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An uninvited enemy: antimicrobial resistance and its relations with environment

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Abstract. According to the reports from the World Health Organization (WHO), AMR (Antimicrobial Resistance) is a rising problem for human beings. AMR could invalidate all efforts that human beings have made in the field of antibiotics. For example, AMR Mycobacterium Tuberculosis has taken away thousands of lives in patients all over the world, while their resistance to the most prevailing medicines, including Rifampicin and Streptomycin no longer works. In the history of the continuous battle between bacteria and human beings, it seems that the emergence of AMR in bacteria is not random; rather, they seem to follow a certain pattern related to climate change. This thesis, through the method of literature and case study, aims to give a hypothesis supported by the data and facts to elaborate on this pattern, which is not yet scientifically proven. According to the perception with the aid of resources, the heat waves happening in the last centu ry until now might have correlations with the emergence of AMR.

Keywords: antimicrobial resistance, bacteria, environment.

1. Introduction

As the most famous and infamous prokaryotes in the world, bacteria have always been in close relationships with human beings. From endosymbiotic theory (that the mitochondria might descend from bacteria) and the colonies in our intestines, bacteria have played an important role in our daily lives. However, bacteria can sometimes be a serial killer, too. In the history books can we learn about every pandemic and plague, most of which are relevant to a certain kind of bacteria–Yersinia Pestis, Staphylococcus Aureus–such names have haunted above the European continent like piles of dark clouds. In 1928, a beam of sunlight penetrated the thick layer of dark clouds–penicillin, the world's first antibiotic, was discovered by Dr. Fleming. Since then, humans have taken the lead in the battle, consistently outperforming bacteria. Nevertheless, in the recent decades, bacteria has gradually equipped themselves with "new weapons", AMR. The existence of AMR calls into question the victory of human beings, implying further years of struggle.

AMR refers to the ability bacteria acquire to resist certain traditional antibiotics for survival. The formation of AMR includes two main steps: random mutation in the bacteria's genome and a following natural selection, which helps the bacteria population identify whether the new trait is useful or not. For instance, Staphylococcus Aureus has been discovered to be resistant to methicillin, a major antibiotic used in the field of curing such diseases [1]. Such multidrug-resistant S. Aureus is given the name "

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MRSA," pushing human beings to invent antibiotics with different mechanisms as methicillin to solve the problem. According to most studies, many researchers have attributed the burgeon in AMR nowadays to the second step of formation–natural selection. Researchers have long argued that the abuse and misuse of antibiotics might inevitably stimulate the bacteria to form AMR, since it gives them an environment rich in survival pressure where the bacteria can find the trait of resistance useful and pass it on to other individuals. Passing is also an important and problematic property of bacteria. In a nutshell, the methods of passing genetic information are separated into two kinds: horizontal transmission and vertical transmission. AMR involves both of these methods. Bacteria already with AMR can pass the genetic material to other bacteria individuals by emitting their plasmids–media for bacterial genetic information– and that other bacteria can pick it up. Bacteria that acquire the resistant gene will possess this AMR ability. This process is called the horizontal transmission. Vertical transmission, on the other hand, means that the resistant gene is passed from mother to son and daughter. The combination of these two methods of transmission empowers the bacteria to form populations and populations of resistant genes in a relatively short time.

This thesis aims to delve into the mechanism of AMR formation, comparing it to the frequency of heatwaves, and carry out a possible hypothesis about the effect of heatwaves on AMR formation. AMR is a severe health problem thoroughly understanding it will by all means be beneficial to the world. The methodology in this thesis includes data analysis and modeling.

