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Review Article

Are antibiotics still the same "Wonder Drugs" they used to be, or will increasing resistance render them useless?

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ABSTRACT

Bacterial infections had been a deadly disease for centuries before antibiotics were first discovered. Since then, antibiotics have brought an era of prosperity in medical field, saving millions of lives. However, our life-saving Wonder Drugs (Antibiotics) are being horrendously threatened by the growing number of resistance bacteria. Meaning, our antibiotics are losing their effectiveness, which in turn could cast us to the dark ages of medicine. Nowadays, Cancer is believed to be the deadliest disease in the world; however, statistics prove that by 2050, this world record would be broken by AMR (antimicrobial resistance) with 10 million deaths annually. Meanwhile, the goal of this project is to fully examine data and statistics available in detail, to reveal the seriousness of antibiotic resistance, if they are still as effective as they used to be and if there is any hope in saving the future of our Wonder Drugs. In order to find a valid answer to our title question, I have collected data from various resources, including books, review papers, Journals papers, conference Proceedings, the NHS and reports published by World Health Organisation (WHO). Furthermore, I have run an online survey to collect data on peoples' awareness towards antibiotics resistance. This is to prove, whether antibiotics will one day be defeated by the growing resistant bacteria or will they remain as effective as they have always been.

Keyword: Antibiotic; wonder drugs; antibiotic resistance

INTRODUCTION

Fatal diseases which used to kill millions of innocent people each year are now nearly wiped out in many countries around the globe. This is mostly due to the crucial development of antibiotics and the use of vaccinations. This important discovery, antimicrobial drugs (antibiotics), is one of the most significant medical achievements of the 20th century. The impact of this fascination drug has been so massive that it has made the world to fall into addiction of using it for treating numerous diseases.

Although the discovery of antibiotics is a new innovation, throughout the century's substances carrying properties of antibiotic have been used to treat various diseases. For instance, traces of tetracycline have been discovered in skeletal remains from ancient Sudanese Nubia dating back to 350–550 CE [1][2]. Other similar

samples have been found alongside skeletons in Dakhleh Oasis, Egypt; form the late Roman era [3].

The impact of this project is to prove the fact that antibiotics are not the same all-good and powerful as they used to be; and that the developing resistance is ceasing its treating effect to the extent of making it useless.

BACTERIA

Basically, bacteria are single-cell microorganism made of a nucleus, cytoplasm, cell membrane, cell wall, bacterial flagellum and hundreds of coiled circular DNA. Nearly, 4,000-10,000 different species of bacteria can be detected in only a single gram of soil alone! Nevertheless, of this terrifying number, only less than 10% are classified as harmful bacteria; leaving the other 90% to be actually 'good' [4]. These statistics prove the genetical diversity of bacteria to be the riches in the universe. This genetical diversity have been due to bioactive chemicals. These chemicals are the direct reason behind the genetical mutation and derivation of natural selection of bacteria which in turn produces a broad spectrum of genetic variation among bacteria. Meanwhile, it is the genetic variation in their chromosomal genes that gives bacteria the ability to gain resistance to certain antibiotics [5].

ANTIBIOTICS

To begin with, the vocabulary, antibiotics literally means "against life"; while, referring to those of pathogens. Antibiotics can simply be defined as substances that are produced my certain types of fungi (microorganisms) as a by-product of respiration; which is cable of destroying bacteria. These fascinating chemicals attack the cell wall of bacteria, inhabiting the enzymes in the cell wall. As a result, cell wall synthesis stops, ceasing its growth which in turn kills the bacteria [6]. On the other hand, the term 'Antibiotic' in day to day context refers to the purified and dozed substances produced by fungi in biological fermenters, which are consumed in the form of tablets and injections to treat bacterial infections [7].

There are typically two main types of Antibiotics; Bacteriocidal and Bacteriostatic. Bacteriocidal antibiotics function as a poison, killing bacteria directly. This is done by crippling the production of bacteria cell wall; thus, making them pregnable to all environmental factors. Meanwhile, Bacteriostatic antibiotics hinder the growth and reproduction of bacteria, by ceasing the production of vitamins and folic acids [8][9].

HISTORY OF ANTIBIOTICS

The discovery of antibiotics was itself an accident. This occurred when Professor Alexander Fleming (Figure 1 (a)) started cleaning up his laboratory on the morning of September 3rd, 1928. He came across a Petri dishes (Figure 1 (b)) in which he previously covered with bacteria staphyloccus for his research. He noticed a small bit of mould grown in the middle of the Petri dish. Meanwhile, the devastating change in the history of medicine occurred when he too noticed that the bacteria staphyloccus covering the glass plate had not actually grown around the mould, rather forming an empty zone around it. He then started a new research on this phenomenon, leading him to discover that the mould, Penicillium Notatum, is capable of producing chemicals which inhabited the growth of bacteria [10].

With Fleming's further research, it was found that these chemicals, which later came to be known as Antibiotics, could also eliminate other bacteria and that animals could ingest it without any severe side-effects. However, Fleming ceased his research and moved to other fields of medical issues. It wasn't till ten years later when Howard Florey and Ernst Chain, from University of Oxford, proclaim the discovery of the world's first antibiotic found in mould – penicillin [10].

After abundant tests to prove the treating effect of Antibiotics, British pharmaceutical companies finally approved the mass production of this drug. Furthermore, the break-out of a fire in in Boston, Massachusetts, USA, had many survivors who had severe skin damages which were susceptible to infections from the Staphylococcus. Doctors used Penicillin as a treatment which made a significant success. As a result, the US government began the strong support of the drug. Later during the World War II, Penicillin received the name "Wonder Drug", due to the fact that, it was tremendously been used to treat soldiers in both hospitals and battle fields, in all parts of the war zone, saving thousands of lives. This huge success in the

history of medicine claimed Howard Florey and Ernest Chain the Nobel Prize of 1945 in Medicine, with Alexander Fleming as their role for creating the world's first antibiotic [11].

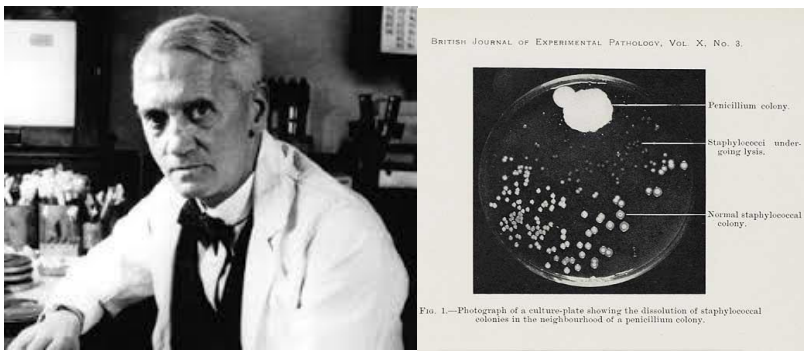


Figure 1: a) Professor Alexander Fleming in his laboratory, b) Fleming's petri dish containing the world's first antibiotic

PROSE AND CONES OF USING ANTIBIOTICS

Advantages

The most obvious advantage of using antibiotics is the fact that it treats various bacterial infections, thus, saving millions of lives every year. Meanwhile, there is still more to antibiotics than just saving lives; as this invincible drug has played a major role in the improvement of medicine more than any drug ever invented before. This is because without the use of antibiotics, chronic diseases such as diabetes, end-stage renal disease, rheumatoid arthritis; or complex surgeries such as organ transplants, joint replacements and cardiac surgeries would have not been even close to being possible; as the infections following these treatments would readily kill the patients within a few weeks [12][13][14]. The Centres for Disease Control, estimates that each year in the US almost 2 million people acquire bacterial infections in hospitals, 70 percent are being treated by antibiotics [15].

