Microbe of the month

Breaking The Chain of Infection

Cutimed®

NOVEMBER 2022 NEWSLETTER

Compiled by
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Featured this month:

MECHANISMS OF ANTIMICROBIAL RESISTANCE (AMR)

Clever moves you need to know about!

Hello readers!

The Microbe of the Month newsletter aims to educate healthcare workers about pathogens of importance, as well as vital facts and clinical guidelines relevant to Infection Control and Antimicrobial Stewardship, in an easy to read and understand format.

18th – 24th November marks World Antimicrobial Awareness Week – a global campaign that is recognised annually to improve awareness and understanding of AMR and encourage best practices among the public, One Health stakeholders and national policymakers – who all play critical roles in reducing the further emergence and spread of AMR.[1]

This issue will review some of the latest research findings on antimicrobial resistance (AMR), especially in view of the 'collateral damage' caused by antibiotic prescribing during the COVID-19 pandemic.

Please use this newsletter as a teaching tool in your workplace, share it widely and start an 'infectious dialogue' about topical issues in infection control!

Microbes are constantly finding new defence strategies, called '**resistance mechanisms**'. Antimicrobial resistance (AMR) occurs when bacteria, viruses, fungi and protozoa change genetically over time – this is to be expected over thousands of years, because of Darwinian natural selection. However, **the overuse and abuse of antimicrobial agents exerts additional *'selective pressure'* on microorganisms which accelerates the development of resistance**.

Antibiotics, antiviral, antifungal and antiparasitic agents are becoming less effective; and outbreaks, severe infection and sepsis are more commonplace - as infections become increasingly difficult or impossible to treat. **Researchers estimated that AMR in bacteria alone caused an estimated 1.27 million deaths in 2019.**[1]

Key words: *antimicrobial resistance (AMR), selective pressure, multidrug-resistant (MDR), multidrug-resistant organism (MDRO), mechanisms of resistance, antimicrobial stewardship (AMS).*

IT'S TIME TO FIGHT AMR
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NOVEMBER 2022 Where do we stand?

A recently published systematic review on the global burden of bacterial antimicrobial resistance[2] used data from literature reviews, hospital and other surveillance systems - covering 471 million individual records and isolates, and 7585 study-location-years.

The findings indicated that bacterial AMR is a health problem whose magnitude is at least as large as major diseases such as HIV and malaria, and potentially much larger. Although bacterial AMR is a problem worldwide, **it was estimated that, in 2019, the highest rates of AMR burden were in sub-Saharan Africa.**

The following **antibiotic-resistant bacteria** were responsible for an estimated **929 000** deaths attributable to AMR, and at least **3.57 million** 'AMR-associated' deaths in 2019[2]:

01 *Escherichia coli*

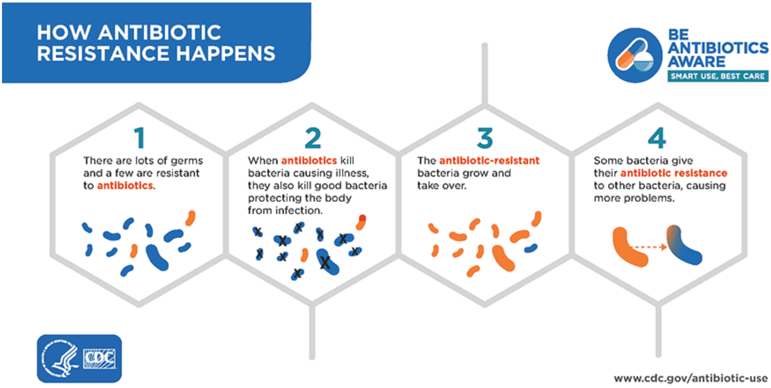
02 *Staphylococcus aureus*

03 *Klebsiella pneumoniae*

04 *Streptococcus pneumoniae*

05 *Acinetobacter baumannii*

06 *Pseudomonas aeruginosa*



HOW ANTIBIOTIC RESISTANCE HAPPENS

1. There are lots of germs and a few are resistant to **antibiotics**.
2. When **antibiotics** kill bacteria causing illness, they also kill good bacteria protecting the body from infection.
3. The **antibiotic-resistant** bacteria grow and take over.
4. Some bacteria give their **antibiotic resistance** to other bacteria, causing more problems.

Methicillin-resistant *Staphylococcus aureus* (MRSA) caused more than 100 000 deaths attributable to AMR in 2019; while MDR tuberculosis, third-generation cephalosporin-resistant *E. coli*, carbapenem-resistant *A. baumannii*, fluoroquinolone-resistant *E. coli*, carbapenem-resistant *Klebsiella pneumoniae (K. pneumoniae)*, and third-generation cephalosporin-resistant *K. pneumoniae* each caused an estimated 50 000–100 000 deaths. [2]

US Centers for Disease Control and Prevention ANTIBIOTIC RESISTANCE THREATS [3]

Urgent Threats

Carbapenem-resistant Acinetobacter spp.

Candida *auris* (fungal pathogen)

Clostridioides *difficile* (C. *difficile*)

Carbapenem-resistant Enterobacteriaceae

Drug-resistant Neisseria *gonorrhoeae*

Concerning Threats

Erythromycin-resistant Group A Streptococcus

Clindamycin-resistant

Serious Threats

Drug-resistant Campylobacter spp.

