NO OPTION

THE HIDDEN CRISIS AND HOPE FOR AMR

AMR DECLARATION TRUST

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No Option: The Hidden Crisis and Hope for AMR
AMR Declaration Trust

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Dedication

This book is dedicated to the memory of the millions of individuals who tragically lose their lives to antimicrobial resistance each year. We also extend our heartfelt dedication to the tireless scientists, global and regional leaders who relentlessly strive to combat the socio-economic challenge posed by AMR. Their unwavering commitment and efforts illuminate our path towards a future where AMR is no longer a threat to humanity

Preface

The AMR Declaration Trust introduces "No Option: The Hidden Crisis and Hope for AMR," an insightful journey into the global issue of antimicrobial resistance (AMR). This anthology, primarily composed of accounts from Indian patients confronting the debilitating effects of AMR, serves as a stark reminder that this challenge transcends national boundaries. It powerfully communicates that AMR is a universally shared problem, echoing across borders and impacting lives globally.

In this book, two dozen eminent doctors recount poignant narratives, shedding light on distressing circumstances where therapeutic options were scarce or non-existent. These stories illuminate the daunting daily realities that individuals and healthcare professionals worldwide face due to AMR. The book, written in plain, accessible language, aims to highlight the gravity of AMR, a silent pandemic that claimed approximately 1.25 million lives worldwide in 2019.

To provide a counterbalance to these sobering realities, "No Option" also features inspiring stories of hope and innovation. Notably, several of these groundbreaking drug and diagnostic development efforts originate from India, highlighting the country's leadership in addressing this global challenge. Contributions from domestic and international innovators, as well as organizations such as the Longitude Prize and AMR Action fund, showcase the power of creative, 'out of the box' thinking in devising solutions to the AMR crisis.

The intention of "No Option" is not to sensationalize AMR but to raise awareness about this significant global issue. We hope readers

will grasp the enormity of the situation and feel inspired to contribute towards finding potential solutions. The inclusion of stories by Indian doctors not only underscores India's commitment to leading the global fight against AMR but also emphasizes the universality of this challenge.

This book stands as a testament to the AMR Declaration Trust's ongoing mission to educate not just healthcare professionals, but the wider public about the urgency of the AMR problem.

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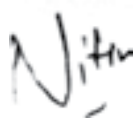
Dr Nitin Bansal

Foreword

Professor Dame Sally Davies

United Kingdom AMR Envoy, Former Chief Medical Advisor, UK

I am a doctor who retired from treating patients to work with the government. I wanted our government and every one across the world to make policies that helped people live better and longer. But I still remember many of my patients and they remain at the centre of my policy work.

Thirty years ago, my patient Kevin died only four years old of overwhelming infection with Pneumococcus. His infecting bacteria was resistant to all antibiotics. This tragic story has been repeating all across the world. Now though we have a vaccine against pneumococcus that works and saves lives every day. In addition, fewer antibiotics are used and this means that antibiotic resistance, also known as AMR with its associated bad outcomes, is less likely. Now 30 years on, had Kevin being vaccinated, he would have been unlikely to catch this infection and die.

Today, we know bacterial resistance to antibiotics (AMR) is on the rise, killing thousands every day round the world. But I am optimistic. We can solve this problem. Let me tell you why. Well, we can start with preventing infections by providing clean water and safe sanitation. Also, vaccination programmes play a key role in preventing infections.

Twenty years ago, I was told that the science to find new antibiotics was too difficult. Yet now we know new antibiotics can be developed

and found! I am optimistic that governments will fund the new medicines we need to save the lives of their citizens.

Ten years ago, only a few scientists were looking for new antibiotics but now we have more scientists working on antibiotics and also on novel and very different treatments, including monoclonal antibodies to treat serious infection or prevent infection, phage therapies that can infect and kill bacteria, heavy metals and so much more.

Five years ago from Britain, we challenged the world on diagnostic tests for AMR, putting up with the Longitude Prize. Now we are seeing new technologies developing that offer real opportunities to treat people's infections fast and with the right drugs.

Science is taking us into a new world where better diagnostics and better treatments will save lives and allow us to continue with the wonders of modern medicine from safe childbirth to effective cancer treatment. We can stop the rise of deaths but it takes more than scientists. It takes funding alongside scientists, companies and governments working effectively together. We need all of us to tell the governments that they have to do this.

We know that when the public rises up action follows. So, it is in the hands of each of us to make a difference - after all health is a human right and health is limited without effective antibiotics.

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LIGHT AT THE END OF THE TUNNEL

Bad Affairs of the Heart

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The allure of infectious diseases medicine lies in its complexity and the cerebral challenge it poses to medical practitioners. Our minds are constantly tested as we strive to solve intricate medical puzzles, employing our knowledge, experience, and instincts to unravel the mysteries that afflict our patients. Yet, despite our relentless efforts, there are occasions when we are faced with a sense of impotence, a gnawing feeling of inadequacy, as we are compelled to witness the slow and painful descent of a patient into the abyss of mortality. The following account is one such instance where my exhaustive repertoire of medical knowledge and experience in the realm of infectious diseases proved insufficient, and I was left to witness the heart-wrenching spectacle of a patient gradually succumbing to death.

On December 6, 2021, the life of a family changed dramatically when the husband, a hardworking carpenter and the sole breadwinner of the family, returned home from work with chest pain. He rested for a while, but the pain worsened, and he started to feel suffocated. The family rushed him to a local hospital where the doctor informed them that he was experiencing early symptoms of a heart attack and required immediate stent placement due to a blockage in his blood vessels. Fortunately, they had insurance that covered the surgery, and after two days, he was discharged. Although he experienced some chest discomfort and fever, he appeared to be recovering.

However, in the last week of January, he started experiencing a high-grade fever, cough, and chest pain again. The family took him to the nearby hospital, where the doctor diagnosed him with pneumonia and hospitalized him for a week, administering antibiotic injections. After he was discharged, the family was hoping for a stable and healthy future, but unfortunately, they were wrong.

One night in March,he suddenly had difficulty breathing, and the family took him to AIIMS, where he was diagnosed with critical breathing issues and admitted to the ICU on a ventilator. He was removed from the ventilator and shifted to a ward, but he still had a fever every day. This was when I, an infectious diseases specialist, was called. We explained that the fever could be due to an infection that had now spread to his heart (Infective Endocarditis). Blood samples were taken, and the test results showed that the bacteria causing the infection was *Pseudomonas aeruginosa*, which was resistant to all the antibiotics that the hospital was currently providing. We then conducted several tests and discovered that the infection was likely due to the stent placed in his heart.

Pseudomonas aeruginosa	
Ceftazidime	R
Piperacillin - Tazobactam	R
Cefoperazone - Sulbactam	R
Levofloxacin	R
Ciprofloxacin	R
Amikacin	R
Gentamicin	R
Meropenem	R
Imipenem	R
Aztreonam	R
Colistin	I
Others	MBL producer

We started him on the last option drug – Ceftazidime – avibactam, but his fever didn't subside even after two weeks. We suggested he undergo heart surgery (stent removal) as the infection was not getting controlled. After few days, he agreed, and post-surgery, he was shifted to the ICU where his fever finally subsided. However, a week after his release from the hospital, he developed a fever again and was taken back to the hospital. The doctors suggested continuing the antibiotic injections, and for a while, he appeared to be recovering.

Unfortunately, after two weeks, his condition deteriorated once again, and he was rushed back to the emergency room where he was once again admitted to the ICU with sepsis and organ failure. The blood samples showed that the bacteria had now become resistant the last of the antibiotics, and we had no option other than to put him on multiple antibiotics and treatments, including ventilator support and dialysis. Despite our best efforts, his health continued to deteriorate, and he eventually succumbed to the infection, leaving the family devastated.

This story is a poignant reminder of the importance of seeking medical attention promptly when experiencing chest pains or other unusual symptoms. It also highlights the devastating effects of antibiotic resistance and the need for more research and development of new antibiotics to treat these superbugs. Lastly, it illustrates how illness can quickly deplete a family's savings and leave them struggling to afford the necessary treatments.

Block Me If You Can – Dengue Virus

Dr. Ankita Baidya

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Mr. Roy and his family were living a comfortable life in New Delhi with a well-established routine when their 24-year-old son suddenly developed a high fever accompanied by chills. Concerned, they took him to their family physician who promptly started him on oral antibiotics and ordered laboratory investigations. However, after two days, the son's condition deteriorated significantly, with the development of a persistent cough, weakness, dizziness, and low blood pressure. Upon further testing, he was found to have dengue fever, with a low platelet count of 132,000.

On the fourth day, he developed a reddish rash over his legs, and his skin and eyes became yellowish in color. He also experienced severe nausea and was unable to eat. Upon arriving at the emergency room, he was found to have low blood pressure, low oxygen levels, and jaundice. Additionally, fluid had accumulated in his lungs and abdomen. Chest x-rays and ultrasound scans were performed, and all necessary blood tests were taken. It was clear that he needed to be admitted to the ICU.

Further blood tests revealed that his platelet count had dropped to 18,000, and his liver function tests were deranged, with a highly elevated bilirubin level of 7.8. He urgently needed a platelet transfusion, but his rare blood group (O negative) made it challenging

to find a compatible donor. After a six-hour search, a family friend with the same blood group came forward to donate platelets, and a single donor platelet transfusion was carried out. All possible supportive care was given, including oxygen supplementation. The son gradually recovered and was transferred to a regular ward after spending five days in the ICU. He continued to improve and was eventually discharged from the hospital, slowly regaining his strength over time.

Dengue fever is a challenging disease that currently has no approved vaccines or medications. Despite being known for many years, it remains a difficult-to-treat condition that requires prompt and intensive medical care. It is definitely a NO option Disease.

The Game of Bones – Superbug Prosthetic Joint Infection

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I am an infectious diseases physician. I treat all types of infections, but people don't typically seek out ID doctors for regular fevers. Other doctors usually call us when they have exhausted all other options, which is why we ID doctors are occasionally referred to as "no option" doctors.

We are attracted to this specialty of medicine because of the challenges it presents. As ID doctors, we solve puzzles and overcome challenges, but there are also times when we feel helpless. This is the story of one such case, where despite using all my knowledge and experience in infectious diseases, I felt helpless as I watched a patient slowly succumb to death.

Six months ago, I was consulted by an orthopedic surgeon for a patient. The patient was a chef in his 60s who had an excellent quality of life, except for severe pain in his right hip. He was diagnosed with osteoarthritis of the hip and underwent hip replacement surgery at another hospital. Everything went well for a month, after which he noticed some fluid leaking from the surgery site. Alarmed, he went to his surgeon, who found that the knee was infected. He tried a joint

wash and gave him antibiotics, but the discharge wouldn't subside. That's when the orthopedic surgeon consulted me, and I was called to the scene.

Bone and joint infections are a nightmare for both orthopedic surgeons and infectious disease physicians. Prosthetic joint infections are particularly difficult to treat, often requiring further surgeries and a prolonged course of intravenous antibiotics. Whenever I encounter a bone or joint infection, I remember Dr. Cherian, my orthopedic professor, who once said, "You may spit into the abdomen, but you should not even breathe into bones and joints." Orthopaedic surgeries must be extremely sterile, or else life is going to be miserable for the patient later, and of course, for the orthopedic doctor too.

In this patient's case, the only option was to perform a two-stage exchange operation. The surgeon would remove the infected joint prosthesis, and I would administer a prolonged course of intravenous antibiotics for at least six weeks. Then, we would wait two weeks to ensure that the infection had subsided before the orthopaedic surgeon could insert another joint. That was the plan.

The first surgery went well, and the orthopedic surgeon removed the diseased joint and surrounding tissue, which were sent for culture. When the culture results came in, the surgeon called me again, and I was shocked to see what bacteria had grown in the culture. There were three organisms: Carbapenem-resistant *E. coli*, Carbapenem-resistant *Klebsiella pneumoniae*, and Vancomycin-resistant *Enterococcus faecium*. Treating just one of these organisms would be a nightmare, but now we had to treat all three. Carbapenems are among our high-end antibiotics, and when bacteria become resistant to them, our options become limited and toxic. However, we couldn't just watch; we had to treat. So, we started the patient on a combination regimen of the antibiotics Ceftazidime-avibactam, Aztreonam, and Linezolid. These are intravenous antibiotics that have to be given through a special intravenous catheter called a PICC line. We administered these antibiotics for six weeks, followed by two weeks of an oral antibiotic called Cotrimoxazole.

Initially, the patient's infection markers returned to normal, and we discontinued the antibiotics, planning for a future operation. However, the patient's discharge reoccurred, and the bacteria had mutated. Both *E. coli* and *Klebsiella* were present, but the previous medication combination was ineffective. Based on susceptibility testing, we administered a combination of cotrimoxazole and ciprofloxacin, which temporarily alleviated the issue. However, the discharge later increased, and further testing identified a new *E. coli* strain that was resistant to the ongoing medication. We added the drug Tigecycline, which is known to cause severe gastritis and vomiting, and the patient could not tolerate it. Eventually, we decided on a regimen of Fosfomycin and Gentamicin, which are toxic drugs with uncertain efficacy, but we had no other choice. The joint continued to harbor multiple organisms, and we tried all possible combinations of medication, adding new drugs and changing regimens for six months. The financial burden of hospitalization was enormous, so we eventually treated the patient on an outpatient basis, with his son administering the drugs through the PICC line. The patient suffered from the side effects of these drugs and developed complications, which we managed with the help of a local small clinic. However, a month ago, he was admitted to our hospital again, too sick to be managed by the clinic.

Much had changed in this gentleman over the past 6 months. He was just a shadow of his old self. His hair had become sparse, and his muscles had lost most of their flesh. His blood pressure was down, and a blood culture grew yeast. We knew this yeast could only have come from the PICC line, so we removed it and started him on antifungal medicine, Caspofungin. However, he did not improve. Slowly, his hypotension worsened and he eventually succumbed. A day later, the yeast was identified as Candida guillermondi, which was resistant to Caspofungin.

A hospital-acquired infection made his life miserable, and another one took his life. This is not an isolated story. All infectious disease physicians will have similar stories to tell. Antimicrobial resistance (AMR) is not just an issue on paper; it is something that will affect us all. It's time to be aware and to act.

Superbugs and The Money Heist

Dr Saurabh Pandey

Consultant Physician & Specialist in Infectious Diseases.

Founder & Director

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Gorakhpur (UP)

I recall a 60-year-old lady from rural Uttar Pradesh with pre-existing diabetes and hypertension who presented to us with fever, burning, and frequency of urination, as well as altered behavior for a few days. She took a few painkillers and waited two days to see a local doctor, where she was administered multiple injections and bottles. Over the next three days, her abdominal pain reduced, but she began to develop altered sensorium with spiking fever.

She was shifted to a hospital in the city where she was diagnosed with a complicated urinary tract infection and multiple organ dysfunction syndrome. She was started on supportive medication and new antibiotics in the form of meropenem, amikacin, and teicoplanin, along with drainage of pus around the kidney. The estimated cost of antibiotics was 5000 INR per day. After three days, her blood culture grew a drug-resistant organism named *E.coli*, and only meropenem was continued.

Over the next four days of treatment, her general condition showed some improvement, and the family breathed a sigh of relief. The following day, she began to experience fever spikes, along with a productive cough, and a diagnosis of hospital-acquired pneumonia

was made. Laboratory investigations were sent, and the physician asked her to choose between a blood and sputum culture and a molecular test like PCR. Blood culture was chosen due to its lower cost. The new antibiotic combination included meropenem with polymyxin B, which cost about 11,000 INR per day. The family expressed concern over the financial crisis they were facing, although they were making arrangements with relatives. We cautioned them that something worse could happen, and they could consider other places to treat, but they denied any transfer. There was minimal improvement in the patient's condition, and after two days, the blood culture reported *Klebsiella pneumoniae*, which was resistant to all known antibiotics. The only option left was the latest antibiotics, Ceftazidime-Avibactam with Aztreonam, and the daily cost of this drug was around 18,000-25,000 INR, apart from other supportive medication and charges. They asked us to proceed with the possible treatment as they were about to receive some financial aid. After two days of treatment, there was some improvement in with reduced fever and improved well-being. Unfortunately, due to a lack of insurance coverage and adequate funds, the treatment was eventually discontinued. They took her to another remote hospital, but they still could not manage this expensive antibiotic. Despite the best efforts of the healthcare staff and rescue medications, she could not complete the treatment due to the expensive medication for the highly resistant organism for which there was "NO OPTION."

