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ANTIBIOTIC RESISTANCE: A REVIEW

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Abstract-Antibiotics are medicines used to prevent and treat bacterial infections. Antibiotic resistance occurs when bacteria change in response to the use of these medicines. Bacteria, not humans or animals, become antibiotic-resistant. These bacteria may infect humans and animals, and the infections they cause are harder to treat than those caused by non-resistant bacteria. Antibiotic resistance leads to higher medical costs, prolonged hospital stays, and increased mortality. The world urgently needs to change the way it prescribes and uses antibiotics. Even if new medicines are developed, without behaviour change, antibiotic resistance will remain a major threat. Behaviour changes must also include actions to reduce the spread of infections through vaccination, hand washing, practising safer sex, and good food hygiene.

Keywords- Antibiotic, Medicines, Resistance, Bacteria, Prolonged

I. INTRODUCTION

Antibiotic medications are used to kill bacteria, which can cause illness and disease. They have made a major contribution to human health. Many diseases that once killed people can now be treated effectively with antibiotics. However, some bacteria have become resistant to commonly used antibiotics. Antibiotic resistant bacteria are bacteria that are not controlled or killed by antibiotics. They are able to survive and even multiply in the presence of an antibiotic. Most infection-causing bacteria can become resistant to at least some antibiotics. Bacteria that are resistant to many antibiotics are known as multi-resistant organisms (MRO). Antibiotic resistance is a serious public health problem. It can be prevented by minimising unnecessary prescribing and overprescribing of antibiotics, the correct use of prescribed antibiotics, and good hygiene and infection control. Some bacteria are naturally resistant to some antibiotics. For example, benzyl penicillin has very little effect on most organisms found in the human digestive system (gut).

Bacteria resistant to antibiotics

Some bacteria have developed resistance to antibiotics that were once commonly used to treat them. For example, *Staphylococcus aureus* ('golden staph' or MRSA) and *Neisseria gonorrhoeae* (the cause of gonorrhoea) are now almost always resistant to benzyl penicillin. In the past, these infections were usually controlled by penicillin.

The most serious concern with antibiotic resistance is that some bacteria have become resistant to almost all of the easily available antibiotics. These bacteria are able to cause serious disease and this is a major public health problem. Important examples are:

- methicillin-resistant *Staphylococcus aureus* (MRSA)
- vancomycin-resistant *Enterococcus* (VRE)
- multi-drug-resistant *Mycobacterium tuberculosis* (MDR-TB)
- carbapenem-resistant *Enterobacteriaceae* (CRE) gut bacteria

One of the central themes of success in human therapeutics in the 20th century was the discovery and development of antibiotics and antibacterial agents, for the treatment of bacterial infections. The introduction of antibiotics helped drop the death rates from infectious disease from 797 per hundred thousand in 1900 to 36 per hundred thousand in 1980, a 20-fold improvement. Two lines of chemical investigation proved fruitful: the isolation of natural products with antibiotic activity from microbial sources and the purposeful synthesis of antibacterial agents by medicinal chemists. The first line of discovery, the isolation of microbial metabolites from Nature, was initiated by Flemming's discovery of a penicillin-producing fungus and was closely followed by systematic search of antibacterial producing microorganisms by pioneers such as Dubos and Waksman. This strategy produced many of the famous classes of antibiotics. These include both the cephalosporin and penicillin branches of the β -lactams, the aromatic polyketides of the tetracycline class, the aminoglycosides



represented by streptomycin, the polyketide macrolactones exemplified by erythromycin, and the glycopeptides of the vancomycin and teicoplanin family. The search by medicinal chemists for antibacterial magic bullets by synthetic efforts has produced the sulfa drugs, the dihydrofolate reductase inhibitors, the fluoroquinolones, and most recently the oxazolidinones. In the course of these discovery efforts, the active natural products and synthetic antibacterials have proven to be valuable probes for deciphering the identity of targets in pathogenic bacteria. Historically, this has turned out to be a target poor

therapeutic area with only four robust targets for widely used groups of antibiotics: bacterial cell wall biosynthesis; bacterial protein biosynthesis; DNA replication and repair; and folate coenzyme biosynthesis.

The golden age of antibiotic discovery in the 20th century was actually quite short (Table 1). The two decades from 1940 to 1960 saw isolation of most of the major classes of natural antibiotics. The sulfa drugs were introduced in the 1930s and have been in continuous use for 70 years. The first versions of the quinolone synthetic drugs were introduced in 1962.