Antibiotics have also been an important aspect of improving life span worldwide. For instance, US citizens used to live up to and estimated age of 56.4 years back in 1900-1920. However, now, this have surprisingly increased to an estimate of 80 years old, due to the use of antibiotics as it can be seen in Figure 2[16].

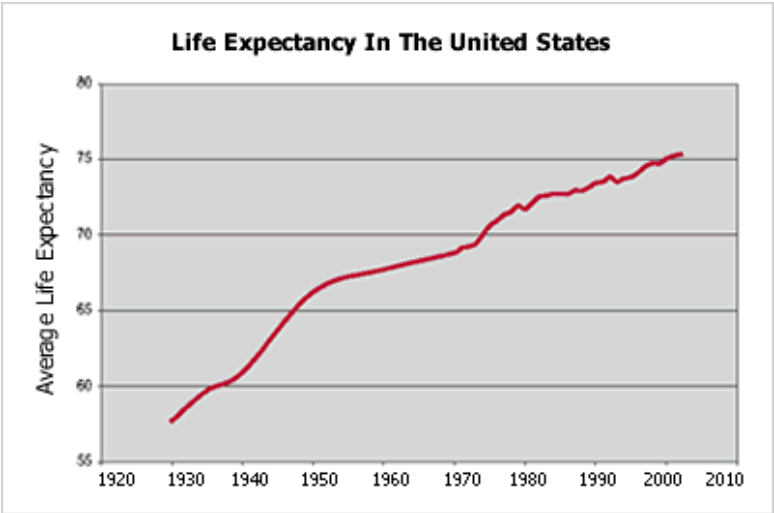


Figure 2: Life expectancy in United State since 1930

The use of antibiotics is the only reasonable solution to food-borne and other poverty-related infections in third-world countries, where sanitation is still a major problem [14]. This is

because the net cost being spent on antibiotics, to treat the citizens is far less than to improve the countries entire living condition and hygiene.

Furthermore, it is due to the use of antibiotics alongside vaccinations, which has put an end to many of the diseases which now seem to be no more threatening in many parts of the world. For example, Smallpox, Rinderpest, Poliomyelitis (polio), Dracunculiasis and Yaws [17].

DRAWBACKS AND SHORTCOMINGS

Firstly, it is important to be known that antibiotics are ineffective against all viral infections. This is because viruses do not have a cell wall for the antibiotics to strike at. Thus, virus is not a target for it at all.

Secondly, number of antibiotics are limited, with most of them dating back to about 40 years ago. Although, some new antibiotics have been discovered since then, but their number is just negligible compared to the number of growing resistant bacteria.

Thirdly, antibiotical residues left in the kidney and liver after ingestion, cause serious problems in both children and elderlies. For example, fluoroquinolone class, which are one of the most popular oral antibiotics used, can cause renal (kidney) failure [18].

Fourthly, is the fact that antibiotics are generally expensive, let alone potentially strong ones needed in case of severe bacterial resistance. For example, the UK NHS alone spends £158 billion annually on antibiotics.

Lastly but not least, is the most important drawback of antibiotic, which is the fact that bacteria can gain resistance against them, making them ineffective and the patients defenceless. Antibiotic resistance is the point I would like to highlight in the upcoming paragraphs in order to answer the title question.

Antibiotic Resistance

Ever since the discovery of antimicrobial agents (antibiotics), patients have been treated for infectious diseases for over 70 years; reducing illnesses and mortality rates significantly [21]. Thus, making antibiotics a huge global success. However, their reputation is being threatened by a phenomenon called, antibiotic resistance [22]. In this situation, the bacteria which once used to be killed by a certain antibiotic, is now capable of resisting it. This happens when the genes in the DNA of the bacteria mutate giving it new properties to survive against that antibiotics.

Although history of antibiotics and their massive usage to treat human infections only dates back to less than a century ago, their practice has produced hard-to-imagine results, proving the incredible capabilities of bacteria to adapt and cope to the destructive strength of antibiotics. This in turn has resulted in the formation of untreatable infections, called 'Superbugs' [19]. Meanwhile, recent studies have shown that superbugs are a product of mutation in bacteria's genes which gives them new properties to survive antibiotic attacks [5]. However, the negative impact of superbugs varies quite differently in developed countries compared to third-world countries.

Natural selection of bacteria for antibiotics resistance is a natural phenomenon which has a strong correlation to the volume of antibiotics used. Thus, the more antibiotics a person uses, the more likely it is that resistant strains of bacteria are produced and spread [23].Figure 3 shows stages in in the development of resistant strains of bacteria.Starting with normal bacteria, process of natural selection and finally forming resistant genes.

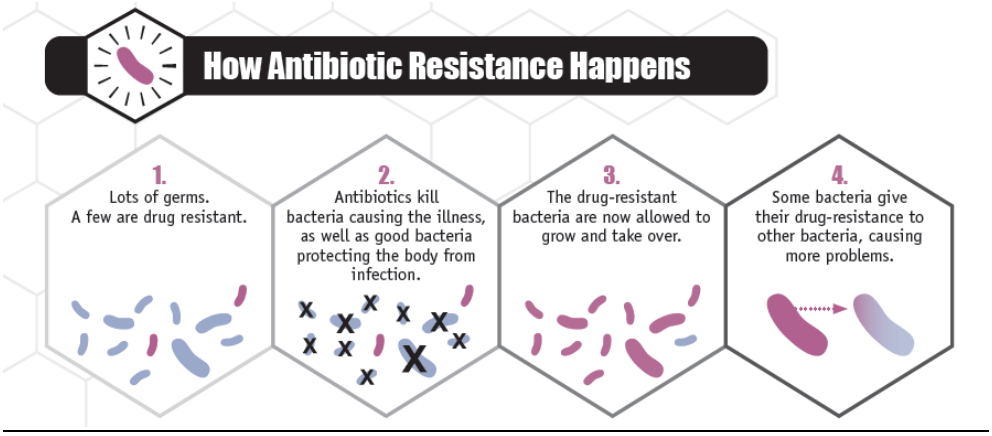


Figure 3: showing the process of antibiotics resistance

Figure 4 illustrates the cycle on how resistance bacteria spreads in the environment. Starting from either humans or food-producing animals and finally ending with the human society. This proves the fact that either uses finally brings harm to the humans.