Sample	Blood
Organism	*Klebsiella pneumoniae*
Antibiotic	Susceptibility result
Piperacillin-tazobactam	Resistant
Meropenem	Resistant
Cefepime	Resistant
Amikacin	Resistant
Tigecycline	Resistant
Colistin	Resistant

This medicine will not work in vivo.

Drug-resistant gonorrhea in a teenager.

Dr Bikram Das

Consultant in Infectious Diseases, Apollo Hospital, Kolkata

We had a 19-year-old college student present to our clinic with complaints of a burning sensation during urination (dysuria) and intermittent whitish discharge from his penis (urethral discharge) for more than two weeks. Upon further questioning, he revealed that he had traveled to Thailand three weeks prior with his friends and had unprotected sexual intercourse with an unknown woman. Five days after the incident, he began experiencing these symptoms. He had taken multiple over-the-counter medications since then but did not find relief. He had received three doses of azithromycin 500 mg tablets in the last two weeks, cefixime 400 mg twice, amoxicillin-clavulanic acid 625 mg three times a day for three days, ciprofloxacin 500 mg twice a day for three days, and doxycycline 100 mg twice daily for the last ten days.

On examination, he was stable and afebrile. He had mild whitish urethral discharge without any ulcers or swelling. We advised him to collect his first morning urine and swabbed the urethral discharge to send for culture and other tests to determine the cause of his discharge. Other blood tests, including kidney and liver function tests, were within normal limits. The urine test showed plenty of pus cells and some bacteria. When the report came back, we discovered that he was suffering from a resistant gonococcal infection, which was why over-the-counter medications did not work and prolonged his suffering.

Organism: *Neisseria gonorrhoeae*	
Drug	Susceptibility
Penicillin	Resistant
Cefixime	Resistant
Ceftriaxone	Sensitive
Ciprofloxacin	Resistant
Azithromycin	Resistant
Tetracycine	Resistant

Considering this as a multi-drug-resistant *Neisseria*, we treated him with the only available drug that was susceptible. His symptoms were resolved in a few days, but the concern is the emerging resistance to multiple antibiotics, which will probably leave us with "NO OPTION" in the near future for the treatment of Neisseria infection. The prior exposure to the use of multiple antibiotics without seeking proper consultation could have contributed to this situation.

The Double Whammy from a Food Platter

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KIMSHEALTH, Trivandrum

Miss T had always wanted to explore India, with its vibrant culture and rich history. She finally got her chance and embarked on a holiday trip to North India. She enjoyed every moment of her trip, immersing herself in the local culture and savouring the delectable cuisine. However, little did she know that her joyous trip would soon turn into a nightmare.

Two days after returning from Delhi, Miss T began to feel sick. She developed vomiting and jaundice, and her condition worsened rapidly. She was taken to a hospital where she was diagnosed with severe jaundice and liver inflammation caused by the hepatitis A virus. But that was not all. She also had bacteria in her blood that caused typhoid, resulting in low blood pressure and further complicating her condition.

Miss T's condition continued to deteriorate, and she developed severe liver failure and slipped into a coma. Her family was devastated as they watched her fight for her life. The doctors informed them that she needed a liver transplant to survive, and thankfully, a relative came forward and donated a part of their liver. The transplant was successful, but Miss T had a long road to recovery ahead of her.

She spent 52 days in the hospital, and her medical bills amounted to a staggering 40 lakhs INR. She suffered physically, struggling to recover from the coma and becoming dependent on others for her daily activities. She received multiple blood transfusions and underwent dialysis to manage complications. The experience left her depressed and traumatized.

Miss T's ordeal highlights the importance of hygiene, sanitation, and vaccination. Both hepatitis A and typhoid are food and waterborne illnesses transmitted through contaminated food and water. They can be prevented by practicing hygienic food habits, boiling water, and other measures. Proper handwashing, sanitation, and hygiene can also prevent transmission through unhygienic practices like improper handwashing and open defecation.

It is worth noting that both hepatitis A and typhoid are vaccine-preventable, but vaccines are not widely used due to cost, lack of awareness, and availability. The majority of those affected by these illnesses are young children and young adults. While the illness may be mild and recoverable in two weeks, this could result in missed school or work.

It is important to note that there are no specific antiviral medicines for hepatitis A, and prevention is the best form of treatment. Additionally, antibiotic resistance among typhoid is increasing, and typhoid resistant to multiple antibiotics is commonly seen. Soon, we may face difficulty in treating common infections like typhoid. Hence, judicious use and disposal of antibiotics without contaminating water and food resources is important to prevent infections and the spread of drug-resistant bacteria.

Miss T's experience is a sobering reminder of the importance of hygiene, sanitation, vaccination, and the urgency to work towards the development of new antibiotics to save patients. Her story serves as a wake-up call to all of us to take responsibility for our health and well-being, and to do our part in preventing the spread of infectious diseases.

"A Black Fungus Horror Story"

Dr Ravi Teja

Registrar in Infectious Diseases, Apollo Hospital, Chennai

The summer of 2021 was a difficult time for many, but for this 50-year-old man with decompensated chronic liver disease and diabetes mellitus, it would be particularly challenging. He presented to the hospital with a fever that had persisted for five days and trouble breathing for two days. He was diagnosed with COVID-19 pneumonia and given corticosteroids, remdesivir, and tocilizumab to help him feel better. After 21 days, he was able to leave the hospital.

However, a few days after being discharged from the hospital, the man began experiencing blood in his urine and decreased urine production. The doctors did a biopsy and found that he had a fungal infection called mucormycosis. They gave him medicine called Amphotericin-B to treat the infection. However, his health got worse quickly, and he had to have surgery to remove both of his kidneys.

After 45 days of receiving Amphotericin B, he had trouble breathing and experienced a fainting spell. The doctors conducted a test and discovered that his heart was not functioning properly. Echocardiography revealed severe LV dysfunction with an EF of 45% (normally >60%). They believed that the medicine he was taking for the fungal infection was the cause, so they discontinued it. They prescribed a different medication called Posaconazole, but unfortunately, he did not improve and passed away.

If he had gone to the hospital earlier, his illness might not have gotten so bad. Additionally, if he had not been given too much steroid medicine or if his diabetes and liver disease had been better controlled, his chances of recovery would have been higher. Unfortunately, he ultimately succumbed to the infection because there was "No Option" to treat.

A yeast can brew your life!

Dr Nitin Bansal, Consultant, Infectious Disease,

Rajiv Gandhi Cancer Institute, Delhi

My wife, a 35-year-old homemaker, started experiencing stomach pain and nausea one night. She took painkillers and a vomiting tablet and went to sleep. Early the next morning, she woke up with severe stomach pain and vomiting. I took her to the emergency room of a large hospital where she was admitted. After initial blood tests and an ultrasound of her stomach, the doctors informed us that she had an infection in her pancreas due to gallbladder stones. They recommended that she be admitted to the ICU for a couple of days. She was then transferred to the ICU and started on various medications. She was given oxygen through a face mask for their efforts and care.

48 hours later, doctors informed me that she had gone into sepsis and her kidneys had failed, for which she needed high-end antibiotics and dialysis. I was informed that she was in critical condition and doctors were doing their best to save her. After a few days, she showed improvement and was able to sit up in bed. All tubes were removed and she started taking oral liquids. In the next few days, she was shifted to a room. I thanked God, the doctors, and the hospital staff for their efforts and care.

On the 3rd day of her stay in the room, she started having a high fever and her breathing became rapid, so she was shifted back to the ICU. Her doctors said that she had gone into sepsis again with organ failure. She was started on treatment, including ventilator

support and dialysis. However, later it was discovered that she now had a fungal infection for which treatment was almost impossible, even though she was on two anti-fungal medicines. The culture report is shown below. Despite the best efforts of the doctors and hospital staff, she lost her life due to an infection for which there was "NO OPTION".

Sample	Blood
Organism	*Candida auris*
Antibiotic	Susceptibility result
Fluconazole	Resistant
Caspofungin	Resistant
Amphotericin B	Susceptible
Micafungin	Resistant
Voriconazole	Resistant

Resistant: This medicine won't work. Susceptible: It may work, but in her case, doctors told her it will be difficult to give as her kidney had failed.

Reflections of a doctor in training: the resident's perspective!

Dr. Parul Kodan

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Tossing at night, tears, fears - an untold saga of a doctor dealing with the antibiotic crisis at a referral center.

The exciting journey of an overworked resident aiming to make a difference soon fades into an everyday struggle. The reality shock knocks back with exhaustion, and that turns into a struggle with the realities of everyday life in the complex system.

Doctor in the midst of an antibiotic crisis!

As a doctor in training, I was excited about the possibility of making a significant impact and saving lives, but the reality of the job soon set in. I was posted for my TB clinic rotation and I reviewed the latest guidelines and articles on advances in the management of tuberculosis and drug-resistant tuberculosis. I was ready with my N-95 mask and all geared up to help the large number of patients I anticipated in the clinic. Or at least, I thought I was prepared. However, on the first day, I quickly learned that this posting was more perplexing and challenging than I could have ever imagined.

Here, I present a page from the doctor's diary when she worked in the TB clinic:

June 1, 2017

Here comes a patient - a young girl who is 16 years old and on XDR treatment. XDR TB stands for extensively drug-resistant tuberculosis. It is a form of tuberculosis (TB) that is resistant to even the second-line drugs used to treat multidrug-resistant tuberculosis (MDR-TB). XDR-TB is caused by tuberculosis bacteria that have developed resistance to multiple TB drugs and is one of the most feared types of bacteria.

She entered the room with a result report but without a proper mask. I reminded her to wear one to prevent the spread of the resistant bacterium. She pleaded not to wear it, stating that it was suffocating and nauseating. I insisted that she wear it, but she remained unconvinced. Eventually, she put on the mask, but a few minutes later, she began vomiting. She explained that she was allergic to the mask material and that it caused rashes and vomiting. I was concerned because she had a sputum 3+ positive and had been around her school, playground, and younger sister without a mask. This could lead to the disastrous spread of the resistant bacteria. She still had a productive cough and should be isolated, but she dismissed this suggestion and claimed that her "chunni" (cloth from her dress) was an effective mask.

No book knowledge had prepared me to handle infection control measures for drug-resistant tuberculosis without isolation measures and prescribed masks. I was not aware of guidelines that required isolation in cases where the patient was carrying on with their daily routines and only had an occasional cough.

It was a real challenge to teach patients in the clinic to isolate or wear an effective mask all the time, but I can now empathize with what the other side of the table feels. Through my interactions with so many patients, I understood how difficult it was to tie a mask around one's face for work.

The stigma, the social outcast (this was pre-COVID, pre-mask era!), the discomfort, the suffocation - the mask was not a good companion for most of my patients.

I wondered, what is the way to stop resistant bacteria? Without effective cough etiquette, our society will continue to perpetuate MDRs and XDRs. Therefore, masks must be worn. But how? I had no answers.

Coming back to the young girl, I diligently went through her records and grinned as I found the cause of her vomiting and deteriorating health. She had pancreatitis and cholelithiasis. Yes, I now knew the cause. I referred her to casualty because this dehydrated and hypotensive girl required immediate fluids and early surgery. However, she was turned away from a busy, crowded casualty in a government hospital with so many patients at risk from this admission.

I called my surgeon friends and was told that as per operation theater guidelines, they couldn't operate on a case of a drug-resistant sputum-positive patient and had no post-surgery isolation cubicle. I referred her to a TB hospital for immediate IV fluids, medical management, and early surgery. The patient's mother called the next day and reported that she was experiencing severe vomiting and couldn't eat or drink. She was refused admission to the TB hospital due to a lack of beds. I referred her to another TB hospital with a letter stating the urgent need for admission. She was admitted, and I assumed all was well.

16 June 2017

She came for a follow-up 4 weeks later; she looked better but was very quiet. This talkative and chirpy girl who spoke endlessly even when she was ill, today looked dull and did not say anything. Her mother told her how she was discharged once she was better and called for a follow-up in the busy OPD. But one night, the girl deteriorated and they could not go to the distant hospital. However, for her daughter's life, they took her to a small nursing home near their house. Yes, the gall bladder was removed and she was symptomatically better...a happy ending to her crisis. She was managed well and she improved.

I thought 'all is well that ends well.' I was happy until she told me the girl's father, who was a taxi driver, sold his taxi for it. The girl's name was removed from the school and she joined her mother's tailoring job to earn money for the family. I missed a heartbeat. The girl would no longer go to school! The girl would no longer be a potential threat to her classmates. But of course, I did not want this!

As I lay awake that night, restless and unable to sleep, I couldn't help but feel the overwhelming sense of helplessness and inadequacy we face in dealing with the countless stories of suffering. The guilt of being unable to offer any meaningful assistance to a young girl simply because she had contracted a resistant bacteria weighed heavily on my mind. How do we handle these bad bacteria?

I experienced a sense of guilt, knowing that there was nothing I could do to help her. However, in an overcrowded environment where resources are scarce, what options do we have for patients who are potentially infectious with resistant bacteria, like the one she had? Is there no solution to alleviate their suffering? Even as everyone is striving to do their best, how do we address the social complexities and miseries caused by these resistant bacteria? Are we simply leaving patients to fend for themselves against these formidable opponents? Perhaps the best approach is to focus on finding solutions to prevent the growth of resistant bacteria, thereby averting the untold suffering they can cause.

Don't Breathe: A Pneumococcal Horror

Dr Vidya Krishna

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This is the story of X, a lovely four-year-old girl from Chennai. She was the only child to her parents and was born after a long period of infertility. Her parents had lost one boy earlier in the newborn period to a suspected blood infection (sepsis). Given this, her parents were always anxious about X's health. They meticulously monitored her diet, immunizations, health check-ups, weight, and development. Even if she had a minor cough or cold, they immediately rushed her to the doctor. They were often unhappy when the doctor just prescribed "cold" medicines and worried if they were missing "sepsis". They felt reassured only when the doctor prescribed antibiotics for X's illnesses. They often switched doctors because of this.

X presented to us with a severe chest infection. It had started with what appeared to be a viral infection, with symptoms of fever, cough, and a cold. X was promptly started on an antibiotic (Amoxicillin-clavulanate) syrup on day 1 of her illness. However, she continued to have fevers and her cough worsened by day 4. Her parents then decided to get her admitted to a hospital, and chose a physician who was their relative to care for her. After admission, X was diagnosed with pneumonia involving her left lung, based on blood tests and a chest X-ray. As per protocol, X was started on antibiotic injections with a drug named Ceftriaxone. Unfortunately, X received a low dose of the antibiotic due to improper calculation. She was given a brand that had a combination of two drugs (Ceftriaxone and Sulbactam),

and the drug dosing was inadequately calculated based on the total dose rather than only the Ceftriaxone component. All she needed was a good dose of Ceftriaxone, but instead, she received a low dose of Ceftriaxone and an unnecessary second drug in the form of Sulbactam. Within the next 4-5 days, X's condition dramatically worsened. She was now breathing hard and needed oxygen to maintain blood oxygen levels. The infection had spread, and she now had pus around her lungs. At this point, she was brought to our hospital.

She had fulminant sepsis upon admission. She required medication to maintain her blood pressure and had to be connected to a ventilator as she was unable to breathe adequately. A chest X-ray revealed completely white lungs on both sides (black lungs indicate healthy lungs as there is air in the lungs). A CT scan showed that she had cavities in her lungs and pus completely surrounding her left lung. The surgical team had to insert a large tube into her left chest to drain the pus and leave it in place so that the pus could drain continually. Despite receiving high-end antibiotics and all of this treatment, her condition continued to worsen, and she had to be put on lung bypass (ECMO). The costs of her ICU stay, surgical procedures, antibiotics, tests, and ECMO were enormous and out of reach for a middle-class Indian family. However, her parents persisted in supporting her care.

