ANTIBIOTIC RESISTANCE

THE MAGIC BULLET'S TOLL

BY 2030

126 BILLION
defined daily dosages of antibiotics*

200%
more than in 2015*

BY 2050

10 MILLION
deaths/year**

More than those killed in the Rwandan genocide

BY 2050

$100 TRILLION
economic loss**

Which is over 15 times of Africa's GDP

What if a saviour turns into a killer? After 80 years of use, overuse and abuse of antibiotics—termed magic bullets—microbes have become resistant to them. Antibiotic resistant diseases are undoing the great strides in modern treatment. **VIBHA VARSHNEY** exposes a growing public health crisis

With reportage by
AGATHA NGOTHO | KENYA
ENGELA DUVENAGE | SOUTH AFRICA
PROSPER K KUORSOH | GHANA
VINCENT YUSUF | NIGERIA
VIOLET NAKAMBA | ZAMBIA
JENIPHER ASIIMWE | UGANDA
ALOK GUPTA | CHINA

Source: *Global increase and geographic convergence in antibiotic consumption between 2000 and 2015, *PNAS*, April 10, 2018, **Tackling drug-resistant infections globally: final report and recommendations, 2016, Wellcome Trust, HM Government, the UK

IN RURAL and urban markets of Nigeria, antibiotics are sold openly and without any prescription by hundreds of vendors such as Sadiq Abdullahi in Kpana Market in Utako district of Abuja. Abdullahi sells antibiotics like amoxicillin, ciprofloxacin, metronidazole, penicillin and clindamycin. It's an open, hot and filthy outlet. People crowd his shop as he sells these antibiotics at prices much lower than those of the registered pharmacy.

Vendors like Sadiq Abdullahi do not ask customers for prescriptions and sell any amount of antibiotics, disregarding treatment guidelines. Abdullahi sources his drugs from sellers based on the outskirts of Abuja. But these medicines do not even have the mandatory codes for verification of the country's National Agency for Food and Drug Administration. Despite his lack of medical qualification, Abdullahi is willing to sell antibiotics to Jumai Abdullahi, a young woman who believes—without medical diagnosis—that she is suffering from typhoid. She represents what is emerging as one of the major reasons for abuse of antibiotics—self-medication. But self-medication is only one of the many ways antibiotics are being misused and this is leading to resistance in microbes.

More than 70,000 people are dying across the world each year due to infectious diseases that have become resistant to antibiotics—the only line of treatment that could have saved their lives. By 2050, the death count will increase to 10 million each year, as much as those killed in the Rwandan genocide—one of the bloodiest in history. Since the development of antibiotics in the 1940s, these drugs have been used extensively. But over the years, the world is using them indiscriminately and inappropriately. Even low- and middle-income countries matched or surpassed consumption in high-income countries between 2000 and 2015. Attempts to combat this resistance only end up throwing new problems. It impacts our overall development agenda now, like the United Nations' Sustainable Development Goals (SDGs) which the world needs to meet by 2030. For example, SDG 1 relates to ending poverty, but this is unlikely as antibiotic resistance (ABR) or antimicrobial resistance (AMR) is striking the poor the most and they have to bear the high cost of treating resistant bacterial infections. Similarly, at stake is the SDG 2 to end hunger. Untreatable infections in food-animals are threatening food security. To achieve the SDG targets, the world has decided to focus on the poorest countries in Africa and Asia.

Unfortunately, it is in these continents that antibiotic misuse is rampant. People in Ghana too abuse the magic bullets. Ibrahim Ahmed, a resident of Wa Municipality in the Upper West Region, grinds tablets of penicillin and mixes it with honey. He feeds this mixture to his three children during the peak of the *harmattan*, a season that

A shop in Nigeria's Kpana Market selling antibiotics without any prescription

PHOTOGRAPH: VINCENT YUSUF

occurs between November and March, when children suffer from cough due to the dry and dusty wind. There is also a practice where people break open a capsule and sprinkle its content over a wound to avoid infections instead of taking it orally.

In Zambia's capital Lusaka, when Friday Malimakau gets a cold, he goes to the pharmacy where the pharmacist recommends antibiotics, antihistamines and antacids. Malimakau has been doing this for as long as he can remember. Similarly, Melody Malawo, also a resident of Lusaka, gets antibiotics whenever she feels feverish. "When I go to a hospital, they too give me antibiotics. So now I just go to the nearest pharmacy to save time," says Malawo.

Bad as the situation might be in Africa, India too fares poorly. A Drug Resistance Index (DRI) developed by researchers from Center for Disease Dynamics, Economics & Policy (CDDEP), Washington and Rollins School of Public Health, Emory University, Georgia was used to track global trends in effectiveness of antibiotic therapy in 41 countries in 2018. The result showed that high-income countries had the lowest DRIs and low-income and middle income countries had high DRIs. Among the 41 countries, India was the worst performer.

CONSUMPTION IS RISING. A paper published in *The Lancet Global Health* in November 2017 says that between 2007 and 2012, total sales rose annually in India. What's worrying is that this increase was driven by fixed-dose combinations (FDCs) most of which are not approved for sale. Of the 118 different antibiotic FDC formulations available in the market, only 43 were approved by India's drug regulator, the Central Drugs Standard Control Organization.

"Unapproved formulations figured prominently in sales figures—270 m units of the FDC antibiotics sold in 2011-12 contained unapproved formulations. The Indian government banned some unapproved FDCs, including antibiotic formulations, most recently in 2016. But the bans have been challenged by the industry and it appears the FDCs remain on sale," write Patricia McGettigan, a clinical pharmacologist at Queen Mary University of London and Allyson Pollock, a professor of public health, New Castle University, the UK, in *The Conversation*, a news website.