2. Environment's Potential Effect

The formation of AMR can be influenced by various environmental factors. Just as is mentioned above, an environment abundant with natural selection and survival pressure can effectively give rise to the opportunity of an AMR population. However, natural selection is only the second step of AMR development, while mutation is actually the first step that matters the most. Mutations are completely random, according to their definitions, but there are many factors that might induce the mutation in the bacterial genome. Figure 1 shows the AMR bacteria discovery timeline:

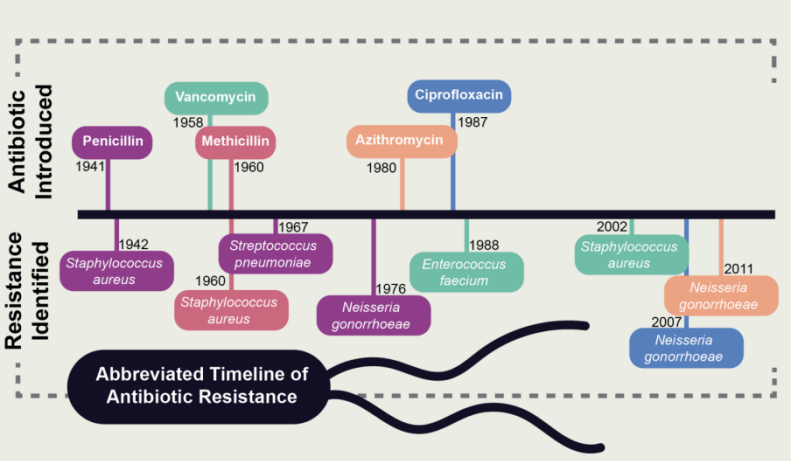

Figure 1. AMR bacteria discovery timeline

Figure 2 illustrates another graph of the timeline of extreme heat in the past century:

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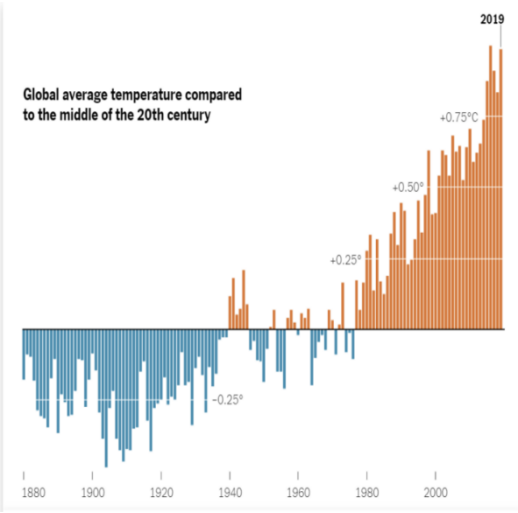

Figure 2. Global Temperature Change from 1880 to 2019 [2]

The two graphs that are presented upwards may appear completely irrelevant to each other. However, when putting the two graphs on one timeline, it is easy to find that the times when AMR appeared are perfectly coincidental or slightly after the years in which a heat wave strikes the globe. Is this just a coincidence, or is one an indicator for the other?

Back to the topic of AMR formation. As previously mentioned, mutation plays a crucial role in the entire process. Due to the special structures of DNA and RNA, a factor that induces mutation must be powerful enough to break the hydrogen bonds between the nitrogenous base pairs in the whole molecule. Intense heat is one of those candidates. There has been substantial evidence pointing out that high temperatures can lead to the denature of DNA molecules, increasing the possibility of mutations. For instance, some researchers in the US have been investigating the genetic mutation of yeast bacteria under elevated conditions, and it turns out that the possibility of genetic mutation is positively correlated to the magnitude of heat [3]. With this conclusion, researchers can try to unveil the mystery between AMR and intense heat. Figure 1 demonstrates that the first AMR bacteria ever recorded in human history is the Staphylococcus Aureus, which causes severe inflammation and used to flourish in wet and warm conditions in the last century. Later, figure 1 shows another MRSA in 1960 and the first resistant Streptococcus in 1967. Among these three are 2 different species of bacteria, and they are resistant to 3 different kinds of antibiotics, meaning that they are formed independently without the possibility of horizontal transmission among species. From Figure 2, there was a cluster of heat waves around 1960, during which the temperature was significantly higher than that of other years since the discovery of the first antibiotic in 1941. Such high temperatures correspond almost perfectly with the time when AMR emerged. Accounting for the fact that discovery time might have been a little bit later than the heat waves, it can be assumed that it would take some time for the mutant gene in a single bacteria to be spread to populations, with which scientists could have determined the presence of mutant resistant traits. Furthermore, scientists needed the chance to treat such AMR bacteria with available antibiotics so they could reveal the AMR bacteria–in other words, AMR genes might have emerged earlier than scientists had expected, like one or two years earlier, which again substantiates the timeline of the emergence of AMR and global heat wave. Apart from the earliest example, current examples also support the claim: another cluster for the emergence of AMR happened around 2000 and 2010 at the border of 2 centuries. Similar to that in about 1960, the cluster in 2000 consistently follows several heat wave peaks around 2000, even if the global temperature was burgeoning in that period of time.

