Bacteria often cause infections, and we take antibiotics to help us recover. Antibiotics are like magic pills that have saved millions of lives. However, the overuse of antibiotics is now making bacteria evolve fast and evade these antibiotics. A few bacteria like the purple one in the petri plate (Figure 1) have evolved a way to dodge and not get killed by one particular kind of antibiotic. The day might come soon when not a single antibiotic would work, and we could die of even tiny paper cuts. In this article, we discuss what antibiotics are, how they target bacteria, and why bacteria are suddenly becoming resistant to antibiotics. We include a list of ten points that each of us must follow and a pledge for everyone to take, to help stop the spread of antibiotic resistance. A small questionnaire is included that we would like you all to answer. Together we can win the battle against antibiotic resistance.

Introduction

The threat is real. Help stop superbugs! This sounds like a line from the latest Marvel movie, but this is in fact, a reality, a hard truth. Once, our friend Amber got a really sore and scratchy throat. The doctor diagnosed it as Strep throat (Streptococcal pharyngitis caused by Streptococci bacteria) and prescribed antibiotics. Her mom insisted that she take all the medicines and at the right time. She grumbled but did so and was cured. It seemed to Amber that antibiotics are magic pills that help one get back into shape from any infection. We already saw what havoc the...
Figure 1. A petri plate growing antibiotic resistant bacteria *Chromobacterium violaceum*. The plate is taken from the group of Dr Anu Raghunathan. Photo credit: Dr Deepanwita Banerjee (NCL, Pune).

Keywords
Antibiotic resistance, superbugs, healthcare, antibiotics, adaptive evolution.

lack of medicines wreck, as in the case of covid-19/coronavirus. But now doctors and scientists are warning us that medicines may not work for bacteria either. It appears that superbugs or antibiotic-resistant bacteria are here! An example of such antibiotic-resistant bacteria is shown in Figure 1. And if we do not act soon, we will be in the post-antibiotic era. What is antibiotic resistance? How did we get here? Will our Strep throats not get cured? Will we now have bacterial infection related lockdowns? Have we lost all hope?

Allow us to take you through an exciting journey in this article, all the way from the discovery of the first antibiotic penicillin to the rise of the superbug and beyond. This is also a call to action; each one of us needs to understand and participate. You too, can prevent the rise of superbugs and reduce antibiotic resistance.

Let us first start with looking at bacteria or ‘bugs’ as they are casually called. They are one of the smallest organisms and made of just a single cell. Bacteria are found everywhere on Earth. Did you know that one square inch of your skin is colonized by about 50 million bacteria? There are also bacteria inside us (about 100 trillion), more than our own cells. Most of these are good bacteria and are not dangerous. These bacteria help in many functions, including digesting the food we eat. The bad bacteria or pathogens are encountered during infections, like the one we had when we
were kids. These are the bad bugs that you want to kill using antibiotics. Bacteria are usually much larger than viruses and unlike viruses, have a well-defined cell structure and usually do not require a living host cell to survive.

1. What are Antibiotics?

Antibiotics are drugs (or medicines) used to treat bacterial infections and have saved millions of lives. These are the natural chemical weapons used by fungi and bacteria to wage war against other bacteria. Most antibiotics we use today are small molecules that we have adopted and modified from nature. In the 1900s, Paul Ehrlich proposed the idea of a magic bullet that selectively targets only the harmful bacteria, but not us. Such a magic bullet was discovered by Alexander Fleming when he accidentally found a fungus growing in his laboratory that was killing the bacteria he was trying to grow. We still use petri plates like the one used by Fleming today (Figure 1). This marked the beginning of the age of antibiotics. Antibiotics fall in the larger class of molecules called antimicrobials. While antibacterial products prevent the growth of bacteria, the term antimicrobials refer to substances that act against all types of microorganisms—bacteria (antibacterial), viruses (antiviral), and fungi (antifungal). In other words, antibiotics act only in case of bacterial infections (see Box 1).

So why are antibiotics so good at killing bacteria? They act by modifying critical functions and preventing the bacteria from repairing or building parts of themselves. Commonly used antibiotics such as penicillin target proteins (enzymes) that make the components of the bacterial cell wall and cell membrane. The cell wall and the cell membrane form two kinds of boundary walls in bacteria. By stopping bacteria from building or repairing them, we can easily stop the growth of bacteria. Several other antibiotics try to block the synthesis and repair of DNA (deoxyribonucleic acid), the central molecule in all cells that encodes genetic information. Another target of antibiotics (e.g. erythromycin) is
Box 1. When do you take antibiotics?