There is also lack of awareness about antibiotics and their correct use, as researchers from Pune-based CSIR-National Chemical Laboratory found when they assessed a cohort of 504 urban Indians for their knowledge, awareness and practice of antibiotic use and antimicrobial resistance.

According to their findings, published in May 2018 in *Current Science*, 47 per cent were unaware of the differences between over-the-counter drugs and antibiotics. One in four were unaware that dose-skipping could lead to ABR. One in 10 bought medicines without a prescription.

OTHER THAN MISUSE by humans, antibiotics are used in rearing animals and to protect plants from diseases. Pressures for a profitable yield with a quick turnover have led to a record increase in global antibiotic consumption—131,109 tonnes in 2013, whch is likely to increase by 52 per cent in 2030, according to research by CDDEP. This is far more than antibiotics used in humans.

South Africa, along with its BRIC partners (Brazil, Russia, India and China), has shown the largest percentage increase in antibiotic consumption this decade. Import data for antimicrobials between 2014 and 2015 estimates procurement for animal health at 23 to 36 per cent and for human use between 74 and 77 per cent. These figures were published in South Africa's first national *Surveillance for Antimicrobial Resistance and Consumption of Antibiotics Surveillance Report* in November 2018.

In China, as much as 70 per cent of antibiotics produced are used in animals. China consumed 162,000 tonnes of antibiotics in 2013, more than half of the global total. About 52 per cent was used on livestock, which is more than that used by humans. While China is at present culling pigs to control the African Swine Fever outbreak, there is a fear that antibiotic use will rise as the country is planning a policy to promote big animal farms. In India, similar misuse is visible in the case of poultry where farmers put one-day old chicks on antibiotics to prevent them from getting sick and also for growth promotion.

Antibiotics are being misused in other ways too. Victor Yamo of the World Animal Protection in Kenya explains how in dairy farming, antibiotics are being misused to treat mastitis—inflammation of the mammary gland—instead of following animal husbandry practices. Instead of cleaning the cowsheds, farmers use large amounts of antibiotics to prevent diseases. Reportedly, dairy farmers also use antibiotics to increase the shelf life of milk. Abubakar Bala Mohammed, who has spent 25 years in veterinary practice in Abuja, says that farmers use antibiotics without consulting professionals, and in many cases, they mix three to five antibiotics in the water and give it to animals.

Dooshima Kwange of the Department of Veterinary and Pest Control Services, Federal Ministry of Agriculture and Rural Development, predicts another scarcity scenario. Nigeria's population will reach 400 million by 2050. Kwange says there will be more pressure on livestock production to ensure food is available to everyone.

Though not much is known about the use of antibiotics in cultivation of crops in India, many are used for this purpose. India's Directorate of Plant Protection, Quarantine & Storage has approved the use of two antibiotics—streptomycin and tetracyline—in plants. However, instead of being used only to treat bacterial diseases, they are often mixed with pesticides and used liberally on even healthy plants.

Antibiotic resistance is making treatment of infectious diseases like leprosy almost impossible

PHOTOGRAPH: VIKAS CHOUDHARY / CSE

In 2019, Delhi-based non-profit Centre for Science and Environment (CSE) reached out to the farmers to understand existing practices of antibiotic use in crops and found that antibiotics are purchased routinely along with other agrochemicals. Jaswant Singh, a rice farmer from Fazilka in Punjab, used streptocycline on his crop despite absence of any infection. Interaction with farmers pointed towards a weaker extension machinery of state agriculture departments in the absence of which, the antibiotic use is guided by agrochemical dealers.

THE CONSEQUENCE OF this indiscriminate use is that the environment is accumulating antibiotic residues. In China, antibiotics are finding their way into the foodchain through waste products. More than 50,000 tonnes of antibiotics ended up being absorbed in the water and soil, found