While this fact substantiates the proposed theory, there are other interesting and dreadful facts that we must focus on. In 1996, levofloxacin, a powerful antibiotic that targets certain kinds of bacterial infections such as UTI (Urinary Tract Infection) and E. Coli infections. Nevertheless, from the timeline

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of AMR emergence, scientists were astonished to find that levofloxacin-resistant S. Aureus (another kind of MRSA) emerged in the same year. This alarming fact demonstrates that in some species of bacteria, the rate of mutation and the time required to develop a resistant population can be unexpectedly fast, surpassing the normal development of AMR at normal temperature and under all other conditions. According to researchers in the US, Shigella samples derived from the southern part of Iran developed string resistance under lab environments in a period of 3 years, while that of levofloxacin-resistant Staphylococcus Aureus only took no more than 2 years [4]. In fact, some researchers have claimed that some species of bacteria can begin to develop AMR in merely 11 days [5]. Such facts have proved that with the aid of intense heat, bacteria might develop AMR much more quickly than before. While the speed of AMR development is an important variable, the magnitude is also a concerning problem. In 2000, the first XRSA (Extremely Resistant S. Aureus) was unveiled by scientists. XRSA is the accumulative result of several decades. Although there is a paucity of research on the relationship of XRSA with intense heat, it can be estimated that intense heat might play an important role in the emergence or distribution of XRSA.

3. The Possible Reasons for the Emergence of AMR–Survival Pressure

Environmental problems, such as natural disasters, deforestation, and erosion, have plagued humans for years. Since bacteria that affect humans typically thrive in environments similar to our own, why does intense heat emerge as a key factor for antimicrobial resistance (AMR), a phenomenon that is also supported by data and research? In order to figure out the mystery, it is necessary to have a deep look inside the second step of the formation of AMR, and the basic mechanisms of certain types of antibiotics. People should first have a clear view of a bacterial individual's overall structure. Compared to prokaryotic cells such as human cells, bacterial cells mainly differ from them in two important properties: the presence of peptidoglycan (PG) cell walls, and the special structure of DNA and organelles such as ribosomes. Most antibiotics initially target the PG cell wall to identify and destroy bacterial cells. Biologists have divided bacteria into two categories: Gram-positive and Gram-negative, in which Gram-positive have a thick layer of PG surrounding the cytoplasm, while the gram-negative has a thin layer of PG inside another layer of lipids. PG always provides strong protection for the inner parts of bacteria, resisting some attacks from the human immune system, no matter what type of bacteria it is. However, PG functions as a polysaccharide, essentially forming bonds with sugar molecules and amino acids like alanine. Research has revealed that high temperatures will likely disrupt the normal function of PG, inhibiting its synthesis. In research conducted in the UK, biologists claim that continuous exposition to temperatures higher than the optimal survival temperature for the bacteria species Bacilli dismantles its PG cell wall:The cycle of processes involved in peptidoglycan formation in particulate preparations from two common bacteria has been investigated, and certain characteristics of the system have been reported. The biological enzyme preparation derived from bacterial species undergoes rapid inactivation at 37°C and to a lesser degree at 30°C. The most sensitive reaction observed is the dephosphorylation of C-55 isoprenoid alcohol pyrophosphate, which directly hinders the synthesis of PG [6].

