

# How action in India can have global impact: The Indian pharmaceutical industry and antimicrobial resistance

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## INTRODUCTION

Antimicrobial resistance (AMR) is increasingly recognised as a growing global health problem. Without effective antibiotics, infections become more difficult to treat, and medical and surgical procedures can become high-risk interventions. Every time an antibiotic is used, bacteria are given a chance to adapt their defences and develop resistance. To minimise this, antibiotics must be used correctly and only when needed – to treat specific pathogens following a specified treatment regimen.

The overuse and misuse of antibiotics in humans and in the agricultural sector is accelerating the increase in resistance. Global AMR strategies are being developed that address the stewardship of antimicrobials: to ensure they are used responsibly by humans and in animals, and to minimise levels of antimicrobials in soil and water. Many AMR strategies focus on developing new medicines to replace the antimicrobials that are becoming less effective.

AMR strategies must also address access issues. People living in less developed and resource-limited settings are on the frontlines for AMR – they generally face higher rates of resistance and infectious diseases, yet get poor healthcare advice and often struggle to access antibiotics when they need them. In fact, millions of people currently live without reliable access to antimicrobials or to good information on how to use them. In a WHO survey, 75% of Indian respondents thought that infections with cold- and flu viruses could be treated with antibiotics. These factors prompt people to use antibiotics in ways that can encourage resistance, for example, by splitting a single course of antibiotics between two sick children to leave both at greater risk of resistance.

## ANTIMICROBIAL RESISTANCE IN INDIA

India has made significant gains in public health in the past two decades. A baby born in India today can expect to live ten years longer than if he or she was born in the 1990s. Mortality among the under-fives has dropped by 65%. Of particular relevance to AMR, the proportion of deaths in India that are caused by communicable diseases (including infectious and nutritional diseases) has dropped from 54% to 27% since the 1990s.

Nevertheless, the burden of infectious diseases in India remains high, bringing a clear need and demand for antibiotics. Lower respiratory infections, diarrhoeal diseases and tuberculosis are among the ten deadliest diseases in India. Out of every 100,000 children aged under 5 in 2016, 115 died due to pneumonia, diarrhoea or another common infectious disease. In 2010, Indians consumed 12.9 billion

antibiotic pills, up from 8 billion in 2001. In comparison, China was estimated to consume 10 billion pills in 2010.

India has some of the highest antibiotic resistance rates globally. This includes bacteria that are a common cause of infection in the community and in healthcare facilities. In 2017, resistance to key broad-spectrum antibiotics (the first-line of defence against an infectious disease) exceeded 70% for common bacteria that cause diarrhoea (*E. coli*) and pneumonia (*A. baumannii*, *K. pneumonia*). This includes strains of these bacteria that are even resistant to the newer antibiotics, such as carbapenems. In Indian hospitals, a range of healthcare-associated infections (HAIs) have been found to have prevalence rates of between 11% and 83%. Globally, this compares to rates of between 7% and 12%, according to WHO estimates. More than half of irrigated agriculture and more than three quarters of drinking water supplies in India are dependent on groundwater. Unsafe water sources, poor sanitation and a lack of access to handwashing facilities are the three largest factors for spreading infectious disease and accelerating resistance. The uneven and weak health system infrastructure also plays a significant role.

## GOVERNMENT ACTION

Bringing AMR under control requires consolidated, concerted action by multiple stakeholders. Infection prevention and control are key. The government has the central enabling role in these areas, including in expanding access to clean water, sanitation and hygiene, in strengthening the health care system, in establishing regulations around antibiotic prescription, in implementing therapeutic guidelines, and in public education and awareness of AMR. The government in India is already taking action. For example, its Red Line campaign involves putting a distinctive red line on all antibiotic packaging to mark it as 'prescription only'. The innovation has been internationally hailed as an important mechanism for ensuring antibiotics are dispensed appropriately. The government also plans to establish a nation-wide AMR surveillance system. Under the plan, a network of 30 laboratories will generate data on antimicrobial resistance for specific pathogens known to pose a particular threat to public health.