CLIMATIC SPIKE

A warming planet will induce the development of antibiotic resistance

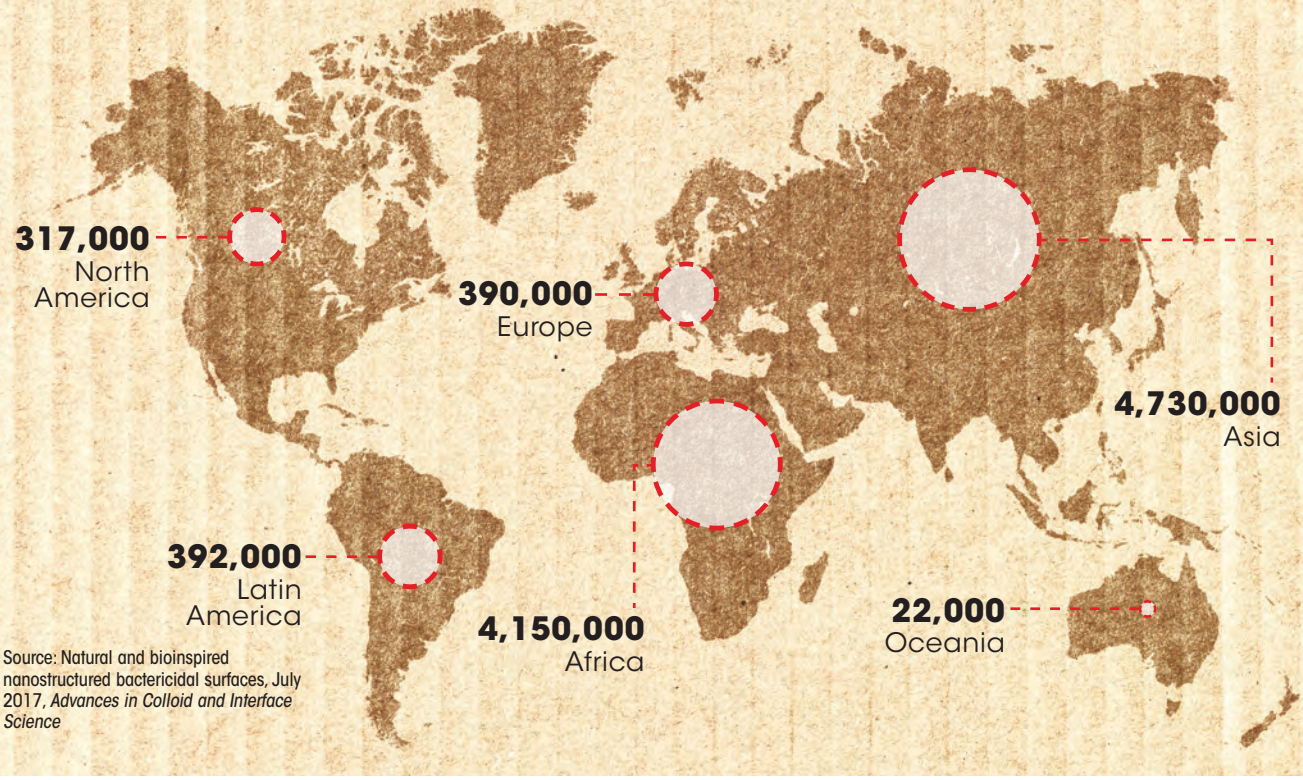
CLIMATE CHANGE is a new trigger for antibiotic resistance. Global warming is increasing the pace of reproduction in bacteria and leading to development of resistance. Researchers from the University Medical Center in Göttingen, Germany, conducted a 30-country observational study on six-year prevalence of carbapenem-resistant *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, multidrug resistant *E coli*, and Methicillin-resistant *Staphylococcus aureus* and found that these were more prevalent during the warm-season mean temperature. "These results reveal two aspects: climatic factors significantly contribute to the prediction of AMR in different types of healthcare systems and societies and climate change might increase AMR transmission, in particular carbapenem resistance," the researchers said at the European Congress of Clinical Microbiology and Infectious Diseases in Amsterdam, the Netherlands in April 2019.

Earlier, a study published in *Nature Climate Change* in May 2018 established this link. Epidemiologists from USA and Canada found higher local temperatures correlated with a higher degree of antibiotic resistance in common bacterial strains. They looked at antibiotic prescription rates and found that increased rate of prescriptions were associated with increased antibiotic resistance across all pathogens investigated. They then compared this database to local temperatures and found a strong correlation between higher local average minimum temperatures and antibiotic resistance. Increase in local average minimum temperature by 10^0C were found to be associated with 4.2, 2.2 and 3.6 per cent increase in antibiotic resistant strains of *E coli*, *K pneumoniae*, and *S aureus*, respectively.

"Warmer temperatures induce the development of antibiotic resistance by spurring enzymatic activity inside bacterial cells, which leads to increase in bacterial populations. Higher temperatures also aid the transmission of resistance genes among bacteria and increase bacterial-animal interactions for nutrients which allows new resistant strains to propagate," says Jyoti Joshi, Head-South Asia, Center for Disease Dynamics, Economics & Policy, New Delhi. Notably, both climate change and antimicrobial resistance are listed among the top 10 global health threats by the World Health Organization.

SPREAD OF RESISTANCE

Asia and Africa will account for 88.8 per cent of AMR deaths



Source: Natural and bioinspired nanostructured bactericidal surfaces, July 2017, *Advances in Colloid and Interface Science*

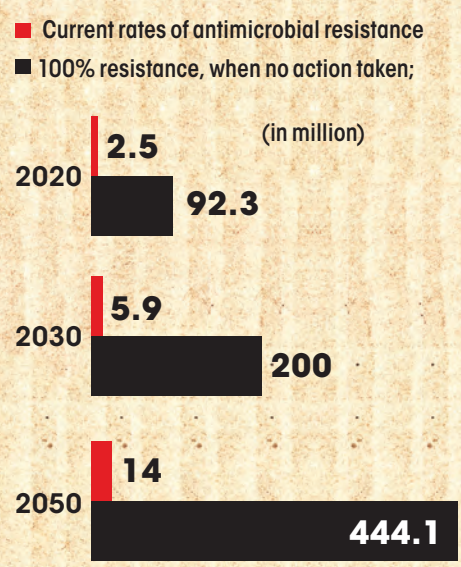
the Guangzhou Institute of Geochemistry of the Chinese Academy of Sciences. The average concentration of antibiotics in Chinese rivers was about 303 nanograms per litre, compared with nine nanograms in Italy, 120 nanograms in the US, and 20 nanograms in Germany. These levels are much higher than AMR industry alliance's safe standards—20-32,000 nanogramme per litre, depending on the antibiotic.