According to Figure 1 in the first section, it can be inferred that heat wave temperatures must be above 37 degrees Celsius.

Thus, the heat waves in the recent decades will have similar effects as those observed in the experiments of British biologists, that the synthesis of PG for bacterial cell walls will be impeded. As a matter of fact, the impediment of the bacterial cell wall is also an indispensable and most pristine method for antibiotics to kill bacteria: penicillin, the first antibiotic in human history, kills bacteria by inhibiting the photosynthesis of PG–specifically, penicillin binds to the beta-lactam ring to DD-transpeptidase, inhibiting its cross-linking activity and preventing new cell wall formation. The similarity between the mechanisms of penicillin and the effect high temperature has on PG synthesis means that heat waves happening in the recent decades provide an environment with survival pressure identical to that of penicillin. In other words, the same problem of inhibited cell wall reproduction confronts bacteria, thereby enabling them to retain the beneficial trait. Therefore, there is a good chance that intense heat

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provokes the bacterial species in the environment to develop a resistant trait even before they are in contact with antibiotics. To test this hypothesis, large amounts of experimentation and research need to be carried out, but since the theory is logically correct, optimism should be applied to this hypothesis.

4. Negative Effects of AMR and Solutions

According to the World Health Organization (WHO), antimicrobial resistance (AMR) is one of the top global public health and development threats. It is estimated that bacterial AMR was directly responsible for 1.27 million global deaths in 2019 and contributed to 4.95 million deaths.The misuse and overuse of antimicrobials in humans, animals, and plants are the main drivers in the development of drug-resistant pathogens. AMR affects countries in all regions and at all income levels. Poverty and inequality exacerbate its drivers and consequences, primarily affecting low- and middle-income countries. AMR jeopardizes many of the benefits of modern medicine. It makes infections harder to treat and makes other medical procedures and treatments – such as surgery, cesarean sections, and cancer chemotherapy – much riskier [7].

Although all properties and data about AMR seem unfavorable to human beings, there is a lot we can do to prevent AMR from emerging and spreading–in environmental ways. From the mechanism of AMR formation, it is clear that extreme conditions such as intense heat and strong radiation will increase the rate of AMR significantly, so it is a must to cut those extreme conditions that are caused by human activities. What people can do includes the reduction of fossil fuel combustion, the promotion of public transportation, and the application of certain kinds of new technology that function as an alternative to carbon-emitting activities. The cut-off in the usage of refrigerants such as Freon can effectively reduce the damage to ozone so that it can block hazardous radiation out. Reduced exposure to extreme conditions gradually eliminates the natural cause of AMR formation. In terms of antibiotic use, another prevailing measure is to oppose the misuse and abuse of antibiotics, especially in certain fields like husbandry and breeding. With the joint effort in different fields from everyone, human beings can overcome the threat of AMR.

5. Conclusion

The thesis has concentrated on the fundamental knowledge and processes of antimicrobial resistance (AMR), and presents significant theories and evidence upon which a hypothesis is formulated. If the concept is substantiated by future research, it will provide invaluable assistance to the pressing issue of AMR. It is a relatively new but already lethal issue, responsible for millions of deaths to date. Its appearance undermines the effectiveness of antibiotics, which have been a crucial treatment for bacterial infections since the previous century. Gaining insight into its fundamental mechanism and its interaction with the environment is undoubtedly advantageous and significant.

Although certain data and facts are included in the thesis to substantiate the assertion, there are still some complicating elements that could undermine the hypothesis. The idea clearly lacks scientific verification and empirical evidence, owing to the scarcity of studies pertaining to this subject. Moreover, the data utilized in the thesis is mostly limited to a quite restricted region, hence it may be inappropriate to generalize the suicide to the entire world.

To address the mentioned concerns, this paper proposes that future studies should prioritize a simulation model or experiment to examine the correlation between antimicrobial resistance (AMR) and the environment. It is recommended that samples be collected from various global locations to elucidate and validate the actual relationship between these two forces. In addition, it is important to take into account several possible confounding variables and endeavor to analyze their collective impact and outcomes.

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