Table 1. History of Antibiotic Classes in Clinical Use

year	antibiotic	class	natural product	synthetic
1929 (activity)	penicillin	β -lactam	√	
1940 (purification)				
1932	sulfapyridine	sulfonamide		√
1944	streptomycin	aminoglycoside	√	
1945	cephalosporin	β -lactam	√	
1947	chloramphenicol	phenypropanoid	√	
1948	chlortetracycline	tetracycline	√	
1950	erythromycin	macrolide	√	
1955	vancomycin	glycopeptide	√	
1955	virginiamycin	streptogramin	√	
1955	amphotericin	polyene (antifungal)	√	
1955	lincomycin	lincosamide	√	
1959	rifamycin	ansamycin	√	
1962	nalidixic acid	quinolone		√
1969	fosfomycin	phosphonate	√	



2000	linezolid	oxazolidinone		√
2003	daptomycin	lipopeptide	√	

How does antibiotic resistance develop?

There are many ways in which bacteria can become resistant to antibacterial drugs. Resistance can be intrinsic, meaning a basic characteristic that naturally occurs in the bacterium, and is essentially always there, or acquired, which means the bacterium is not naturally resistant but has become resistant somehow overtime. One fantastic example of intrinsic resistance would be *Mycoplasma* species' resistance to beta-lactam antibiotics, like penicillin. These specific drugs attack the cell wall of bacterial cells; however, *Mycoplasma* species do not possess cell walls. As a result, *Mycoplasma* are intrinsically resistant to this class

of antibiotic. Acquired resistance can be the result of one bacterium sharing genes with another, an accidental transmission of genes from one bacterium to another through bacteriophage (viruses that only infect bacterial cells), or a bacterium picking up resistance genes from it's environment (from DNA left behind after another bacterium died for instance). These three mechanisms of acquired drug resistance are referred to as methods of 'horizontal gene transfer'. Resistance can also arise from random mutations in the genetic sequence that happen to be beneficial, and persist as a result.

Why does antibiotic resistance develop?

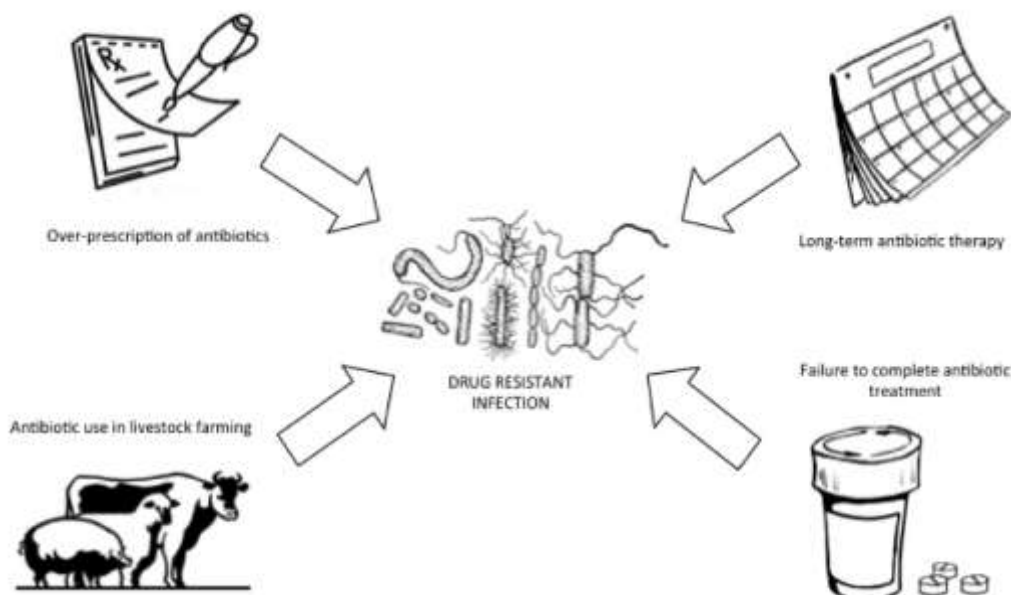


Figure1: Factors Contributing to antibiotic resistance

Microbes (bacteria included) are very skilled at the delicate art of survival. Existing virtually ubiquitously in the environment, there is an intense amount of competition between microorganisms for available resources. This competition drives microbes to develop survival mechanisms. Some microbes even make their own antibiotic compounds. In such a case, the microbe itself would be unharmed by the compound it produces (think intrinsic resistance), but surrounding microbes would be affected (possibly killed), thus increasing the initial microbe's chances of survival. This was the whole basis of how