Data from surveillance systems shows an interesting picture of antibiotic use in China. The level of antibiotics in the waterways of the populous eastern region was six times higher than concentrations in the central and western regions. Southern regions consumed much more antimicrobials than those in North China. Reason: warmer temperatures in the South led to more outbreaks of diseases compared to north China's colder climate (see "Climatic spike", *p*33). An assessment of antibiotic pollution in rivers across the world shows similar scenarios. Researchers from University of York tested samples from 711 sites in rivers of 72 countries across six continents for the presence of 14 antibiotics. Antibiotics were found in 65 per cent of the samples. In Bangladesh, the antibiotic metronidazole was found to be 300 times the safe level. Trimethoprim, an antibiotic used to treat urinary tract infections, was found at 307 of the 711 sites tested. Ciproflaxacin frequently exceeded safe levels, surpassing the safety threshold at 51 places. The team found that safe limits were most frequently exceeded in Asia and Africa—primarily in Bangladesh, Kenya, Ghana, Pakistan and Nigeria. "Our data shows that antibiotic contamination of rivers could be an important contributor to AMR," says Alistair Boxall of the York Environmental Sustainability Institute.

Bacteria in the Ganga in Varanasi too are resistant to commonly used antibiotics, says a study released in March 2019. Varanasi region receives over 309.8 million liters of treated and untreated domestic waste daily, which has high levels of

Skeletals of antimicrobials

Rise in deaths due to AMR is stark if no action is taken by governments



Source: *Estimating the economic costs of antimicrobial resistance: Model and Results,* 2014, RAND Corporation, USA

antibiotics. Similarly, samples collected from two lakes in Bengaluru showed the presence of antibiotics and microbes resistant to 10 commonly-used antibiotics. The results showed that Bellandur lake also has high number of antibiotic resistant bacteria. This water is used for irrigation and while most residential associations test it for contamination, they don't get samples tested for the presence of antibiotics.

CONSTANT PRESENCE OF antibiotics in the environment leads to resistance. The revenge of the bug on human health is already visible in Nigeria, where epidemics of meningitis and inflammation of brain tissue are quite common. While meningitis can be caused by viral and fungal pathogens, three predominant bacteria—*Neisseria meningitidis, Haemophilus influenzae b* and *Streptococcus pneumoniae*—are responsible for more than 70 per cent of bacterial meningitis cases. Even after mass vaccination campaigns using a conjugate

"SOME BACTERIAL PATHOGENS ARE RESISTANT TO ALL ANTIBIOTICS"

Tobias Dörr, a microbiologist at Cornell University, New York, is researching on protecting beneficial microbes from antibiotics. He speaks to **Megha Prakash** on how antibiotic exposure can alter beneficial gut microbes

On how antibiotics alter gut bacteria

Broad spectrum antibiotics suppress microbial growth in the gut. Since our gut microbes play an important part in digestion, this reduction in microbial numbers can cause digestive problems like diarrhea. Also, the microbial community in the healthy gut is well-balanced, but the use of antibiotics affects some microbes more than others and disturbs the balance. Another side-effect is that antibiotics reduce the protective effect of the native microbiota. Normal gut bacteria help exclude dangerous bacteria (pathogens) from the gut by filling up the "niches" or the micro-environment that permits the growth of bacteria. If you kill of the bacteria in the gut, you open up more niches for pathogens to grow. A study has shown that the ability of the microbiota to recover from antibiotics differs between individuals (humans) and also between individual groups of bacteria. In some cases, the changes can be long-term. The consequences of such long-term alterations are poorly understood.

On how antibiotic resistance can be handled

It is a literally life-threatening issue. Antibiotic resistance is rising and there are some bacterial pathogens that are resistant to all available antibiotics—patients infected with such bacteria sometimes have little hope of recovery. This is especially dangerous since antibiotics are not only used to fight infections when you are ill, but also are essential for invasive procedures like surgery, chemotherapy and, for example, bone marrow transplants. For the last two procedures, antibiotics are given prophylactically because the immune system is damaged (chemotherapy) or suppressed to allow for transplantation (bone marrow). These procedures only work if, in the absence of the immune system, antibiotics can protect these patients. Antibiotic resistance is a very difficult problem to handle, and it requires collaboration of a wide variety of people.

On how to improve gut microflora

One of the most drastic consequences of realising that the microbiota plays an important role in gut health (especially after antibiotic exposure) is the ability to restore a "good" microbiota composition using fecal transplants—the transfer of fecal material from healthy patients to somebody with a disturbed microbiota. This practice has shown some positive results, but there are still challenges that have to be overcome.

vaccine, MenAfriVac, the National Centre for Disease Control's (NCDC) report in December 2019 shows about 2,770 suspected cases. Garba Iliyasu, an infection disease expert at the Aminu Kano Teaching Hospital and a Lecturer at the Department of Medicine, College of Health Sciences, Bayero University Kano says that the major challenge with meningitis is the increasing resistance to penicillin.

Antimicrobial Use and Resistance in Nigeria: Situation Analysis published in 2017, says that 30.8 per cent of all *N meningitidis* isolates, 66.7 per cent of *H influenzae* isolates and 45.2 per cent of *S pneumoniae* isolates were resistant to penicillin. Iliyasu says that this resistance is making it difficult for the poor to access the treatment. In Nigeria, resistance is not limited to meningitis. Adefolarin Opawoye, an infection diseases expert at the Aminu Kano Teaching Hospital in Kano, North-western Nigeria, says cases of resistant to antibiotics are growing in hospitals and some patients are resistant to all the available antibiotics in the country.