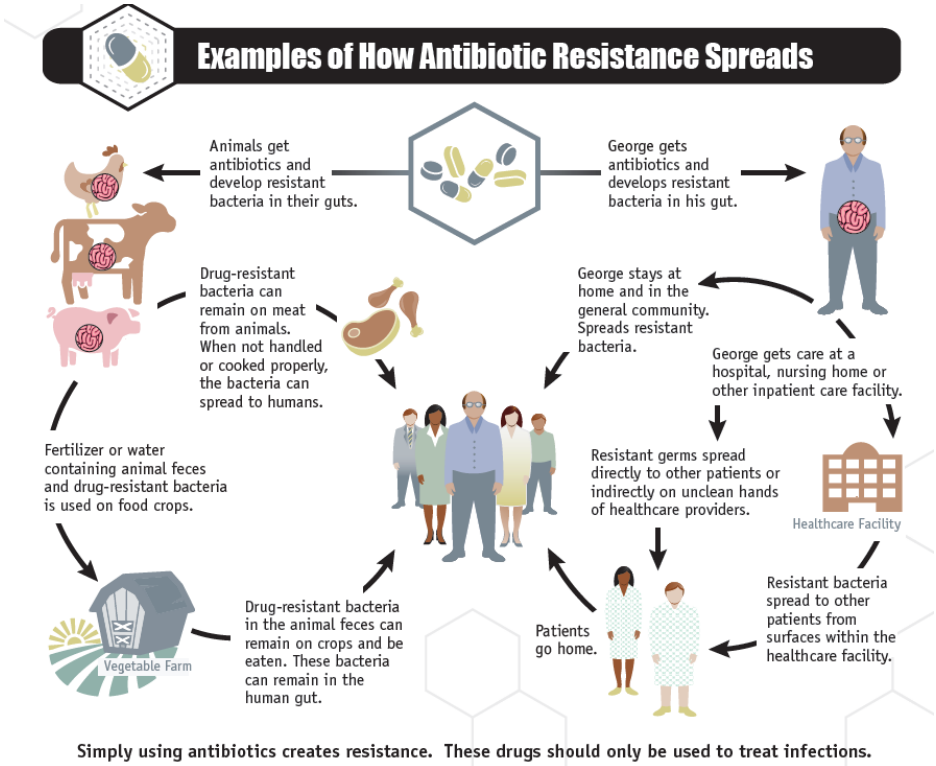


Figure 4: The spread of antibiotic resistance [24].

The more resistant bacteria spread the more new-resistant strains develop causing the threat to increase exponentially. According to the NHS, a resistant bacteria gene, known as MCR-1 was discovered on a Chinese pig farm in November 2014. This special gene is known to be resistant to Colistin—a very strong antibiotic kept to serve doctors at the last resort when almost nothing else works. Meanwhile, what truly is alarming is the fact that by Jan 8th 2015, the same gene was found in UK, Canada, France, Germany, and Vietnam. What makes the situation worse is the fact that resistance to Colistin is not the only life-threatening part, but the fact that this gene combines with other factors to create an ultimate-superbugs resistant to 3 more potentially strong antibiotics [25]. The evidences above suggest the fact that it wouldn't take much long time before resistance spread to all the antibiotics which are the only weapons

we have to save our patients lives. It is believed that the only way apart from developing new antibiotics (which has not been much successful as most of the antibiotics use date beach to at least 50 years ago) is to use them responsibly. Unfortunately, despite all the warnings, data show that the use of antibiotics in agriculture and livestock has increased by 23%-- totalling to 70% of antibiotics sold this year globally. The sad part is the fact that these antibiotics used are not on sick animals needing medication but rather to make them grow faster and fatter [25]!

Antibiotic resistance can occur and be accelerated due to both overuse and misuse. Meanwhile the reasons behind this misuse are:

- Poor prescription by doctors: prescribing antibiotics when not required, incorrect dosage and wrong choice of medicine.
- Self-prescription in countries where antibiotics can readily be bought by the public.
- Not fully finishing an antibiotic course prescribed by the doctor, after feeling better.
- Overuse of antibiotics in husbandry and agriculture [26].

DEVELOPED COUNTRIES VS THIRD-WORLD COUNTRIES

Epidemic caused by antibiotic resistance is a global issue effecting all countries of all strengths. However, the intensity if this epidemic and how well each country is trying to counter-attack it varies greatly.

Third-world Countries and Antibiotics

World Health Organization (WHO) has begun a deep concern over the issue of antibiotics resistance in third-world countries. "The world is poised to enter a 'post-antibiotic' era, " said the chairman of the World Health Organization. Meanwhile, it cannot be argued that this eerie era has already arrived in some part of the world at this current moment. For instance, research has proven that as much as 88% of Nigerians being infected with Staphylococcus aureus infections, can no longer be treated with methicillin—once a prominent weapon against this microbe [27]. Furthermore, nearly 95% of Pakistani and Indian adults carry bacteria, resistant to ß-lactam antibiotics, in which is considered to be of the 'last resort' by Timothy Walsh, a medical microbiologist at Cardiff University, UK. Meanwhile, only about 10% of adults in Queens area of New York carry such bacteria. "The spread of resistance is more than we could have imagined", said Walsh [27].

Antibiotics can be bought without a prescription in many under developed countries, and overuse of these drugs is fuelling the evolution of resistant bacteria. Up to 90% of antibiotic purchased is without a prescription, and non-prescription sales are common in every drug store [28].

Figure 5: A woman buying antibiotics in Nigeria

Antibiotic prescription plays an important role in making incentives for many institutions; especially, in poorer countries, where medical funds are not readily available by the government. For instance, many hospitals in China rely about a quarter of their revenue from the incomes made by the sales of medical drugs. In India, drug sellers pay huge compensations to

doctors who direct their patients to their pharmacies. This in turn, means that pharmacies sell more drugs or charge patients a higher price in order to sustain their profit [29]. Another study suggests that insured patients are prescribed more antibiotics than those without insurance, as costs would no longer be much of a matter [30]. These are only wee examples of how underdeveloped or developing countries waste antibiotics for their own benefits, putting patients' lives in danger.

Nowadays, developing and third-world countries are in desperate need of antibiotics. This is because it is the poorer countries who have to tangle massively with bacterial infections such as tuberculosis. Meanwhile, poor prescribing practices and lack of regulation or guidelines are fuelling the growth of resistance bacteria [31].

Poor hygiene, dirty water supplies, civil wars, and increasing numbers of immunocompromised people with HIV infection, facilitate both resistant bacteria and their rapid spread in third-world countries [32].

Many parts of the world are now on the move to monitor antibiotics resistance in various parts of the globe in order to figure out methods for controlling it. For instance, Xiao Yonghong, deputy director of the Institute of Clinical Pharmacology at Peking University in Beijing, China, is working with a research group to monitor drug resistance in China for several years. After years of research, he wrote," In China itself, resistance to strong drugs causes about 60–70 per cent of infections from common bacteria — such as Escherichia coli that causes intestinal infection and Pneumococcus that causes pneumonia [16]."

Diagnostic test for antibiotic resistant are often unavailable or too expensive in developing countries and the cost of it is directly paid by the patients. Thus, it is easier and cheaper to use antibiotics and observe the result first. This in turn means a greater threat of antibiotic resistance. For example, in Malaysia, only a wee number of hospitals have diagnosis equipment with less than 20% of cases being tested for resistance [33][34].

Poor immunisation in third-world countries directly relates to a tough burden of potentially dangerous diseases, this in turn means higher usage of antibiotics, resulting in even more antibiotic resistance throughout the country. For example, data shows that in India, less than half of children are fully immunised with the essentially required vaccines. Thus, more children are vulnerable to various diseases needing more antibiotics [35]. On the other hand, the use of the pneumococcal conjugate vaccine (PCV) has initially reduced infection rates by a third and therefore antibiotic use in the US has declined greatly [25] [36]. These studies, finally revealed the fact that the use of vaccinations for child serotypes of pneumococci would reduce the burden of pneumococcal resistance; thus making this antibiotic a potential weapon against HIV infection in developing countries.

In many developing countries doctors have to bow to the pressure form patients, wanting antibiotics as a means of treatment. As this is the only way to keep their reputation and salary. This in turns means more unnecessary antibiotics being prescribed.

Drug resistance in developing countries is becoming made even worse by the poor infection control in healthcare system and the fact that they are more overcrowded than they should be. According to a recent study 1265 healthcare units in 75 countries had about 51% patients having infections (including those who did not require any antimicrobial drugs), but about 71% received antibiotics [37]! Some of this usage was for prophylaxis (precaution for any infection) which was somewhat higher than the reported data from 17 west European countries [38].

