When the Drugs Don't Work

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The Hidden Pandemic That Could End Modern Medicine

Anirban Mahapatra

juggernaut

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For Rituparna, whose unwavering support makes all things possible

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Preface

What This Book Is About

In recent years, there have been several books written about the rise of bacteria that can't be treated with common antibiotics for scientists, physicians, economists, historians, and policymakers. This, however, is not one of them.

This book has been written to raise awareness of a health crisis that affects you, me, and everyone else. The idea came from a frank disclosure made by a family member, someone who had a nightmare encounter with superbugs – a bacterial infection that did not respond to antibiotics.

Perhaps you know someone who has faced a similar crisis. A premature newborn confined to an intensive care unit (ICU) struggling for life with a superbug infection. Or a urinary tract infection that just wouldn't go away. Maybe a routine surgical procedure or a Caesarean section that led to a prolonged stay in a hospital.

If you live in India, Bangladesh, Pakistan, or a similarly populous and dense country where antibiotics are readily accessible, it's highly likely you've directly encountered a superbug or know someone who has faced this threat. The rapid spread of antibiotic-resistant bacteria has made superbugs a global issue, with their proliferation increasing every day at an alarming rate.

The hidden pandemic of superbugs could end medicine. This is the simple truth. If you think I'm exaggerating, let's consider the facts.

Antibiotics are crucial for protecting the health of individuals both in India and worldwide. The first person to receive the first antibiotic, penicillin, had developed an infection after scratching the side of his face while pruning roses: he died when his supply of the miracle drug ran out. We might be going back to a period where even minor scratches pose lethal risks. Additionally, diseases like tuberculosis (TB), pneumonia, gonorrhoea, and even seemingly minor infections like strep throat may become untreatable.

People with chronic conditions like diabetes, which affects over 100 million people in India alone, are susceptible to infections due to weakened immune systems. Further, cancer patients receiving chemotherapy are at a high risk of developing serious infections. Recipients of organ transplant and those undergoing dialysis for advanced kidney disease also face a heightened risk of infection. Thus, antibiotics play a vital role in protecting these vulnerable populations – and modern medicine requires antibiotics that work.

Sepsis, a response to infections typically caused by bacteria, affects at least 11 million Indians every year and often results in death. It's especially prevalent in ICUs in India, where up to half of the patients may develop it. Patients undergoing surgery risk life-threatening infections, and antibiotics are necessary for surgical procedures to be viable. This is particularly important for the growing number of Caesarean sections, which account for about one in every five births in India.

India is at the forefront of the global battle against superbugs. In India, in 2019, superbugs were directly responsible for around 300,000 deaths and were a contributing factor to one million more. The confluence of India's dense population, environmental challenges, inadequate sanitation, and healthcare systems, as well as low levels of public awareness of this problem, creates a fertile ground for the spread of superbugs. The situation is exacerbated by the easy over-the-counter availability of antibiotics, leading to widespread self-medication and a general tendency among healthcare providers to prescribe antibiotics as a go-to solution. Additionally, the market is flooded with untested and unapproved combinations of antibiotics.

India's role as a major producer of pharmaceuticals, including antibiotics, adds another layer of complexity to the problem. Cities like Hyderabad, known for their pharmaceutical industries, have reported dangerously high concentrations of antibiotics in local waterbodies. This problem extends to many of India's urban and industrial areas, such as Delhi, where antibiotics are found in both water supply and sewage systems.

Surprisingly, around 70 per cent of medically important antibiotics sold in the world are not used in human health but to plump up animals for consumption. In 2020, India ranked among the top five countries, along with China, Brazil, the US, and Australia, in terms of antibiotic usage for livestock including cattle, sheep, chickens, and pigs.

Tackling the superbug crisis requires a multifaceted approach that goes beyond the reach of only doctors and scientists. While these experts play a critical role in advising on policy and revising prescription practices, a broader societal effort is needed to combat the spread of superbugs. In response to this growing threat, in 2022, India, along with thirty-eight other countries, committed to a significant reduction in the use of antibiotics in animal agriculture by 30 per cent to 50 per cent by the end of the decade.

To address the root causes of antibiotic resistance, it's essential to enforce stricter regulations on pharmaceutical companies to prevent dumping antibiotic waste into the environment. Physicians must resist the urge to prescribe antibiotics without a diagnosis of a treatable bacterial infection. Similarly, pharmacies must be regulated to limit the sale of antibiotics to only those with prescriptions. Crucially, public awareness and behaviour, must also change. Educating the public about the risks of antibiotic misuse and the importance of not demanding antibiotics for minor illnesses is vital.

