

Antibacterial stewardship in India

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Executive Summary

Widespread abuse of life-saving antibiotics has led to the emergence antibiotic-resistant bacteria which significantly threaten public health, food security, and the world economy. India is the largest global consumer of antibiotics, and the Indian Ministry of Health and Family Welfare recently finalized a comprehensive National Action Plan (NAP)ⁱ to tackle antibiotic resistance. This policy memo provides actionable recommendations to complement this plan. Firstly, education of medical personnel and patients, in partnership with national media can help raise awareness about the consequences of antibiotic misuse. Second, the government must enact regulations on antibiotic use in human and veterinary medicine, and, crucially, enforce stringent regulations for waste management from both antibiotic manufacturing and sewage treatment plants. Finally, incentivizing local technology through government and international agencies can aid the development of diagnostic tests essential for antibiotic conservation.

**To: Mr. J. P. Nadda,
Hon'ble Minister of Health and Family Welfare**

Re: Antibacterial stewardship in India

Antibiotic resistance (ABR).

While antibiotics constitute a critical line of defence against bacterial infection, excessive and improper use of this vital technology undermines its effectiveness by promoting resistance among disease-causing bacteria. An infamous example is the emergence of the 'New Delhi' superbug in 2008, and its rapid spread across the globeⁱⁱ. Moreover, the increase in ABR is outpacing the rate of new drug development, and an independent UK review predicts a death toll of 10 million people per year by 2050, with over \$100 trillion in costs, if ABR is not aggressively addressed.ⁱⁱⁱ Given the devastating potential implications for human health, the world economy, and food production, ensuring the efficacy of this global common resource is paramount.

India currently suffers bacterial populations with high levels of resistance to all major classes of antibiotics. Antibiotic use has almost doubled in the past ten years^{iv}, making India now the largest global consumer. The government is well aware of the urgent need for investment in public health infrastructure, reform of state and national regulations on antibiotic use, and awareness raising education campaigns.

Source 1: agriculture. India is currently the fourth largest user of antibiotics in livestock agriculture, mostly as "growth promoters" in the poultry and swine industries^v (since adding sub-therapeutic doses of antibiotics to animal feed increases the efficiency at which the feed is converted into muscle mass). By 2030 this use is projected to double, due to increasing adoption

of intensive farming methods to meet popular demand for animal-derived foods. ABR is currently widespread within herds and places significant burden on animal health, farm viability, and food production. It also poses severe threats to human health, as 18 of the 27 classes of antimicrobials commonly used in animals are important for human medicine^{vi}. One study found 100% of tested chickens harboured infections resistant to the antibiotic sulfadiazine, and resistance to the 'last-resort' antibiotic colistin is also widespread^{vii}. ABR in animal populations may be transmitted to humans through direct contact, or through consumption or handling of contaminated animal products^{viii}. Industrial farms furthermore cause high levels of antibiotic residue in surface and groundwater, as up to 90% of antibiotics fed to cattle, swine and poultry are excreted intact^{ix}.

Source 2: human misuse. India is the foremost consumer of antibiotics for human health. Medical advice is unaffordable for a significant proportion of Indians, who must rely heavily on over-the-counter (OTC) medications from pharmacists, which are frequently used improperly. Even with prescriptions, lack of adherence to dose schedules and futile antibiotic use for viral infections contributes to ABR--either by failing to eliminate the infection but providing pathogenic bacteria exposure to the antibiotic, and/or by disrupting the populations and genetics of the body's existing bacterial flora, respectively. In 2012, FDA (India) canceled or suspended licenses of nearly 500 pharmacies in the Aurangabad division, that were dispensing drugs without prescriptions and/or without a pharmacist present, in addition to educating retailers through district-level meetings. These regulatory efforts by FDA (India) with non-compliant antibiotic dispensing are steps in the right direction^x. Still, 58,000 infants in India were infected by superbugs in 2013^{xi} as a chilling reminder of the urgency and priority of tackling ABR.

Source 3: water contamination. Rapid expansion of India's pharmaceutical industry has made it the second largest drug manufacturer worldwide. But it has also led to contamination of surface and ground water with antibiotic residues throughout the country. In India's drug manufacturing capital, Hyderabad, researchers reported a daily release of 45kg of ciprofloxacin from a single plant^{xii}, leading to unchecked growth of antibiotic resistant bacteria in downstream sediments. Even after treatment, water-borne ciprofloxacin levels exceeded human therapeutic blood plasma concentrations by 3-fold^{Error! Bookmark not defined.}. Despite efforts to close 12 units in Hyderabad for violating regulations, a February 2016 report^{xiii} documents the ongoing failure to curb pharmaceutical pollution, and perpetuation of substandard conditions in drug manufacturing plants.