Both her blood and pus cultures grew *Streptococcus pneumoniae*, a common bacterial cause of lung infections in children. This bug is quite sensitive to "basic" antibiotics in almost 98-99% of cases. However, in X's case, most likely due to repeated antibiotic exposures and prior inadequate Ceftriaxone dosing, the bug was resistant to all but 2-3 drugs. The problem was that X needed a long duration of antibiotics for about 6-8 weeks because of her severe lung infection. We initially gave her an antibiotic, but it did not reach good levels in her blood. The ECMO machine has large pipes going from the patient to the machine and machine to the patient. The antibiotic got sequestered in the circuit and did not reach the patient. We changed to a second antibiotic, but we could not give it for more than 2 weeks as it causes a drop in blood counts and affects the nerves if used longer. We had only one more antibiotic left, but this is generally not approved in growing children because it can cause damage to bones

and tendons. We had "NO OPTION" but to give her the deadly drug to save her life, if not her limb.

She had to undergo one more surgery to completely strip her lung covering and remove all the pus. Finally, after three weeks on ECMO and enormous emotional and financial strain, X was shifted to the ward. We did further tests to make sure her immune system was good, as it was very unusual to develop such a severe and resistant infection after having received pneumococcal vaccines. Luckily, she had no immune defects. She was discharged after 10 days on the ward and received a total of six weeks of antibiotics. Fortunately, she had no side effects at discharge, but we continue to monitor her during follow-up.

This case highlights the problems associated with unnecessary antibiotic exposure and improper dosing of antibiotics. Both doctors and parents need to take the time to discuss the natural course of illness instead of relying on antibiotics as a cure-all for infections. Otherwise, it will only lead to antibiotic resistance with no options left to treat a truly deserving infection.

Super Pseudomonas and a broken foot

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I am an engineering student aged 20 years from South Tamil Nadu. My father works as a mason, and his only dream in life is to make his kids successful. He was diagnosed with diabetes 10 years ago, and although he takes medicine regularly, he doesn't do routine check-ups because of his busy work schedule. He is the only breadwinner in our family.

One day, when I returned from class, I saw my father lying in bed with a dressing on his right leg. Later, my mom told me that he had been injured at work and that the doctor had prescribed antibiotics and painkillers. We took him to the same doctor for regular dressing of the wound every other day. Despite taking the medication, the wound was not healing completely. The doctor tried different antibiotics each time we visited, but eventually, he suggested that we admit my father to the hospital and administer injectable antibiotics as his culture test showed that only injectable antibiotics would work. Following the doctor's advice, my father was admitted to the hospital and received antibiotics for a week, after which the wound showed partial improvement, and he was discharged.

But after five days, he started experiencing severe pain in his leg, along with increased swelling around the wound. This time, we decided to

take him to a higher center where there is a specialist in treating diabetic foot infections. The doctor examined him and decided to take a CT scan of the leg and admitted him for injectable antibiotics. The doctor said that his foot had a severe infection and we needed to remove the dead tissue, or else his life would be in danger. Though we were hesitant, we agreed. We were hoping that the medicine would work wonders. The next day, my father underwent foot surgery, and the doctor informed us that his bone tissue had a severe infection, as per the CT report, and had a lot of pus collection, which was all removed. The doctor said that he had sent the bone for culture, and we would decide after the culture reports were back.

Father was shifted to a ward after his surgery and was doing well. However, one day later, he began to feel very cold and when the nurses examined him, they discovered that he had a high fever. Suddenly, after three hours, he began to talk irrelevantly and the nurses rushed to examine him. They called the doctor, who determined that his blood pressure was very low. The doctor rushed in to examine my father and decided to move him to the ICU. We were slowly losing hope and were completely disheartened by the way things were going. Father was immediately transferred to the ICU. The doctors informed us that they had increased his antibiotics to the highest level and started medication to increase his blood pressure. We waited outside the ICU, hoping for improvement.

The next morning, the doctor came and examined my father, and asked us to meet him in his office. When we met him, he said that my father's blood pressure had improved, but his kidneys and liver had started to fail, and we needed to remove his right foot immediately if he was to survive. We couldn't believe what we heard. Immediately, I asked the doctor why we couldn't try expensive antibiotics, which I had googled by that time. In response, the doctor showed me a report with a heading that read "Pus Culture." All I could see were a series of "R"s alongside a long list of antibiotics given in that report. The doctor explained clearly that we knew the organism causing the problem, and that bacterium was called Pseudomonas. However, the issue was that every antibiotic available in the world was resistant to it, including the latest expensive antibiotics.

We felt as if the whole world was collapsing in front of us. However, we agreed to the doctor's plan, and he underwent one more surgery. The doctors removed his right foot below the knee. After two days, he started to show improvement and was shifted outside of the ICU. He got discharged after 10 days from there. Though we had his life back, we are still struggling financially and emotionally due to this no-option bacteria.

The Proteus and the Pandora's Box

Dr Soumya Sridharan

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It was a pleasant Sunday morning. I was greeted by my wife with a strong coffee and a beautiful smile. "How fortunate I am to be blessed with everything one could ask for," I thought to myself as I sat down with the newspaper on the balcony. I had a loving family, a good job with a decent salary, caring parents, and I owned a big house in a small town. I had everything a middle-class family man could want out of life. Little did I know that this Sunday would be the last one I spent with such complacency and peace.

My wife was having difficulty passing urine and had been running a fever for the past few days. She had tried an antibiotic that our neighbor had used for a similar problem, but she had no relief. As any caring husband would, I took her to a small clinic that was open on Sunday, unable to bear the distress she was in. The general practitioner gave her another course of antibiotics for five days and said she would be fine. I gave her the medicine that night and tucked her in to sleep. The next morning, she woke up with a broad grin, saying she felt much better. She was kind enough to make breakfast and see me off at the entrance as I left for work. However, on the fifth day, the fever came back with a vengeance, and my wife could not get out of bed. When I asked her if she had finished the course of medicine the doctor gave her, she said she had stopped after two days because she felt better. I reassured her that she would feel better by the end of the day as she had taken paracetamol. I took a day off from work and stayed with her. By evening, the fever hadn't stopped,

and she was drowsy. I rushed her to the emergency room at a nearby hospital. A battery of tests was ordered, along with a CT scan of her abdomen. They started her on saline and antibiotics. The doctor came to me and said in a serious tone, "Sir, your wife is seriously ill and will need an ICU admission. I'm afraid she has a kidney infection." I pleaded with the doctor to do whatever was best for my wife. He said it was a common infection, and she would be better in a couple of days. When I came home from the hospital, my 10-year-old daughter asked me what happened to Mama. I told her that Mama was down with a simple infection and would be back home in two days. I took the lunch my 80-year-old mother had prepared for her dear daughter-in-law to the hospital. I was in for a shock. I was not allowed to see my wife. The doctor informed me that my wife had become very sick, and her blood pressure had dropped. They had put her on a breathing machine and were supporting her with injections to maintain her blood pressure. They told me she was in a coma and could not speak to me. My mind became fuzzy with all the information given suddenly. I was aghast! Just a few hours ago, the doctor had told me she would be home in a couple of days, and now she was in a coma!

The scans done overnight showed that she had pus in her kidney, and I signed an emergency consent for the surgery to remove it. My heart was heavy, and my mind was numb with pain. I prayed that my wife would be fine. After three long hours that seemed like an eternity, the doctor came and said that the operation was successful, and my wife would be shifted back to the ICU. I felt so happy. The next day, she continued to have a fever and was still on BP medicines. I was informed that her urine culture, sent two days before, had come back and showed a bacteria with no medicines that were effective against the infection. I watched my wife wither away in front of my eyes with no drugs to cure her. There were no options for her to be treated with. Do I deserve this?

Name of the patient	XXXX
Age /Sex	38 years/F
Specimen	Urine
Organism identified	*Proteus mirabilis*
Colony count	>1,00,000CFU
Ceftriaxone	R
Cefotaxime	R
Aztreonam	R
Meropenem	R
Imipenem	R
Ciprofloxacin	R
TMP/SMX	R

Salmonella and the nightmare of shattered dreams!

Dr Suresh Kumar

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A 22-year-old Ms. Rani was ready to pursue her master's degree in the US and was a famous food blogger on YouTube. She had experienced different types of food at various venues. She cleared her exams and visa, and was now ready to move abroad in a few weeks.

All of a sudden, she developed a fever, loose stools associated with abdominal pain, and vomiting for two days. She self-prescribed T. Paracetamol and T. Bifilac, which provided some symptomatic relief for two days. However, her symptoms worsened after the third day, and she approached a pharmacy and took OTC medication (T. Azithromycin, T. Loperamide, and T. Paracetamol) for two days. After a week, she again developed a fever, fatigue, and abdominal pain. These symptoms worsened her condition and finally made her consult a nearby doctor.

He prescribed some antibiotics (Norflox-tinidazole), but there was no improvement. He ordered some blood tests, and her results for Widal, dengue, lepto, and scrub typhus came back negative. She went to another doctor who started her on T. Ciprofloxacin for three days. Following this, she was symptomatically better for the next seven days. However, after seven days, her symptoms worsened, and she

developed persistent fever associated with bloody stools, abdominal pain, nausea, and fatigue.

She was admitted to a specialty hospital emergency room for further treatment. Lab investigations were conducted and blood cultures were sent. The blood culture showed *Salmonella Typhi* positive, but it was resistant to ceftriaxone and azithromycin, which are the most commonly used antibiotics. Therefore, she was started on Inj. Meropenem, the highest and most powerful antibiotic. Later, she was diagnosed with intestinal perforation, a rare complication of typhoid in modern times. She was treated with Inj. Meropenem for two weeks. Although typhoid is simple to treat with just 7-10 days of oral antibiotics, people in 2023 are going back to the era of Typhoid Mary, where typhoid was difficult to eradicate and passed on to many people, killing some. Similarly, nowadays, people are transmitting resistant typhoid (with no oral option) to others, which might kill or make people suffer.

This lack of an 'oral' option for typhoid has killed Ms. Rani's dream of pursuing her career, as her parents not only cancelled her flight but also her study plans.

"No options not only kill patients, but also rob them of their dreams and cause them to suffer."

Infections require not only antibiotics, but also proper diagnosis and appropriate tests, which can be another hidden problem.

The TB diaries

Dr. Subhashree Samantary

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A 26-year-old female patient was on the verge of completing her master's degree in biotechnology. She was all set to finish her thesis project and start preparing for her final exams. But then one morning, she started having a disturbing headache and vomiting. She thought it could be because of exam stress and sleepless nights from exam preparations. But over the next few days, she also started having a mild fever more often in the evening, which would relieve on its own with a lot of sweating. She kept it hidden from her family as she did not want to add any more trouble to her already troubled family. After all, her father was a grocery shop owner who had just completed his one-year treatment course for drug-resistant pulmonary TB infection last month. It was a tough year for him as well as the entire family. He had to face financial and emotional difficulties, dealing with lots of side effects of the drugs, like vomiting, tingling sensation in legs, psychological disturbances, and multiple visits to the doctor to manage them.

But then again, she started having a fever and headache almost every day. All she wanted was to finish her exams well. She secretly consulted a local doctor who gave her some analgesics and an antibiotic (levofloxacin, as she could remember) for seven days. With that, she got some symptomatic relief. Gradually, she lost her appetite and lost weight drastically. This could not go unnoticed by her family. They thought it could be due to exam stress, but this much stress was unwanted. When her mother spoke to her, she told her about the health issues she had been having for the past month.

Then she agreed to go for a doctor consultation as the symptoms had started worsening and were already disturbing her studies. But the same night, she had multiple episodes of vomiting along with a fever and severe headache, for which she had to be rushed to our hospital emergency. She was stabilized in the emergency, and the next morning she was shifted to the ward. We examined her thoroughly. Everything seemed normal except for some amount of neck tightness. All the routine blood work-ups were done. The next morning, she again had a fever and could not lift her left leg. We convinced her family and performed a lumbar puncture, a procedure that is performed by inserting a specific needle into the spinal cord to obtain the clear fluid called CSF, which flows in and around the brain and spinal cord. The next day, we received the blood and CSF reports, along with the findings of physical examination and strong contact history. We had a high suspicion of TB brain for her. We also got her MRI brain done and sent the CSF sample for a specific test called GeneXpert Ultra, which is a single test that can detect both tuberculosis bacteria and preliminary drug resistance status within two hours. To confirm our suspicion, we obtained the reports of geneXpert Ultra, which were positive for TB, but fortunately, it was a sensitive strain. We counselled the family that this was just a preliminary investigation, and we would have to wait for higher drug susceptibility tests before starting appropriate treatment. However, before that, she needed to be started on basic drugs for drug-susceptible TB. We initiated her on the anti-tubercular treatment (ATT) provided by the government from the DOTS centre attached to our hospital (known as HRZE), along with the steroid dosage indicated for brain TB.

On day 3 of treatment, she started experiencing itching and rashes all over her body. This was suspected to be an allergic reaction due to ATT and it was immediately stopped. Then, she was given the individual drugs one by one, and it was found that one of the ATT drugs (pyrazinamide) was the culprit. From that time, her regimen was modified to HRE, which was still available at the DOTS centre free of cost. On day 7, she started experiencing sudden confusion and speech difficulties and could not identify her family members. By then, the drug susceptibility report for other drugs was with us, according to which she had drug-resistant TB. However, we had limited options

of ATT to treat her as she had developed TB meningitis, unlike her father, whose was a drug-resistant pulmonary TB. We put her on a combination of second-line drugs, which would effectively treat the brain TB, but her family had to purchase those drugs for her treatment. We made a few of the drugs available free-of-cost for her as long as she was hospitalized, but her clinical condition did not improve. We counselled her family that there were limited options available for the treatment of brain TB and there would be a slow response because of her delayed reporting to the hospital and extensive brain involvement that was confirmed in a repeat MRI brain. She remained hospitalized with us for 48 days, but it was a great psychological and financial burden for her family. Finally, they decided to discharge her from the hospital against medical advice, leaving us with 'NO OPTIONS' to treat her.

They sold everything, but in return, got nothing

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James was around 20 years old and from my native place, Guwahati. He was not very good at studies but was a brilliant singer. Naturally, he was extremely popular in his college. One day, he told his father, "Papa, I get tired very easily for the last couple of weeks." The father took him to a doctor who advised some blood tests. His hemoglobin came out to be only 5gm/dl, so he was referred to a hematologist. A bone marrow biopsy was done, and he was diagnosed with leukemia. The news was a bolt from the blue for the family. The doctor advised him to have a bone marrow transplant. His father was a teacher, and it was difficult for him to bear the huge cost of the treatment. He sold some of his ancestral property, withdrew money from his PPF, and came to Delhi. Before coming to Delhi, James was having some urinary tract infection for which he took some injectable antibiotics. In Delhi, he was admitted to a corporate hospital and underwent several tests. The doctors said that a bone marrow transplant might cure James of the disease. The bone marrow transplant was done, and the postoperative period was uneventful until the third day. The family was hopeful that they would go home soon. On the fourth day, James had a fever. Samples

from different sites were sent for culture and sensitivity, and empirical antibiotics were started. Unfortunately, he was not responding to the treatment. He was shifted to the ICU. He developed respiratory difficulty, for which he was put on ventilatory support. His kidneys started failing, for which dialysis was started. His medical bills far exceeded what was initially estimated. James' father started taking loans from whomever he could. Back home, James' friend started collecting money by crowdfunding, but this was not enough to meet the expenses. James's family did not have any option but to sell their house. In the hospital, doctors informed them that his blood culture grew bacteria that were resistant to all antibiotics that were tested. So, a combination of antibiotics was tried with the hope that the combination would work if not alone. His condition did not improve for several days. His blood pressure started falling, and there was no sign of recovery. James fought for 32 days. In the early hours of the 33rd day, James breathed his last.

James's family was devastated. They sold whatever they had, but they did not even have enough money to transport his mortal remains. The government and other social agencies came forward to help them, and finally, they returned to Guwahati with lots of loans to repay, memories of James, but no home to stay.