This challenge is for all of us. In this book, I will inform readers about the remarkable discovery of antibiotics, the consequences of their misuse that led to the terrifying emergence of superbugs, and the actions we can collectively take to safeguard the future of modern medicine and our own well-being.

Perhaps one way to understand the dimension of the danger is by comparison to the most recent global pandemic. The mayhem caused by COVID-19 is well known. We all bear the trauma of the pandemic years. Many of us will need time to heal. Others will try to forget about it as soon as possible.

Many of us are also acquainted with some of the major challenges facing humanity such as climate change, the threat of a close encounter with an asteroid, and rogue artificial intelligence. But another insidious threat hides in plain sight in our daily lives and that is the silent, or hidden, pandemic of superbugs. We ignore this calamity at our peril.

A hundred years ago, infectious diseases were one of the leading causes of death worldwide. The use of antibiotics and the implementation of modern public health measures, such as vaccinations, sanitation, and improved living conditions, have since significantly reduced the impact of infectious diseases on global mortality. Today, this trend is being reversed.

The writing is on the wall. Today, superbugs present a greater threat than COVID-19. If left unchecked, they will inflict a heavier burden on the economy and result in a more significant loss of life. It is clear to me that the discussion of antibiotic-resistant superbugs needs to move beyond microbiology conferences and conversations with doctors in white coats. It needs to move from the corridors of hospitals into the chat groups of ordinary citizens and into the halls of power.

To understand the superbug pandemic, we must examine our relationship with antibiotics because the two are deeply interconnected. The discovery and subsequent widespread use of antibiotics revolutionized modern medicine. The golden age of discovery of antibiotics lasted from the discovery of penicillin in 1928 to around 1964. The rate of discovery and development of antibiotics slowed over the next sixty years. The slowdown is often referred to as the 'innovation gap' in antibiotic research, and today, there are not nearly enough antibiotics for deadly superbugs.

Overreliance on and misuse of these drugs have given rise to superbugs. Today we are faced with a crisis, since many of these wonder drugs don't work any more. **The last new major class of antibiotics that reached the market was daptomycin, discovered in 1984 and approved for use nearly two decades later.**

No truly innovative antibiotics have hit the market in over twenty years. At the same time, bacteria that are resistant to every one of the antibiotics we have at our disposal are

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Year of introduction of common antibiotics and year when credible reports of antibiotic resistance were first reported

Antibiotic	*Antibiotic Deployed to the Public*	*Antibiotic Resistance*
Penicillin G	1942	1947
Streptomycin	1944	1946
Chloramphenicol	1948	1950
Erythromycin	1952	1955
Tetracycline	1952	1959
Vancomycin	1956	1982
Cephalosporins	1964	1982
Linezolid	2000	2001
Daptomycin	2003	2006
Ceftolozane/Tazobactam	2014	2021

Table modified from data from the United Nations Environment Programme report *Bracing for superbugs: Strengthening environmental action in the One Health response to antimicrobial resistance* (2023).

Other sources may provide somewhat different dates based on the country of deployment of the antibiotic and the criteria for determining resistance.

showing up with alarming frequency. Superbugs resistant to multiple antibiotics are moving from being increasingly difficult to tackle to being impossible to treat. The words of an infectious diseases specialist breaking the news to a patient who had acquired a superbug infection after an amputation still ring in my ears: 'We don't know how to treat you.'

Antibiotics are used in almost every sphere of our lives. If they stop working, it will truly be the end of modern medicine. Let me tell you about two personal events that occurred during the writing of this book which illustrate my own complex relationship with antibiotics.

My eleven-year-old son came home from school one day feeling sick. He developed a fever the next day and a sore throat with a cough. These respiratory symptoms are common, but they're also non-specific and tell us nothing about the cause of illness. We tested for COVID-19 at home with a rapid antigen kit, which came back negative. Appreciating that most respiratory infections that kids pick up get better on their own, my son rested at home for the next few days and drank plenty of fluids. The only medicine we gave him was a low dose of a fever reducer available without a prescription

When the symptoms had not resolved in a week, we took him to his paediatrician, who tested for COVID-19 again, influenza A and B, and the bacterium that causes strep throat. These tests are usually accurate if they render a positive result but are less reliable when the results come back negative. My son tested negative in all cases.