penicillin was discovered! Of course we wouldn't have such a rich diversity of microbes in the world if some didn't develop, either through random mutation or horizontal gene transfer, means to defend themselves from these naturally occurring antibiotics. When we use antibiotics to treat infections, we are treating microbes with compounds similar to those they have been battling for centuries. As such, resistant populations can arise very quickly following the tried and true process of evolution.

Antibiotic resistance can arise, and has arisen, for many different reasons. Exposure to antibacterial drugs provides a



selection pressure, killing off bacteria that are susceptible to the drug, while the few that happen to possess resistance genes survive and multiply. Factors contributing to the development of resistance include (Figure 1):

- Over-prescription of antibiotics (for example, giving antibiotics for an infection that isn't caused by bacteria, like the cold or flu)
- Overuse of antibiotics in livestock farming
- Lengthy courses of treatment with antibiotics
- These scenarios expose bacterial populations to antibiotics at unnecessary times, putting pressure on resistant bacteria to over-take the population and making them more difficult to treat in the future.
- Patients not finishing the whole course of antibiotics prescribed to them
- This may seem counter-intuitive considering the other three scenarios, but a short treatment regiment might wipe out bacteria that are completely susceptible to a drug while a full course of treatment is required to wipe out those bacteria that are partially resistant. If you stop a treatment early, you may be un-wittingly selecting for less susceptible bacteria that will be more difficult to treat later. A similar situation can occur if you treat a bacterial infection with a lower than optimal drug concentration. Drug resistance is not a black or white issue. Sometimes bacteria are resistant to lower concentrations of a drug, but will be killed by a higher concentration, or sometimes more exposure time is needed for the drug to work... if the instructions for treatment aren't followed closely, you could be doing more harm than good, even with the best of intentions. The take-home? Always take your medication as prescribed.

Causes of Antibiotic Resistance

Antimicrobial resistance is mainly caused by the overuse of antimicrobials. This leads to microbes either evolving a defense against drugs used to treat them, or certain strains of microbes that have a natural resistance to antimicrobials becoming much more prevalent than the ones that are easily defeated with medication. While antimicrobial resistance does occur naturally over time, the use of antimicrobial agents in a variety of settings both within the healthcare industry and outside of has led to antimicrobial resistance becoming increasingly more prevalent.

Natural occurrence

Antimicrobial resistance can evolve naturally due to continued exposure to antimicrobials. Natural selection means that organisms that are able to adapt to their environment, survive, and continue to produce offspring. As a result, the types of microorganisms that are able to survive over time with continued attack by certain antimicrobial agents will naturally become more prevalent in the

environment, and those without this resistance will become obsolete. Over time most of the strains of bacteria and infections present will be the type resistant to the antimicrobial agent being used to treat them, making this agent now ineffective to defeat most microbes. With the increased use of antimicrobial agents, there is a speeding up of this natural process.

Self-medication

Self-medication by consumers is defined as "the taking of medicines on one's own initiative or on another person's suggestion, who is not a certified medical professional", and it has been identified as one of the primary reasons for the evolution of antimicrobial resistance. In an effort to manage their own illness, patients take the advice of false media sources, friends, and family causing them to take antimicrobials unnecessarily or in excess. Many people resort to this out of necessity, when they have a limited amount of money to see a doctor, or in many developing countries a poorly developed economy and lack of doctors are the cause of self-medication. In these developing countries, governments resort to allowing the sale of antimicrobials as over the counter medications so people could have access to them without having to find or pay to see a medical professional. This increased access makes it extremely easy to obtain antimicrobials without the advice of a physician, and as a result many antimicrobials are taken incorrectly leading to resistant microbial strains. One major example of a place that faces these challenges is India, where in the state of Punjab 73% of the population resorted to treating their minor health issues and chronic illnesses through self-medication.