The story is an unfortunate but not rare one. The cancer and its treatment lowers immunity and making them prone for various infections. These infections are often caused by multi drug resistant organisms. These infections increase morbidity, mortality, hospital stay, need of organ support, need of second line of antimicrobials, increased duration of antimicrobial treatment and increase the cost of treatment exponentially which is already expensive.

It is difficult to calculate the cost of treatment attributable to antimicrobial resistance. However, in recent times, several cost analysis studies have been carried out in patients infected with MDR organisms. A retrospective analysis in the USA showed that attributable costs were $30,998 for methicillin-resistant *Staphylococcus aureus* and $74,306 for carbapenem-resistant *Acinetobacter*. The cost of treatment for MDR infections was estimated to be $4.6 billion in

2017 in the US. According to the CDC, in the United States alone, antibiotic resistance could add about $1,400 to the hospital bill for treating patients with any bacterial infections. The CDC says that antimicrobial resistance adds a $20 billion surplus in direct healthcare costs in the United States.

According to different studies, it is projected that AMR could cost from $300 billion to more than $1 trillion annually by 2050 worldwide.

We also have limited national data regarding the increased healthcare costs due to AMR. A recent study on the health economics of multi-drug TB treatment in Mumbai found that an individual could spend two years of their total income to eliminate virulent TB bacteria. One family who participated in the study spent 25 lakhs in two years on various ATT, doctor fees, hospital stays, and other expenses. Another study estimated that the treatment cost of MDR TB is approximately 6.5 lakhs, which is quite high for many Indian families. Catastrophic costs, defined as costs exceeding 20% of annual family income, were experienced by 7% to 32.4% of drug-sensitive TB patients and by 68% of drug-resistant TB patients.

A statistical model estimated that human consumption of antibiotics in India would be 20 to 22 billion doses per year, and the economic cost due to AMR would be around 640 to 700 billion per year. Thus, AMR may reduce at least 0.5% of our total Indian GDP.

With an Angel, At Midnight

Miss Hena Parveen

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A man got out of a car, dressed in a blue short-sleeved top and pants, with a white lab coat. His dark blue tie was loosely worn, spectacles tilted to the side, and his greyish-white hair disheveled and shaggy. He wasn't expected at the hospital at 12 AM on Sunday. The parking lot was dark under a cloudy sky with occasional dim lights in the gloomy corners. He sprinted towards the entrance of the hospital building, glancing at a watchman sitting on a plastic chair, sleeping with his mouth hanging wide open. The LED lights on board on the top of the building flashed: "MIJ Hospital."

The man rushed in, and the glass doors opened. He walked towards the elevator and pressed the button for the second floor. His footsteps could be heard in the silence of the night. He opened the door of an office with a large nameplate that read "Dr. Arjun Nair." Quickly grabbing his stethoscope, he walked towards the Intensive Care Unit next to his office. The light in front of the ICU was dim, reflecting the expressions of a few people sitting on a couple of chairs lined up outside. They looked like a family: a man with a dark beard dressed in a plain green t-shirt and trousers, a woman dressed in a faded sari, barefoot, and a baby wailing in her hands. Dr. Nair pushed open the door, revealing the brightly lit intensive care room. Suddenly, he turned back, listening to the man outside calling his name. The family who was standing behind walked up to the doctor.

"We have been trying to reach you multiple times, doctor! Please-"

Dr. Nair put his hands on the shoulder of the man as if his gentle touch could wash away the perils facing the man and his family.

"Doctor, please come in quickly."

He was quickly interrupted by the nurse, who poked her head out through the partially opened door. The doctor patted the shoulder of the weeping man and said, "Don't worry, we will do everything possible to save your daughter."

Harishma, a girl of eleven years, was lying on the bed with a blue hospital gown partly covering her thinned-out hands and legs, and her bald head shining in the bright light of the room. A metal bracelet hung loosely on her hand, making way for an intravenous fluid line. She could barely open her mouth, which was now full of large wounds, making it painful even to drink a glass of water. The temperature recording in the bedside chart was so sharp and steep, like the rise and slope of the Himalayan peaks, that the doctor pondered.

"Where is the blood culture report?" inquired the doctor.

The team was waiting for the blood culture report from the microbiology laboratory. The report would direct Dr. Nair on the correct antibiotic he could select to save Harishma from the clutches of death.

Harishma was diagnosed with blood cancer a month ago. Dr Nair had injected her with powerful chemo drugs that would help destroy the cancer cells in her blood.

The doctor paced around the room, adjusting his tie and spectacles while looking at Harishma, who was trying to remain conscious. Suddenly, the printer buzzed, interrupting the doctor's deep thoughts. The nurses quickly stood up from their chairs. Even the angel in the picture on the side table seemed to turn her gaze towards the printer. However, the devil remained silent.

Within a few seconds, a single piece of paper slid out of the printer. A nurse grabbed it, pinned it onto the clipboard, and handed it over to the doctor. He looked at the paper, his eyes transfixed, and wiped drops of sweat from his forehead with his hands.

The nurse shook her head, too, hopelessly.

"All of them resistant, sir."

"Yes, all of them are resistant. Is there no hope?" declared the doctor, his face frowning.

Dr. Nair handed over the clipboard to the nurse. All she saw on the white sheet were bold red "R" letters and the name "*Klebsiella*" written in bold italic font at the top of the page. No antibiotic can kill the *Klebsiella* bacteria brewing in Harishma's blood.

"Oh God, this *Klebsiella* is a superbug," the nurse announced.

Antibiotics have the power to kill bacteria and cure infections. However, if the bacteria are resistant to all antibiotics, they will survive, and the patient may die.

The doctor and the three nurses had no choice but to inform the parents that their child was going to die soon.

Dr. Nair walked out of the intensive care unit to find the family still standing there with their hands in the air, as if praying for a miracle. Their eyes widened as soon as the doctor walked up to them.

"And?" asked the father, his voice trembling. He sensed hope in his voice, but with the doctor's expression, he knew what had happened. The father's eyes swelled up with tears as he shook his head in disbelief.

"I am sorry," the doctor said.

"We have no cure."

Zika the zombie

Dr. A. Rajalakshmi,
Consultant in Infectious Diseases,
KIMSHEALTH, Trivandrum

I am a “gnat.”
I love to buzz
I thrive on blood
I spread what I get
But still seen as a menace.
Why?

I get blamed and batted
Dengue, chikungunya
Malaria, filaria, zika
There are just a few.
Why?

I, too, am a living being.
I need to survive.
I need to eat and drink.
I prefer human “resources”.
Am I to be blamed?

Now I have a new name.
Zika zombie
Do I look like a zombie?
Is it named just to rhyme?
I am a tiny little tot.
Am I to be blamed?

Yes, I give Zika
Mostly mild
Fever, rash, red eye
Aches and pains.
Quick recovery.

In pregnant women
Zika causes terror
There is a small risk of having abnormal babies.
For a healthy baby.
Counsel and screen

Zika the zombie
There are no antivirals to treat.
Treat the symptoms
No vaccine to prevent
Prevent me from biting.

I do cause diseases
For which there are no treatment
But, am I the problem?
With my increasing population.
I need to thrive and survive

I love stagnant water
I live and breed there.
Humans, help me.
To breed and multiply.
But why am I blamed?

Bring in hygiene.
Prevent waterlogging.
Use protective clothing.
And mosquito nets
I may slowly disappear
Gone would be the zombie days!

Melancholy of a mosquito

Zika is a virus that is spread by mosquito bites. It is generally a mild disease and requires treatment to reduce symptoms as there is currently no antiviral medication available against Zika. Rarely, it causes neurological complications in the general population. The major concern about Zika is during pregnancy, as it carries a risk of fetal anomalies. Pregnant women need to be careful in regions where Zika is common (endemic) and take measures to prevent mosquito bites. Women who develop fever and rash during pregnancy need to be carefully evaluated for possible causes, as there is a list of diseases that can present like Zika and can affect the fetus.

LIGHT AT THE END OF THE TUNNEL

Creating Ripples of Inspiration: The Chennai Declaration's Role in Addressing AMR Globally

Dr Abdul Ghafur, Coordinator, Chennai Declaration and Managing Trustee, AMR Declaration Trust

Antimicrobial resistance (AMR) has been recognized as a growing global threat that affects public health, animal health, and the environment. To tackle this complex and multifaceted issue, various national and international initiatives have been established, and one of the most influential ones is the Chennai Declaration. This initiative was launched in 2012 in India, with the participation of multiple medical societies and other organizations, to develop a roadmap to tackle AMR from the Indian perspective. The Chennai Declaration aimed to mobilize momentum towards the implementation of a national policy to control the rising trend of AMR by initiating efforts and consultation with all relevant stakeholders. The initiative played a significant advocacy role in the ban on the growth promotional use of colistin in 2019 and the formulation of the H1 rule on the over-the-counter sale of antibiotics in 2013 in India. The Chennai Declaration played a significant role in the formulation of the H1 rule on the over-the-counter sale of antibiotics in India in 2013, and then played a significant advocacy role in the ban on the growth promotional use of colistin in 2019.

The Chennai Declaration has been hailed for its impact on creating an attitude change among Indian medical societies, authorities, and even the international community towards AMR. After the

declaration, the medical community and Indian authorities became more receptive to the issue of AMR, opening up to discussions on the topic. The Chennai Declaration also helped the international academic community to change their approach towards India and other developing countries, becoming sympathetic and not critical. The efforts of the Chennai Declaration team undoubtedly sped up the publication of new regulations in India and also played a crucial role in convincing the government to initiate efforts towards the implementation of the National policy for containment of AMR. The impact of the Chennai Declaration was not limited to India. During a parliamentary discussion on AMR in the UK, the Chennai Declaration was highlighted as an example of positive progress. In addition, the Chennai Declaration has served as a model for other low- and middle-income countries (LMICs), inspiring experts to initiate AMR action in their own countries.

The success of the Chennai Declaration is attributed to the tireless efforts, perseverance, and persistence of the team behind the initiative. The Chennai Declaration is an excellent example of how persistence and perseverance can create a significant impact in addressing global health challenges. The initiative shows that even small, localized efforts can create ripples of change that can have a lasting impact on global health.

The Chennai Declaration also highlights the importance of collaboration and stakeholder engagement in addressing complex public health issues. The initiative brought together medical societies, representatives of governmental bodies, and other stakeholders, and their collective efforts resulted in significant progress in addressing AMR in India. The impact of the Chennai Declaration is not limited to India, as it has become a model for other countries to follow in their efforts to address AMR. The initiative has demonstrated that it is possible to make significant progress in addressing global health challenges through persistent efforts and collaboration among stakeholders.

In 2022, the AMR Declaration Trust was established as a public charitable trust that builds on the success of the Chennai Declaration

and provides a platform for stakeholders to continue working together towards the goal of addressing AMR globally. The Trust recognizes the need for a One Health approach and promotes collaboration across human, animal, and environmental sectors. The establishment of the AMR Declaration Trust is a significant step in the fight against AMR and demonstrates the continued commitment of stakeholders to addressing this global health threat.

In conclusion, the Chennai Declaration is a significant initiative that has created an attitude change among Indian medical societies, authorities, and the international community towards AMR. The initiative shows that persistence, perseverance, and collaboration among stakeholders can make a lasting impact on global health challenges. The success of the Chennai Declaration is a model for other countries to follow in their efforts to address AMR and other global health challenges.

Bugworks is a beacon of hope in the discovery of novel antibacterial agents

Santanu Datta & Vasan Sambandamurthy

Bugworks Research India Pvt. Ltd., Bangalore.

Antibiotics have revolutionized modern medicine over the last 80 years by protecting us from the deadliest bacteria we are exposed to in our daily lives. However, over the years, a majority of bacteria have evolved defense mechanisms to overcome the effectiveness of antibiotics that are currently in use. The situation is worrisome when treating infections caused by Gram-negative bacteria that usually thrive in the hospital environment and are notorious for exhibiting widespread resistance to multiple classes of antibiotics. The discovery and development of new antibiotics are scientifically challenging, and the entire development process can take 10-12 years and could cost upwards of one billion dollars to launch a new, differentiated class of antibiotic. Given the enormous costs and scientific barriers, pharmaceutical companies need more financial incentives to invest in developing new antibiotics, as they are typically used for a short course of treatment and are not as profitable as other drugs used to treat chronic conditions. The perpetual cycle of new antibiotic development owing to resistance development has been seen as a negative incentive for the industry, resulting in a significant slowing down of the antibiotic discovery process. These factors have contributed to a steady decline in the number of approved antibiotics due to inadequate investment, reduced interest in antibiotics R&D from big pharmaceutical companies, and a broken market model

for commercial success of new antibiotics. These factors have put the onus on small biotech companies to innovate and develop novel antibacterial drugs to address AMR.

One such ray of hope stems from the ongoing efforts of a small biotech company based out of Bangalore - Bugworks Research. Bugworks is focusing on developing an innovative, broad-spectrum antibacterial drug that targets Gram-positive, Gram-negative, and bacterial bio-threat pathogens. The genesis of Bugworks has a definitive link to the erstwhile AstraZeneca R&D center and its predecessor, Astra Research Center in Bangalore. The scientific founders of Bugworks and its key members, with a collective global drug discovery experience of over 200 years, were trained in infection biology and drug discovery from these two centers. The closure of AstraZeneca R&D center, Bangalore, due to business reasons was a catalyst for the creation of Bugworks in 2014.

The global exposure to the scientific and business nuances of modern drug discovery and development was the cardinal principle embedded into the ethos of Bugworks. The need for driving innovation via global partnerships, leveraging cost benefits via national and international CROs, guided by global key opinion leaders, provided the necessary impetus to drive innovation at Bugworks. Building these enabling ecosystems paved the way for Bugworks to raise non-dilutive funding from multiple agencies within India and overseas and helped generate high-quality data that matched global benchmarks. Developing a broad-spectrum antibiotic is an arduous task and requires the demonstration of two key features: firstly, the molecule should be effective against the highly drug-resistant ESKAPE pathogens (comprising some of the most deadly Gram-positive and Gram-negative pathogens known to cause severe illness and known to exhibit drug-resistant mechanisms). Secondly, the molecule should have a very low propensity to develop resistance in the laboratory and eventually in the clinic.

The discovery of new antibiotics involves several stages, starting with identifying a potential new target in a bacterial species and designing a chemical molecule (using a combination of high throughput

screening, molecular modeling, and creative chemical synthesis) that can effectively bind and neutralize the target function. Using an iterative process consisting of design-test-analyze and several rounds of optimization followed by an extensive test for safety, tolerability, and efficacy in preclinical animal models results in a clinical drug candidate. This candidate drug is manufactured in large-scale quantities under good manufacturing processes (GMP) to ensure safe use in human volunteers. Over the next several years, the drug undergoes extensive safety, tolerability, and efficacy testing in healthy volunteers, followed by studies in diseased patients, generating a body of evidence demonstrating benefit versus risk to treat a life-threatening infection. The entire clinical development and study in human volunteers and diseased patients is a highly regulated process with extensive control mechanisms to ensure there is no harm to the participants and a clear demonstration of benefit to needy patients at the end of this long and expensive journey.

Bugworks has built successful partnerships with two tertiary care hospitals in Bangalore, St. John's Hospital and Narayana Health City, to readily access and screen its compounds against a huge panel of drug-resistant bacterial isolates from patients. This provided real-world evidence and guided the selection of molecules from thousands of diverse compounds that met stringent global standards to progress further into drug development. To circumvent the risk of developing resistance, Bugworks employed a unique strategy to design drugs that work against two essential targets in the bacteria, thereby reducing the emergence of drug-resistant mutations on the target genes. After four years of systematic and concerted efforts by a multidisciplinary team led by Bugworks, BWC0977 was selected as the clinical candidate drug to progress into expensive and lengthy clinical studies in humans. This could be the first novel, broad-spectrum drug discovered in the last five decades after the introduction of the fluoroquinolone class of drugs. Currently, BWC0977 is undergoing Phase 1 studies in healthy volunteers to establish safety, tolerability, and pharmacokinetics of this drug. In the next 3-4 years, Bugworks hopes to progress BWC0977 into further clinical studies in patients infected with a spectrum of bacterial pathogens, such as complicated urinary tract infections, complicated intra-abdominal infections, and

bacterial pneumonias. The totality of evidence from these clinical studies will provide a robust data package to seek regulatory approval for commercial launch of BWC0977 in global markets. Bugworks hopes that the key learnings and insights from this ongoing research will help them to continuously innovate and provide solutions to tackle antibiotic resistance and spur a legion of innovators to follow in this journey. If Bugworks succeeds in this endeavor, it would be the first biotech company to create an innovative solution to treat the global pandemic of AMR.