In patients who get infected by organisms that produce Extended Spectrum Beta Lactamases (ESBL), drugs like ciprofloxacin and augmentin no longer works. "Then you have to move on to much more powerful substitutes like piperacillin-tazobactam and meropenem. The cost of drug treatment alone rises to 100,000-150,000 Naira ($260-$420)," he says.

Cases of antibiotic-resistant Urinary Tract Infections (UTIs) caused by bacteria which produce ESBL is one of the leading causes of clinic visits by women in Nigeria. According to the 2017 AMR country report, 63 studies on UTIs conducted in 26 States and Abuja showed that the pathogens were resistant to all drugs commonly prescribed for UTI in the country. Resistance rates were highest for ampicillin and cotrimoxazole where most organisms show 100 per cent resistance.

In Zambia too, Jereme Kanika, a pharmacist says most of the antibiotics especially the first line drugs like penicillin are now failing to work on the patients because of being abused the most. "When penicillin fails to work on a patient, we introduce them to a more strong and expensive antibiotic," he said. Other than the cost of newer antibiotics, the extended periods of treatment too takes its toll on the patients. In Uganda, Joy (name changed) who lives is Wobulenzi, Luwero District in Central Uganda contracted an UTI from a dirty toilet. "The infection was itchy and painful and I bought some tablets from the pharmacist, but they didn't work on me and I changed medication. This time, I was given an ointment that I had to insert and some tablets. I got well but it took seven months," she says. In Uganda there are reports which show that antibiotics are becoming useless. A study *Antimicrobial-Resistant Infections among Postpartum Women at a Ugandan Referral Hospital* published in 2017 shows that at the Mbarara Regional Referral Hospital, of the 25 UTIs studied, nine of 11 (82 per cent) caused by Enterobacteriaceae tested positive for ESBL production (and therefore multi drug resistant) and 17 out of 22 (77 per cent) were resistant to ciprofloxacin, one of the most sought-after antibiotic to treat bacterial and fungal infections.

RESISTANCE IS STRIKING THE POOR THE MOST AND THEY HAVE TO BEAR THE HIGH COST TO TREAT RESISTANT BACTERIAL INFECTIONS

Alex Owusu-Ofori, head of the Clinical Microbiology Unit of the Komfo Anokye Teaching Hospital in Kumasi in the Ashanti Region of Ghana, says that about 70 per cent of the most common bacteria that cause urinary tract infections are resistant to the commonly-used antibiotics in some hospital. Patients with resistant infections remain sick for longer periods, stay longer in hospitals, pay more for their treatment and are more likely to get complications and die. Multi-drug resistant cases of tuberculosis are common and a cause for concern, says Angela Ama Ackon, deputy director, Ghana's Ministry of Health.

SOUTH AFRICA, LIKE many other countries, has entered a post-antibiotic era, according to Marc Mendelson, chair of South Africa's Ministerial Advisory Committee on AMR. Mendelson sees doctors

PHOTOGRAPH: EPA

^ Unrestricted use of antibiotics by poultry, fish and pig farmers and food producers is a serious problem in China

struggling to treat pneumonia and infections of the urinary tract, bloodstream, skin and soft tissue, all caused by bacteria.

Things are worse in Kenya as a study published in *PLOS* in February 2019 reveals. Researchers analysed 624 samples collected from Kenyatta National Hospital, situated in Nairobi, and found AMR rates higher than local and international reports.

Eveylne Wesangula, a member of the Pharmaceutical Society of Kenya, says there is not much data available on AMR and no action can be taken without data. Wesangula says the Ministry of Health has rolled out a surveillance strategy that will recruit 28 hospitals as sentinel surveillance sites by 2022. This will help the process of collecting and analysing data at the national level.

Before this, a study published in *BMC Infectious Diseases* in 2017 had shown that prevalence of antibiotic resistance in Africa was comparable with the rest of the world, but information is not available for 42.6 per cent of the countries in the continent.

Drug resistant diseases are on the rise in India too. Recently, the Indian Council of Medical Research (ICMR) published the annual report of the Antimicrobial Resistance Surveillance Network for January-December 2018. In the study, ICMR tested samples from 20 top medical institutes from across the country. From these centres, ICMR collected 60,497 isolates in 2018 to check susceptibility of several antibiotics to different bacteria groups like Enterobacteriaceae, typhoidal *Salmonella*, non-fermenting gram negative bacteria, diarrheal pathogens, Staphylococci and Enterococci and fungal pathogens.

The findings were again shocking. Take the case of Enterobacteriaceae. Only half (52 per cent) of the isolates were susceptible to piperacillin-tazobactam. As per the findings, maximum susceptibility was shown against colistin (92 per cent) followed by amikacin (68 per cent) and carbapenems (60-65 per cent).

Antibiotic resistance is making treatment of infectious diseases like leprosy almost impossible in India. This, when India had pledged to eradicate leprosy by 2019. Since 2014, India is a part of a growing list of countries, including Brazil and China, where leprosy can no longer be treated by the conventional multidrug treatment (MDT). What's worrying is that new patients are now showing resistance to MDT, whereas drug resistance was earlier experienced mostly by those who discontinued treatment. More than 13 per cent of the new cases and 44 per cent of the relapsed cases are showing resistance to rifampicin, one of the three drugs of MDT, say researchers with Stanley Browne Laboratory in Delhi, a WHO centre for surveillance of drug resistance in leprosy. The study was published in *Clinical Microbiology and Infection* in November 2015. "Rising cases of drug resistance since 2014, particularly among new patients, shows that resistant strains are actively circulating in India," says Mallika Lavania, a researcher with Stanley Browne Laboratory. So how are countries trying to combat resistance that seems to be a disruptive development for public health?