Infections like the common cold, influenza and covid are caused by viruses; rhinovirus, influenza virus, and coronavirus, respectively. Antibiotics cannot kill viruses, and hence taking antibiotics doesn’t help in these situations. While taking antibiotics against non-bacterial infections doesn’t help relieve symptoms, it may make the scenario worse in the long run. Only when you have a secondary infection, after a viral attack, such as from *Streptococci* bacteria, would an antibiotic work.

Antibiotic resistant bacteria or superbugs are bacteria that are not controlled or killed by antibiotics.

Antibiotics do not kill Viruses & Fungi

Antibiotics kill Bacteria

the ribosome, the machinery that makes more proteins. If the bacteria can no longer make their own cell parts like cell wall, DNA or protein, they will die. Although antibiotics have superpowers, bacteria are now getting smarter and evading them. Viruses (such as the coronavirus) don’t have the machinery to make their own cell membrane or ribosome and can’t be targeted by such antibiotics.

Antibiotic-resistant bacteria or superbugs are bacteria that are not controlled or killed by antibiotics. They can survive and even
multiply in the presence of an antibiotic. Most infection-causing bacteria can become resistant to at least some antibiotics. Similarly, antimicrobial resistance—which is a larger area—involves microbes that do not respond to current antimicrobial drugs. Doctors and scientists, including many from India, have been working on different aspects of antibiotic resistance. See Box 2 for a word puzzle of some famous scientists who have contributed in different ways to our understanding of antibiotics and antibiotic resistance. Antibiotic resistance is a serious global health concern. If we want antibiotics to continue having their superpowers and save our lives, we need to do something about it.

**Box 2. Super Scientist Jumble Quiz**

*Put the jumbled up alphabets together or analyze the clues to find the name of the scientist.*

**Starupe:** Louis is renowned for his discoveries of the principles of vaccination and a technique of treating milk to stop bacterial contamination. He developed the first vaccines for rabies and anthrax.

**Cwirhov:** Carl was the first to describe and name diseases such as leukaemia and thrombosis. His description of the transmission cycle of a roundworm *Trichinella spiralis* established the importance of meat inspection.

**Chok:** Robert identified the specific causative agents of tuberculosis, cholera, and anthrax. He postulated a series of four generalized principles linking specific microorganisms to specific diseases.

**Meflign:** Alexander discovered the very first antibiotic penicillin, accidentally. While cleaning his lab bench, he saw a petri plate contaminated with a mould, having wiped clear all the bacteria like it was secreting poison. That mould was *Penicillium* and the antibiotic isolated from it was penicillin. Penicillin was so valuable that it was re-extracted from the urine of patients who were given the antibiotic.

**Ehes:** Fanny is best known for her work in microbiology alongside her husband, Walther. Together they were instrumental in developing agar as a medium for culturing microorganisms in petri plates.

**Skonihy:** Roy recently led a team of scientists who made a huge petri plate coated with different concentrations of antibiotics to visualize the process of antibiotic resistance. Bacteria placed on the outer edges had to adapt to higher and higher levels of antibiotics as they moved toward the centre of the plate. This was a beautiful example of evolutionary biology!

**Knoghid:** Dorothy developed crystallography techniques and was the first to decipher the complete structure of penicillin. She also discovered the structure of insulin and vitamin B12.
2. What Is Causing It? How Do Bacteria Become Antibiotic Resistant?

2.1 Bugs Getting Smart

Antibiotic resistance is not new. Alexander Fleming had seen penicillin-resistant bacteria not long after penicillin was discovered. Bacteria may have several ways to become antibiotic-resistant (see Box 3). For instance, *Staphylococcus* may become resistant by learning to build bacterial cell walls faster than antibiotics can break it down. Other bacteria have learnt how to destroy these antibiotics before they have done their job. Bacteria can acquire these superpowers by random mutations in their DNA (or genome). They can also exchange parts of their DNA (called genes) by a process called gene transfer. They can swap their genes for resistant genes from other bacteria, even dead ones.