Existing Measures and Recommendations

In 2011, the Ministry of Health and Family affairs published a detailed national ABR policy (NAP) pushing for sweeping measures to contain OTC antibiotics and enhance ABR surveillance in hospitals. However, a significant proportion of Indians find medical advice unaffordable and rely heavily on OTC medications from pharmacists. Indeed, India sees more infant death due to drug inaccessibility than from drug resistance. To reconcile the NAP's implementation hurdles and the burgeoning threat of ABR, Indian medical societies, policy makers, and the WHO drafted the 2012 Chennai Declaration^{xiv}. They recommended a 'step-by-step' approach to phase out OTC antibiotics over five years, to maintain access to life-saving antibiotics while combating ABR. The Chennai Declaration mobilized concerned stakeholders and garnered significant international attention. In 2014, the Indian government classified third and fourth generation cephalosporins, carbapenems, newer fluoroquinolones as Schedule H1 drugs, requiring a special color coding on the pack and a prescription for sale^{xv}

The 2011 NAP briefly touched upon antibiotic misuse in seafood but not in other categories of livestock. The discharge of antibiotics into water bodies from pharmaceutical plants also requires immediate attention. Commendably, the proposed 2017 NAP on ABR covers a wider range of factors that drive ABR. Our policy memorandum is meant to serve as an addendum to complement the recommendations proposed by NAP 2017 strategic priorities:

Comments on NAP Goal 1 and 3: Improved awareness of ABR through effective communication and Reducing the incidence of infection through prevention and control. To raise awareness improved ABR awareness amongst all stakeholders, including clinicians, hospital staffs, policy makers, general public, as well as farmers is crucial. In addition to educating current medical students, there is need for continuing medical education for existing doctors. Physicians need to emphasize to their patients the importance of completing prescribed antibiotic courses. Raising public awareness on hospital and personal hygiene through formal education and media broadcasts can aid in civic engagement and promote shared decision making. Promotion by celebrities can prove to be very effective as well. Introducing the concept of ABR to young children through school books is a viable bottom-up approach to inculcate responsible practices. Bolstering NGOs' efforts can help improve basic sanitation and reduce infection incidence at the grass-root level.

Comments on NAP Goal 2: Strengthening knowledge and evidence through surveillance. Introduction of certifications of ABR-policy compliance as well as performance based-awards or incentives compliant clinics and pharmacies can help ABR containment. The general public would simultaneously need to be informed about the importance of these certifications. Preference for positive versus negative incentives depends on ease of implementation/enforcement, the

administrative burden on local government, and minimizing opportunities for unfairly gaming the system and corruption. Each local authority in India could be given the freedom to enact policies in favor of incentives that suit the community better.

In addition to traditional medical facilities, ABR surveillance needs to be extended to the Indian telemedicine market (set to double in size by 2020). A US-based study found that Teladoc physicians tend to prescribe broad-spectrum antibiotics at a 30% higher rate compared to a doctor's office. Finally, in the future, primary care doctors could benefit from training in algorithm-based distinction between bacterial and viral infections, which often present similar symptoms. The past decade has witnessed the development of fast and cheap techniques for facilitating these diagnoses (e.g. ^{xvi} and ^{xvii}); equipping microbiology labs with such technologies, and incorporating their use into the standard practice of primary physicians will lead to better patient outcomes and more appropriate use of antibiotic resources.

Comments on NAP Goal 4: Optimizing the use of antimicrobial agents in health, animals, and food. We consider three principal components to this goal. First, on the subject of antibiotics sales, we note that Schedule H1 did not cover several types of antibiotics such as gentamicin and piperacillin-tazobactam, and all older fluoroquinolones, beta-lactams, and microlides, which remain available OTC. Demand for these drugs has now increased to compensate for restricted sales of the stronger prescription antibiotics. Gradual phasing out of OTC sale of all antibiotics would be crucial, as bacterial cross-resistance is a commonly observed phenomenon where a single resistance gene renders an entire class of antibiotics ineffective^{xviii}.