Developed countries

In developed countries, where the burden of infectious diseases is less prominent, other challenges are on the rise. This refers to the decrease in effectiveness of first-line antibiotics (weak and cheaper ones), causing an increase in the demand of more expensive second and even in severe cases third-line antibiotics. On the other hand, this challenge is even far greater in third-world countries where the burden of diseases is in its highest level. This is indeed due to the fact that patients with resistant infections may not be even able to afford simple antibiotics, let alone super-expensive treatments [39].

According to Centre of Disease Control and Prevention (CDCP), a Nevada woman in her 70s was hospitalized in August last year after she returned from an extended trip to India. Doctors' report suggested that she was suffering from a carbapenem-resistant Enterobacteriaceae (CRE)

infection. Unfortunately, she died of septic shock due to the fact that all the 14 types of antibiotics available at the hospital were ineffective against the resistant bacteria. Meanwhile, what truly is a shock, is the fact that none of the 26 antibiotics available in America would have either worked [40].

Each year in European Union (EU) nearly 400,000 patients are infected with resistant strains of bacteria, of whom 25,000 die. This in turn has a dramatic economical implication on the EU. This is because, AMR (Antimicrobial resistance) in the EU alone causes an economic loss of more than £1.3 billion each year [41].

The same story goes in the U.S., with an estimate of two million people being sickened by resistant infections of whom 63000 die each year [24]. Nevertheless, it is anticipated that by 2050, up to 10 million people will lose their lives due to AMR—more than those of cancer. This is maybe why the UK's government chief medical officer (Prof. Dame Sally Davies) compared the treat of antibiotic resistance, as being equivalent to terrorism and that it should be put on UK National Risk Register [42].

"If we fail to act, we are looking at an almost unthinkable scenario where antibiotics no longer work and we are cast back into the dark ages of medicine" said David Cameron, the former UK Prime Minister [43]. In July 2015 the UK Prime Minister announced antibiotic resistance as a global threat and called in for ideas to defeat it [44].

The implications of antibiotic resistance are so devastating that it is nearly beyond imagination. This is because routine surgeries and minor infections will become life- threatening once again and all victories earned against infectious diseases will be just history. In addition, all hospital expenses will increase exponentially, to an extend where no public patient will be able to effort it [43]. RAND Europe and KPMG are two projects responsible for collecting data and estimating the loss due to AMR. It is predicted that within the next 35 years about 300 million people will die due to AMR. This in turn causes the world's GDP to fall by 2 to 3.5%. meaning, by 2050 the world is expected to lose between £66 and £80 trillion if antibiotic resistance is not tackled today [44].

PUBLIC AWARENESS

In Brazil, Anvisa, together with the Pan American Health Organization (PAHO), has begun a project called Rede RM (Network of Microbial Resistance Monitoring and Control) in order to monitor levels of antibiotic resistance in Brazil. Resistance to antibiotics is a global phenomenon. This is because resistant infections are readily increasing mortality among patients of all ages, putting every citizen at risk. Thus, Anvisa is strongly emphasizing the importance of raising awareness of the problem of antibiotic resistance, in both the medical community and among patients [31].

Another step in preventing antibiotic resistance is to make sure patients fully finish their antibiotic courses even after felling fully healed; unfortunately, even a third of Canadian fail to do so, considering the fact that they are living in a developed country! This is because incomplete course kills most of the bacteria but the remaining bacteria will gain resistance. Val Montessori, an infectious diseases specialist in Vancouver said," what truly drives me nuts, is when people give their left over antibiotics, which end up in cupboards to their cousin who has a cold!"

This is why doctors are now trying to reduce the amount of unused antibiotics by prescribing advanced, but shorter courses [45].

25% of people responded that it is acceptable to give friends and relatives leftover antibiotics as long as it is the same illness. And a further 43% believe that it is totally acceptable to request the same antibiotic from a doctor or pharmacy, if that antibiotic help their friend to feel better. All these actions in turn result in a growing antibiotic resistance!

With all the advertisements of WHO to take the full prescription even after feeling better, still responds from Sudan, Egypt, and China with 62%, 55% and 53% respectively, is to stop taking the medicine when they feel better! The goal is to promote doctors into reducing unnecessary prescription of antibiotics not avoiding antibiotics when a child truly needs them [45]. This data shows how unaware are the public.

GOVERNMENT EXPENDITURE AND ENFORCEMENT

Governmental expenditure and enforcement varies greatly from country to country. For instance, in some countries, antibiotics can be

purchased "over-the-counter", meaning without doctor's prescription. While, other countries have laws to allow patients to buy antibiotics only with prescription. However, even with the presence of such laws, this does not really mean that they are fully enforced. This is why the government can play an important role in the fight against antibiotic resistance. This can be done, if the government issues sever laws against unnecessary prescription and illegal purchase of antibiotics.

In 2016, expenditure rate for NHS was 5.2%, while the growing rate is anticipated by UK GDP to be around 15.2% between 2014/15 and 2020/21 [46]. This will be around £7 billion which stands for an increase from £135 billion to £142 billion in 2020/21. It would be wondering that only UK NHS will be spending £158 billion on antibiotics in 2020/21. Meanwhile, reports from the US Department of Health and Human suggested that the US spends about $1.3 billion per year on just six common resistant bacteria [45].

Some governments have already begun to implement new methods. For example, the US has started to train better doctors and improve practice across all healthcare units and hospitals. The target is to reduce antibiotic usage among outpatients by 50% and inpatients by 20% by 2020 [52]. Meanwhile, the UK plans to optimise its prescription practice with the use of genomic technology for diagnosis of various diseases. This plan also includes promoting the use of narrow spectrum antibiotics over broad spectrum. Furthermore, the UK is also on the course to develop new drug treatments and diagnosis methods. This also includes establishment of a new AMR Research Funders Forum under the Medical Research Council (MRC) lead, as well as a research unit under the National Institute for Health Research (NIHR) lead [51]

Furthermore, various institutions have taken the fight into their own hands by issuing "Antibiotic Policies", this is to ensure the rational use of antibiotics within the institute.

DISCUSSION

In my opinion, the best approach to this question is to examine all the factors directly responsible for antibiotics resistance; in order for us to come up with complex ways to oppose it.

To begin with, Figure 6 shows how much antibiotics are purchased with(red) and without(blue) prescription. This terrifying data totally proves the unawareness of people and the main factor deriving us closer to the "Post antibiotic era".

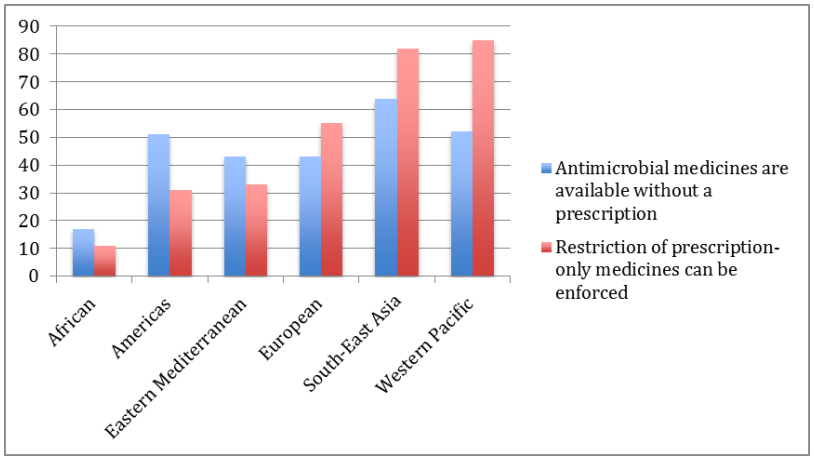


Figure 6: Graph demonstrating Practices related to use of antimicrobial medicines across main areas of the world [26].