A new dose

How the world is gearing up to fight antibiotic resistance

A patient receives medicine for multidrug-resistant tuberculosis; about 78 per cent TB patients are multidrug resistant, according to the *Global Tuberculosis Report 2019*

PHOTOGRAPH: REUTERS

URMI BAJPAI, an associate professor at the department of Biomedical Sciences, Acharya NarendraDev College in south Delhi's Govindpuri and her students, are finding bacteriophages—viruses that can kill the bacteria—from soil samples collected from some of the dirtiest corners of the city. From the genetic sequences of these bacteriophages, they hope to find enzymes that could lead to cures for multidrug resistant TB—over half a million new cases of rifampicin-resistant TB were reported globally in 2018. Of these, 78 per cent were multidrug resistant TB patients according to the *Global Tuberculosis Report 2019*.

Gopal Nath, who is head of the department of microbiology at the Institute of Medical Sciences at the Banaras Hindu University, Varanasi, is testing bacteriophages through clinical trials to treat chronic wounds that don't respond to standard treatment. When tested on 20 patients with chronic non-healing wounds, seven patients were completely healed within 21 days. In the US, biotech giant PhagePro, is planning to test their product, ProphaLytic-VC, against strains of cholera.

Research on alternatives has become critical considering that many pharmaceutical companies have abandoned R&D in antibiotics. The *2017 Antibacterial Clinical Pipeline Report* of the World Health Organization (WHO) revealed that there are only a few innovative antibiotics in developmental stages.

As the world wakes up to the fact that failure to control AMR could lead to economic losses equivalent to US $100 trillion by 2050, action against antibiotic resistance is mounting both at the local and global levels. From finding new treatments to ensure existing drugs are used judiciously to reduce the inappropriate use of antibiotics, it is a multidimensional battle in which each of us has a role to play.

SOUTH AFRICA, WHICH reported its first case of MDR-TB before 2000, has found success in shorter treatment protocols. Usually, MDR-TB patients have to undergo treatment for 24 months, but South Africa has shifted to new oral drugs which translate to shorter, injection-free treatment of nine months. According to Norbert Ndjeka, director of drug-resistant TB, TB and HIV, in South Africa's department of health, 67 per cent of MDR-TB patients are now treated successfully compared to 40 per cent a decade ago. South Africa has also adopted decentralised healthcare since 2011 for TB patients. Now patients can access diagnoses and treatment close to where they live, and even receive it at their homes. "These days only very sick, bedridden patients or those who react badly to medication are admitted to TB hospitals," says Jacques Cronje, medical manager of Sonstraal TB hospital in Paarl, a town in the Western Cape province.

China too launched action on AMR way back in 2005 when the country launched two major networks to keep track of antibiotic resistance—China Antimicrobial Resistance Surveillance System (CARSS) and the China Antimicrobial Surveillance Network (CHINET). While the former collects data on antibiotic usage, the latter is a database of bacterial resistance collected from 960 million people. In 2011, China launched a special campaign aimed at "rational use of antimicrobials in healthcare systems". Authorities set targets to reduce antibiotic prescriptions—they should make up less than 60 per cent of all prescriptions for hospitalised patients, and less than 20 per cent for outpatients. For Mao Yuan, a doctor at Hegang People's Hospital in Heilongjiang Province, the policy changed the mindset of both medical staff and patients. "We realised as doctors that our role is not only to diagnose patients, but also patiently explain to them why they don't need antibiotics," she says.

To reduce heavy antibiotic use in animal farms, China has established an animal health administration system to monitor, supervise and provide assistance to farmers regarding the use of chemicals. In 2015, the Ministry of Agriculture (MoA) banned the use of four antimicrobials—lomefloxacine, pefloxacine, ofloxacin, norfloxacin in animals. Colistin sulphate was prohibited as a feed additive in 2017. China is be one of the biggest manufacturers of antibiotics and has taken steps to ensure antibiotic residues do not make their way into the environment. To control effluents released by the antibiotic manufacturers, China issued strict guidelines in the National Action Plan 2016. The norms made Environmental Impact Assessment more stringent.

But global action came only in 2015,

when it was recognised that AMR could derail the progress towards meeting SDGs. To ensure all countries had coordinated action on antibiotic resistance, WHO, along with the Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE) proposed the Global Action Plan on antimicrobial resistance at the 68th World Health Assembly in May 2015, which urged member nations to develop national action plans on antimicrobial resistance by 2017. WHO, FAO and OIE provided a common template which the countries could use and prepare their National Action Plans (NAP) suited to domestic conditions. By January 2019, 117 countries had prepared NAPs, and another 62 had plans in progress.

In response, China roped in 14 ministries to initiate a five-year national action plan from 2016 to 2020 in continuation with their existing plans. The 2019 annual report from CARSS shows a significant decrease in antimicrobial consumption in the country. Among inpatients in hospitals, usage decreased 0.5 percentage points from 36.9 per cent in 2018. The decadal comparison shows a much stronger picture; it declined from 59.4 per cent in 2011 to 36.4 per cent in 2018. The use of antibiotics in surgeries decreased from 41.5 per cent in 2011 to 21.9 per cent in 2018. However, antibiotic use in tertiary general hospitals remains high. "In the case of China, population and geographical size make the job of tackling the antibiotic resistance a challenging one. But the slowdown in antibiotics consumption is happening with the joint action by government, medical staff including doctors and even patients," C K Lee of the World Health Organization China Office told *Down To Earth*. But it took the country more than a decade to achieve this.