And so, we were no closer to identifying the cause of my son's ailment. And it wasn't getting better. What's worth noting is that the paediatrician did not prescribe any medicine, but instead asked us to keep monitoring symptoms and come back if they worsened or didn't get better on their own. What the paediatrician *did not do* was prescribe an antibiotic.

My son could have been suffering from an infection that was not routinely tested for, or from allergies, or another ailment for which there were no rapid tests. More accurate cultures could have confirmed if there was indeed a bacterial infection. But thankfully for us, and as you might have expected, my son did get better on his own.

My spouse and I are well aware of the dangers of over-prescription of antibiotics. We currently live in the US where antibiotics are not available without prescriptions. A similar situation with a different child, parent, or physician might have played out differently in a different time or in a different part of the world. We could have pushed the physician to prescribe an antibiotic. Additionally, she might also have been expected to prescribe an antibiotic or two, even if the chance that they were needed was low.

Rapid diagnostic tests might not have been available or been more expensive than antibiotics. Also, they are not entirely accurate. When the gold standard for identifying bacteria and matching them to antibiotics that work against them takes two days or more, a physician must move beyond the textbook to apply practical experience. They must consider the resources they have at their disposal, what other infections they have seen recently, and whether the patient is likely to wait for a confirmatory diagnosis. A physician might ask themselves the question: 'Will I ever see this patient again?'

When antibiotics first went into broad use starting in the 1950s, it was common for physicians to prescribe antibiotics not after the confirmation of a bacterial cause, but simply by observing symptoms. Even then, it was appreciated that most respiratory infections are not caused by bacteria. As such, antibiotics that have specificity against bacteria are useless in treating infections caused by viruses or seasonal allergies. In fact, as we will see, they can be harmful not only to broader society, but also to the person who takes them.

More recently, around 60–80 per cent of patients treated for COVID-19 were prescribed an antibiotic, such as a cephalosporin or azithromycin. This was despite the common knowledge that these antibiotics are not effective against the coronavirus that causes COVID-19. Even if physicians suspected that there was an associated bacterial infection lurking alongside the coronavirus, they would've known that the odds of such a co-infection were small. According to a recent study, only 5 per cent of patients had both the coronavirus and a bacterial infection treatable with an antibiotic.

What about the parents of a sick child? In countries like India where many antibiotics are easily available without a prescription, parents watching a suffering child may be tempted to get them from a local pharmacy themselves and give them without an understanding of whether they are required or how they work. They may remember a time when they popped antibiotics for a couple of days and got better and assumed that it was the antibiotics that had healed them. We tend to overestimate the effect of actions we take. As a result, action, even if taken without a logical basis, despite being actively harmful, is often seen as preferable to inaction. I understand the urge.

The second incident I want to highlight occurred recently, when I was having a conversation with my aunt. A resilient woman well into her seventies, she had weathered a litany of health challenges over the years. As the conversation flowed, the topic of this book surfaced. My aunt shared an unsettling belief that she had become resistant to antibiotics. She felt there was an inherent flaw within her, making her vulnerable to infections that antibiotics could not remedy.

This misconception struck a chord with me. It was not the first time I had encountered the sentiment, and it made me realize why this book needed to be written. I explained to my aunt that our bodies do not become resistant to antibiotics. Instead, antibiotics are ineffective in treating infections caused by the resistant bacteria that are inside us.

I also explained to my aunt that not all bacteria are harmful: there are trillions of bacteria inside us that contribute positively to our health. These beneficial bacteria inhabit various parts of our bodies like the gut, skin, and mouth. They assist in digesting food, producing essential vitamins, regulating our immune responses, and even influencing our mood and mental health. Beyond these beneficial bacteria, a significant number remain neutral, causing neither harm nor providing any explicit benefit.

This nuanced relationship with bacteria stands in contrast to our interactions with viruses. Let's consider COVID-19, a viral disease. There's never a circumstance in which the presence of the causative coronavirus in a human body is considered normal or natural. Whether it manifests with pronounced symptoms or remains silent, it is an invasion by a foreign entity. The virus exists to replicate and spread at the host's expense.

Many harmless bacteria can become disease-causing given the opportunity. Some may enter from outside, but many others live within our bodies. When disease-causing bacteria acquire resistance to antibiotics, they become superbugs.