Antibiotic use is increasing, especially in Asian and Latin American countries where increase in incomes provide a wider public access to medicine. Reports show that 42% of people in lower income countries used antibiotics as compared to 29% of people in higher income countries. In India itself, antibiotic use has increased by 37% from 2005 to 2010, while the fastest growth was in broad-spectrum penicillins and cefalosporins, previously unaffordable [47]. Nevertheless, in developing countries where HIV burden is a highlighted problem, the use of cotrimoxazole to treat opportunistic diseases due to Aids, has increased resistance to pneumococci

and E coli up to twice the normal rate [48]. The perfect balance in developing countries can be achieved by the appropriate use of antibiotics—consider the one million deaths of children each year from pneumonia, much of it untreated—and the overwhelming tendency for inappropriate use of antibiotics for coughs, colds, and diarrhoea [48].

Hard-to-imagine estimates produced by the British government truly proves the seriousness of AMR. This is due to the fact that the global loss of £80 trillion in gross national product and over 10 million death (more than cancer) cannot be even relatively compared to other disasters [6].

Different countries are coming up with various plans to act against antibiotic resistance. Figure 7 illustrating death toll in 2050, although developed countries have better plans, the number of deaths in Europe will be about 390,000 per year, which is still horrifying. This number is around 5 million and 4.2 million for Asia and Africa respectively. This shows that the antibiotic resistance is increasing dramatically. Based on these anticipations, it is not difficult to prove that our life-saving Wonder Drugs will no longer be useful in 2050.

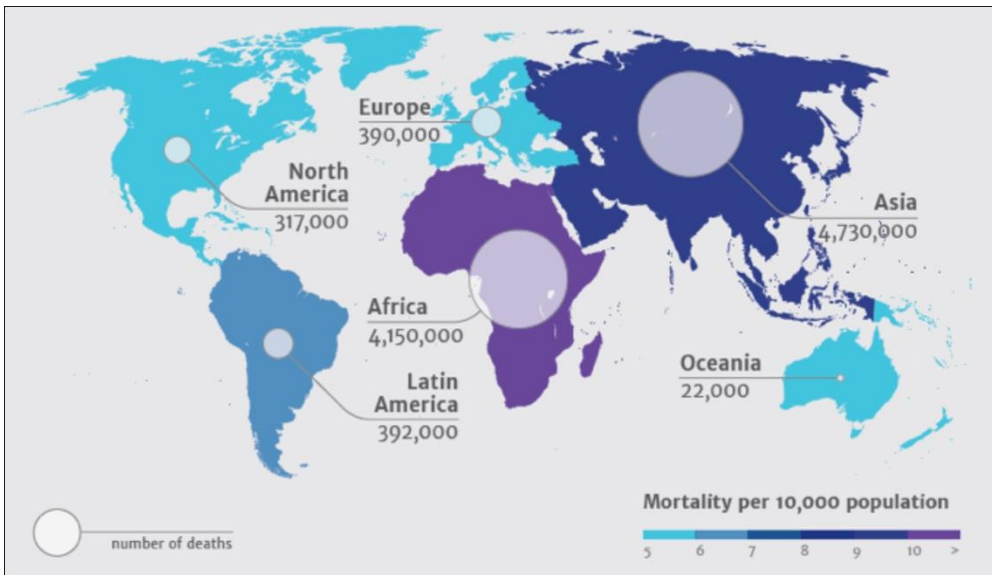


Figure 7: showing number of death due to antibiotics resistance in all the continents by 2050 [44].

Mortality rates because of hospital-acquired bacterial infections are shooting up steeply. For instance, about 63,000 patients from the 2 million infected patients lose their life in United States every year and a further 25,000 in the EU, due to multidrug-resistant bacterial infections. Nevertheless, massive additional costs are created for the ministry of healthcare which cannot be ignored easily. This can readily be portrayed by estimated economic data from the NHS, suggesting an extra 1.5 billion EUR being spent on multidrug-resistant in 2009 [49]. The annual additional cost of treating hospital-acquired infections from just six species of antibiotic-resistant bacteria was estimated to be at least £1.04 billion in 1992 – more than the annual expenditure on influenza [49]. These statistics show how much money is being nearly wasted on excessive use of antibiotics which itself consumes a great deal of money.

Economic impacts associated with AMR are as horrifying as the death tolls. For instance, current rates due to AMR in OECD countries are about 0.03% of GDP. This is to increase to 0.07% in 2030 and 0.16% in 2050. This in turn would result in loss of a further £2.3 trillion [51].

In common people's minds, cancer is the most dangerous disease in the world but based on the report from AMR [4], number of death due to antibiotics resistance will be 1.22 times of cancer in 2050 as shown in Figure 8. It means in the competition between these two mass murderers, antibiotics resistance is the winner. These unfortunate statistics reveal that we are to think of better Wonder Drug from now on.

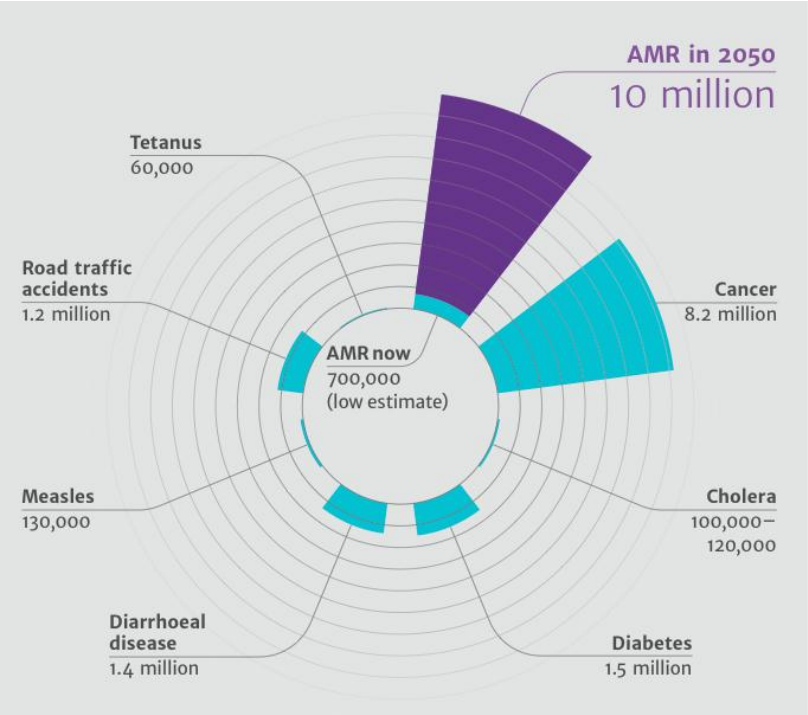


Figure 8: AMR anticipation for antibiotic resistance [44].

With such a horrendous threat ahead of us, most countries do not take it as serious as they should. World-wide, only 25% of the countries actually have implemented national policies to fight antibiotic resistance, and 40% have coordinated control programs to AMR. However, the other 35% had nothing done towards this matter.

Globally, heavy antibiotic consumption is not by humans, rather it is given to food-producing animals. For instance, in US alone, 80% of the nation's antibiotics are used on livestock. And it is further reported that is going to increase by 67% within the next two decades [51].

We have designed a survey (Appendix 1) of our own using online SurveyMonkey and posted it in Facebook to collect data on how people use antibiotics and if they face any problem about it. In this survey, I focused on cold as the main disease. This is because cold does not require antibiotics and any positive response shows how unaware are people towards the use of antibiotics.