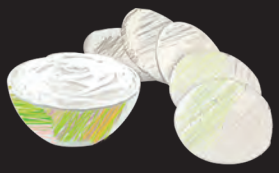
India too worked quickly in 2015 to prepare the NAP on AMR. It set up the Intersectoral Coordination Committee, Technical Advisory Group and Core Working Group on AMR for technical coordination and oversight in September 2016 and the National Action Plan on Antimicrobial Resistance (NAP-AMR) was released by this group on April 20, 2017. The National Health Policy, 2017, also addressed AMR and gave priority to the development of guidelines on antibiotic use. To promote appropriate use of antibiotics in humans, the Red Line campaign was launched in India in February 2016 to curb over-the-counter sale of antibiotics. Under this campaign, a red line is printed on antibiotic packages as warning.

AS OF JANUARY 2019, 117 COUNTRIES HAD PREPARED NATIONAL ACTION PLANS ON AMR AND ANOTHER 62 HAD PLANS IN PROGRESS

Most countries in Africa started working on AMR only after WHO's intervention. In November 2016, an AMR coordinating body was set at the Nigeria Centre for Disease Control (NCDC). In January 2017, the "One-Health" AMR Technical Working Group was launched to conduct a situation analysis on AMR and the NCDC developed the Antimicrobial Resistance National Action Plan (AMR-NAP). Inweregbu Stella of NCDC says the government conducted a situation analysis in 2017 and found there was no AMR laboratory surveillance system, no dedicated funding to control AMR and limited collaboration among the health, animal-health and environmental health sectors on AMR. Since then, NCDC has established nine surveillance sites to begin collection of AMR data.

Zambia too has prepared an elaborate Multisectoral National Action Plan, which was launched in November 2017. One of the focus areas of Zambia's NAP is to collect high quality data on the prevalence of AMR and drug resistant infections and on the use of antimicrobial medicines in humans and animals. The Zambia National Public Health Institute, the technical disease intelligence arm of the ministry of health is establishing a national public health laboratory network that will further improve the ability to monitor AMR. "We have mounted a very effective surveillance system, which at hospital level, routinely collects specimens to check how effective our drugs are to the various diseases," says Kennedy Malama, permanent secretary, Ministry of Health. This has already yielded results as data shows that while there is resistance to some antibiotic drugs in one

HOW TO REDUCE CONSUMPTION OF ANTIBIOTICS



Consume probiotics

Including probiotics in diet can help. It was seen that when infants and children consumed foods rich in bacterium like Lactobacillus and Bifidobacterium, they were at least 29 per cent less likely to need antibiotics.

Stop smoking

Cigarette smoke makes Methicillin-resistant Staphylococcus aureus (MRSA) more resistant to antibiotics and makes it more invasive and persistent. Exposure to cigarette smoke increases the rate of mutation in microbial DNA, resulting in microbes that are resistant to antibiotics.

Promote breastfeeding

Breast milk boosts immunity. It has been observed that infants breastfed for at least six months had fewer resistant bacteria in their gut than babies who were breastfed for a shorter period or not at all.

Support safe pregnancies

Antibiotics should be avoided during pregnancy. It has been observed that number of antibiotic resistant bacteria in an infants gut are higher if their mother consumed antibiotics during pregnancy. Even breast milk of these mothers had resistant bacteria which can be passed on to the child.

Embrace new technology

New technologies that can help reduce exposure to antibiotics are being developed. For example, tiny amounts of antibiotics embedded in corn-based nanoparticles help reduce the amount of antibiotic required. This also protects the microbiome in the intestines.

Embrace prophylactic foods

High-fiber foods like whole grains, beans, fruits and vegetables help the growth of healthy bacteria in the gut. They should be eaten after taking antibiotics. As a precaution, these high fiber foods should not be consumed while taking the antibiotics as this reduces the absorption of the drug.

Keep the house dust free

Presence of antimicrobial substances such as triclosan in indoor dust can make microbes resistant. This chemical is used in many consumer products such as toothpaste and hand washes and persist in the environment.

Consume foods that have natural antibiotics

Some foods like honey, garlic, mushrooms, onions and spices like turmeric have antibiotic properties and should be consumed regularly to reduce chances of falling sick. Molecules derived from cranberry fruits is said to increase the sensitivity of pathogenic bacteria to antibiotics.

Avoid foods that reduce the activity of antibiotics

Fruit juices, dairy products or alcohol reduce the body's ability to absorb drugs. Do not forget to maintain a gap of up to three hours eating these and antibiotics.

Get vaccinated

Vaccines can reduce the chances of contracting bacterial diseases and reduce the need for antibiotics. Where efficacy is proved, such vaccines should be used.

Source: Body Burden: Antibiotic Resistance, 2019, DTE/CSE

part of the country, the same drug continues to be effective in other parts. The country has also strengthened the surveillance system through the Zambia National Health Strategic Plan (2017-2021), which has proposed that laboratory services will be set in hospitals and health centres across the country. Additionally, the Ministry of Health also provides point of care testing to the rest of the health centres and some health posts as part of the National Biomedical Laboratory Strategic Plan 2018-2022. The country has also put in place systems to monitor the environment.

