

2020-11-10

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<http://hdl.handle.net/10026.1/16668>

10.21955/amrcopenres.1114927.1

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COVID-19 and Antibiotic Resistance - The calm before the storm...

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The human race has been affected by the continuing pandemic of SARS-CoV-2, with even the farthest reaches of the planet testing positive for the virus. At the time of writing this, a novel coronavirus (COVID-19) has infected over 40 million people worldwide, and the global death rate has reached almost 1.2 million^[1]. However, this pandemic could potentially be overshadowed by a more significant threat to humankind... bacterial resistance to antibiotics.

Incessant battle.

Humans and microorganisms have always been in a constant battle with each other. However, not all of these diverse prokaryotes cause infection and disease. Some are beneficial in maintaining a homeostatic balance of microflora within our bodies. Nevertheless, with the dawn of the 'antibiotic era', humans developed a new set of 'chemical weapons' to use against pathogenic microbes. Unfortunately, the microbes fought back, evolving to become resistant to these "weapons".

It is an entirely natural process for bacteria to evolve resistance to chemicals that target it - they have been doing it for billions of years. However, as modern medicine has progressed, bacteria have become more exposed to newly developed antibiotics and survive. The surviving bacteria then pass down antibiotic-resistant genes to their offspring^[2]. Our misplaced reliance and

overuse of antibiotics has compounded the problem, making bacteria even more robust.

Given the evolution of antibiotic-resistant bacteria has overtaken the development of new antibiotics, and no new classes of antibiotics have been discovered for over 30 years^[3], it is clear that the continuing COVID-19 pandemic pales into insignificance with what is around the corner.

When treatment is an issue.

COVID-19 (caused by virus SARS-CoV-2) is highly contagious, more so than any recent virus we have encountered. It is transmitted from person to person through a number of different pathways, like respiratory droplets, direct contact with the infected, and indirect contact with surfaces^[4]. When a patient is suffering from COVID-19 infection, opportunistic bacterial pathogens can persist and enter into the equation. This bacterial co-infection, along with secondary infection, are additional factors causing morbidity and mortality.

From 24 separate studies that were recently conducted, figures have shown that 72% of hospital inpatients testing positive for COVID-19 were given antibiotics as a prophylactic to treat a suspected bacterial infection. However, only 17.8% of COVID-19 patients were confirmed as having co-infection or developed secondary infections like bacterial *pneumonia*^{[5][6]}. This is a perturbing fact, as many of these patients might have never had a bacterial infection, however, they were still treated with antibiotics.

Clinicians are forced to do this in the hope of preventing patient death from co/secondary infections because they are unable to diagnose an infection in a more expeditious way. Nevertheless, the education regarding antibiotic stewardship in both the community and hospital environment (where the majority of human broad-spectrum antibiotics are prescribed^[7]) needs to be improved. Additionally, reluctance to use newly developed agents because it is more cost effective to use older antibiotics has led to antibiotic overuse^[8]. It is these issues that have been key factors in the evolution of “superbugs”.

Vertical & horizontal gene transfer.

Understanding bacterial evolution and how super strains are mutating is paramount to tackling this issue. Bacterial organisms have varied mechanisms to resist the antibiotics created to destroy them; like the ability to produce specific enzymes that can make an antibiotic inactive against it. Consequently, these genetic mutations are passed down through vertical transfer from a parent cell to its offspring, making the bacteria harder to eliminate.

There is also the issue of horizontal transfer, a process where a bacterial organism is able to transfer its genetic material to another bacterial organism that is not an offspring. During this transfer, it is possible that much of the bacteria's genome is changed. Plasmid-mediated resistance is an example of this process. Antibiotic resistant genes are carried on plasmids, which can be transferred between bacteria of the same species, or even, more worryingly, between different species. Moreover, this type of bacterial resistance to antibiotics is a far greater challenge to control. An example of gene transfer is *Staphylococcus aureus*, which was once easily treated by methicillin (a β -lactam penicillin class antibiotic).

However, this bacterium evolved the ability to produce an enzyme called penicillinase, giving the microbe penicillin resistance. This resistant organism is more commonly known as MRSA (methicillin-resistant *Staphylococcus aureus*).

Poverty = Infection.