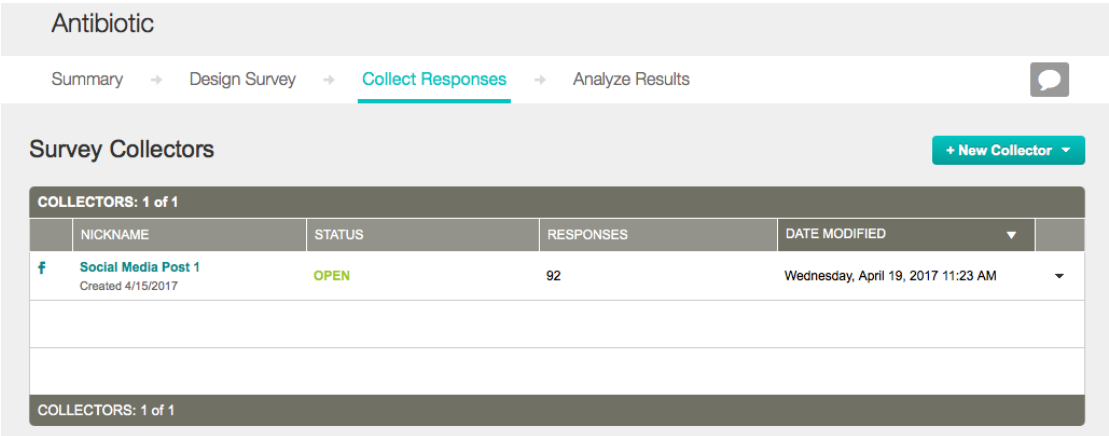
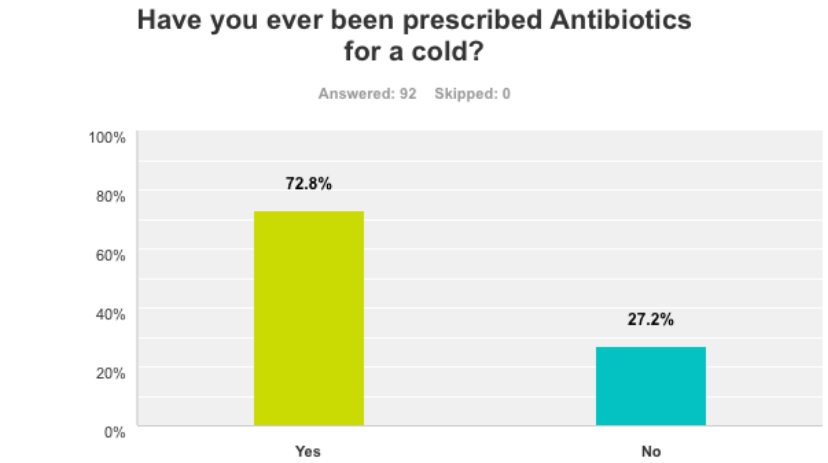


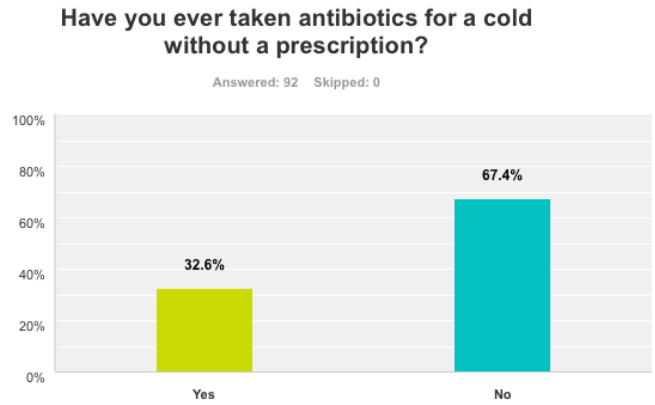
Figure 9: Total number of responses to our online survey



Answer Choices	Responses	
Yes (1)	72.8%	67
No (2)	27.2%	25
Total		92

Basic Statistics				
Minimum	Maximum	Median	Mean	Standard Deviation
1.00	2.00	1.00	1.27	0.44

Figure 10: Bar chart illustrating percentage of people who take antibiotics for cold



Answer Choices	Responses	
Yes (1)	32.6%	30
No (2)	67.4%	62
Total		92

Basic Statistics				
Minimum	Maximum	Median	Mean	Standard Deviation
1.00	2.00	2.00	1.67	0.47

Figure 11: Bar chart illustrating percentage of people who take antibiotics with/without prescription for cold.

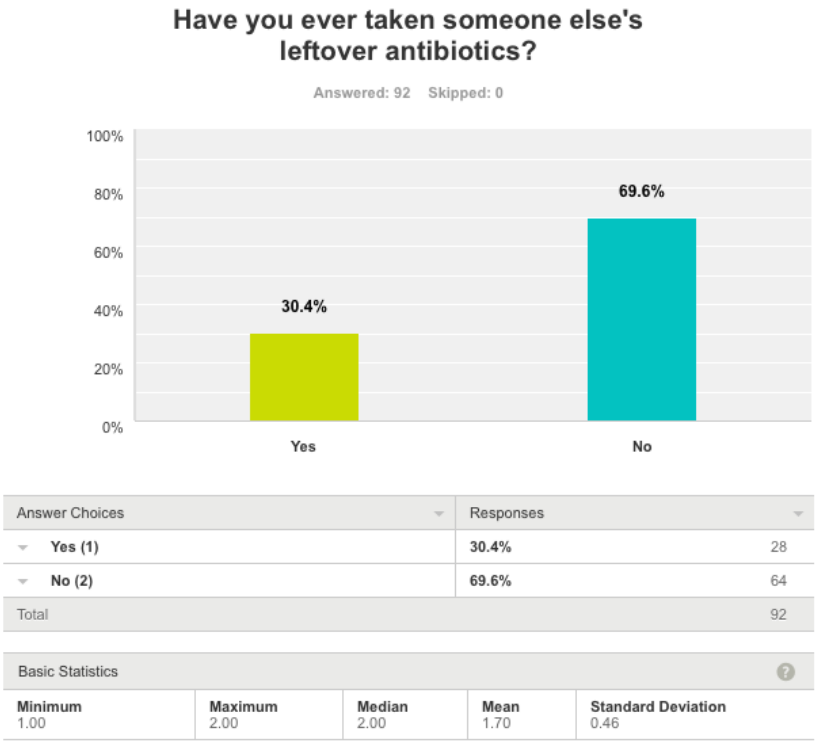


Figure 12: Bar chart illustrating percentage of people who take someone's else leftover antibiotics.