In 2017, the Indian government published its National Action Plan on Antimicrobial Resistance (NAP-AMR). The NAP-AMR spells out six strategic priorities, including improving awareness through communication, education and training, strengthening surveillance, and promoting investment for AMR activities, research and innovation (for example, to develop alternative approaches to managing infectious diseases). As it begins implementing the NAP-AMR, the government is now working to consolidate the data available on AMR in India. Also in 2017, India introduced two National Strategic Plans (NSPs) for controlling infectious diseases: one for ending the HIV/AIDS epidemic and another aiming for Tuberculosis Elimination. The NSP-TB, for example, has set out a framework for reducing TB incidence to zero by 2025, while also ensuring cost of treatment is not catastrophic to patients or their families. Private sector engagement is one of the NSP-TB's four focus areas.

## HOW INDIAN ANTIBIOTICS COMPANIES CAN BRING CHANGE

Pharmaceutical companies also have an opportunity to play a key role; they can determine to a large extent where their products are available and how they are priced and promoted, and have significant influence on manufacturing chains, as well as expertise in researching, developing and commercialising new medicines. For example, pharmaceutical companies can take clear policy measures to address over-the-counter sales of antibiotics.

India has the world's third largest pharmaceutical industry, accounting for 10% of the global market by volume. In 2017, revenue is estimated to have grown by 7.4%, making India's one of the fastest growing pharmaceutical sectors globally – the market is projected to be worth USD 100 billion in revenue by 2025. India is also one of the largest exporters of pharmaceuticals, reaching USD 16.8 billion in pharmaceutical exports in 2016-17.

India's pharmaceutical market is dominated by generic medicines, which account for 70% of market share by revenues. India's generics market was worth USD26.1 billion in 2016. Generic medicine manufacturers can be characterised as either bulk producers of active pharmaceutical ingredients (APIs) or producers of finished (generic) products. In practice, generic medicine companies commonly produce both APIs and finished products. Indian pharmaceutical companies are generally seen as leaders in the production of finished antibiotic products. A large proportion of APIs used by Indian companies are produced in China. Compared to the global average, the cost of pharmaceutical production in India is approximately a third lower. Indian generic companies have been traditionally known for supplying lower-cost antimicrobials to low- and middle-income countries, helping to increase access to, for example, anti-retroviral therapies for HIV/AIDS in sub-Saharan Africa during the 90s and early 2000s, in cooperation with international agencies such as The Global Fund, UNICEF and Gavi the Vaccine Alliance.

Given its share of the global market and position in global supply chains, the potential for Indian pharmaceutical companies to control AMR is significant. Their core role is to guarantee a reliable supply of high-quality antibiotics and prevent shortages. They can also expand their activities in antimicrobial R&D, particularly in the incremental improvement of existing products. With many hundreds of antimicrobial products in their portfolios, companies' efforts to ensure responsible use could also have a major impact, for example by educating pharmacists and doctors about the risks of resistance. The main challenge for these companies, however, will be to move beyond the traditional low-cost/high-volume generic medicine model, as this is seen as undermining strategies to control AMR through the responsible use and promotion of antibiotics.

### **A NEW TOOL: THE 1<sup>st</sup> ANTIMICROBIAL RESISTANCE BENCHMARK**

The 2018 Antimicrobial Resistance Benchmark is the first independent comparison of what pharmaceutical companies are doing to bring antimicrobial resistance under control. The goal of the AMR Benchmark is to identify good practices that are already being implemented by the industry as guidance for how to make further progress. By giving pharmaceutical companies public recognition for their actions on AMR, the Benchmark provides accountability as well as an incentive to expand their activities. It evaluates companies' activities in antimicrobial R&D and their antibiotic manufacturing policies, as well as the steps company take to ensure antimicrobials are available and being used wisely

The Benchmark has been independently developed by the Access to Medicine Foundation, funded by the Dutch and UK governments. The Access to Medicine Foundation is an independent non-profit organisation based in the Netherlands. It has more than ten years' experience analysing how pharmaceutical companies are addressing global health priorities and then using its results to stimulate positive change.