<table>
<thead>
<tr>
<th>Box 3. Emergence of antibiotic resistance</th>
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<tbody>
<tr>
<td>Superbugs are created through the following pathways:</td>
</tr>
<tr>
<td>restricting antibiotic entry: Decreased cell permeability</td>
</tr>
<tr>
<td>removing the antibiotic: Antibiotics are pumped out of the cell</td>
</tr>
<tr>
<td>destroying the antibiotic: Enzymes can cut up or deactivate the antibiotic</td>
</tr>
<tr>
<td>bypassing antibiotic action: Produce a Trojan horse to bypass the inhibited molecule</td>
</tr>
</tbody>
</table>

2.2 Security Guards At the Cells Boundary Walls

Antibiotics usually work after they enter the bacteria by crossing the cell walls and cell membranes. Antibiotics can cross the membrane directly or via pores formed by proteins called porins. Superbugs have been shown to reduce the number of these porins or alter how these porins function. This results in reduced entry of the antibiotic. Some other bacteria like *Staphylococcus* have found a way to build bacterial cell walls faster than antibiotics can break them down. Resistant bacteria may increase the exit of the antibiotics as well. Multidrug resistance efflux pumps are proteins
made by the bacteria that help it to pump out different kinds of antibiotics. These pumps are present in many organisms and usually help good bacteria by pumping out toxins such as heavy metals and pollutants. Superbugs can acquire antibiotic-specific pumps by random mutations or from other bacteria. They can then make many more of these pumps and remove all the antibiotics from inside their cells, making them resistant to these antibiotics. For instance, Salmonella containing these multidrug-resistant pumps are becoming a worry in food-related infections.

2.3 Making the Antibiotics Inactive

Another way superbugs can acquire their powers is by destroying the antibiotic. One of the superbugs was found to contain the now-famous New Delhi metallo-enzyme 1 (NDM-1). It is a protein that can modify the chemical structure of antibiotics (called beta-lactams). These drugs target the cell wall and make the pathogen resistant to a broad range of antibiotics. The most common bacteria that make this enzyme are gram-negative bacteria, such as Escherichia coli and Klebsiella pneumoniae. The gene for NDM-1 can spread from one bacteria to another by gene transfer, making it particularly fast in spreading. NDM-1 was first detected in a Swedish patient of Indian origin in 2008. Bacteria containing these enzymes can be found everywhere in the world, not just in New Delhi!

2.4 Adaptive Evolution and Natural Selection

Bacteria have a head start of billions of years over us humans and hence ample opportunity to evade antibiotics and develop resistance. If nature has developed an antibiotic, it probably also has developed a way to fight it. Several organisms have evolved mechanisms to counter antibiotics.

The antibiotic action is an environmental pressure; those bacteria which have a mutation allowing them to survive will live on to reproduce. These could be from random mutations or acquired from bacteria previously exposed to this antibiotic. They will

Antibiotic resistance is an inevitable result of evolution.
then pass this trait to their offspring, which will be a fully resistant generation. In 2016, a group of scientists including Dr Roy Kishony and Dr Michael Baym (Harvard Medical School, USA) used a giant petri plate to visualize this process. They added varying amounts of antibiotics and found that antibiotic resistance increased consistently. At the start, bacteria were only living at the edges of the mega petri plate, where there was none or a low amount of antibiotics. Over time, and hundreds of generations of bacteria, they slowly evolved to acquire resistant genes and were able to spread over the entire petri plate, even at the centre with a very high amount of antibiotics.

2.5 Humans Getting Complacent

So are we helping the superbugs rise? Unfortunately for mankind, we are doing our part to make the superbugs succeed. Repeated and improper uses of antibiotics are the primary cause of the increase in drug-resistant bacteria. In fact, Fleming had already predicted the phenomenon of antibiotic resistance caused by the overuse of antibiotics and said, “The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily under-dose himself, and by exposing his microbes to non-lethal quantities of the drug make them resistant”. While antibiotics should be used to treat bacterial infections, they are ineffective against viral infections like the common cold, most sore throats, and the flu. Antibiotics are being prescribed incorrectly for viral infections. And every time you don’t finish the full course prescribed, you run the risk of creating superbugs and leaving super-strong bugs behind.

Unplanned and rampant use of antibiotics is making them less useful.