Here's the sobering reality: we will never completely eliminate superbugs because bacteria living within us can develop antibiotic resistance. But there's a silver lining. By reshaping our approach to antibiotics and understanding our relationship with bacteria, we can change the narrative. The pandemic of superbugs looms large, but the future isn't set in stone.

Through this book, we will consider the causes – that's plural – of the superbug crisis. Make no mistake, there is no single cause or simple solution. One of the many reasons is the overprescription of antibiotics, a significant driver of the rise of superbugs. Unnecessary exposure to antibiotics gives bacteria a chance to adapt and become resistant. Agriculture exacerbates the issue, with the overuse of antibiotics in livestock and fish farming. These antibiotics then enter the environment and the food chain, leading to widespread exposure and again, the evolution of superbugs.

Poor infection control leads to the rapid spread of superbugs. This is worsened by substandard hygiene and sanitation practices in communities. Here, communities and governments also play a vital role in stopping the spread of superbugs. Policymakers must enforce stricter regulations to curtail the rampant overuse of antibiotics and also to incentivize the development of new drugs. The pharmaceutical industry needs to prioritize and accelerate research on superbugs and the next generation of antibiotics.

Ultimately, as individuals we must embed good habits in our daily life, such as refraining from self-prescribing antibiotics or veering from a recommended prescription course. Just as we teach our children to look both ways before they cross the street and drill it into them until the habit becomes instinct, we need to drill it into everyone that antibiotics must be used with caution until that idea becomes instinct. This is essential to combat superbugs and slow down the rise of antibiotic resistance.

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A Daily Tragedy

'Every medicine, every antibiotic they gave her, it did nothing. Her body was tiny, but her battle was immense.' Anjali struggled to maintain her composure as she retold her daughter's story for the documentary film's crew. 'As a mother, you feel so helpless.'

Anjali's daughter was born prematurely and spent a heart-wrenching seven days in the ICU of a hospital in Amravati, a small town in Maharashtra. Those seven days were filled with a roller coaster of emotions for Anjali: hope, despair, and a mother's fervent prayers. Yet, despite the valiant efforts of the medical team, a parent's worst nightmare came true for her and her family. The tiny girl died, before she could even leave the hospital, before she had been introduced to the world. She had not even been named.

The paediatrician who treated Anjali's newborn was reflective, but gave a telling assessment of the tragedy. The baby died of neonatal sepsis, a life-threatening medical condition which occurs when a newborn acquires a severe infection that spreads throughout the body. The infection was caused by an untreatable bacterial strain – a superbug that didn't respond to any antibiotic. There was nothing that could've been done to save the baby.

Sadly, this tragedy is far from an isolated incident in India today. Anjali's daughter is one of the approximately 60,000 babies in the country who die each year from infections caused by bacteria that don't respond to front-line antibiotics. These superbugs threaten to upend modern medicine and push back decades of progress in improving the quality of life in India.

'What happened to me shouldn't happen to anyone else. It's a pain you can't put into words,' says Anjali, her voice tinged with a sorrow that she knows will never completely go away.

Unfortunately, we are heading towards a catastrophe in which many mothers like Anjali will regularly mourn the loss of their children. India is at the forefront of a crisis, a hidden pandemic of superbugs, that is killing our most vulnerable populations. We must act now or face the consequences because we have created this crisis. Unfortunately, there is a lack of public awareness about how we got here and what we can do to solve the problem.

This book covers the tragic circumstances of the decisions that brought us to this point, the dangers we face, and what we need to do to emerge from this dark shadow that threatens to take healthcare back into the pre-antibiotic era.

However, before we talk about superbugs, we need to acknowledge how much life has improved in the last few decades for most of us. India, now the most populous country in the world, has witnessed a healthcare transformation that is nothing short of miraculous. Consider this: if you were born in India around Independence, you could expect to live only until your early thirties. Life was fraught with challenges such as malnutrition, inadequate sanitation, and widespread infectious diseases.

Fast forward to the present, and the average Indian can expect to live up to around the age of seventy, a monumental advance. And while today there are indeed large disparities between genders, communities, and economic classes, the overall progress we have made in improving the lives of common people is undeniable. We must take a step back and appreciate this.

There isn't one single benign factor that led to this revolution, but rather many things working in tandem. Better education and economic progress played an important role in health awareness. An educated populace can make more informed choices. Economic progress has also enabled advances in health. Further, knowledge without the capability to act is futile, and that ability came from relative advances in prosperity, which allowed for improved well-being in successive generations.