Ghana launched its National Action Plan in 2017, which will ensure collaboration between various ministries. The policy and action plan regulates efforts to improve awareness and knowledge of AMR; provide evidence-based knowledge to reduce the burden of AMR; reduce the occurrence of infections in establishments; optimise the use of antimicrobials in animal and human health; and, create an enabling environment for sustainable investment in AMR reduction. To back the implementation of the AMR policy, President Nana Akufo-Addo has asked the Ministry of Health and the Attorney-General Department to move selected aspects of the policy into legislation. Some of the features in the policy could become legislation and this may include rules regarding prescribing of antibiotics and good laboratory practices and restricting the use of antibiotics in animal husbandry. This action according to Angela Ama Ackon, deputy director, Ministry of Health is a display of high level of commitment by the government to combat the threat of AMR in the country.

THE INTERAGENCY COORDINATION

Group (IACG) on Antimicrobial Resistance was set up in 2016 by the UN to formulate a blueprint to fight against antimicrobial resistance. It recommended a "One Health" response in April 2019 to deal with the problem. One Health approach keeps humans, animals, the foodchain, the environment, and the inter-connectedness between them as one entity while taking step to fight the problem. Under this, while the countries will need to ensure that those who need antimicrobials, vaccines and diagnostics should not be deprived, at the same time, their use for growth promotion in animals and agriculture has to be phased out. The group also recommended that funds should be made available to increase innovation in new antimicrobials, diagnostics, vaccines and waste management tools.

In 2018, an assessment of NAPs by IACG pointed out that more than formulating action plans, implementation is a challenge, especially in resource-constrained settings of low- and middle-income countries. The group identified the major challenges in implementation—lack of awareness and

Thailand's health ministry is encouraging people to exchange their expired and old medicines for eggs

PHOTOGRAPH: REUTERS

political will, finance, coordination, monitoring and data and technical capacity. To ensure implementation, IACG suggested that interventions must be mainstreamed into broader health, agricultural and environmental projects. Availability of funds is also crucial for the success of the NAP. Moreover, increased regional cooperation is essential for the effective implementation of NAPs.

The world has taken a multipronged attack on AMR. In May 2018, the Global Antimicrobial Resistance Research and Development Hub was launched during the 71st session of the World Health Assembly to help countries decide the allocation of resources for R&D on AMR by identifying gaps and overlaps. It will also promote coordination among governments in the fight against AMR. In September 2019, India joined the partnership that has 16 countries, the European Commission, two philanthropic foundations and four international organisations (as observers). The hub proposes to develop a dynamic dashboard, establish operational activities and procedures and engage experts in ad-hoc expert advisory groups to understand the range of R&D incentives and gaps in the incentive toolbox.

In June 2019, FAO, OIE and WHO launched the AMR Multi-Partner Trust Fund to scale up efforts to support countries to counter the threat of AMR. The AMR Trust Fund has a five-year scope (through 2024) and has received an initial contribution of US $5 million from the Government of the Netherlands. The immediate funding requirement is US $70 million, which will provide technical support to countries designing NAPs and scale up local action.

To achieve this countries could also modify their NAPs based on learnings from within and outside the country. The Centre for Science and Environment, a New Delhi-based non-profit, is working with the Zambian government to improve implementation of their NAP. It has helped the country to reprioritise NAP based on current ground level scenario, implementation progress and available resources. It also provides an understanding of how each sector—human health, animal and environment—perceive each activity and what timeline each would prefer to implement them. The two stakeholders have also worked on AMR surveillance.

A five-year roadmap to phase-out antibiotic misuse in food-animal sector, particularly non-therapeutic antibiotic use and use of critically important antibiotics in therapeutic applications has been developed as well.

EVIDENCE OF THE rampant misuse of antibiotics is overwhelming. The question is how to ensure that medical practitioners and people know what is "right" for their health. We should ensure that doctors do

^ A child in Bangladesh gets an oral cholera vaccine, distributed by the World Health Organization

not over-prescribe; people do not misuse. In India, Gurugram-based Public Health Foundation of India showed that prescription rate of antibiotics in India is 412 per 1,000 persons per year. This is less than other countries like Italy (957 prescriptions per 1,000 persons), Germany (561 prescriptions per 1,000 persons) and the UK (555 prescriptions per 1,000 persons).

However, when it comes to third and fourth-line of antibiotics, India beats others. The percentage of prescriptions with cephalosporins and quinolones (38.2 per cent and 16.3 per cent) in India is significantly higher than in the US (14 per cent and 12.7 per cent). The third-line of antibiotics, which should be prescribed only at the hospital level, are prescribed at the primary care level in India. These antibiotics make their way into the environment and trigger resistance. It is clear that environmental triggers to antibiotic resistance have to be urgently controlled. There are many alternatives to antibiotics and they are cost-effective too. There are also methods to treat antibiotic residues in effluents from industry and homes and these should be installed.

An opportunity lies in SDGs. The environmental dimensions that support AMR are part of SDGs. Though antibiotic resistance has not been given adequate attention in SDGs, course correction is underway. In 2019, WHO proposed to track two priority pathogens in bloodstream infections, namely *E coli and Staphylococcus aureus* to serve as sentinels of progress. This indicator connects the Monitoring and Evaluation Framework put together by WHO, FAO and OIE.

This indicator is part of SDG 3(d), which is to strengthen the capacity of countries for early warning, risk reduction and management of national and global health risks. While using AMR as an indicator to track progress on SDGs is an important stepping stone, we must keep in mind the fact that only 10 years are available for efforts to take effect on the ground. However, the very fact that there are multiple areas in the SDGs where action on AMR can take place is an opportunity. DTE

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PHOTOGRAPH: REUTERS