The major issue with self-medication is the lack of knowledge of the public on the dangerous effects of antimicrobial resistance, and how they can contribute to it through mistreating or misdiagnosing themselves. In order to determine the public's knowledge and preconceived notions on antibiotic resistance, a major type of antimicrobial resistance, a screening of 3537 articles published in Europe, Asia, and North America was done. Of the 55,225 total people surveyed, 70% had heard of antibiotic resistance previously, but 88% of those people thought it referred to some type of physical change in the body. With so many people around the world with the ability to self-medicate using antibiotics, and a vast majority unaware of what antimicrobial resistance is, it makes the increase of antimicrobial resistance much more likely.

Clinical misuse

Clinical misuse by healthcare professionals is another cause leading to increased antimicrobial resistance. Studies done by the CDC show that the indication for treatment of antibiotics, choice of the agent used, and the duration of therapy was incorrect in up to 50% of the cases studied. In



another study done in an intensive care unit in a major hospital in France, it was shown that 30% to 60% of prescribed antibiotics were unnecessary. These inappropriate uses of antimicrobial agents promote the evolution of antimicrobial resistance by supporting the bacteria in developing genetic alterations that lead to resistance. In a study done by the American Journal of Infection Control aimed to evaluate physicians' attitudes and knowledge on antimicrobial resistance in ambulatory settings, only 63% of those surveyed reported antibiotic resistance as a problem in their local practices, while 23% reported the aggressive prescription of antibiotics as necessary to avoid failing to provide adequate care. This demonstrates how a majority of doctors underestimate the impact that their own prescribing habits have on antimicrobial resistance as a whole. It also confirms that some physicians may be overly cautious when it comes to prescribing antibiotics for both medical or legal reasons, even when indication for use for these medications is not always confirmed. This can lead to unnecessary antimicrobial use.

Environmental pollution

Untreated effluents from pharmaceutical manufacturing industries, hospitals and clinics, and inappropriate disposal of unused or expired medication can expose microbes in the environment to antibiotics and trigger the evolution of resistance.

Food production

Livestock

The antimicrobial resistance crisis also extends to the food industry, specifically with food producing animals. Antibiotics are fed to livestock to act as growth supplements, and a preventative measure to decrease the likelihood of infections. This results in the transfer of resistant bacterial strains into the food that humans eat, causing potentially fatal transfer of disease. While this practice does result in better yields and meat products, it is a major issue in terms of preventing antimicrobial resistance. Though the evidence linking antimicrobial usage in livestock to antimicrobial resistance is limited, the World Health Organization Advisory Group on Integrated Surveillance of Antimicrobial Resistance strongly recommended the reduction of use of medically important antimicrobials in livestock. Additionally, the Advisory Group stated that such antimicrobials should be expressly prohibited for both growth promotion and disease prevention.

In a study published by the National Academy of Sciences mapping antimicrobial consumption in livestock globally, it was predicted that in the 228 countries studied, there would be a total 67% increase in consumption of antibiotics by livestock by 2030. In some countries such as

Brazil, Russia, India, China, and South Africa it is predicted that a 99% increase will occur. Several countries have restricted the use of antibiotics in livestock, including Canada, China, Japan, and the US. These restrictions are sometimes associated with a reduction of the prevalence of antimicrobial resistance in humans.

Pesticides

Most pesticides protect crops against insects and plants, but in some cases antimicrobial pesticides are used to protect against various microorganisms such as bacteria, viruses, fungi, algae, and protozoa. The overuse of many pesticides in an effort to have a higher yield of crops has resulted in many of these microbes evolving a tolerance against these antimicrobial agents. Currently there are over 4000 antimicrobial pesticides registered with the EPA and sold to market, showing the widespread use of these agents. It is estimated that for every single meal a person consumes, 0.3 g of pesticides is used, as 90% of all pesticide use is used on agriculture. A majority of these products are used to help defend against the spread of infectious diseases, and hopefully protect public health. But out of the large amount of pesticides used, it is also estimated that less than 0.1% of those antimicrobial agents, actually reach their targets. That leaves over 99% of all pesticides used available to contaminate other resources. In soil, air, and water these antimicrobial agents are able to spread, coming in contact with more microorganisms and leading to these microbes evolving mechanisms to tolerate and further resist pesticides.

II. PREVENTION OF ANTIBIOTIC RESISTANCE

Only use antibiotics for an infection caused by bacteria

Antibiotics are effective against infections caused by bacteria. They don't work against infections caused by viruses such as the common cold and the flu. Having green or yellow-coloured mucous, phlegm or snot isn't always a sign of a bacterial infection. Read more about snot and sputum.