Then there's what we eat. Enhanced diets significantly reduced malnutrition and starvation, leading to healthier and longer lives. India has not experienced a single serious famine since its independence. The Green Revolution of the 1960s and 1970s helped the country significantly increase its agricultural production through the introduction of high-yielding crop varieties and modern farming techniques. This allowed India to not only feed itself, but to post annual surpluses for many staple crops, and even become a food exporter.

It's not easy to transform the infrastructure of a country, but India has persevered on this front too. Improvements in sanitation and sewage systems have made living conditions cleaner, reducing the risk of diseases. While open defecation remains a persistent issue, strides have been made to reduce it.

Let's not forget healthcare. From basic medical centres to specialized hospitals, the quality of medical facilities and professionals has seen a marked improvement in the country. More can and should be done, but we should appreciate the efforts of healthcare professionals in modern India. Take cholera, for example. Historically, six of the seven cholera pandemics that occurred globally originated in India before Independence. However, not a single cholera pandemic has occurred in India in the past few decades. While smaller cholera outbreaks do still occur, the risk of contracting cholera and dying from it has greatly diminished.

These facts are not just academic for me. My family, like millions of others, benefited from this progress. We were lifted out of poverty and joined many others as part of the 'Great Indian Story'. My father was born before Independence in a village that had no electricity. He grew up without access to clean water and sanitary sewage disposal. Despite meagre means, he went on to complete his education at one of India's premier medical institutions, the All India Institute of Medical Sciences, which was founded in New Delhi in 1956. My mother also came from a similar background. She received her postgraduate medical degree from the same institution. Their education prepared them for further training abroad, after which they returned to treat patients at a district town in India.

Although my own story took a slightly different path, there are some similarities. Like my parents before me, my own education was almost entirely subsidized by the Indian taxpayer. Although the following statement might sound fantastic, I've crunched the numbers, and it is absolutely true: the total cost of my college education to my family was less than that of a high-end smartphone today. This number neglects to account for inflation of course, but it is still a startling realization.

When I arrived in the US to continue my studies in microbiology, the move was made possible by the generous fellowships I received, and the research grants awarded to my mentor and PhD adviser. I did not have to pay for doctoral training. Indeed, this is why I have always felt indebted to taxpayers in two countries.

The benefits of widespread vaccination are also personal for me. My father nearly died from a severe smallpox infection while he was in college. I was born the same year that *Roti, Kapada, Aur Makaan* (translated to Food, Clothes, and Shelter in Hindi) with Manoj Kumar in a lead role and the up-and-coming Amitabh Bachchan in a supporting role was the biggest Hindi blockbuster. Later, I would be immunized around the same time that the last known case of smallpox was reported in the country in 1975. Born after smallpox was eradicated, my son has never needed to be vaccinated against it. Polio is no longer the concern it once was in India either.

Even for other diseases that have not been eradicated, vaccination drives have substantially reduced mortality. Fresh in public memory is the massive COVID-19 vaccination drive that India launched to ensure citizens were protected. Today, India not only vaccinates its own but produces many of the vaccines used around the world.

If vaccines have helped prevent some infectious diseases, then antibiotics have treated other persistent ones. Ask anyone what some of the greatest advances of the past century are and you might hear answers that include the personal computer and internet revolution, global air travel, and television. But let me offer a serious contender. Antibiotics are among the greatest technological triumphs in human history. Without question, these drugs are an indispensable aspect of modern life, transforming once-fatal bacterial infections into manageable conditions.

Do you think I'm exaggerating? Antibiotics are the drugs that made modern medicine possible. Before antibiotics existed, a scratch or a scraped knee could result in a deadly infection. Today, antibiotics are used preventatively in surgeries, to treat chronic conditions like cystic fibrosis, and to stave off infections in high-risk scenarios. They have saved uncounted millions of lives, and an estimated 40 billion doses of these medicines are consumed every year.

But the pressing and unavoidable question remains: what do we do if and when these life-saving drugs become ineffective?

When bacteria develop resistance to antibiotics, everyday medical procedures become high-risk. Childbirth and the initial months of a baby's life turn precarious. Even routine hospital visits and minor surgeries carry significant danger. Simply housing patients together in the same ward introduces risk.

