Antimicrobial resistance: How substandard medicines contribute

By Roger Bate

The possibility of reverting to the pre-antibiotic era is increasing. With dirty hospitals, poor prescribing practices by physicians, and poor patient adherence to correct antibiotic use, the threat was already real. But now an increase in the production of substandard medicines is probably accelerating antibiotic resistance. The UK government predicts that antimicrobial resistance (AMR) could cost society a fortune within decades. The threat of AMR is increasing because of poor-quality medications, and India is ground zero when it comes to most of the problems. Given that antibiotics are so cheap in India, antibiotic use is, in effect, a substitute for proper sanitation. It is not surprising that new versions of AMR are now emanating from India. My team’s research shows that at least 6 percent of thousands of antimicrobial medicines sampled from 19 emerging nations are substandard. In nearly every nation, poor-quality medicines made in India were found. Of the substandard products we procured, 40 percent were made by legal and government-protected Indian manufacturers. But India is not the only problem case, and a global effort is required to identify sloppy production and prevent these products from being used.

The British government recently assessed the risks of antimicrobial resistance (AMR) undermining health systems in emerging markets and the developed world. Returning to a pre-antibiotic era would mean that many surgical procedures now taken for granted would become high risk, and currently treatable diseases could become a likely death sentence. The potential costs are enormous, undermining trade and economic growth over the next few decades. The UK government report suggests that by 2050, perhaps 6.2 percent of global production ($14.2 trillion) would be lost because of AMR (KPMG 2014). Right now, few major pharmaceutical companies prioritize manufacturing antimicrobial agents, because the profits are far lower than in other areas of research, such as cancer, hypertension, or diabetes. So with few financial incentives for companies to find new antimicrobial agents, the future may be bleak—with old medicines becoming obsolete and few new medicines emerging.

Most causes of AMR are well-known and covered by the UK government report. Dirty hospitals have encouraged dangerous strains of disease, such as methicillin-resistant Staphylococcus aureus (MRSA) and Clostridium difficile. The main drivers of AMR in the West are probably doctors prescribing antibiotics for viral infections and patients not completing courses of antibiotics as they should. But one aspect of this debate that has not been addressed sufficiently is medicine quality, which is especially a problem in emerging markets. Poor-quality medicines are a danger to patients, but they also are a risk to everyone because they accelerate resistance.

In the cutthroat world of cheap generic drug production, the lowest-cost provider usually wins the contract to supply—whether it is for a pharmacy chain, a hospital, or even an entire health service. As a result, legitimate manufacturers are constantly looking for ways to lower costs and beat the competition.
In the West, decent regulators and good feedback from physicians means that poor-quality producers are not likely to survive in the market. But in emerging nations, sloppy production is unlikely to be detected (Bate 2012). And in some emerging nations, notably India, where the government prioritizes protecting the industry over public health, sloppy production is effectively defended by government (Eban 2013).

**Substandard Drugs in the Marketplace**

Perhaps one-third of antimalarial drugs in emerging markets are substandard in some way (Nayyar et al. 2012). Such products may be responsible for approximately 122,000 deaths a year across the 39 African nations analyzed, the equivalent of 4 percent of all deaths of those under five years old (Renschler et al. 2015). With the rise of resistance to the best antimalarial cocktails, which is a significant problem in parts of the Mekong Delta, such poor-quality antimalarials may have an even larger impact in the future (Tun et al. 2015).

Drug quality in malaria treatment is evaluated far more than other infectious diseases, primarily because treatment failure can rapidly result in death. But even for malaria, no estimations of the contribution of poor-quality medicines to drug resistance have been undertaken.

Tuberculosis (TB) is another global infectious disease of major importance, with around one-third of the Earth’s population latently infected. According to research on drug-resistant strains, this translates to at least two billion people as possible incubators for tuberculosis that is difficult or impossible to treat (World Health Organization 2014; Bate et al. 2013; Binagwaho et al. 2013).

My team conducted a study of isoniazid and rifampicin, two of the main first-line antituberculosis medicines, to determine if substandard medicines are available and if they potentially contribute to drug resistance in cities in low- and middle-income countries (Bate et al. 2013). We expand on that paper with previously unanalyzed data from different pharmacies in the same cities of the 19 countries covered in that study: Angola, Brazil, China, Democratic Republic of Congo, Egypt, Ethiopia, Ghana, India (three cities), Kenya, Nigeria, Russia, Rwanda, Thailand, Turkey, Uganda, United Republic of Tanzania, and Zambia.

In the previous paper we had assessed 713 treatment packs from a selection of pharmacies in 19 cities. We now add 392 samples that were procured in 2014 and were tested before expiration in 2014 and 2015. Of the original 713 samples tested, 9.1 percent failed basic quality testing for requisite levels of active pharmaceutical ingredient (the chemicals that actually combat infection). The failure rate was 16.6 percent in Africa, 10.1 percent in India, and 3.9 percent in the other middle-income countries listed.

Similarly, of the new 392 samples, 8 percent failed basic-quality testing. Once again African failure rates were the highest at 16 percent, Indian failure rates were at 9 percent, and other middle-income nations were at 2 percent. Overall, 8.4 percent of the total combined sample of 1,105 medicines failed.