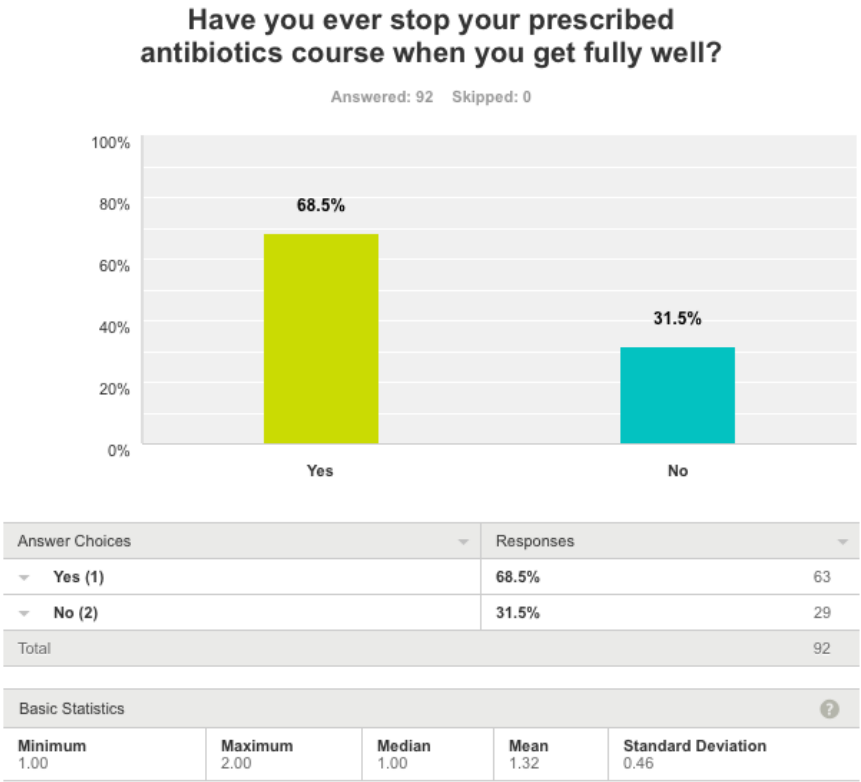
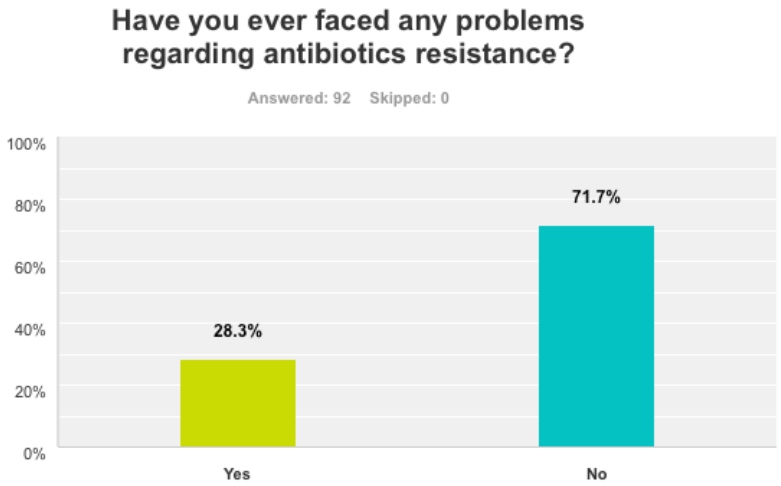


Figure 13: Bar chart illustrating percentage of people who stop antibiotics course when they got well.



Answer Choices	Responses	
Yes (1)	28.3%	26
No (2)	71.7%	66
Total		92

Basic Statistics				
Minimum	Maximum	Median	Mean	Standard Deviation
1.00	2.00	2.00	1.72	0.45

Figure 14: Bar chart illustrating percentage of people who face antibiotics resistance.

The general overview on the results of our survey shows that people are still not aware enough on how serious antibiotics resistance is. Figure 10 shows the improvement in practice of doctors compare to some decades ago when most people were prescribed antibiotics for cold. However, Figure 14 shows almost one third of people facing the problem of antibiotics resistance. This proves the fact that at this current stage I have a great threat of resistance, let alone how this would increase by 2050. Hence, revealing our desperate need of new innovation to fight antibiotic resistance.

WHAT TO CONSIDER IN ORDER TO FIGHT ANTIBIOTIC RESISTANCE?

The real issue with antibiotics is the fact that soon after their discovery and massive consumption, antibiotics resistance arises in an exponential manner. This scenario as happened almost with every single antibiotic produced. This in turn has resulted in a race between antibiotics development and antibiotic resistance [53]. So, a good question is how to retain the power of antibiotics for the longest time as possible?

One of the best ways to counter attack antibiotic resistance is to use the newly developed "laboratory synthesised" ones. These antibiotics are far more effective than their naturally produced partners. This is because the "laboratory synthesised" are better absorbed by the body and kill resistant bacteria more effectively. This in turn can be used as a defence against the growing number of resistant strains bacteria [50].

A significant factor which should be strongly considered is the use of antibiotics by humans, animals and plants. This is due to the fact that the levels of antibiotic-resistant infections strongly correlate with the level of antibiotic consumption [54]. Therefore, the less antibiotics we use, the lesser the chance of resistance.

Another solution, is to make sure patients fully finish their antibiotic courses even after patients fell fully healed; unfortunately, even a third of Canadian fail to do so, considering they are living in a developed country! This is an important factor; this is because incomplete course kills most of the bacteria but the remaining bacteria will gain resistance. Val Montessori, an infectious diseases specialist in Vancouver said, what truly drives me nuts, is

when people give their left over antibiotics, which end up in cupboards to their cousin who has a cold! This is why doctors are now trying to reduce the amount of unused antibiotics by prescribing advanced, but shorter courses [20].

There is a question that if making new antibiotics is a solution to resistance? In this era, where we are again threatened by bacteria, which have gained resistance, new interest to finding new antibiotics or even newer ways to kill bacteria are on the rise. However, the process of producing antibiotics is very long and expensive, requiring nearly ten years and $3oo million. Meanwhile, there still have been lots of effort to find new ones, but most of the newly discovered are much like or related to the ones previously discovered. As a result, bacteria gain resistance to them as little as within two years [55].

Another approach suggests, using "decoy" molecules along with antibiotic. This molecule helps to make a diversion, causing the resistant enzymes produced by bacteria to attack the molecules instead of the antibiotic. As a result, the antibiotic has a chance to attack the bacteria. However, this method has its own drawback, as finding decoy molecules to match each certain antibiotic is itself a challenge [55]!

Ways to effectively fight antibiotic resistance are:

1- People should take antibiotics that are prescribed by doctors and not of their own choice.
2- People should finish antibiotic courses and not keep them for later.
3- Parents must ensure their children's vaccinations are up to date
4- Doctors should prescribe antibiotics only when they are truly required.
5- Farmers should prevent usage of antibiotics on food-producing animals.
6- Media should increase awareness of the civilians.
7- Universities should train better, more caring and careful doctors.
8- Governments must place awards for new discoveries against antibiotics.
9- Pharmaceutical companies should increase the development of new antibiotics.

It is also believed that, a global system for tracking antibiotic resistance is essentially required, in order to locate "hot-spots" of resistance and measure trends. This allows us to recognize positive effects of our moves against antibiotic resistance [45].

CONCLUSION

In conclusion, with all the research and data collected, it is obvious to say that antibiotic resistance is a major global problem which cannot be ignored. Nevertheless, if we fail to address this issue today, we are looking at a time bomb that is waiting to blow up.

Although at the current stage, our life-saving Wonder Drug might still be as useful and essential as it has been since its discovery, it cannot be argued that antibiotics are desperately losing their power. Furthermore, if we cannot find a way to stop resistance or control it, the race between new antibiotic development and resistance would be a battle in vain. As resistant bacteria are far more active that our industries.

Therefore, we have to act now and it should be fast, if we are ever to save our Wonder Drug. And this can only be achieved if every single one of us, our patients, doctors, media and the government play their roles correctly and effectively. Patients should fully finish their prescribed course, never take leftover antibiotics and stop expecting antibiotics for simple diseases—those not requiring antibiotics such as cold. Doctors should make more accurate diagnosis of bacterial or viral infections, they should reduce unnecessary prescription and be more careful of their choice of antibiotic. The media must help to increase public awareness on how serious the threat of antibiotic resistance is and how everyone can be a part of the fight against it. The government should highly encourage the development of new ways to fight antibiotic resistance, increase funds for research and give a good credit to how important antibiotic resistance actually is.

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CONFLICT OF INTEREST STATEMENT

The authors confirmed that there is no conflict of interest for this research paper.

