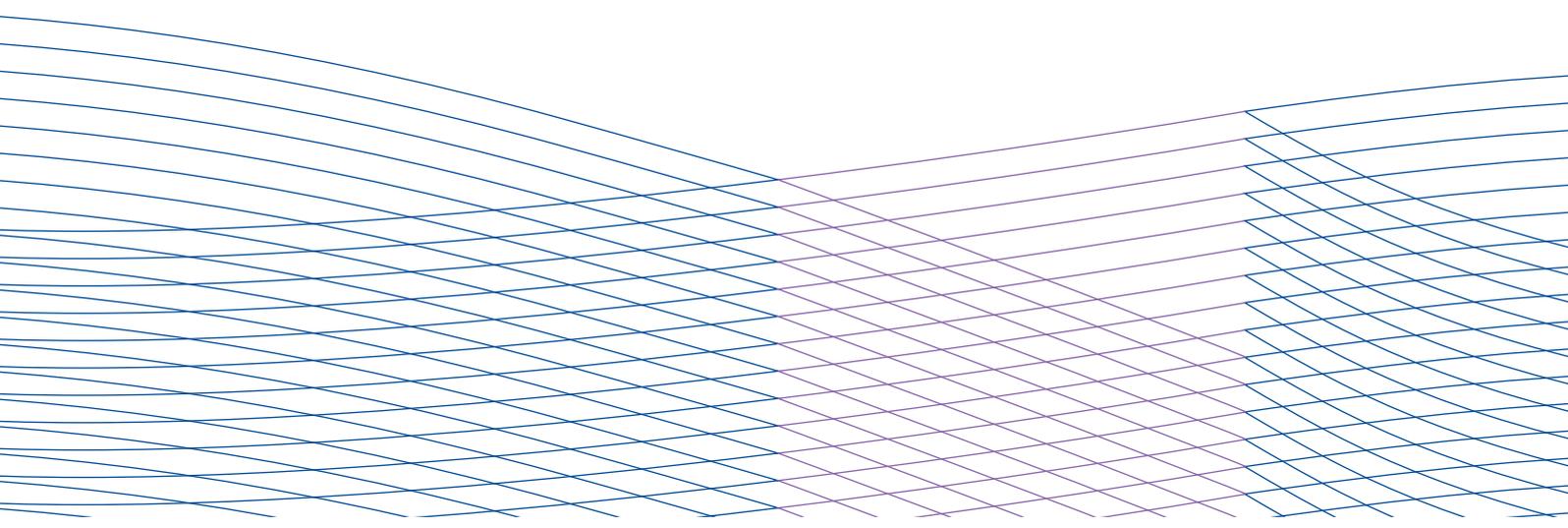
Finally, there is a role for industry to play too. Acknowledging that many antimicrobials will not reach patients via well-regulated supply chains in temperate climates, greater efforts are needed to understand the degradation of antimicrobial products and how this can be prevented – for instance through better packaging or re-formulation. Major global manufacturers – ‘big pharma’ and generic producers alike – can play a crucial role in improving the handling of antimicrobial products (and raising the awareness of the problems of mis-handling by clinicians) across the length of their supply chains, complex though they may be. Manufacturers also have a responsibility – ethically, as well as commercially – to ensure that levels of quality are the same regardless of the markets into which they sell.

CONCLUSION

These issues represent just two individual elements of the enormously complex and multi-faceted problems of drug resistance. However, they provide helpful demonstrations of two key difficulties that sit at the heart of the global response to the wider issues of AMR: the need to coordinate regulatory activities across national and organisational boundaries, and the complex interactions between government policy and human behaviour. Both of these aspects need to be properly considered when tackling these issues specifically, and the mounting global crisis of AMR more generally.

ACKNOWLEDGEMENT

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