Knowing how resistant bacteria are evolving is not the only way to curb the rising trend of superbugs. Following basic hygiene practises, like regularly washing hands/surfaces, using sanitiser when hand washing is not available, preventing cross-contamination between foods/surfaces, and sneezing onto the inner elbow, rather than onto hands, are just some of the ways to help prevent the transmission of any microbial infection^[9]. Obtaining clean, safe water is also a major problem. Microbes can spread rapidly in developing regions that do not have access to clean water and good sanitation^[10]. Unfortunately, in these areas where the poverty level is high, necessary hygiene regimes cannot be achieved. Poverty is leading to a greater level of antibiotic misuse, for example, the unregulated manufacture of inferior quality drugs, patients sharing or not finishing a course of antibiotics, and using out of date drugs. These are all too familiar scenarios leading to increased antibiotic resistance^[11].

How does climate change fit in?

Bacteria have also evolved to withstand several different environmental factors, such as extreme changes in temperature. With climate change at the forefront of recent scientific media coverage, it is crucial to link these two significant issues together. Generally, an increase in temperature can augment enzyme activity, thus increasing bacterial growth. Recent studies have shown

antibiotic-resistant bacteria are surviving for longer at warmer times of the year as global temperatures rise^[12]. This proves there is a clear association between antibiotic resistance and temperature, meaning pathogens may be getting stronger and more resilient over time because of global warming^[13].

Where is the money?

Another big challenge faced by scientists is obtaining the funding needed to combat antibiotic resistance. The field of antibiotic research and development is grossly underfunded, so more investment is needed to support recent improvements and solutions being established. While some private companies within the industry understand this issue and invest money into an 'alliance' they have created, the public sector is falling behind drastically. Data from 2018 has shown that the total European public sector investment fund for antibiotic development totalled roughly €430 million annually^[14]. This is less money than the annual income made by the top 10 footballers in the world combined^[15], proving humanitarian priorities are grossly obscured. Even though the European Commission has made funding available through the Horizon research and innovation programme, along with AMR Action Fund expecting to invest \$1 billion in response to the antimicrobial resistance (AMR) threat, it is still not enough to make the impact that is sorely needed to strengthen the fragile antibiotic pipeline which is almost at breaking point^[16].

No borders, no boundaries.

The uncontrolled increase of antibiotic resistance is a serious global health concern that affects everyone. Microbes are silent in their movement and have no regard for world boundaries or country

limits. International travel and trade have an obvious impact on infectious disease transmission. However, due to the current COVID-19 situation, there has been a reduction in international travel^[17], which could possibly have an effect on reducing transmission of antibiotic resistant microbes. Limiting travel and trade, conversely, is not an ideal reduction method. Therefore, it is up to the worldwide community to unite in order to fight these microscopic adversaries, as no single initiative by any individual country or region will be enough to reverse this trend. All sectors, whether it be political, medical, economic, environmental or industrial, have a responsibility to help tackle antibiotic resistance, along with the other concerning factors associated. Scientists around the world are continuing to make advances in the pursuit of new antibiotic treatments for infection, and fast detection methods to identify antibiotic-resistant genes from pathogens^[18]. These endeavours are examples of what is needed to restrict and slow down antibiotic resistance.

What if a scratch could kill?

Governments must take steps to invest more time, funding, and effort into all aspects of this global crisis. A much-needed increase in public spending towards the antibiotic development pipeline would relate to an increase in output by scientists. The public also needs to be confident that their money is going towards combatting an issue that will not only affect us in our lifetime but have massive consequences for our children's lifetime thereafter. As antibiotics play a considerable part in healthcare, the ramifications if nothing is done are unthinkable. A simple scratch could kill a child, cancer treatments could kill a patient, and childbirth could kill an expectant mother and her baby^[19]. Currently, the global loss of life

caused by antibiotic resistance is estimated at over 700,000 deaths per annum. This is predicted to climb exponentially to over 10 million deaths per annum by the year 2050 if no action is taken^[20]. These figures show the need for scientists and clinicians to start educating a broader demographic to understand global and personal impacts caused by antibiotic resistance.

COVID-19 has demonstrated how vulnerable the human race is to an infectious agent. The pandemic has been a massive struggle for all, putting people and services under enormous pressure. However, to prevent this sort of scenario from becoming a regular occurrence with even greater loss of life, the global community must act now. New solutions are on the horizon, and with every new solution, no matter how big or small, comes the possibility to reduce death caused by antibiotic resistance, simultaneously bringing hope to so many of those already affected by this microbial war.

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