REFERENCES

1. Bassett EJ, Keith MS, Armelagos GJ, Martin DL, Villanueva AR. Tetracycline-labeled human bone from ancient Sudanese Nubia (AD 350); 1980.
2. Nelson ML, Dinardo A, Hochberg J, Armelagos GJ. Brief communication: mass spectroscopic characterization of tetracycline in the skeletal remains of an ancient population from Sudanese Nubia 350–550 CE. American J Physical Anthropol 2010; 143(1):151-154.
3. Cook M, Molto EL, Anderson C. Fluorochrome labelling in Roman period skeletons from Dakhleh Oasis, Egypt. American J Physical Anthropol 1989; 80(2): 137-143.
4. Available from: https://answersingenesis.org/ natural-selection/antibiotic-resistance/bacteria-more-good-than-bad-and-ugly.
5. Obuli A. Antibiotic Resistance in the Environment: a Link to the Clinic?. Microrevi Cell Mole Biol 2017. 1(1):589-594.
6. Broderick, M and Chadwick, T. Cambridge IGCSE Biology textbook. UK: Cambridge University Press; 2015.
7. Available from: https://en.wikipedia.org /wiki/Antibiotics
8. Available from: https://www.healthychildren.org/English/health-issues/conditions/treatments/Pages/The-History-of-Antibiotics.aspx
9. Rajendra S, Anshumali M, Manoj K, Praveen KM. Microbial Proteases in Commercial Applications. J Pharm Chem Biol Sci 2016; 4(3):365-374.
10. Available from: https://www.historylearningsite.co.uk/a-history-of-medicine/antibiotics/
11. Available from: http://www.microbiologysociety.org /education-outreach/ antibiotics-unearthed/antibiotics-and-resistance/history-of-antibiotics.cfm
12. Centers for Disease Control and Prevention, Office of Infectious Disease. Antibiotic resistance threats in the United States, 2013. April 2013. Available from: http://www.cdc.gov/ drugresistance / threat-report-2013. Accessed January 28, 2015.
13. Wright GD. Something new: revisiting natural products in anti- biotic drug discovery. Can J Microbiol 2014; 60(3):147-154.
14. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. Pharm Therap 2015; 40(4):277.
15. Available from: http://www.sustainabletable.org/257/antibiotics
16. Rossolini GM, Arena F, Pecile P, Pollini S. Update on the antibiotic resistance crisis. Clin Opin Pharmacol 2014; 18: 56-60.
17. Available from: https://en.wikipedia.org/wiki/Eradication_of_infectious_diseases
18. Available from: http://www.vancouversun.com /health/Common+antibiotic+linked+kidney +damage+study+finds/8470993/story.html
19. Wright, G.D., 2010. Antibiotic resistance in the environment: a link to the clinic?. Current opinion in microbiology, 13(5), pp.589-594.
20. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20420303/
21. Available from: https://www.cdc.gov /drugresistance/
22. Available from: https://www.healthychildren.org/English/health issues/conditions/ treatments/Pages/The-History-of-Antibiotics.aspx
23. Goossens H, Ferech M, Vander Stichele R, Elseviers M, ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005; 365: 579-587.
24. Centres for Disease Control and Prevention (US). Antibiotic resistance threats in the United States, 2013. Centres for Disease Control and Prevention, US Department of Health and Human Services; 2013.
25. Available from: https://www.theatlantic.com/health/archive/2017/01/colistin-resistance-spread/512705/
26. WHO Press, World Health Organization. Worldwide country situation analysis: response to antimicrobial resistance; 2015.
27. Reardon S. Antibiotic resistance sweeping developing world: bacteria are increasingly dodging extermination as drug availability

outpacesregulation. Nature2014; 509(7499): 141-143.
28. Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S. Non-prescription antimicrobial use worldwide: a systematic review. Lancet Infect Dis 2011; 11: 692-701.
29. Sweidan M, Zhang Y, Harvey K, Yang YH, Shen X, Yao K. Proceedings of the 2nd national workshop on rational use of antibiotics in China, Beijing, 28-30 November 2005:1-18. Available from: www.docstoc.com/docs/44755790/Proceedings-of-the-2nd-National-Workshop-on-Rational-Use
30. Dong H, Bogg L, Rehnberg C, Diwan V. Association between health insurance and antibiotics prescribing in four counties in rural China. Health Policy1999; 48: 29-45.
31. Available from: http://www.scidev.net/global/health/feature/antibiotic-resistance-and-the-developing-world.html
32. Okeke IN, Laxminarayan R, Bhutta ZA, Duse AG, Jenkins P, O'Brien TF, et al. Antimicrobial resistance in developing countries. Part I: recent trends and current status. Lancet Infect Dis 2005; 5: 481-493.
33. Berkley JA, Mwangi I, Ngetsa CJ, Mwarumba S, Lowe BS, Marsh K, et al. Diagnosis of acute bacterial meningitis in children at a district hospital in sub-Saharan Africa. Lancet2001; 357:1753-1757.
34. Lim VK, Cheong YM. Bacteriology turnaround time in seven Malaysian general hospitals. Malays J Pathol 1992;14: 41-43.
35. Laxminarayan R, Ganguly NK. India's vaccine deficit: why more than half of Indian children are not fully immunized, and what can—and should—be done. Health Affine 2011; 30(1): 1096-1103.
36. Dagan R, Klugman KP. Impact of conjugate pneumococcal vaccines on antibiotic resistance. Lancet Infect Dis 2008;8:785-795.
37. Vincent J, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009; 302: 2323-2329.
38. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) study. JAMA 1995; 274: 639-644.
39. Laxminarayan R. Economic issues related to antimicrobial resistance. In, Roberts JA, eds. The economics of infectious disease; Oxford University Press, 2006; p49.
40. Available at: http://www.usatoday.com/story/news/health/2017/01/15/woman-dies-of-superbug/96611540/
41. Available from: http://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-resistance/data-and-statistics
42. Available from: http://www.independent.co.uk/news/science/chief-medical-officer-dame-sally-davies-resistance-to-antibiotics-risks-health-catastrophe-to-rank-8528442.html
43. Available from: https://amr-review.org.
44. Review on Antimicrobial Resistance. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. Review on Antimicrobial Resistance. London, United Kingdom; 2014.
45. Available from: https://www.todays-parent.com/kids/kids-health/antibiotic-resistance/
46. Available from: https://www.kingsfund.org.uk/blog/2016/01/how-does-nhs-spending-compare-health-spending-internationally
47. IMS Health. MIDAS market segmentation data. IMS; 2011.
48. Hamel MJ, Greene C, Chiller T, Ouma P, Polyak C, Otieno K, et al. Does cotrimoxazole prophylaxis for the prevention of HIV-associated opportunistic infections select for resistant pathogens in Kenyan adults? Am J Trop Med Hyg 2008;79: 320-330.
49. Aminov RI. A brief history of the antibiotic era: lessons learned and challenges for the future. Front Microbiol 2010; 1(1):134.
50. O'Connor TF. The Columbia Encyclopedia. Ref User Serv Quart 2001; 40(3): 297-297.
51. Cecchini M, Langer J, Slawomirski L. Antimicrobial Resistance in G7 Countries and Beyond: Economic Issues, Policies and Options for Action. Paris: Organization for Economic Co-operation and Development; 2015.

52. The White House. Executive Order Combating Antibiotic Resistant Bacteria. Washington DC: White House; 2015.
53. Available from: https://www.oecd.org /els/health-systems/Antimicrobial-Resistance-in-G7-Countries-and-Beyond.pdf
54. Goossens H, Ferech M, Vander Stichele R, Elseviers M.. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. The Lancet 2005; 365(9459): 579-587.
55. Available from: http://emerald.tufts.edu /med/apua/about_issue/wh

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