Symptoms such as cough, sore throat, earache and fever don't always mean that you have a bacterial infection. While some people with these symptoms will need antibiotics, most people won't because the infection can be caused by viruses. In those cases, the infection will get better without antibiotics.

Only use antibiotics when prescribed by a doctor

Your doctor will assess your condition and use their clinical judgment to prescribe a particular antibiotic if they think it is needed. Before prescribing, they will consider your symptoms, exposure to infection and test results, other medicines you are taking and any allergies you may have.

Never share antibiotics with others



Antibiotics you are prescribed may not work for your family/whānau member, friend or neighbour's illness. They might not need antibiotics at all. If they do, they might need a different dose or type of antibiotic. They may have an allergy or another condition or be taking other medicines that mean your antibiotics are not suitable.

Using antibiotics when they are not needed, or taking the wrong antibiotic, exposes bacteria to antibiotics unnecessarily, which encourages antibiotic resistance.

Don't use antibiotics left over from a previous prescription

The type, dose and amount of antibiotics left over may not be enough to fight a new infection. This creates more opportunity for resistant bacteria to develop and multiply. Different infections may need different treatments, even though you might have similar symptoms. If your condition is caused by bacteria, to treat it effectively you need to get the right antibiotic, at the right dose, for the right period of time. Using antibiotics when they are not needed or taking the wrong antibiotic exposes bacteria to antibiotics unnecessarily, which encourages antibiotic resistance.

Another thing to keep in mind is that just like food, antibiotics go off. Keeping leftover antibiotics may lead you to take expired medicines, which means they may not work when you need them or may make you feel more ill. Liquid antibiotics often need to be kept in the fridge and expire quickly; other antibiotics may not be labelled with a specific expiry date.

Should you finish a course of antibiotics?

Often you will feel better before your course of antibiotics is finished. More studies are showing that shorter courses of antibiotics are just as effective as longer courses. However, treatment guidelines are being updated with this new information, so your prescriber will take this into account when they decide your treatment.

For some infections it is important to take antibiotics for a while after you feel better to make sure the infection is gone, so it is always best to complete your antibiotics as advised the prescriber. If in doubt, talk to your prescriber.

Dispose of antibiotics correctly

Take unused antibiotics to the pharmacy for safe disposal. If you have leftover antibiotics from previous use, dispose of them correctly by returning them to your pharmacy for safe disposal.

Don't put them down the toilet or sink. There is a risk that antibiotics poured down the sink or flushed down the toilet may pass through treatment systems and enter rivers, lakes and even drinking water supplies. In homes that use septic tanks, antibiotics flushed down the toilet could leach into the ground and seep into ground water.

Antibiotics that get into the environment may drive bacteria to become more resistant. Appropriate disposal of antibiotics by the pharmacy minimises this risk. Unused medicines taken to pharmacies are disposed of by specialist waste disposal companies.

Prevention and control

Antibiotic resistance is accelerated by the misuse and overuse of antibiotics, as well as poor infection prevention and control. Steps can be taken at all levels of society to reduce the impact and limit the spread of resistance.

Individuals

To prevent and control the spread of antibiotic resistance, individuals can:

- Only use antibiotics when prescribed by a certified health professional.
- Never demand antibiotics if your health worker says you don't need them.
- Always follow your health worker's advice when using antibiotics.
- Never share or use leftover antibiotics.
- Prevent infections by regularly washing hands, preparing food hygienically, avoiding close contact with sick people, practising safer sex, and keeping vaccinations up to date.
- Prepare food hygienically, following the WHO Five Keys to Safer Food (keep clean, separate raw and cooked, cook thoroughly, keep food at safe temperatures, use safe water and raw materials) and choose foods that have been produced without the use of antibiotics for growth promotion or disease prevention in healthy animals.

Policy makers

To prevent and control the spread of antibiotic resistance, policy makers can:

- Ensure a robust national action plan to tackle antibiotic resistance is in place.
- Improve surveillance of antibiotic-resistant infections.
- Strengthen policies, programmes, and implementation of infection prevention and control measures.
- Regulate and promote the appropriate use and disposal of quality medicines.
- Make information available on the impact of antibiotic resistance.