A story of escape from "No Option."

Nitin Bansal

Consultant of Infectious Diseases at Rajiv Gandhi Cancer Institute, Delhi.

In a very famous neurological institute in the city, many patients have been getting brain infections over the last few weeks. This has been particularly happening to patients after brain surgery. Most of them eventually succumbed to this infection, and the few who survived were left debilitated. Although these patients were operated on by different surgical teams in different Operation Rooms (OR), and all patients were operated on different days, one thing was common in these patients: their cause of infection was the same bug.

Organism: *Acinetobacter baumannii* Sample: CSF	
Cefazidime	Resistant
Ciprofloxacin	Resistant
TMP-SMX	Resistant
Colistin	Sensitive
Meropenem	Resistant
Minocycline	Resistant
Amikacin	Resistant

Doctors used varying antibiotic regimens to clear this infection. In fact, they used to give antibiotics directly inside the brain. Unfortunately, very few patients improved. It looked as if life-saving neurosurgeries

were turning out to be life-taking procedures. Surgeons and hospital administrators were extremely distraught and were having sleepless nights.

Eventually, a team led by an infectious disease physician and a clinical microbiologist from another hospital was asked to investigate this scenario. The team gathered and reviewed the hospital's old records. They discovered that this infection had been observed many times in the past several years, but the incidence of infection was very low. According to their estimates, the incidence of this infection was only 1 in 100 patients in the last two years. However, in the last two months, it has infected 18 patients, and 16 out of 18 had undergone neurosurgery.

The team took rounds of the OR, CSSD unit (the place where surgical instruments are cleaned and sterilized), ICU, and wards. It took them nearly one week, and then they pointed out some observations to the surgeons and hospital administrators.

- The CSSD unit was closed last month for renovation, and surgical instruments were sent to a different location for sterilization. This location supplied instruments to multiple small hospitals nearby, and they discovered that many patients in these hospitals also had the same infection.
- Some instruments were sent to the hospital without proper labels indicating sterilization. In fact, it was found that a few protocols, such as the timing of autoclaves and bio-indicators, were overlooked due to an extra burden.
- The ICU did not have hand sanitizers at the bedside, and the consumption of hand sanitizer has decreased from 10 liters per week last year to 2 liters per week in the last two months.
- They also pointed out that the same bottles were getting filled with sanitizer without proper cleaning.

After these observations, several corrective actions were taken, which included regular audits of the outside CSSD unit and feedback was given to that location. Within 2 months, the hospital was able to fast-track the renovation of its own CSSD unit and started sterilizing instruments in-house.

Importance of hand sanitization was re-emphasized to hospital staff and hospital administrators were convinced to invest in hand rub stands which could be placed at all appropriate locations.

After these and several other changes, the rate of infection came down to a minimum.

This story highlights the importance of good infection control practices that need to be followed at all times to reduce infection rates. This is a good example to show how doctors can help their patients avoid infections for which there was NO-OPTION.

LAMPing the Way: Fighting AMR with Molecular Diagnostics

Dr Emma Hayhurst, CEO of Llusern Scientific

I am Emma, the CEO of Llusern Scientific, a purpose-driven enterprise that specializes in creating accessible and user-friendly molecular diagnostic solutions. As a self-professed microbiology enthusiast, I am deeply fascinated by the remarkable potential of microbes and their capacity for both positive and negative impacts. Thus, I sought to apply my knowledge and skills to tackle one of the most pressing global health concerns today – the rapid escalation of antibiotic resistance. The good news is that, similar to addressing climate change, this issue is entirely solvable, requiring only determination, ingenuity, and significant funding.

Antimicrobial resistance (AMR) results from a basic process of evolution through natural selection, whereby microorganisms develop resistance to drugs as their use increases. Reducing the utilization of drugs is one of the most effective ways of curbing AMR. Ensuring proper diagnosis of infections is critical to achieving this goal, as it guarantees the selection of the most appropriate medication. In 2016, while conversing with my colleague Jeroen, a molecular genetics specialist, we discovered an underutilized molecular diagnostic technique known as LAMP, which could be integrated into a simple and cost-effective point-of-care (POC) test for detecting urinary tract infections (UTIs). We recognized that UTIs were a common bacterial infection, affecting millions of people annually worldwide. However, the lack of reliable POC tests had led to incorrect diagnoses and unwarranted prescription of antibiotics.

Given the dire need for improved UTI diagnosis, we collaborated with our engineering colleague Ali and applied for seed funding from the Longitude Prize. As individuals with no prior experience in diagnostics, securing traditional research grants or private investments would have been a daunting task. Nevertheless, we overcame the challenges, developed a passionate video application, and succeeded in securing funding from the Longitude Prize.

Since then, our journey has been a rollercoaster ride, transitioning from academic researchers to industry professionals in the diagnostic field. We have progressed from proof-of-concept to full-scale commercial production of our UTI test, which comprises a simple sampling tool, a molecular reaction test kit, and an easy-to-use portable electronic reader device. We have secured multiple grants and seed investments and are proud to work with investors who share our values and vision for a purpose-driven enterprise that addresses not only AMR but also enhances patient outcomes. Additionally, we have embraced a One Health approach, applying our UTI test in veterinary settings as well.

Moving forward, early clinical results for our UTI test are promising, and we believe that we are fulfilling an unmet healthcare need. Our test will empower clinicians to make evidence-based treatment decisions at the point of care, selecting the most effective antibiotics based on the bacterial strain responsible for the infection, and considering the patient's unique context. This, in turn, has the potential to reduce the overuse of antibiotics and improve patient outcomes.

By improving UTI diagnosis in community and primary care settings, our test can also mitigate the burden of UTI-associated complications, which are prevalent in secondary and emergency care units. While UTIs present complex issues across various patient groups, our test is a step towards addressing this problem, with potential applications in the diagnosis of numerous infectious and non-infectious diseases.

As a start-up enterprise, our future remains precarious, and securing adequate funding is a constant challenge. Nevertheless, we are excited

about the possibilities of our technology as a platform for addressing various diagnostic needs. We aspire to make our tests accessible to everyone, not just those who can afford them. As a small team with a vision to create positive change, we remain optimistic that our journey has just begun!

Keep your eyes open!

Dr Kusum S. Chand

M.B.B.S., M.D.(Med), MF Hom. (London)

Sr. Physician Homeopath

Max Super Speciality Hospital

Author of the book 'Dare to Differ'

Ignoring the "NO VISITORS" signage, I entered the microbiology laboratory, knowing I could do so as I had recently finished a few months of training in the department. Holding the drug sensitivity plate, my hand shook slightly as I checked and rechecked the laboratory number. I wished it was not the urine culture sample number I had gone to check first thing in the morning before starting the daily routine at the hospital, but it was. The yellow bacteria around the white discs on the red culture medium of the microbiology culture plate were staring at me. Bacteria had grown around all the antibiotic discs placed in the culture medium. The bacterium named Staphylococcus aureus was defying me, laughing at me. It seemed to be saying, "treat me if you can." Its growth indicated that it was resistant to all oral antibiotics available then. I was crestfallen, and all the complications of a drug-resistant urinary tract infection flashed in my mind. But my confidence and faith in modern medicine soon perked me up. Science rapidly progressed in every field, and new drugs were discovered every other day. I was confident that soon an appropriate antibiotic with fewer side effects would be found for this bug. Until then, all that was required of me was to take precautions and check the infection. However, the frequent urine examinations and yearly intravenous pyelographs created a fear of having an incurable disease. All I wished for was something that would relieve the nagging symptoms and give peace to my mind.

As luck would have it, a gentleman in my husband's office practiced homeopathy as a hobby. My husband asked him if he had something for my condition in homeopathy. "Yes," was the prompt and confident reply. I was reluctant to meet him because, in my mind, homeopathy was only good for skin problems and vague psychological symptoms, not for severe infections such as mine. But, on my husband's insistence, I decided to give homeopathy a try. After a few months, grudgingly, I had to admit a reduction in the frequency of symptoms and urine examinations.

This is my story. I was about thirty when it happened. This incident proved to be a game-changer, as it changed the course of my life. Qualified with an M.B.B.S. and an M.D. in General Medicine, I was passionate about the medicine of my learning. However, my suffering from repeated urinary tract infections, where antibiotics couldn't help me, disillusioned me and led me to alternative medicine. I spent two decades experimenting, learning, and validating homeopathy – a system of therapeutics I had ridiculed. When, as a general practitioner, I was convinced of the efficacy of integrating homeopathy with modern medicine, I took the plunge to become a homeopath by taking the M.F. (Hom) examination. The decision has been rewarding. I have successfully treated many patients with drug-resistant infections or drug intolerance, which would not have been possible with only modern medicine. (Excerpt from my book 'Dare to Differ')

No doubt, antibiotics are miracle molecules and the cornerstone of modern medicine. However, antimicrobial resistance has created a scenario where we must look for other evidence-based solutions. Homeopathic medicines can provide a solution in many situations where antibiotics do not work, or the patient is intolerant to antibiotics.

How do homeopathic medicines act in infections?

All living beings possess a powerful self-defense mechanism: the immune system. This is something by which any living cell, tissue, or body responds to all external stimuli, beneficial or malevolent. It can be defined as a complex biological system endowed with the capacity to recognize and tolerate whatever belongs to the self and reject what

is foreign. It constantly acts and keeps the functions of the living being within the normal level of homeostasis. When it is healthy and intact, no change in health is evident. It is not a constant factor, which is a general perception, but waxes and wanes with various physical or emotional stresses.

Allopathic medicines, such as antibiotics, focus on targeting the microbe, whereas homeopathic medicines used in infections aim to boost the individual's immunity. It is the microbe that becomes resistant to antibiotics, not the person. A strong immune system can overcome microbes, regardless of the pathogen's antimicrobial susceptibility profile.

My experiments and experiences have shown that homeopathy and allopathy are complementary. The complementary use of homeopathy with allopathic antibiotics reduces recovery time, morbidity, and increases drug compliance. It can be helpful in patients intolerant to antibiotics and drug-resistant bacterial infections, including Multidrug-Resistant Tuberculosis. We have carried out a Randomised Controlled Trial on the utility of homeopathic drugs administered in conjunction with conventional allopathic anti-TB drugs. Experiments show that homeopathic medicines give reproducible results when given in a regime form. The regime is patient-specific and is guided by the symptoms of the patient.

Randomised Controlled Clinical Trials (RCTs) are the acid tests for the evidence of any therapeutic modality. As a qualified doctor in Modern Medicine (allopathy) and Homeopathy, I believe all relevant stakeholders should collaborate and initiate RCTs to explore homeopathic medicines in various infectious disease clinical syndromes. I believe homeopathic medicines can withstand the acid tests in these clinical syndromes and help the global community fight against AMR. It is high time we kept our eyes open!

Serendipity led me to work on the global issue of AMR….

Dr Laura JV Piddock

Professor Emeritus at the University of Birmingham, UK; Scientific Director of the Global Antibiotic Research and Development Partnership (GARDP).

I never thought I would end up working in the field of antibiotics and antibiotic resistance. After finishing my undergraduate degree in Biological Sciences, I had planned to work in forensic science, but there were no job openings at the time. Instead, I ended up starting a basic Biochemistry PhD, which I quickly found was not to my liking. However, a job offer to do a PhD while working at a hospital in Birmingham with Professor Richard Wise, a global expert on antibiotics, changed everything.

My PhD research focused on the target of penicillin, which had only been discovered shortly before, in a bacterium. It was not known why this drug did not work. But it was my work on antimicrobial resistance (AMR) that really piqued my interest. I was exposed to pre-clinical and clinical research and development of new antibiotics, which gave me a great understanding of the challenges and opportunities in the field.

After completing my PhD, I stayed on with Richard for two years as a senior scientist in the hospital before moving to the University of Birmingham Medical School to set up my own research team. I became a full professor in 2001 and sat on numerous national

and international advisory bodies and boards, including the World Health Organization advising on antibiotic resistance. I was also the President of the British Society for Antimicrobial Chemotherapy from 2008 to 2011. In 2013, I co-authored the first report to the World Economic Forum on AMR.

As the crisis of drug-resistant infections became more apparent in the 2000s, I led a global public awareness initiative called Antibiotic Action, which called on governments to address the challenges facing the development of new antibiotics. In my academic research, I continued to focus on mechanisms of antibiotic resistance and mode of action, but I was increasingly engaged in public awareness events and policy-making.

At one such event, I was asked what I was doing in my own research to tackle the crisis of AMR and lack of new drugs. This question prompted me to reorient my research towards drug discovery projects based on the knowledge gained about drug-resistance mechanisms. This ultimately led to my joining the Global Antibiotic R&D Partnership (GARDP) in 2018.

GARDP was created to fulfill the global action plan to address AMR and the challenges of R&D of new antibiotics. It brings together different entities in partnership to work together to get new antibiotics to those who need them. I lead the GARDP Discovery and Exploratory research program, which aims to fill gaps in the global discovery and pre-clinical pipeline, and the GARDP Scientific Affairs education and outreach program under the brand REVIVE. The latter aims to prevent the depletion of expertise and wisdom and ensure that the antimicrobial R&D community can access the technical knowledge needed to develop new treatments. I am also a member of the GARDP Policy & Advocacy team and the GARDP management team.

GARDP also has clinical programs focusing on serious bacterial infections, children's antibiotics, including neonatal sepsis, and sexually transmitted diseases. We are eagerly awaiting the results from the zoliflodacin phase 3 clinical trial to treat drug-resistant

gonorrhea, the data from which will be available later in 2023. I am hopeful that the data supports the approval of this much-needed new treatment.

Looking back on my career, I realize how many opportunities, often serendipitous, I have had and the privilege of working on many different aspects of AMR and contributing to solving the crisis of the lack of new treatments. It has been a fulfilling journey, and I hope to continue making a positive impact in the field of antibiotics and antibiotic resistance for years to come.

From Boom to Bust: The Economics of Antibiotics R&D

John Alter

Head of External Affairs, AMR Action Fund

Those who work on antimicrobial resistance (AMR) are accustomed to unsettling statistics. There are 1.27 million people who die annually from drug-resistant bacterial infections, and one in five AMR deaths occur in children. Additionally, 10 million people are projected to die from drug-resistant infections by 2050, and the World Bank estimates that AMR will cost the global economy $100 trillion by the same time.

Each of these statistics is deeply concerning, but I am not a clinician or a scientist on the frontlines of patient care. Instead, I have spent the past quarter of a century working for a large multinational pharmaceutical company that develops medicines and recently transitioned to a fund that invests in small companies developing - or trying to develop - new antibiotics. So, I bring a different perspective to the AMR crisis and dwell on a different set of statistics. There's one AMR-related data point that I find especially troubling, a number that rattles around my head on a near-daily basis and makes me wonder whether we'll ever be able to contain this threat. That number is 27.

That is the total number of antibiotics in clinical development that might work against one of the drug-resistant bacterial pathogens that the World Health Organization considers critical. For the sake of comparison, it is estimated that there are 700 oncology drugs in

late-stage development. All 27 of the antibiotics are experimental, and very few of them will successfully make it through the long, rigorous process of clinical testing and achieve regulatory approval. The distressingly thin pipeline of clinical-stage antibiotics says as much about the remarkable history of these lifesaving drugs as it does about their perilous future.