If bacteria that are resistant to many, or all the available, antibiotics spread widely, it isn't just a minor or temporary setback, it is a public health crisis. The rise of antibiotic-resistant superbugs adversely affects life expectancy. The consequences are severe, putting immense pressure on healthcare systems and in India, it rolls back the clock on the hard-won medical advances of the past few decades.

But it is time to brace yourself. This dystopian future is not a hypothetical scenario: it's already manifesting right now. In recent years, a worrying trend has emerged – there are an increasing number of powerful superbug variants of bacteria that were treatable with antibiotics just a few years ago but have now grown resistant to them.

From around 1950, there was always a backup antibiotic that physicians could resort to. When bacteria gained resistance to one class of antibiotics, physicians moved on to the next one. But there is now an ongoing race, one that humanity is losing. In recent years, superbugs have been gaining the upper hand, and the medicine cabinet is running bare. As a result, patients are dying of untreatable infections. And what's worse is the pipeline is also running dry. No new major class of antibiotics has been made commercially available in decades, and we are close to entering the post-antibiotic era.

You might ask how this is possible. In nearly every other realm of science and technology, as time passes and we learn more, we get better at doing things. Moore's Law (which states that the processing power of a computer doubles every few years) is a famous observation that explains why the smartphone in my pocket is much more powerful than the guidance computer used to land the first humans on the moon in 1969.

Natural Selection of Antibiotic-Resistant Bacteria

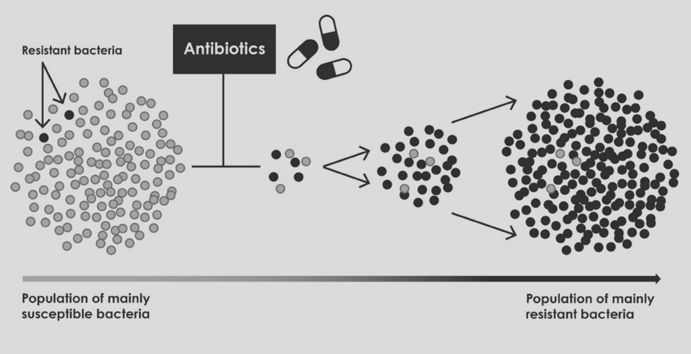

Image credit: The ReAct toolbox on 'mutations and selection'

Initial Population: Initially, there is a diverse population of bacteria, most of which are susceptible to antibiotics (represented by the grey dots). A few bacteria are naturally resistant due to random mutations that exist in populations (shown here in black).

Application of Antibiotics: When antibiotics are introduced (the pills icon), they kill most of the susceptible bacteria. Resistant bacteria survive because they have certain traits that protect them from the effects of the drug.

Multiplication of Resistant Bacteria: The resistant bacteria (black dots) survive the antibiotic treatment. Since the susceptible ones (grey dots) are now largely eliminated, the resistant bacteria face less competition for resources and can multiply freely.

Change in Population: Over time, as resistant bacteria replicate, the population shifts from being mostly susceptible to being primarily composed of resistant bacteria. This means the antibiotic is now much less effective since most of the bacteria present can tolerate it.

But nature has a secret advantage over machines. Carbon-based life forms have extra capabilities that silicon-based transistors don't have: they can evolve. Life has had plenty of time to figure out how to do things better than humans.

Even when we find ways to defeat bacteria, they come back. A new generation of bacteria can grow very fast – some even double in population every twenty minutes. Bacteria are incredibly versatile, and they've been here for billions of years. Modern microbiology is not even a few hundred years old, and does not have much of a chance against these formidable foes. British chemist Lesley Orgel aptly summed up this dynamic with his observation: 'Evolution is cleverer than you are.'

Now, I will let you in on another little secret. Humans can make great smartphones and rocket ships, but so far, our track record at making drugs that beat bacteria is pretty lousy. Technically, antibiotics are natural products made by the bacteria and moulds that can kill or retard the growth of certain bacteria. Sometimes, the definitions are broadened to include natural products that kill fungi or parasites, but we'll stick to the original definition for clarity.

What about drugs that chemists design and make from scratch? To differentiate them from antibiotics, we will call these synthetic compounds antibacterials. There are not as many antibacterials as there are antibiotics. In fact, most of the antibiotics in use even today are ones we took from (mostly soil) bacteria. We've tinkered with antibiotics that soil bacteria naturally make to produce them at scale, improve their effectiveness, and make them last a little bit longer. But massive projects to create antibacterials from scratch have little to show for the money and effort that have been put into them. That's one of the reasons that most major pharmaceutical companies have moved on from the effort to create new antibacterials altogether. Nature is still the best weapon against nature.