Health professionals

To prevent and control the spread of antibiotic resistance, health professionals can:



- Prevent infections by ensuring your hands, instruments, and environment are clean.
- Only prescribe and dispense antibiotics when they are needed, according to current guidelines.
- Report antibiotic-resistant infections to surveillance teams.
- Talk to your patients about how to take antibiotics correctly, antibiotic resistance and the dangers of misuse.
- Talk to your patients about preventing infections (for example, vaccination, hand washing, safer sex, and covering nose and mouth when sneezing).

Healthcare industry

To prevent and control the spread of antibiotic resistance, the health industry can:

- Invest in research and development of new antibiotics, vaccines, diagnostics and other tools.

Agriculture sector

To prevent and control the spread of antibiotic resistance, the agriculture sector can:

- Only give antibiotics to animals under veterinary supervision.
- Not use antibiotics for growth promotion or to prevent diseases in healthy animals.
- Vaccinate animals to reduce the need for antibiotics and use alternatives to antibiotics when available.
- Promote and apply good practices at all steps of production and processing of foods from animal and plant sources.
- Improve biosecurity on farms and prevent infections through improved hygiene and animal welfare.

Development of new drugs

Since the discovery of antibiotics, research and development (R&D) efforts have provided new drugs in time to treat bacteria that became resistant to older antibiotics, but in the 2000s there has been concern that development has slowed enough that seriously ill people may run out of treatment options. Another concern is that doctors may become reluctant to perform routine surgeries because of the increased risk of harmful infection.^[159] Backup treatments can have serious side-effects; for example, treatment of multi-drug-resistant tuberculosis can cause deafness or psychological disability. The potential crisis at hand is the result of a marked decrease in industry R&D. Poor financial investment in antibiotic research has exacerbated the situation. The pharmaceutical industry has little incentive to invest in antibiotics because of the high risk and because the potential financial returns are less likely to cover the cost of development than for other pharmaceuticals. In 2011, Pfizer, one of the last major pharmaceutical companies developing new antibiotics, shut down its

primary research effort, citing poor shareholder returns relative to drugs for chronic illnesses. However, small and medium-sized pharmaceutical companies are still active in antibiotic drug research. In particular, apart from classical synthetic chemistry methodologies, researchers have developed a combinatorial synthetic biology platform on single cell level in a high-throughput screening manner to diversify novel lanthipeptides.

In the United States, drug companies and the administration of President Barack Obama had been proposing changing the standards by which the FDA approves antibiotics targeted at resistant organisms.

On 18 September 2014 Obama signed an executive order to implement the recommendations proposed in a report by the President's Council of Advisors on Science and Technology (PCAST) which outlines strategies to streamline clinical trials and speed up the R&D of new antibiotics. Among the proposals:

- Create a 'robust, standing national clinical trials network for antibiotic testing' which will promptly enroll patients once identified to be suffering from dangerous bacterial infections. The network will allow testing multiple new agents from different companies simultaneously for their safety and efficacy.
- Establish a 'Special Medical Use (SMU)' pathway for FDA to approve new antimicrobial agents for use in limited patient populations, shorten the approval timeline for new drug so patients with severe infections could benefit as quickly as possible.
- Provide economic incentives, especially for development of new classes of antibiotics, to offset the steep R&D costs which drive away the industry to develop antibiotics.

Scientists have started using advanced computational approaches with supercomputers for the development of new antibiotic derivatives to deal with antimicrobial resistance.

III. CONCLUSION

Antibiotic resistance has increased worldwide in bacterial pathogens leading to treatment failures in human and animal infectious diseases. Resistance against antibiotics by pathogenic bacteria is a major concern in the anti-infective therapy of both humans and animals. Bacteria are able to adapt rapidly to new environmental conditions such as the presence of antimicrobial molecules and, as a consequence, resistance may increase with increasing exposure to antimicrobials. Serious concerns about bacterial antibiotic resistance from nosocomial, community-acquired and food-borne pathogens have been growing for a number of years, and have been raised at both national and international levels.



Emerging bacterial resistance against different types of biocides (including disinfectants, antiseptics, preservatives and sterilants) has been studied and characterised only recently. Only limited scientific evidence is available to correctly weigh the risks of antibiotic resistance induced by resistance to biocides and some controversies remain. Furthermore, research indicates that biocides and antibiotics may have some similar and common interactions and target sites with bacteria, which might express shared resistance mechanisms to both antimicrobials.

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