Antibiotics emerged as a viable treatment option in the early 1940s and were immediately heralded as a wonder drug. They vanquished previously untreatable infections and made other medical interventions, such as surgery, organ transplantations, and chemotherapy, significantly safer. The pharmaceutical companies that brought these early antibiotics to market made sizable profits and reinvested a good chunk of those profits into global R&D efforts aimed at discovering and commercializing more antibiotics. The mid-20th century is often referred to as "The Golden Age of Antibiotics," and for good reason. Between the 1940s and 1980s, scientists developed a dozen different classes of antibiotics, representing scores of medicines that could kill a huge range of dangerous bacteria. By some estimates, the advent of antibiotics extended the average human lifespan by 23 years. The drugs worked, the market worked, and humankind benefited.

But then bacteria evolved, and the market changed. It became harder and costlier for scientists to discover new classes of antibiotics and harness their therapeutic potential. It also became evident that given the rapid emergence of "superbugs" - bacterial pathogens resistant to first-line treatments - any new antibiotic that gained regulatory approval should be used sparingly to preserve its effectiveness, a practice that's good for public health but difficult for companies that need to recoup their R&D investments from sales of the finished medicine. From a business perspective, antibiotics became a losing proposition, a high-risk investment with little potential upside. Many of the leading pharmaceutical companies stopped investing in this cornerstone of medicine and put their money to work in other, more lucrative fields, such as rheumatology and oncology.

I saw firsthand how this exodus of pharma companies played out: promising antibiotic programs were shelved, exquisitely talented

chemists and biologists applied their skills in other therapeutic areas, and the pipeline of antibiotics that clinicians depend on stagnated. According to the Institute for Health Metrics and Evaluation (IHME), 63 new antibiotics were approved for clinical use between 1980 and 2000. Between 2000 and 2018, just 15 additional antibiotics were approved. Now, the pipeline of antibiotics is unacceptably thin at a time when the world is losing more than 1 million people every year to drug-resistant bacterial infections.

The situation is dire, and there is significant work to be done, from the hallways of hospitals where antibiotics are administered to the offices of policymakers and boardrooms of multinationals where global health challenges are prioritized. But there's reason for optimism. In fact, I'm personally more optimistic now than I have been at any other point in the last decade about the future of antibiotics.

For the last two years, I have been working at the AMR Action Fund, an investment fund that was set up by the World Health Organization, the Wellcome Trust, and more than 20 pharmaceutical companies to invest US$1 billion in small biotechnology companies that are developing promising antibiotics. One thing that has amazed me during my time with the Fund is how committed these companies are to filling the void left by those who have left the space and replenishing the pipeline. According to the Biotechnology Innovation Organization, small companies are responsible for 80 percent of antibiotics that are in development. They have set up operations around the world, from Bengaluru to Basel to Boston, and their willingness to take on one of the biggest global health challenges of our time despite the significant financial and scientific risks is truly laudable.

The other reason I am more optimistic than ever is that governments are increasingly coming to terms with the fact that antibiotics are precious resources that cannot be lost to the pitfalls of the free market or poorly crafted health policy. Across the G20 and the G7, health and finance leaders are pursuing meaningful reforms to change how antibiotics are valued, sold, accessed, and administered. They are working across sectors and identifying opportunities for

improvement across the whole spectrum of drug development and healthcare delivery.

Momentum is finally changing in the fight against AMR. However, momentum alone cannot solve the problem. To reverse course and meaningfully address the grim statistics that are a hallmark of AMR, we need to take action—and we need to take it now.

Broadening the mantra for the fight against antimicrobial resistance: Vaccines must play a greater role

David L Heymann, M.D.

Professor, Infectious Disease Epidemiology

London School of Hygiene and Tropical Medicine

A young medical doctor and master's student from a lower-income country in Asia once told me that his government was planning to pass legislation requiring laboratory diagnosis before prescribing antimicrobial drugs for an infectious disease. He was concerned about this decision because he felt that it would severely constrain access to antimicrobials among patients in rural areas, who at present were being treated based on clinical diagnosis because of limited clinical laboratory testing possibilities. And because laboratory testing systems were not in place, he was convinced that this would lead to increases in severe illness and death.

This student's concerns are clearly valid in many other lower- and middle-income countries around the world where laboratory testing before treatment is not feasible. In fact, feasibility will only come when there are affordable point-of-care diagnostic tests that help solve the problem of scant or non-existent laboratory systems.

I mulled over these concerns for several days, and as time passed, I began to think about some of the vaccine-preventable diseases,

such as pertussis, and how they have been decreased in incidence by childhood vaccination systems and affordable vaccines that are present in all countries. In fact, I later asked this student and others like him when they had last treated pertussis, diphtheria, or tetanus with antibiotics. Many had never seen these once-common childhood diseases during their medical training and early practice, nor had they learned about their management while in school.

Increasing coverage of existing vaccines including DTP, Hib and the pneumococcal vaccines will prevent sickness and death, and at the same time decrease the need for antibiotics and relieve the selective pressure caused by their misuse.

During the COVID-19 pandemic, new vaccines and vaccine platforms have been developed, and they are now being restructured to produce vaccines for other viral infections, including influenza and polio. These vaccine platforms - mRNA and virus-like particle vaccines, to name two - are also being, or will soon be, adapted for vaccines to prevent bacterial and parasitic infections as well.

The prospect of developing and using these new vaccines to prevent infections such as antibiotic-resistant gonorrhoea, multi-drug resistant tuberculosis, and hospital-related infections such as MRSA is promising, and exciting. They offer a vision of not only preventing infections and the associated sickness and death, but of slowing the development of antimicrobial resistance to existing and newly developed antimicrobial drugs.

We must broaden the mantra for the fight against antimicrobial resistance from the treatment of infections to prevention by vaccination. Investment must be made in both the development of new antimicrobials and the development of vaccines. We can already begin by increasing vaccination coverage of both children and adults using vaccines that already exist.

Help is on the way

Dr Sudeshna Adak

Founder and CEO

OmiX Research and Diagnostics Laboratories Private Limited, Bangalore, India.

It was the year 2015. We were a startup, less than a year old, and discussing the development of RT-PCR-like tests that could diagnose infections in remote locations. A mentor and advisor, who was a research microbiologist, suggested that we should develop a test for antimicrobial resistance. Our naïve response to him was, "What is antimicrobial resistance?" That conversation started us on a journey for the next eight years.

We were a team of scientists and researchers, unaware of the looming crisis of antimicrobial resistance. We began talking to doctors, patients, and caregivers. The stories were heartbreaking, and the numbers were already staggering even in 2015. Stories narrated by doctors stunned us: a family who lost their only earning member from a simple injury on the farm and had an 11 lakh hospital bill, a story of a highly drug-resistant tuberculosis patient in a village who had never been anywhere outside the village – completely mystifying as to how the infection happened, a 1-year-old child with a highly resistant bacterial infection, and many more stories. Age-old culture methods being used were too late and often did not work, especially in bloodstream infections. In order to not lose the patient, the doctors were treating with the highest grade antibiotics, and resistance to those higher-grade antibiotics was starting to grow. There were no new antibiotics on the horizon. In this perfect storm, doctors and

patients were asking, "Can you not help find a test that will tell us which antibiotic will work?"

There were RT-PCR tests available in the market that looked at the organism causing the infection, but did not indicate whether it would respond to antibiotics. These tests were expensive, costing between Rs 25,000 to Rs 30,000 for the patient.

In 2020, we launched a service that would determine whether a patient would respond to the highest-grade antibiotics, Carbapenem and the last resort of Colistin. The cost to the patient was a mere Rs 5000.

When we began, we were given tough cases. One patient had undergone a liver transplant and had three sites of infection, and was in a bad condition. Within 24 hours of receiving the samples, we informed the doctor that the infection that was resistant was in the lung, despite the patient having had a liver transplant. We also noted that the patient would not respond to carbapenem alone, but was sensitive to a new combination treatment of Ceftazidime-Avibactam (CAZ-AVI). Another patient, whom the transplant surgeon had thought was lost, was successfully treated for the lung infection.

Our reputation in Bangalore hospitals was spreading, and we received a call from a doctor regarding a patient. The patient was very poor and was receiving free treatment at a charitable hospital. However, after being there for two weeks, her condition had not improved. The doctor had heard of our services, but the patient could not afford a Rs 5000 test. Although we were a small company struggling to grow, this case was special to us, and we offered our services for Rs 1000, which only covered our transport and manpower costs. The patient was found to be sensitive to Carbapenems, which was not on the list of free medicines prescribed at the charitable hospital. Based on our report, the family was able to find the money for the treatment, and the patient was released after ten days.

We then decided to take on sepsis, the challenging work of identifying drug resistance in bloodstream infections. The bacterial load is so low

that it is like searching for the proverbial needle in a haystack. The bigger problem was that only 10% of blood cultures were positive. The doctor wanted to know if we could identify the bug and resistance in the 90% of cases where blood cultures did not work. However, the laboratory personnel were concerned that our molecular test may report false positives. Therefore, we had to prove that our results were accurate. We designed a study where a sample was taken from a blood culture bottle after three days and subjected to our test. Our agreement with the blood culture was 95%, but we missed fungal infections because our test did not include fungi. However, we had no false positives. If the culture was negative, so was our test, proving that we were only going to identify correctly. We then began testing directly on bloodstream infections, and within four hours, we were reporting results, which was unheard of earlier. We identified 11 cases among 30 patients as positive where culture had failed. All of these were also tallied with the SOFA score, a symptom-based score used by doctors to identify sepsis. Finally, we had a test that could be used for bloodstream infections.

It was March 2020 when we had finished our first 30 cases, and the pandemic hit, changing our plans and outlook. Today, we are taking what we have developed and turning it into a product that can be used even in remote locations. Help is on the way.

Rapid Antibiotic Susceptibility Testing at the Point of Care - The Astrego Story

Johan Elf

Uppsala University and Sysmex Astrego AB.

The use of antibiotics to treat non-bacterial infections contributes to the global increase in AMR. For want of rapid diagnostic tools, doctors also prescribe broad-spectrum antibiotics preemptively because infections might be resistant to the first-line options. This text is a personal perspective of the path to Astrego's 30-min antibiotic susceptibility test, which will hopefully play a key role in the fight against AMR.

The Astrego story began in my lab at Uppsala University in Sweden, where we developed methods to make sensitive optical measurements of molecular processes in bacterial cells. In 2010, PhD student Mats Wallden transferred the techniques for making PDMS microfluidics from Jeff Hasty's group in the US. This method was critical for conducting accurate and reproducible experiments on bacterial cells. Other individuals at the university who made vital contributions on the path to Astrego were David Fange, Alexis Boucharin, and Jimmy Larsson, who worked with fluidics, microscopy, and image analysis.

Our work with antibiotics began in 2012 with PhD student Özden Baltekin, who used fluidic tools to measure the growth rates of individual bacteria to investigate cell-to-cell variation in response

to antibiotics. In discussions with microbiologist Dan Andersson, we concluded that the chip could also be used to measure a rapid response to antibiotics. Initial tests showed a faster response than any of us had expected; susceptible bacteria responded to Ciprofloxacin in less than five minutes. The response was highly reproducible and specific for different antibiotics, which made us realize that we were looking at the actual phenotypic response time to the antibiotic. We could monitor the phenotypic response faster than the division time of the bacteria because we measured the length increase in individual bacterial cells during a short time instead of the number of cells after a long time, as you would do with turbidity in liquid culture or the number of colonies in an agar plate.

At roughly this time, Dan Andersson told us about a new prize for fast susceptibility testing announced in the UK. Özden and I did not know much about the challenges of making a user-friendly and inexpensive product, and we had little comprehension of the complexity of clinical samples. Had we been better informed, we would probably have realized that signing up for the competition in 2015 was premature. But as it was, the goals of the Longitude prize defined what we had to achieve: a susceptibility test that was simple, dirt cheap, and faster than 30 minutes.

To advance the project beyond proof-of-principle, it had to leave academia. User-friendliness, design for manufacturing, and large-scale clinical testing are not strengths of the university. We patented the technology with support from the Swedish Foundations for Strategic Research (SSF), who had encouraged me to do something useful for several years. This encouragement included assigning me an industrial mentor, and thus, I had already pitched a few business ideas to serial entrepreneur Ove Öhman. Ove rapidly shot down each idea until I explained the antibiotic susceptibility test to him. Together with Özden and my friend Martin Lovmar, Ove convinced me that we should start a company to commercialize the rapid AST. Unlike Özden and me, Ove knew what he was getting into since he had founded several companies and developed commercial processes for microfabrication in the diagnostics space.

In the fall of 2016, the idea for Astrego was born, but we needed people and investors. We intended to hit the ground running and carefully selected the founding team to cover the critical competencies of microbiology, microfabrication, and mechanical engineering. Experienced IVD entrepreneurs brought product development, QA/RA, and management skills to complete the founding team. Uppsala University Innovation provided us with the funding to create a prototype instrument, Ove brought in investors, and after a few shaky demonstrations of the prototype, we secured capital to start the company in March 2017.

We decided that the first product should be an AST for urinary tract infections (UTIs) since we knew from academic work that E. coli responds quickly to the most common antibiotics for UTIs. We also thought that obtaining patient samples would be easy since there are 100 million cases of UTIs per year in Sweden, and the sampling is non-invasive. UTIs are responsible for 15% of all antibiotic use in human medicine, and resistance is common. Antibiotic stewardship in this area could thus have a significant impact.

The AST that we developed over the next five years features a single-use cartridge into which we load a fresh urine sample. If the urine contains bacteria, these are trapped in >10,000 microfluidic traps in parallel arrays that we expose to five different antibiotics at five different concentrations. We insert the cartridge into a reader instrument where the growth of individual bacteria is monitored by phase-contrast imaging. The response to the antibiotics is analyzed by an expert system that reports “sensitive” or “resistant” for each of the five antibiotics in 30-45 minutes, depending on the species and antibiotic.

The product development phase was intense. We made a few choices that were likely crucial for our success. Firstly, we made both the single-use test cartridge and the reader instrument in-house, which shortened the integration and troubleshooting cycles. Secondly, we continued to use silicon fluidics. Thirdly, we dried in all reagents on the test chip in-house. Lastly, we continuously tested every step on hundreds of reference isolates.

So many brilliant people have been critical in the development and manufacturing that their contributions do not fit here. The most challenging part was, to everyone's surprise, to get clinical urine samples from suspected UTI patients. This group of patients apparently gets antibiotics prescribed without seeing a doctor or leaving a urine sample.

Like most start-ups, we had our fair share of financial near-death experiences. However, from May 2022, funding ceased to be a problem as Astrego Diagnostics AB was acquired by the global diagnostics company, Sysmex. Sysmex Astrego AB in Uppsala will continue to develop and manufacture AST products, while marketing and sales will be handled by Sysmex's regional branches.

The Astrego instrument will allow doctors to make personalized prescriptions of appropriate antibiotics. With susceptibility testing, even old antibiotics with high resistance frequencies can be used effectively to treat infections. We believe personalized, evidence-based treatments will be critical to limit the increase in AMR and to guide prescriptions in high-resistance environments.

Innovation in Rapid UTI Diagnostics: A Step Towards Curbing Bacterial Resistance

Sachin Dubey

Co-founder and CEO

Module Innovations

During the summer of 2014, our family was thrilled when my sister-in-law announced her pregnancy. As her pregnancy progressed, she experienced symptoms such as burning sensation during urination, abdominal pain, and increased urine frequency. Her gynecologist suspected a urinary tract infection (UTI) and prescribed a course of antibiotics, even though they aren't ideal during pregnancy. To our surprise, her test results came back negative for UTI, leading us to question the lack of rapid, point-of-care tests for UTIs and the unnecessary antibiotics she had consumed. This experience inspired the founding of Module Innovations, a healthcare technology startup focused on precision diagnostics for infectious diseases and antimicrobial resistance (AMR).

UTIs are a global problem, affecting 150 million people annually, with 1 in 3 women under 24 experiencing at least one UTI in their lifetime. Developing countries like India face higher risks due to the widespread practice of empirical antibiotic prescription and easy access to over-the-counter antibiotics, contributing to the emerging pandemic of AMR.

To address this issue, Module Innovations has developed USENSe™, a simple, easy-to-use, point-of-care test to detect four major bacteria responsible for UTIs. The test is as straightforward as a home pregnancy test and delivers visually readable results in just 15-20 minutes. This rapid diagnostic tool allows healthcare providers to offer accurate guidance to patients presenting with UTI symptoms.