I can trace the first shoots of my inspiration for writing this book back to 2010. In August of that year, a scientific article in the medical journal *The Lancet Infectious Diseases* became the unlikely subject of discussion across India, even making its way to Parliament. The research article described the spread of a gene and an enzyme that gave bacterial resistance to certain antibiotics, making them superbugs. It was named NDM-1 after New Delhi. Perhaps you vaguely remember the controversy even if you've forgotten the details.

During the next few months, the issue (or non-issue depending on who you asked) of antibiotic resistance and superbugs gained significant attention from high-profile medical experts on traditional and social media in India and elsewhere. Soon, politicians got into the act as well. Much was written at the time, but it was impossible to know what would follow. We did not know how NDM-1 would spread or how serious it would become.

Fourteen years have passed since that initial episode with NDM-1, and it is natural to wonder what has happened. Were the *Lancet Infectious Diseases* authors making a huge fuss over something that wasn't a real threat? The truth is that good science takes time. Experiments are conducted and results are formulated methodically. Ideas are discussed and debated, often over a span of years. New studies refine, dispel, or build on previous work. Science has no chance to compete when pitted against the news cycle which strives to find the latest controversy to attract eyeballs and online engagement. The topic was buried and forgotten.

No doubt media outlets do sometimes mention antibiotic resistance when there's a specific incident. But there's rarely the time or space to delve into any details or to provide context. You would think that every incident is isolated, but it's not.

The second spark for writing this book came in 2016 with the publication of an influential report that you've probably never heard of. The report titled 'Tackling Drug-resistant Infections Globally' by the Review on Antimicrobial Resistance framed the problem of superbugs and their terrible impact on health and economy in stark terms. This study was commissioned by the government of the UK, and it was informally dubbed the O'Neill Report after the economist Jim O'Neill who chaired the Review.

In 2014, the then prime minister of the UK, David Cameron, asked O'Neill to survey the scale of the problem of resistance, which isn't simply a health crisis, but potentially a long-term economic calamity that could derail global development and security. O'Neill was no stranger to discerning current trends and tying them together to create a big picture. While at the investment bank Goldman Sachs, he had coined the acronym BRIC to refer to Brazil, Russia, India, and China after identifying them as emerging powerhouses poised for economic growth. As chair of the Review on Antimicrobial Resistance, he immediately commissioned expert teams at consultancy firms to come to terms with the economic underpinnings of this worldwide menace.

Before moving on, I need to clarify a few terms. Antimicrobials are a group of substances including antibiotics, antivirals, antifungals, and antiseptics. These are powerful tools in the arsenal of modern medicine. Antibiotics are a subset of natural antimicrobials that work on specific bacteria.

Let's be very clear. As a class of drugs, antibiotics work against bacteria. They are ineffective against viruses. In addition, some antibiotics are geared to act against specific bacteria and not all of them. To treat a viral infection, we'd need to be prescribed a very specific antiviral. And to treat fungi, we'd need to be prescribed an antifungal. Each class of drug works only because of the very distinct biology of its target.

Bacterial resistance is part of a broader scheme of antimicrobial resistance. Apart from bacteria, many other microbes (such as disease-causing fungi) develop defences against the effects of antimicrobials. In this book, we narrow our focus to the bacterial superbugs which present the main threats to conventional antibiotics. Fungi are also spreading and developing resistance, but that is perhaps the subject of another book.

The O'Neill report found that if left unchecked, by 2050, the problem of antimicrobial resistance could inflict a staggering cost of US$100 trillion on the global economy – an economic apocalypse by any measure. For comparison, this would correspond to a loss equivalent to roughly nearly 4 per cent of the annual global gross domestic product by 2050. It would cast an estimated 28 million people into poverty and swell annual healthcare costs.

The report also predicted that by 2050, 10 million people would die from antimicrobial resistance every year. Of this number, 7.5 million would die from bacterial infections caused by superbugs. To put that large number in perspective, that is more people than currently die from cancer. Even this number probably didn't account for the true toll from secondary impacts like compromised surgeries and increased vulnerability to epidemics.