This resembles the giant petri plate experiment—a few bacteria that survive the low amounts of antibiotics become stronger and thrive in these conditions and become superbugs. Soap can by itself kill bacteria and it is unnecessary to add more antibiotics. Those antibiotics don’t make us safer but make the bugs stronger. Antibiotics added to food (for preservation), livestock (for the health of animals), and fisheries are aiding the increase of antibiotic resistance. Bacteria are finding ways to fight the an-
tibiotics very soon after they are developed. The number of ways in which we can target bacteria but not harm our own cells is reducing quickly. We need millions of dollars to come up with new antibiotics. Pharmaceutical companies are currently not investing to develop these drugs. There are very few antibiotics in development across the world today.

3. Why Do I care if Bacteria Develop Resistance?

The number of bacteria that are resistant to antibiotics is alarming. Antibiotic-resistant bacteria comprise a real risk to human health and are a major concern around the world. We may be entering into an era where antibiotics may not be effective, i.e., a post-antibiotic era. The danger of antibiotic resistance is that treatable illnesses such as pneumonia, tuberculosis, or minor infections could become incurable. You could die to something as minor as a paper cut. In that last century, in addition to clean drinking water and vaccinations, antibiotics have saved millions of lives. Imagine if I couldn’t easily cure the strep throat infection I had as a child? What if we have to live without antibiotics? I can only begin to dread the nightmare.

3.1 Situation in India

Antibiotic resistance is increasing in India. A recent report initiated by the Department of Biotechnology (India) says that we have some of the highest rates of antibiotic resistance. For instance, a study led by Dr Laxminarayan from the Center for Disease Dynamics, Economics and Policy (New Delhi), reported an increasing resistance to antibiotics that are used as a last-resort measure. Similarly, Dr Sharma and co-workers from World Health Organization (WHO) showed that in Salmonella typhi, the bacteria that causes typhoid, resistance to common antibiotics has increased from 8% to 28% in the last six years. Antibiotic-resistant bacteria are present not just in hospitals and clinics but have also been detected in chicken and fish. Several waste-water treatment plants were found to have high levels of antibiotic-resistant or-
ganisms. These superbugs are everywhere!

In 2012, Indian medical societies adopted the Chennai Declaration, a set of national recommendations to promote antibiotic stewardship. Still, the threat of antibiotic resistance remained real, and it was realized that containing it would require concerted effort. A set of regulations were formulated by the Indian Health Ministry, controlling over-the-counter sales of antibiotics. This is the ‘red line campaign’, which demands that prescription-only antibiotics be marked with a red line. The red line campaign was started to discourage and limit the over-the-counter sale of antibiotics.

3.2 Is All Hope Lost?

All hope is not lost, and research is underway to find new ways to fight harmful bacteria. Scientists are trying different ways to target the growing problem. New antibiotics similar to the ones we have are being tested, but are not enough. We need absolutely new methods and out of the box thinking. For instance, faecal transplants to fight *C. difficile* infections of the digestive system are being tested. State of art research involving phage therapy, metabolite supplements and synthetic biology are underway. Our good bacteria (microbiome) can be perhaps taught to fight the bad ones. But, we also have to control the use of antibiotics in clinics, farms, poultry and fisheries. These can contaminate the environment and drive the evolution of superbugs. We are playing a three-way game of co-evolution with our health at stake. Antibiotics and bacteria are like cheetahs and deers. When the cheetahs get faster, the deer have to speed up to survive. Only that we have become the deers, as the pathogens are attacking us. I am not sure how much faster we can run.
4. What Can We Do?

4.1 Gear Yourself Better: Awareness, Interaction

The first step is that you should know what is antibiotic resistance, what causes it and how we can combat it. Reading this article is a good first step. Also, have a look at the suggested reading list at the end of this article. Talk to your friends, your classmates, your family. You could try a storytelling or a draw-
ing competition (Figure 2). We have prepared a questionnaire that you can try to answer to test your awareness (Box 4). You could also fill up the questionnaire in your class and send us the answers at mulledscience2020@gmail.com. For some questions, there are no right or wrong answers. We will compile these answers, and it will help us understand the current scenario and in the future, may help policymakers in deciding what steps to take, given the current awareness. We also urge you to participate in a survey “Not All Bugs Need Drugs” to understand your knowledge, attitude and practice to antibiotics (Ref: https://goo.gl/forms/LanxaAWARrfjQGeu2).