It is possible some of the failing products were falsified or counterfeit. But with more detailed analysis of the packaging, especially comparisons with known good-quality versions, we are confident that at least 6 percent of the total sample was not falsified or degraded through poor storage but was substandard with under-dosed content that would probably not treat the patient but would almost certainly drive resistance.

Substandard TB drugs are readily available in the private marketplace and probably contribute to antituberculosis drug resistance in low- and middle-income countries.

**How Substandard Medications Drive Resistance**

In 1945 Alexander Fleming won the Nobel Prize for his discovery of penicillin. In his acceptance speech he warned of the inevitable rise of resistance to the wonder drug he had found. He understood that pathogen resistance to medicines is a natural process, whereby over time successful mutations in pathogens will render medicines useless even when antibiotics are used correctly. Seventy years after Fleming’s Nobel, his forecast of resistance has proved prescient, with numerous drug-resistant strains for myriad diseases.

Research indicates that during a mutant-selection window, resistant strains breed while antibiotic-sensitive strains are killed (Abdul-Aziz 2015). Such a window can be enhanced for many reasons. It can occur when a patient fails to finish a course of medicine, so mutations might be successful with a resistant strain flourishing. But even worse are medicines manufactured with subtherapeutic concentrations of active ingredient because of inferior production methods or ingredients. Such medicines might act as perfect drivers of resistance development.
countries—and possibly the richer world too. This issue warrants further investigation through large-scale studies of drug quality in all markets.

A new study (covering the same cities as the TB study mentioned earlier) shows that at least 5 percent of 1,500 samples of the broad-spectrum antibiotic ciprofloxacin were substandard (Bate, Jin, and Mather 2015).

To be clear, these products are sold as generics but should not be regarded as generic because they are not bioequivalent to innovator or generic products, and many do not even pass basic physical and chemical stability analysis, as I will discuss. They are simply poorly made by legal if illegitimate manufacturers. Badly made products undermine trust in real generics, which are essential to combatting disease.

The problem in rich nations is generally not poor quality but insufficient therapeutic equivalence. Many products are not truly therapeutically or biologically equivalent (Food and Drug Administration 2015).

Lack of equivalence has been demonstrated across a range of antibiotic agents including vancomycin, amoxicillin, oxacillin, meropenem, gentamicin, and ciprofloxacin (Vesga et al. 2010; Del Tacca et al. 2009; Agudelo et al. 2013; Zuluaga et al. 2010; Weir et al. 2005). And for vancomycin, a potential therapeutic failure of an allegedly generic vancomycin reportedly led to very nasty diseases, notably MRSA peritonitis and bacteremia (Rodriguez et al. 2009; Rodriguez et al. 2010; Rodríguez et al. 2012).

India’s Key Role in the Problem

In China, hospitals and clinics receive financial incentives for prescribing, and antibiotics are overused as a result (Reardon 2014). In India the practice is less organized but still prevalent (Bate 2009).

Additionally, millions of Indians do not have access to potable water and proper sanitation, and antibiotics are often used as a substitute for better hygiene. Furthermore, there are probably ineffective antibiotic-prescription practices for community-acquired (the normal spreading of disease through the air) respiratory and diarrheal infections, many of which are viral in origin, and hence antibiotics are useless. Moreover, India is one of the largest producers of cheap generic drugs, including antibiotics, and some manufacturers worryingly release antibiotics into wastewater (Reardon 2014). With other negligent manufacturing practices in India, it is not surprising that antibiotic-resistant organisms proliferate (Harris 2014; “France, Germany Suspend,” 2014).

My research team found crucial AMR-controlling medicines (such as the carbapenem antibiotics) available in most pharmacies they visited in India. In a handful these were sold to us without a prescription. Yet in Western nations these medicines are considered crucial for controlling AMR and are administered only in hospitals by trained medical staff.

Another example of the roulette being played in India is the startling number of multidrug-resistant bacteria that were isolated in the public water supply in New Delhi. Concurrently, the German government suspended 80 Indian products made by 16 companies because of failed standards, including bioequivalence (“France, Germany Suspend,” 2014).

India is not alone in this continued substandard manufacturing. But in India the confluence of cheap medicines, sometimes of dubious quality; widespread use of antibiotics instead of more traditional methods of hygiene; physician incentives to overprescribe; and vast, dense urban settings create the perfect storm for resistance emergence.

The global spread of the New Delhi metallo-beta-lactamase 1 (NDM-1) plasmid may have been exacerbated by substandard antibiotics. NDM-1 was first identified in a Swedish patient returning from India with Klebsiella pneumoniae. Although travel is the cause of cases spreading throughout South Asia, it is now probably being transmitted most rapidly in India (Gelband et al. 2015).

It is time for the international medical community and regulatory bodies to agree on a more effective way to identify substandard antibiotics and, once identified, remove them from the supply chain as far as possible. If we do not, we increase the likelihood of reverting to the pre-antibiotic era of untreatable infections.

About the Author

Roger Bate is an economist who researches international health policy, with a particular focus on tropical disease and substandard and falsified medicines.

References