The Foundation builds consensus among stakeholders on what pharmaceutical companies are responsible for regarding specific global health issues. It uses a rigorous data-collection, scoring and evaluation process to analyse companies' policies and practices and identify best practices. The Foundation identifies opportunities for companies to contribute to issues such as AMR, in line with their individual portfolios and expertise.

In March 2018, the Access to Medicine Foundation is in India to meet with Indian pharmaceutical companies that are already actively addressing antimicrobial resistance (AMR) as well as with government representatives. The objective is to identify concrete opportunities for adapting business practices to match current best practice for controlling AMR: in the areas of R&D and incremental innovation, responsible manufacturing, and appropriate antibiotic promotion and access.

## INDIAN COMPANIES DEMONSTRATE WILLINGNESS TO ENGAGE

The Benchmark compares the actions of 30 pharmaceutical companies, including those with the largest R&D divisions, major market presence and specific expertise in developing new antimicrobials. Seven of the companies evaluated are from India: Aurobindo, Cipla, Dr. Reddy's, Lupin, Macleods, Sun Pharma and Wockhardt. All seven produce lower-cost antibiotics; low price is a key enabler for expanding access to these mainstays of modern medicine.

Looking across the group of Indian companies, the level of engagement in AMR is varied. Where some companies are engaged in educating healthcare professionals on the risks of AMR, others are actively monitoring where resistance is emerging and spreading, sharing their results with the Indian health community. Four out of the seven are also active in antimicrobial R&D, including to develop new vaccines and paediatric antibiotics.

### R&D: adapting antimicrobials

While traditionally not known for their R&D activities, these companies have a crucial role in adapting products through R&D to achieve specific attributes. For example, by using their knowledge of the product's chemistry and usage, the companies can develop new doses or courses of treatment, or to adapt the product to improve adherence by specific populations, such as children. Several Indian companies are already active in this area, as demonstrated by the Benchmark's analysis. Here are some examples:

- **Aurobindo** has developed a new combination medicine for HIV/AIDS: a fixed-dose combination of dolutegravir/lamivudine/tenofovir disoproxil fumarate. The company is using licensing agreements to increase access to this medicine. It is also planning its first vaccine launch in 2018, of a pneumococcal conjugate vaccine.
- **Biological E** is working with GSK and Wellcome Trust on a new vaccine for typhoid/paratyphoid fever (Enteric fever). The bacteria that cause this disease show high rates of antibiotic resistance in India.
- **Cipla** is adapting an HIV/AIDS medicine to make it more child-friendly: it is developed taste-masked granules of an abacavir/ lamivudine/lopinavir/ritonavir combination for paediatric patients with HIV/AIDS in collaboration with the Drugs for Neglected Diseases initiative (DNDi).
- **CSIR-IMTECH** is partnering with Johnson & Johnson and the Institute of Microbial Technology (IMTECH) to explore potentially more effective, safer, oral treatment regimens for multidrug-resistant TB (MDR-TB), as well as new molecular entities to treat all TB patients.
- **Macleods** is developing ten new formulations of tuberculosis medicines for children, in collaboration with TB Alliance. Many are dispersible tablets, which are easier for children to take.
- **Merck & Co., Inc.** is in a joint venture with Hilleman Laboratories and Wellcome Trust specialising in vaccine development, including for Shigella, which causes diarrhoea. With Orchid Pharma Ltd., Merck & Co., Inc. is working on the discovery, development and commercialisation of new agents to treat a range of bacterial and fungal infections.

- **Wockhardt** is developing new antibiotics that target some of the highest-risk bacteria for AMR. This includes broad-spectrum antibiotics for treating the superbug MRSA, among others.

### Stewardship: educating India's doctors about AMR

The misuse and overuse of antibiotics is driving the emergence of AMR. To change how these medicines are used, one of the first steps is to raise awareness of AMR and build knowledge about how to prevent resistance from emerging. Pharmaceutical companies have a rich depth of knowledge and expertise about antimicrobial resistance and can play an important role in changing prescribing behaviours among healthcare professionals. The Benchmark identified several examples of how pharmaceutical companies bring information about AMR to healthcare professionals in India:

- **Cipla** is raising awareness about AMR among healthcare professionals in India. It uses a mix of roundtables, panel discussions and meetings.
- **GSK** uses various methods to reach healthcare professionals with AMR-related information in India, including webcasts and meetings. It has covered a range of topics, including the management of community-acquired pneumonia and the role of antibiotics in managing dental infections.
- **Johnson & Johnson** runs physician training programmes on TB and MDR-TB in four regions of India: Ahmedabad, Mumbai, Nagapur and Patna. It also supports case detection and diagnosis through an e-health application.
- **Wockhardt** has established a fleet of mobile clinics that provide treatment and raise awareness of AMR in India. They provide diagnosis, treatment and referral services, as well as information about, for example, vaccinations, HIV/AIDS and TB infections, as well as safe water, hygiene and sanitation.

### Tracking resistance as it emerges and spreads

Curbing AMR depends on knowing which pathogens are developing resistance and where. Yet there are major gaps in this knowledge globally, with countries having differing levels of capacity to gather and harmonise data. The pharmaceutical industry can make an important contribution in this area. The Benchmark found that nine of the 19 companies reporting such efforts are running or supporting 19 AMR surveillance programmes across 147 countries, including in India:

- **Cipla** is gathering data on drug-resistant pathogens in Indian hospitals, specifically in Intensive Care Units. Its pilot programme surveyed physician's about the prevalence of gram-negative pathogens with varying levels of resistance, including pan-resistant bacteria that can no longer be treated with antibiotics.
- **GSK** and **Pfizer** run separate international surveillance programmes focused on AMR trends, which also gather and report on trends in India
- **Johnson & Johnson** is running a 5-year surveillance programme to assess the evolution of drug resistance among the bacteria that causes tuberculosis.
- **Wockhardt** is engaged in tracking antibiotic resistance in hospitals across India among more than 20 different bacteria. It tests samples at its own research center to establish their susceptibility to antibiotics, and to explore any mechanisms of resistance.

### Conclusion

India has some of the highest antibiotic resistance rates globally, as well as high rates of infectious disease. Infection prevention and control, as well as antibiotic stewardship and efforts to provide appropriate access to antibiotics are top priorities for bringing down the disease burden and controlling

AMR. Resistant pathogens, once they have emerged, can spread globally. Tackling AMR in India will have a global impact.

Where bacterial infections occur, pharmaceutical companies have a role to play in ensuring that a reliable supply of the antibiotics is in place, and of high quality. Companies can support the responsible use of antibiotics (known as stewardship) by educating doctors and the public on the risks of AMR. Companies must also take comprehensive and consistent actions to ensure antibiotics are manufactured responsibly, at their own plants and their suppliers', to ensure active antibiotic ingredients are not released into soil and water.

The AMR Benchmark has found evidence of good practices by Indian companies in all of these areas, showing a willingness and a capacity by these companies to control AMR. All companies have potential to do much more. For generic medicine manufacturers in particular, the challenge is in adapting the traditional low-cost/high-volume model to ensure antibiotics are used and promoted responsibly. Information sharing is a critical enabler for good practice to spread across the Indian pharmaceutical sector, and to help coordinate efforts for curbing AMR.

India is home to more than a billion people facing rising rates of resistance and an increasing risk of infectious disease. These factors are driving demand for access to treatment. This brings an opportunity for manufacturers based in India. This demand must be met responsibly, to ensure antibiotics are used wisely. When this is achieved, India-based manufactures will be a core pillar in the public health ecosystem now working to provide effective antibiotics to Indians today and into the future. The result will be the global preservation of life-saving antibiotics, and will not only impact on the treatment of infectious disease, but also on the safety of organ transplants, cancer therapy, surgeries and a host of other treatments that depend on antibiotics and antimicrobials.

#### **About the Access to Medicine Foundation:**

The Access to Medicine Foundation, which publishes the AMR Benchmark, is an independent non-profit organisation based in the Netherlands. It aims to advance access to medicine in low- and middle-income countries by stimulating and guiding the pharmaceutical industry to play a greater role in improving access to medicine. For 10 years, the Foundation has been building consensus on the role of the pharmaceutical industry in improving access to medicine and vaccines. It publishes the Access to Medicine Index every two years, with the next Index due in late 2018.

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