Another challenge is determining antimicrobial susceptibility (AST) when bacteria are resistant to prescribed antibiotics. Patients cannot afford to wait three days to learn whether their prescribed antibiotic is effective. The rise of AMR is a real threat, with the possibility of antibiotics becoming ineffective against common bacterial infections.

To tackle this issue, Module is developing ASTSENSe, a compact device that determines bacterial resistance or susceptibility to over 15 antibiotics within two hours. ASTSENSe provides the minimum inhibitory concentration (MIC) to help clinicians make informed decisions about antibiotic treatment. The system can run multiple patient samples and deliver results to the clinician's phone for efficient decision-making.

At Module Innovations, we are committed to creating rapid point-of-care diagnostics that can change the status quo. We aim to empower clinicians with the right tools, ensuring that antibiotic prescriptions are evidence-based rather than empirical.

Our work has been generously funded and supported by agencies such as BIRAC-Government of India, the Longitude Prize on AMR, and CARB-X US. We are deeply grateful for their continued support.

Viral Warriors: Bacteriophages Taking on Antibiotic Resistance

Pranav Johri, Founder, Vitalis Phage Therapy

It was the beginning of summer in 2016. I, a 33-year-old man, enjoyed the health of a young person with little to no complaints and all the energy to achieve my goals – both personal and professional. I had recently been invited to multiple global platforms to represent my publishing business, and I was pushing the envelope towards the successes that seemed to be just within my grasp. The hectic travel and lack of rest did not matter to my mind, which was raring to go, to elevate myself and my business to the next level in the coming months and years.

One evening, I felt a twinge of pain in my groin. "Just a muscle pull," I thought, "nothing a good stretch won't fix." Little did I know, this pain was the beginning of something that would change the course of my life.

I exercised and stretched in the following days, but the pain persisted. It started spreading to my flanks, and I began to feel ill. My wife suggested that this may not be muscular and that I should see a doctor. I went to my GP, who referred me to a urologist at a well-reputed hospital in Delhi. He listened to my symptoms and diagnosed me with a condition called Chronic Prostatitis. "It's a very common condition, nothing to worry about," the doctor reassured me as he prescribed a course of antibiotics - Azithromycin and Doxycycline.

I returned home from the appointment with the antibiotics, confident that this issue would soon be behind me.

With this diagnosis and the course of treatment with antibiotics, I started to go about my days as normal. However, it became increasingly difficult as time went on, as my symptoms only kept increasing. I now had a daily fever of 100-100.5°F that drained my energy levels. I finished the course of Azithromycin and Doxycycline and returned to the urologist with symptoms worse than before my treatment had started. I was prescribed another course of antibiotics, this time Ofloxacin for four weeks. As the next month passed and the course of Ofloxacin was finishing, my symptoms were getting worse, and I was beginning to get frustrated with my situation. Activities that I could normally do, like going for hikes and going to the gym, were no longer doable. Going to work became a challenge, and I could see my goals and dreams slipping away.

In a state of despair, I sought a different urologist and went to one of the best that the city could offer. He ordered a diagnostic urine test, which was the first time that I was being tested for my condition. The antibiotics prescribed to me to date were done so empirically. With inconclusive test results, I was put on yet another course of antibiotics – the heavy artillery, as the doctor described it – a combination of Ciprofloxacin and intravenous Amikacin. The doctor said that combined with the previous three courses of antibiotics, this oral plus IV dose should clear up the infection. To me, this was the last throw of the dice with antibiotic treatments. If this did not work, my life as I had known it would never be the same again.

When the course of "heavy artillery" antibiotics finished, leaving me in the worst shape of my life, I went back to the doctor and asked, "What now?" He replied with those dreaded words, "We have no options left to treat you. We have tried all the antibiotic groups that we could have prescribed for your prostate infection, and none have been able to provide you with any symptomatic improvement. The best we can do now is symptom management for as long as you live." With a daily low-grade fever, pains all over my urogenital tract, back, and sides, urinary symptoms like frequency and urgency

with poor flow, and no energy to deal with this anymore, this was a death blow to me.

From just a few months ago, when I was soaring in my life, how had it come to this - a battle with a bacterial infection? I couldn't accept this as my fate. But what could I do? As I delved into research on bacterial infections that don't respond to antibiotics, I discovered the alarming issue of antibiotic resistance. Everywhere I looked, hundreds and thousands of people were struggling with antibiotic-resistant bacterial infections, with no end to their suffering in sight.

One day, while reading about alternative treatment options for antibiotic-resistant infections, I came across the term "phage therapy." It is an age-old antibacterial treatment protocol that pre-dated antibiotics. I learned that phage therapy uses bacteriophages, which are viruses that attack bacteria, to treat bacterial infections. It gained popularity in the early 20th century worldwide, with the first phages being found in India's Ganga and Yamuna Rivers. The treatment died out in most of the world with the advent of antibiotics, but Georgia, a small country in Eastern Europe, kept the science alive. I contacted the Eliava Institute in Georgia, founded in 1923, which seemed to be the premier research and development institute for phage therapy worldwide. They said they could conduct thorough diagnostic testing and treat my condition with their phage preparations that were sensitive to my bacterial strains. This was my "Eureka" moment. As I delved deeper into all things phage, I wondered if I could let myself believe that I had found "one option" from "no option." Could my enemy's enemy be my friend?

After four months of research into phage therapy, and with nothing to lose and my whole life to reclaim, I decided to travel to Tbilisi, Georgia, to try phage therapy. My family was skeptical but supportive, and after addressing all their concerns as much as I could, I visited the Eliava Institute's clinic to undergo diagnostic testing and treatment. Testing revealed that I had a multi-bacterial infection, and the strains of Staphylococcus aureus and Enterococcus faecalis were resistant to all the antibiotics that I had been prescribed. My treatment with phages started, and the low-grade fever that I had

been living with every single day for six months broke on the fifth day after starting phage therapy. It was nothing short of a miracle to me. As my treatment progressed, all my other symptoms started resolving one by one.

One year and three courses of phage therapy later, I was free of symptoms and had regained my energy. I could look in the mirror and see not the beleaguered man who was once told to live and die with his infection, but someone who had come back from the clutches of an unbearable life, living once again with vitality and to the fullest of my potential.

Phage therapy saved my life. As I went through this rollercoaster of an experience, I realized the scale of the problem of antibiotic resistance and the potential solution that phage therapy could offer. In the beginning of 2018, my wife and I set up Vitalis Phage Therapy, a first-of-its-kind initiative to facilitate phage therapy for people suffering from AMR infections and to create the infrastructure to bring phage therapy to India. In 2020, Vitalis Phage Therapy established diagnostic testing facilities in India with phages from the Eliava Institute, which enabled localized diagnostic phage sensitivity testing for patients suffering from antibiotic-resistant infections and wanting to explore the treatment option of phage therapy. Since we started the initiative in 2018, more than 200 patients in India suffering from antibiotic-resistant infections/chronic infections have been able to undertake phage therapy and treat their infections that had been declared as 'untreatable'.

2019: A Call to Action

Tara deBoer, Ph.D.,
and Nicole Jackson, Ph.D.,

Leaders at BioAmp Diagnostics, San Francisco Bay Area, CA

In 2019, we, the team at BioAmp Diagnostics, came together with a common goal: to counteract antibiotic resistance by developing tests and technologies that provide critical information needed to guide the treatment of infectious diseases. Our team consists of researchers and globally recognized experts trained in the fields of global health, infectious diseases, epidemiology, medicine, chemistry, biochemistry, and bioengineering. Together, we're working collaboratively to address a global healthcare challenge and make a real-world impact on the treatment of infectious diseases.

Our foundational research was performed at the University of California, Berkeley, as part of a larger diagnostic consortium dedicated to developing non-traditional diagnostic solutions to combat antibiotic resistance. Under the guidance of public health and epidemiology expert Prof. Lee W. Riley, we focused on creating diagnostic tests that encourage the use of antibiotics with the narrowest spectrum of action possible, reducing the selection of drug-resistant pathogens. Prof. Riley emphasized the importance of designing tests that are compatible with standard treatment workflows and are simple to use and interpret, ensuring accessibility across all clinical settings.

With these guideposts in place, we developed the DETECT (dual-enzyme trigger-enabled technology) diagnostic system to improve care delivery for urinary tract infections (UTIs). We chose UTIs as our first

target because they're one of the most common infectious diseases for which antibiotics are prescribed. Additionally, an increasing number of UTIs are being caused by drug-resistant bacteria, creating an urgent need for novel diagnostic interventions.

The premise of our first test was simple: the current standard of care for patients suspected to have a UTI is empiric treatment, meaning that a first-line antibiotic is prescribed based on symptoms alone. However, the rising number of antibiotic-resistant UTIs necessitates the development of diagnostic tests to help clinicians determine which patients are suffering from a resistant infection. Our test aims to rapidly identify common antibiotic resistance markers from a clinical urine sample. A positive result indicates that a stronger antibiotic is needed, while a negative result allows the use of first-line antibiotics. This approach helps reserve broad-spectrum antimicrobials for when they are truly necessary, reducing the selection pressure that promotes antibiotic resistance.

Our team methodically designed, created, and iterated around a core technical approach inspired by conventional biochemical test methods. These classical tests are simple and affordable but require purified bacteria and can be labor-intensive and time-consuming. Our research led to the development of an assay kit that only required mixing test components with a small amount of the patient's urine in a standard multiwell plate. The test results were measured using a standard absorbance reader that collected changes in color intensity within minutes. Our first-generation test, named DETECT, was engineered to capture antibiotic resistance biomarkers produced by common bacteria that cause UTIs and can break down β-lactam antibiotics, which are typical first-line therapy options.

Over two years, we completed the ideation, creation, optimization, and validation of our target test system. In 2019, we demonstrated the clinical potential of the DETECT diagnostic approach in a pivotal proof-of-principle study. Around this time, multiple pharmaceutical companies with antimicrobial discovery programs closed their research and development pipelines or shut down entirely. This alarming shift in the antibiotic discovery market made it clear to

us that diagnostic tools capable of empowering clinicians to use antibiotics effectively and sparingly had become essential.

Thus, in 2019, we spun DETECT out of the university, giving rise to BioAmp Diagnostics. Since its inception, we have been dedicated to translating the validated DETECT system into meaningful diagnostic tests for use in clinics, at home, or in low-resource settings. Our lead test is a simple dipstick test designed to support the care of UTIs caused by multidrug-resistant bacteria. This test represents the first of a pipeline of tests that we are designing to improve outcomes for patients suffering from antibiotic-resistant infections, curb the use of last-resort antibiotics, and surveil the most problematic antibiotic-resistant organisms around the world.

As we move forward, our commitment remains strong in addressing the global challenge of antibiotic resistance. We believe that our work on the DETECT diagnostic system and the tests that will follow can make a significant impact in guiding the appropriate use of antibiotics and helping preserve their effectiveness for generations to come.

By fostering collaborations across disciplines and translating our research into practical applications, we are confident that BioAmp Diagnostics can play a crucial role in transforming the way we approach the treatment of infectious diseases. Our dedication to innovation, accessibility, and real-world impact will drive us to continue exploring and developing new diagnostic solutions that can help combat antibiotic resistance and safeguard public health globally.

With the continued support of the scientific community, healthcare providers, and policymakers, we are optimistic that together we can make a difference in the ongoing battle against antibiotic resistance and create a healthier future for all.

Longitude Prize on AMR: A new generation of diagnostics to slow the spread of antibiotic resistant infections.

Longitude Prize Team

"The simple knowledge of what antibiotic resistance is could have made such a difference to me. You can see the damage that has been done to my face – yes, that was from a car accident, but it was a lot worse. It was to the point where I didn't think I would have a face left. I could have stopped that. And, of course, all the trauma that went with it as well. You know, the trauma of not just me, but my kids seeing my face being eaten away by an infection. It's frightening. It's very frightening to think that this pill that you're taking is not going to make a difference."

Vanessa Carter – AMR Voices film, Longitude Prize on AMR (2020)

The increasing ability of bacteria to resist lifesaving antibiotics is a global tragedy unfolding before us. In this era of modern medicine, it is all too easy to take for granted that when we have an infection, a quick trip to the doctor and a week-long course of pills can fix everything.

A little over a century ago, a scratch from a branch, a broken bone from a fall, or a toothache could result in an infection that would prove deadly. Smallpox, cholera, diphtheria, pneumonia, typhoid fever, tuberculosis, typhus, syphilis, and even the plague could not be

stopped. Before the 20th century, life expectancy was only 47, even in the industrialized world.

The discovery of antibiotics in the 1920s and their development in the subsequent two decades consigned some of the most rampant diseases to the pages of history, not least in high-income countries. Diseases like diphtheria and consumption (tuberculosis) became the stuff of Dickens, not day-to-day life, thanks to antibiotics. Modern medicine was born, and our relationship to surgery and medical treatment was transformed.

Childhood mortality rates have plummeted. Surgeries such as knee replacements, hip replacements, and cataract removals have become routine thanks to antibiotics, which make them easily survivable. Pioneering cancer treatments that wipe out a patient's immune system are made possible because doctors have antibiotic drugs that can fight off infections.

Our world is built on antibiotics. They are the foundation of healthcare, but those foundations are crumbling before our eyes.

As early as 1942, just two years after the introduction of penicillin, four Staphylococcus aureus strains were found to resist treatment. Eight decades later, with no new class of antibiotics discovered since the 1980s, bacterial resistance to antibiotics is rapidly outpacing our ability to stay one step ahead. Without antibiotics in our medical arsenal, the entire global health system will collapse. We know this because it is already happening.

In 2019, antibiotic-resistant infections directly killed 1.3 million people and contributed to the deaths of 3.7 million more. It is estimated that by 2050, antibiotic-resistant infections will kill 10 million people a year – that's more than the population of New York City, or the equivalent of the population of Scotland, Wales, and Northern Ireland combined.

In India, it has been reported that the rate of mortality due to drug-resistant infections is 13%, independent of the reason for admission to the hospital. That means if you are admitted to a hospital, you

have a one in ten chance of dying from a drug-resistant infection, regardless of the reason for admission.

With a relentless slew of devastating data illustrating the scale of what many have called a "silent pandemic," it may seem like tackling antibiotic resistance is a hopeless cause. However, it is not hopeless. There is much that can be done, and it is being done.

We need new antibiotic and antimicrobial treatments, with increasing funding and research to bring new treatments to the market.

To preserve the effectiveness of the drugs we do have, we need to increase global awareness among doctors, nurses, and pharmacists about the role they must play in prescribing antibiotics only when necessary. We need the public to understand that antibiotics are precious and should be taken only when essential and as instructed.

However, we cannot expect doctors and patients to play their part unless they have confidence in the choices they make, and this is where diagnostic tests will be essential.

We have witnessed, through the Covid-19 pandemic, the power that diagnostic tests played in slowing the spread of the virus, helping people make informed choices about self-isolating to protect others, and helping clinicians identify who needed to receive Covid-appropriate treatments. The diagnostics were easy to use, quick, affordable, and accurate.

We need the same for treating bacterial infections: rapid, affordable, and accurate tests that can identify the presence of a bacterial infection and, importantly, advise a clinician which specific antibiotic will kill that infection the first time. Targeting the right antibiotic to an infection reduces the chances of promoting resistance and ensures that only the necessary drugs are being prescribed.

This is where the Longitude Prize on AMR has made an impact.

In 2014, the Longitude Prize committee was re-established by the UK's Astronomer Royal, Lord Martin Rees of Ludlow, and Challenge

Works, to commemorate the 300th anniversary of the original Longitude Prize. The 1714 prize had offered a reward to anyone who could accurately measure longitude at sea, a challenge that had outwitted even the smartest minds for millennia.

Eventually, the prize was won by John Harrison, a carpenter and self-taught watchmaker who invented a timepiece capable of keeping Greenwich time while at sea. Knowing the local time compared to Greenwich allowed sailors to accurately calculate their longitude. Harrison was not a mariner and had no formal training. In winning, he proved that the brightest and most transformational ideas can come from the most unexpected sources.