4.2 Call to Action: Take the Pledge and Follow the Ten Point Plan

Each one of us can do something NOW so that paper cuts and sore throats do not kill people in the future. We have prepared a top ten points plan which we request you to follow (Box 5). Something as simple as washing hands can help stop the spread of these superbugs. Did you know that washing hands was a big step towards reducing hospital and surgery-related deaths in Europe in the late 1800s? An important point to note: do not take antibiotics directly from the chemist/pharmacist (over-the-counter). This is true for all medicines marked with a red line in India. Wait for the doctor’s diagnosis through a culture test, and make sure you have a bacterial infection before you take antibiotics. We must together raise awareness of the red line and help to fight drug abuse and the problem of antibiotic resistance.

Even doctors have not been very clear about the spread of antibiotic resistance. Dr Victoria Fraser, MD made a pledge in 2015, and we urge you all to take it (Box 5). When you take the correct amount of antibiotics at the correct time, you ensure that all bad bacteria are dead and there is little chance of them evolving into superbugs. If we all follow a basic antibiotic etiquette we can together fight the rise of antibiotic resistance. Antibiotics have superpowers and have saved millions of lives. We all want them to continue having superpowers and save us.
Box 4. QUESTIONNAIRE

True or False
1. The red line on a medicine package indicates that it is a prescription drug.
2. If taken too often, antibiotics are less likely to work in the future.
3. Antibiotics can cure viral infection.
4. Bacteria are germs that cause cold and flu.
5. Paracetamol (crocin) is an antibiotic.
6. Antibiotics can reduce any kind of pain.
7. Antibiotics can kill “good bacteria” present in our body.
8. Antibiotic resistance is an important and serious public health issue both in our country and the world.

B. Rate between 1 and 5 (1: Strongly disagree and 5: Fully agree)
1. When I have a cold or fever, I should take antibiotics to prevent getting a more serious illness.
2. Skipping one or two doses does not contribute to the development of antibiotic resistance.
3. I take antibiotics only when prescribed by the doctor.
4. I have, at times started an antibiotic therapy after a simple doctor call, without a proper medical examination.

C. Personal information
Have you used antibiotics in the last year? Yes or No
If yes, how many times?
1–2
3–5
> 5
Name: __________________
Age: __________________

4.3 Can I Contribute in the Future?

The fight against the rise of a post-antibiotic era is multidisciplinary and multidimensional. At the forefront are doctors who are central to this battle. If you are planning to train to be a doctor or know others who are, we urge you to take the pledge (Box 5). It is critical that more and more doctors are aware of this threat and actively combat it. Scientists including biologists, chemists, and chemical engineers are already researching new ways to combat bacterial infection. This is a long ongoing process, and we need
out of the box thinking to tackle this fight. But this shouldn’t be an endless process—if the emergence of antibiotic-resistant bacteria outpaces our research for new disease control methods, it would be too late. To slow down antibiotic resistance, we need social scientists, public health workers, and social workers to make people aware and join this fight. So today and tomorrow, you can contribute in your own way and join this fight for a healthier future.

Box 5. Top Ten Things you Can Do and the Antibiotic Pledge

1. Wash your hands
2. Remind others to wash their hands
3. Practice cough hygiene
4. Stay home when sick
5. Prepare food safely
6. Choose antibiotic free foods
7. Ask if you really need antibiotics
8. Don't ask for antibiotics
9. Get vaccinated
10. Spread the word

I pledge to always use antibiotics appropriately and safely.

That means:
The right antibiotic at
The right time in
The right dose and for
The right duration

Victoria Fraser, MD
May 28, 2015
5. Conclusion

Antibiotic resistance is an emerging threat that we all need to contribute to counteract. Antibiotic resistance is often caused when bacterial populations, exposed to low doses of antibiotics, evolve mechanisms to counter their mode of action. We contribute to antibiotic resistance when we take antibiotics for non-bacterial infections (such as flu) or don’t finish the prescribed dose in the correct time. We hope that more people will be aware of this looming crisis and each of us will take steps to counteract this.

Acknowledgement

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Suggested Reading

[10] S Gandra, Mojica, E Y Klein, A Ashok, V Nerurkar, M Kumari, U Ramesh et al., Trends in antibiotic resistance among major bacterial pathogens iso-
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