Let me put it another way. The World Health Organization (WHO) estimates that around 15 million people in all died directly or indirectly from COVID-19 across 2020 and 2021, the two deadliest years of the coronavirus pandemic. So, on the current trajectory, antimicrobial resistance is poised to be more devastating and more unrelentingly lethal than the most lethal pandemic of our lifetimes. In fact, the WHO reports that antimicrobial resistance is among the top global public health threats facing humanity.

O'Neill made several urgent recommendations.

First, a global public awareness campaign needed to educate the populace, particularly the younger generation, about the dangers of antibiotic resistance.

Second, financial incentives needed to be set in place to drive the creation of new antibiotics. Estimating the cost of bringing a new antibiotic to market, the report proposed that market entry rewards of around US$1 billion for each new antibiotic would be suitable.

Third, technological advances needed to be made in rapid diagnosis so that drugs could be pinpointed to target specific bacteria.

In agriculture, where antibiotics are frequently overused, better surveillance and national targets were recommended to guide more responsible usage. Restricting or banning use of antibiotics crucial for human health in animals was another recommendation. The review called on wealthy countries to do their fair share and to take the lead, recommending that all antibiotic prescriptions be guided by rapid diagnostic tests and up-to-date surveillance.

The O'Neill report which outlined the shape of the impending crisis with antimicrobial resistance was discussed among policymakers and politicians. It provided quotable statistics for microbiologists like me. But much like other position papers and policy reports, it failed to capture the imagination of the broader public including taxpayers and the politicians who determine how to allocate tax revenues.

If the O'Neill report was a wake-up-call that few heeded, then a study published in 2022 in *The Lancet*, one of the world's most prestigious medical journals, by a global consortium of antimicrobial resistance collaborators should've been a slap in the face. This study in *The Lancet* study didn't extrapolate bacterial resistance into the future – it convincingly showed that this is already a very real and present danger. It synthesized data from 204 countries and territories and painted an unsettling picture. For the first time, we had reliable estimates of the death toll from superbugs. Not only were the numbers bad, but they were a lot worse than expected.

In 2019 alone, nearly 1.3 million people died directly from antibiotic-resistant infections. In total, antibiotic resistance contributed to almost 5 million deaths that year from complications. What this indicated was that we were two-thirds of the way to the estimated 7.5 million annual deaths from bacterial infections by 2050 in the O'Neill report. So, if anything, the O'Neill assumptions might well have been an underestimate.

What *The Lancet* study had also found was that antibiotic-resistant bacteria already cause more deaths than HIV/AIDS, TB, or malaria. The toll is especially high among the youngest: one in five of these deaths occurred in children under the age of five. The study also provided a clear indication of the worst culprits. Six bacteria that can thwart antibiotics used to treat illnesses were estimated to have caused 80 per cent of the fatal infections from antimicrobial resistance. These superbugs are *Escherichia coli* (often just called *E. coli*), *Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.

Together, these six pathogens were linked to over 3.5 million deaths in 2019. I will refer to them as the 'Deadly Six' superbugs, and they will show up repeatedly in this book. Out of these six, one superbug, methicillin-resistant *Staphylococcus aureus* has its own nickname, 'Mersa' after the abbreviation MRSA.

Despite these alarming facts and figures, the public remains largely oblivious to the scale and urgency of the problem of antibiotic-resistant superbugs. You may even be asking yourself this: if the threat of superbugs is so severe, why don't we hear more about it? It's an important question that strikes at the heart of why the rise of superbugs is a hidden danger and a silent pandemic. I don't think there's a single good reason for this low-key response. Here's what I do know though. When I wrote *COVID-19: Separating Fact from Fiction*, I had to explain the trajectory of a pandemic for a virus with a relatively simple biology. The fact of the matter is, the problem of superbugs is far more complex and more difficult to get across, in terms of lay understanding, and of course, it is far more difficult to research and counteract as well.

Bacteria are cellular organisms with far more complex life cycles than viruses. A single kind of coronavirus caused the COVID-19 pandemic. In contrast, there's not one disease-causing superbug we can point to as the sole cause of deaths due to antibiotic resistance.

I mentioned the Deadly Six superbugs we will focus on in this book. But there are many other bacteria such as multidrug-resistant (MDR) TB that are also lethal. I've chosen to focus on a subset here, but the problem is there isn't a single culprit: there's a whole host of characters that are potential superbugs.

While the coronavirus that caused the COVID-19 pandemic was a virus we had never seen before, the bacteria that develop resistance and turn into superbugs live among us. This adds an additional level of complexity in explaining and understanding the threat.