The 2014 prize sought to solve an equally difficult challenge, and incentivise solutions with an £8 million prize. A national media campaign, which included documentaries on BBC television and profiles in the Daily Telegraph, Guardian and New Scientist, called on the British public to vote for the focus of the prize from six options. More than 15,000 votes were cast, and the winner was Antimicrobial Resistance.

£8 million would be awarded to a rapid, affordable, and accurate point-of-care test that could determine whether an infection was bacterial, whether antibiotics were necessary, and if so, which drug to prescribe. It is no easy feat, but if achieved, it would be transformative in tackling antibiotic-resistant infections.

In the eight years since its launch, hundreds of teams of diagnostic innovators and researchers from around the world have put their minds to solving this extraordinarily difficult challenge. In doing so, the prize has created an international network of test developers who would not have otherwise been focused on the challenge.

Only one team can win the Longitude Prize on AMR, but its legacy is multiple companies developing rapid diagnostic tests for bacterial infections, creating a new market of life-saving diagnostics that did not exist in 2014.

They include Llusern Scientific, a company based in Wales that started life in a university lab. Its founders came from very different disciplines: one understood the challenge of AMR but not the molecular science needed to tackle it, while the other was a molecular expert who knew little about AMR. The prize incentivized them to come together and develop Lodestar DX, which detects urinary tract infections from a drop of urine.

"Because of the Longitude Prize, we were able to develop a urinary tract infection test, and it's because of that initial help and funding that we received from them, we were very clear what we were trying to achieve," explained Dr. Jeroen Nieuwland, Co-Founder of Llusern Scientific.

In India, Module Innovation has developed USENSe - a rapid, point-of-care test that detects four major uropathogens in just 15 minutes. The test can be conducted at the point of care, and the results are visible to the naked eye, enabling evidence-based treatment with antibiotics.

Being a Longitude Prize on AMR competitor has connected Module Innovations with key technological advisors and enabled the team to refine USENSe to become an accessible, rapid, point-of-care test applicable in global settings.

Thanks to the Longitude Prize on AMR, diagnostic innovators from around the globe are focused on delivering a new generation of rapid diagnostic tests to transform decision-making about antibiotic prescription.

Antibiotic resistance is a human tragedy unfolding in front of us – we cannot afford to turn a blind eye. It wrecks lives, steals loved ones from families, renders doctors impotent to provide treatments, and causes immense suffering to those living with an untreatable infection.

Antibiotic resistance threatens the survival of the healthcare systems that hold our societies together. The new diagnostic tests developed by Longitude Prize on AMR competitors are just one of the many tools we will need to win this battle.

There is no option but to combat superbugs

Viveka Roychowdhury, Editor of Express Pharma and Express Healthcare

How does a journalist figure in combating the Superbug problem without being accused of hyping it up. She suggests that journalists should constantly remind the public and all stakeholders that we have no options left and must fight this battle.

Because sooner or later, we will all feel the impact of this problem in our lives. We will all know people in our circle of acquaintances, friends, or family members who spent a long time in the hospital because they acquired a hospital-acquired infection. More tragic are the cases where we lost a loved one to a superbug like MDR TB.

Let us analyze where the missing links are in this chain. Many times, it is several months later, after treatment from multiple doctors and antibiotics, before the right diagnosis is made. The patient ignores it because of their full focus on exams or career. Parents don't take the initial symptoms seriously enough, and we live in denial, refusing to believe that disease can touch us.

So, we need constant reminders that disease doesn't recognize demographic profiles or socio-economic status. Disease is an equalizer, and we must not take it lightly. COVID-19 has been a harsh teacher of these lessons, and we must not forget them, or we are bound to repeat the same mistakes. Therefore, as journalists, we need to find different angles and perspectives, new research and reports, and

experts who can help us decipher the science and tell the story more accurately and convincingly. As reporters on the pharma and health beats, it can be challenging to get pharma companies, government, and policymakers to comment and come on record. However, thanks to experts like Dr. Ghafur, we receive regular updates on the AMR situation that alert us. Readers of publications like Express Pharma and Express Healthcare are from these sectors and are generally more informed than patients on the Superbug problem. What, then, is the focus of coverage of the Superbug problem in our publications?

The targeted readership of Express Pharma includes professionals connected to the pharma sector, ranging from CXO to general manager level, across manufacturing to marketing. In Express Healthcare, we cover healthcare management professionals, as well as clinical staff from nurses to doctors. In Express Pharma, we spread information about how effluents from antibiotic manufacturing plants have polluted water systems and caused AMR. We advocate for better effluent treatment processes and the use of cleaner, greener technology. The climate change crisis has helped force pharma companies to green their manufacturing processes, but we must be vigilant that this is not merely a 'greenwash'. Doctors and nurses need to be urged to speak up and become advocates of rational antibiotic use. The role of pharmacists needs to change from selling antibiotics without prescription to counseling patients to not take antibiotics at the first sign of a runny nose.

Pharma companies and the medical fraternity have become more aware of their role in the Superbug problem and are taking initial steps to clean up their manufacturing processes, but more needs to be done. All stakeholders, including patients, pharma companies and their employees, hospitals, and doctors, need to be made more aware of the consequences of indiscriminate antibiotic use to prevent unnecessary deaths. We have run out of options and must take drastic steps and be alert to the consequences.

"Reviving Antibiotic Discovery: Wockhardt's Battle Against Superbugs"

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The book's title, 'No Options' aptly captures the current helplessness in tackling the infections caused by the superbugs. However, it is pertinent to note that this state of affairs is the result of complacency that set in after the "Golden Era" of antibiotic discovery (1960–1990). This period, led by the big pharma, witnessed the launch of a steady stream of novel antibiotics that not only saved lives but also played a pivotal role in making the modern clinical science (complex surgeries, cancer treatment, organ transplant, etc.) successful. But unfortunately, now the prestige of antibiotics has fallen to that of a commodity due to complacency, especially among policymakers and global healthcare agencies who mistakenly believed that humanity has defeated the superbugs and new antibiotics are no more a necessity. As a result, the society now equates antibiotics to water or pizza – need to be easily available at a similar cost. Even for the pharmaceutical industry, the development of antibiotics became a low-priority business model compared to other therapeutic areas, such as cancer, obesity, diabetes, or blood pressure/hypertension. It is paradoxical that only antibiotics provide disease 'curing' outcome rather than merely symptomatic relief, yet they have been eclipsed/overshadowed by the medications used to treat lifestyle disorders or cancer. This led to the down fall of once thriving antibiotic discovery ecosystem which was further hastened by big pharma exiting this research area. Eventual hiatus of 20-25-year in the discovery of antibiotics created a situation of overdependence on older antibiotics

which in turn triggered the evolution of diverse resistance mechanisms giving rise to 6-7 different superbugs.

After 1990, humanity started to pay a price for the lack of effective antibiotics as infections caused by certain bacteria, such as methicillin-resistant *S. aureus* (MRSA), Pseudomonas, Klebsiella, and Acinetobacter, rapidly became almost untreatable, particularly in the ICU settings. The current resistance situation is such that the clinical community is waging a daily battle against infections in ICUs and wards, a situation, similar to the "pre-antibiotic era". Thus, superbugs dragged the medical and scientific communities to their knees and forced them to 'learn' utilizing toxic antibiotics that were long abandoned, including polymyxin and colistin. Superbugs exposed the world to yet another harsh reality - while building a research infrastructure is plausible, developing experienced multi-disciplinary scientific talent for antibiotic discovery is not easy. Further, there was a belief that newer 'superbug-active' antibiotics cannot be evolved from a clinically well-established older antibiotic classes. Because of this misleading perception, discovery teams focused on entirely new classes of antibiotics largely relying on in-silico models. This approach utterly failed to produce any worthwhile antibiotics, despite heavy investments and such sorry outcome effectively put an end to the antibiotic discovery research.

When Wockhardt began its quest for new antibiotics approximately 25 years ago, the top management as well as discovery team remained steadfast in its conviction that an already-proven class of antibiotics could be creatively altered to combat modern superbugs. The research team consciously stayed away from in-silico-, vaccine-, monoclonal antibody-, and bacteriophage-based approaches as these approaches could take decades to produce a clinically-viable antibacterial drug, whereas the need for a novel, superbug-active antibiotic is 'today'. At the grave risk of appearing old-fashioned and therefore not worthy of attracting deserved public attention and funding support, Wockhardt remained traditional and continued to build end-to-end capabilities through a multidisciplinary team of >135 scientists fully dedicated to the antibiotic discovery. The track record of antibiotic discovery at Wockhardt proves that it could replicate the successful discovery

ecosystem of 'big pharma' prevalent during the 'Golden Era' leading to a steady flow of innovative antibiotics that are able to combat the superbugs causing life-threatening infections.

Wockhardt's sustained focus in addressing the problem of AMR led to 6 novel antibiotics with two of them already approved for clinical use, three at the last-stage of Phase 3 development and one at Phase 1 stage. All the new antibiotics from Wockhardt have been designated as qualified infectious disease product (QIDP) by US FDA as all of them target currently prevalent superbugs listed by WHO and US CDC. The recently launched antibiotics, code named WCK 771 (Emrok, injection) and WCK 2349 (Emrok O, tablets), are anti-MRSA and till date benefitted >47,000 patients. MRSA is known to cause life-threatening pneumonia, blood stream infections, complicated skin infections, diabetic foot ulcers, infections in cancer/organ transplant patients and bone/joints infections. Prior to the availability of Emrok and Emrok O, patients had no access to IV/oral anti-MRSA drugs with safety features required for the longer duration treatment or home treatment for infections such as diabetic foot ulcers, bone infections and infections in cancer/organ transplant patients.

Another novel antibiotic from Wockhardt is nafithromycin (WCK 4873), which would, for the first time offer an ultra-short course treatment for MDR pneumonia caused in the community settings (i.e. outside the hospitals). Due to high resistance among bugs causing respiratory infections (Pneumococci, Haemophilus, etc.), currently available drugs do not provide assurance of safety and efficacy, particularly in most vulnerable population such as children and older age patients. These are also the patients for whom the presently available antibiotics need to be taken for 7-10 days and at least twice a day and therefore are challenging to comply with the treatment schedule. Nafithromycin which is nearing the completion of last leg of development (Phase 3) is expected to provide a unique treatment option targeting resistant pathogens that too with compliance-friendly once-daily, three-day treatment!

Wockhardt's efforts to tackle another set of superbugs belonging to Gram-negative group have yielded WCK 4282 (high dose cefepime/

tazobactam 2g/2g injection) and WCK 5222 (cefepime/zidebactam injection). Together, when available, these antibiotics will provide a lasting solution to complicated urinary tract infections (cUTI), complicated intra-abdominal infection (cIAI), hospital and ventilator-acquired pneumonia and bloodstream infections. WCK 4282 targets commonly encountered resistant pathogens in wards such as *E. coli*, Klebsiella, Enterobacter and Citrobacter. This novel first-line antibiotic of future will minimize the infections related complications that may land the patients into ICUs/ventilator. A Phase 3 study of WCK 4282 is slated to begin early next year. The discovery of WCK 5222 is a perfect example of looking at a problem from a fresh angle and choosing to go down an untried path while appreciating how superbugs are always coming up with newer ways to evade the antibiotic action. A deep-diving study of existing antibiotics and those in the development pipeline made the Wockhardt discovery team realize that the approaches followed until now were no match to the multiple mechanisms of resistance already acquired in deadly pathogens such as Klebsiella, Pseudomonas and Acinetobacter. This led to the discovery of novel class of antibiotic termed as β-lactam enhancers. Such exciting is the coverage profile of WCK 5222, that >50 publications from world-renowned specialists have appeared in leading scientific journals. These publications show that WCK 5222 has a potential to offer a life-saving destination therapy (an antibiotic helping patient reach the ultimate destination of cure) for ICU infections caused by extreme- drug-resistant superbugs such as *E. coli*, Klebsiella, Pseudomonas and Acinetobacter. Acknowledging the unmatched pathogen/resistance coverage of WCK 5222, recently Drugs Controller General of India (DCGI) approved its use under the compassionate grounds for the critically ill patients that were not responding to any of the available antibiotics. WCK 5222 rescued five such patients, few suffering from cancer or organ transplant. This drug is expected to change the paradigm in the treatment of sepsis and hospital and ventilator-acquired pneumonia and blood infections. The global Phase 3 study of WCK 5222 has been progressing smoothly in Europe and the drug could reach worldwide patients by 2025.

Finally, in response to the requirement of an MDR-active drug with a convenience of treating patients outside of the hospital, Wockhardt

team discovered WCK 6777 (ertapenem/zidebactam) which is a once-daily treatment for resistant infections of UTI or gastrointestinal tract. The need for such a drug was strongly felt during the COVID-19 pandemic as the hospital infrastructure was overburdened and there was a need of a drug that could help treat resistant infections outside the hospitals. Acknowledging such unique clinical profile of WCK 6777, the world's foremost health research organization, National Institutes of Health (NIH), USA has selected WCK 6777 for conducting Phase 1 studies in their facility.

Besides, the insights drawn from 'Golden Era', the success of Wockhardt in the field of antibiotic discovery is attributed to a number of other supportive factors, including scientific freedom, persistent focus and easy access to organizational resources and the capability to weave international collaborations with top researchers and teams. However, in the longer run, so as to address the ever evolving AMR problem, such antibiotic discovery programs would continue to need enormous resources and therefore, both push (incentivizing antibiotic discovery and development) and pull (rewarding innovative antibiotics making a difference) incentives are necessary to offset the poor return on investment linked with antibiotic drug class.

Despite the fact that the several funding organizations have been set up over the past ten years, the project selection criteria has been far from pragmatic. It is of utmost importance that the funding agencies strike a balance between long- and short-term objectives. Longer term, high-risk projects (for example, bacteriophages, vaccines, or those involving chemical classes that were clinically not used) might be supported, but in light of the acute current need of effective antibiotics, these organizations must give priority to funding 'well-differentiated' clinical viability-assured projects. Such projects can be readily identified based on independent studies that support the project concept, a positive review from drug regulators, and safety from Phase 1 studies.

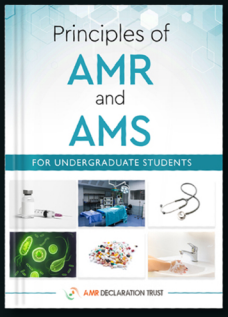
From Indian perspective, it is of even higher urgency that the country quickly achieves self-sufficiency in safe and effective antibiotics that are tailored to tackle country's enormous resistance problem. For this,

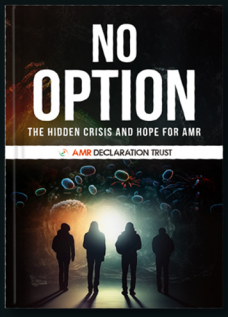
a stable, multi-year incentives and funding mechanism needs to be put in place promptly to support high-level antibiotic discovery and development programs. The criteria of clinical viability, independent research substantiating project concept, favorable assessment from drug regulators, patentability and safety from Phase 1 trials may again be the guiding parameters to evaluate deserving/worthy projects of national relevance.

NO OPTION

THE HIDDEN CRISIS AND HOPE FOR AMR

"No Option: The Hidden Crisis and Hope for AMR," presented by the AMR Declaration Trust, is a compelling anthology of real-life stories illuminating the global crisis of antimicrobial resistance (AMR). While the narratives in "No Option" are penned by committed Indian doctors, they mirror a reality that exists across the globe, underlining the universality of the antimicrobial resistance (AMR) crisis. These stories emphasize that the struggle against AMR is not confined to any single country but is a shared global challenge requiring collective action. This book also highlights India's leadership in innovative solutions while encouraging readers to comprehend and contribute to tackling this urgent issue. It's a tribute to the millions who lose their lives to AMR annually and the tireless scientists and leaders dedicated to combating this challenge. "No Option" is a testament to humanity in the global fight against AMR.





AMR Declaration Trust is a public charitable Trust founded on the principles of Chennai Declaration- a land mark Indian initiative to tackle the global challenge of AMR.

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