The second component of Goal 4 concerns India's livestock industry, which has entered a phase of rapid growth. Damaging practices must be abandoned as soon as possible to mitigate

serious economic impacts in the future. Though some limits on antibiotic use exist for meat exported to wealthier countries, these standards need to be applied more uniformly to encompass domestic consumption. Banning medically important antibiotics from veterinary use must be a top priority for countries at every income level, and in India, the Prevention of Food Adulteration Act and existing collaborations between the Department of Animal Husbandry and the State Drug Controllers provide a framework to quickly implement such bans. Indiscriminate use of antibiotics to promote growth may be similarly regulated, though in this case enforcement poses greater challenges. The experience of countries such as the Netherlandsⁱⁱⁱ has demonstrated that impacts on agricultural productivity can be minimized with sensible policies at the farm level, and so the government must work with industry groups to devise ambitious country-wide regulations on livestock densities, nutrition, and facility sanitation. Animal vaccination programs, already supported by the Biotechnology Industry Research Assistance Council and the Department of Biotechnology's Animal Health Division, must be enlarged to reach more farmers while ramping up investment in thermostable feed-administered vaccines research^{xix}. The long-term economic benefits of these measures will initially be overshadowed by up-front costs, so government departments will have to allocate funds to support farm infrastructure development. These governmental interventions will not be popular with the pharmaceutical and agrichemical industries, so complementary consumer/retailer initiatives must be supported. The fast food industry, for instance, is both highly visible to consumers and extremely influential in the food system, and may be harnessed to reform standard livestock practices.

The third component of Goal 4 also seeks to address the antibiotic pollution of sewage water. Strong regulations need to be imposed on

pharmaceutical plants to ensure the pre-treatment of contaminated waste-water before release. This will benefit sewage treatment plants, whose organic 'activated sludge' technique for eliminating organic material is compromised by antibiotic-laden waste-water. And while sewage plants are not currently equipped to remove antibiotics, this can in fact be done very cheaply using bamboo-derived biochars and/or UV treatment^{xx} (although no maximum contaminant levels have been set by any international organizations for antibiotics, antibiotic levels 1000-fold lower than the minimum therapeutic dose is considered safe^{xxi}). Drug manufacturing and distribution are multilateral associations, and checking ABR is the responsibility of all stakeholders in that supply chain. India can leverage its status as a premiere low-cost drug manufacturer to impose strict environmental guidelines on multinational companies with the support of the United Nations antibiotic resistance summit.

Comments on NAP Goal 5: Promoting investments for ABR activities, research and innovations. A major road-block to the development of new antibiotics is the low return on R&D investment for the pharmaceutical industry. Phage therapy using special virus that specifically target bacteria has recently been shown to be a safe and effective alternative to antibiotics^{xxii, xxiii}. A National 'ABR Innovation Fund' to boost investment in early-stage research may be established to offer monetary prizes to companies and academic institutions that successfully develop new antibiotics or phage therapy, thus decoupling profit from final sales volume.

Comments on NAP Goal 6: Strengthening India's commitment and collaborations on ABR at international, national and sub-national levels. ABR tops the priorities of respected organizations such as USAID, DFID, Bill and Melinda Gates Foundation, and the Swedish International Development Cooperation Agency. India can effectively benefit from global will to curb ABR and draw in financial incentives and

mobilize its indigenous talent. The recent £10m Longitude Prize from the UK to reward the development of an accurate, rapid, and affordable diagnostic test to preclude unnecessary antibiotic prescription is an excellent example.

Conclusion

A single strategy cannot address the global problem of antibiotic resistant bacteria, and conserve antibiotics for a sustainable future. While the most comprehensive and successful programs to combat ABR have been implemented in small, wealthy nations (such as members of the EU), a developing country like India may still learn from both their successes and shortcomings. We have discussed strategies

for raising awareness among the public, and supporting medical practitioners in making accurate diagnoses. We stressed the need for effective surveillance and reporting of ABR incidence—both in the doctor's office and on farms where most antibiotics are consumed worldwide. The burden of agricultural antibiotics may be reduced through a variety of legislative measures and the education of veterinarians and farmers in best practices. Finally, we note that India's world-class pharmaceutical manufacturing is under-regulated in terms of its polluting externalities; while the industry, and Indian economy as a whole, may benefit from governmental incentive for drug R&D.

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At the time of writing, Cato Sandford was struggling through a physics PhD at New York University. Now that it's over he has more time to fret about industrialised livestock agriculture.