Drug-resistant Candida spp. (fungal pathogen)

Extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae

Vancomycin-resistant Enterococci

Multidrug-resistant Pseudomonas *aeruginosa*

Drug-resistant non-typhoidal Salmonella spp. and serotype S. *typhi*

Drug-resistant Shigella

Methicillin-resistant Staphylococcus *aureus* (MRSA)

Group B Streptococcus

Drug-resistant Streptococcus *pneumoniae*

Multi-drug resistant Tuberculosis

WHY DOES ANTIMICROBIAL RESISTANCE EMERGE WITHIN A MICROORGANISM? [4,5]

Microbes - as a group or species - are not necessarily uniformly susceptible or resistant to any specific antimicrobial agents, and levels of resistance may vary within related bacterial groups. ***Most antimicrobial drugs in use today are naturally produced by microorganisms -*** including environmental fungi and saprophytic bacteria (i.e., those which feed off decaying material) - or are synthetic modifications of them. Only a few drugs (e.g., sulphonamides and fluoroquinolones) are wholly synthetic.

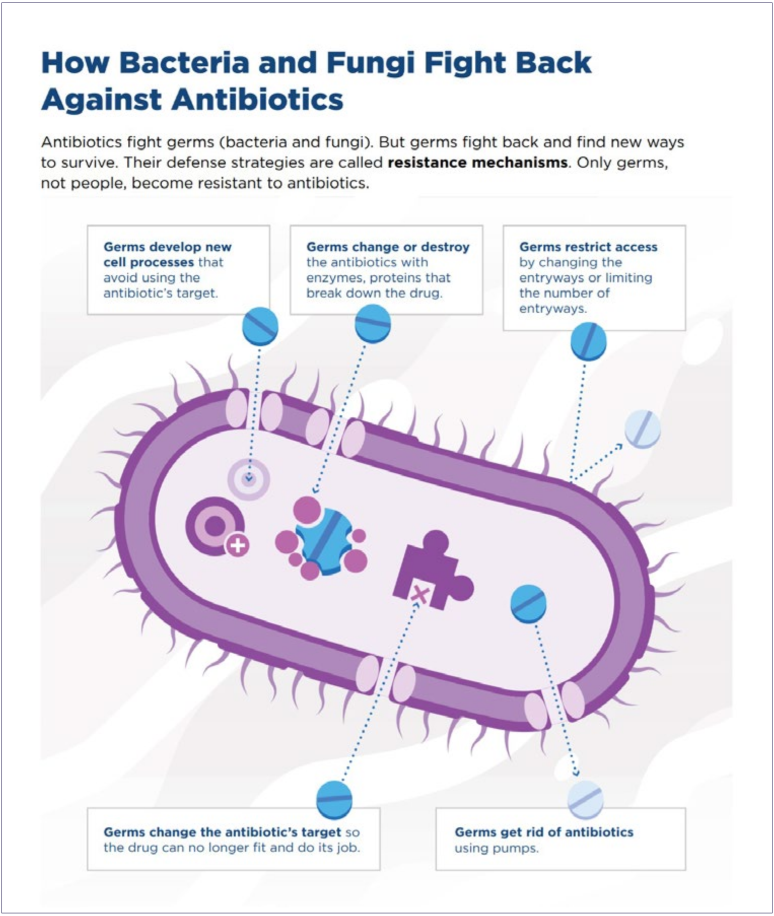
'**Natural resistance**' may be ***intrinsic*** (always expressed in that species) or ***induced*** (i.e., the genes are naturally occurring within the microorganisms, but resistance is only expressed after exposure to an antimicrobial drug). Even the use of low concentrations of antimicrobials (i.e., sub-inhibitory levels) can lead to the selection of high-level resistance in successive bacterial generations, and this may select for '***hyper-mutable***' strains (bacteria with an increased mutation rate) and may also increase their ability to acquire resistance to other antimicrobial agents, from the movement of '***mobile genetic elements***'.

Basic antimicrobial protective mechanisms include:

- preventing entry to, or 'pumping' the antimicrobial drug out of the cell
- producing enzymes that destroy or modify the antimicrobial agent
- making changes to the antimicrobial target (e.g., antimicrobial receptors on the cell wall).

Clinical relevance?

Gram-negative bacteria (e.g., *E. coli, Klebsiella pneumoniae, Acinetobacter* species) make use of all these mechanisms; whereas the ability to limit the uptake of an antimicrobial drug, or the capacity for certain types of drug efflux (pump) mechanisms, is less common in Gram-positive bacteria (e.g., *Staphylococci, Streptococci* and *Enterococci*) because they do not have a lipopolysaccharide outer cell membrane.[5]



How Bacteria and Fungi Fight Back Against Antibiotics

Antibiotics fight germs (bacteria and fungi). But germs fight back and find new ways to survive. Their defense strategies are called **resistance mechanisms**. Only germs, not people, become resistant to antibiotics.

Germs develop new cell processes that avoid using the antibiotic's target.

Germs change or destroy the antibiotics with enzymes, proteins that break down the drug.

Germs restrict access by changing the entryways or limiting the number of entryways.

Germs change the antibiotic's target so the drug can no longer fit and do its job.

Germs get rid of antibiotics using pumps.

Have you ever received a microbiology laboratory culture report which states 'ESBL +ve' next to the bacterial species cultured?

This acronym refers to the production of an '*extended spectrum beta-lactamase' (ESBL)* enzyme and serves as an '**antibiotic resistance alert**' to the prescriber.

Beta-lactam antibiotics cannot be used to treat infections caused by bacteria which produce beta-lactamase enzymes. This is especially problematic, because it leaves very few options for

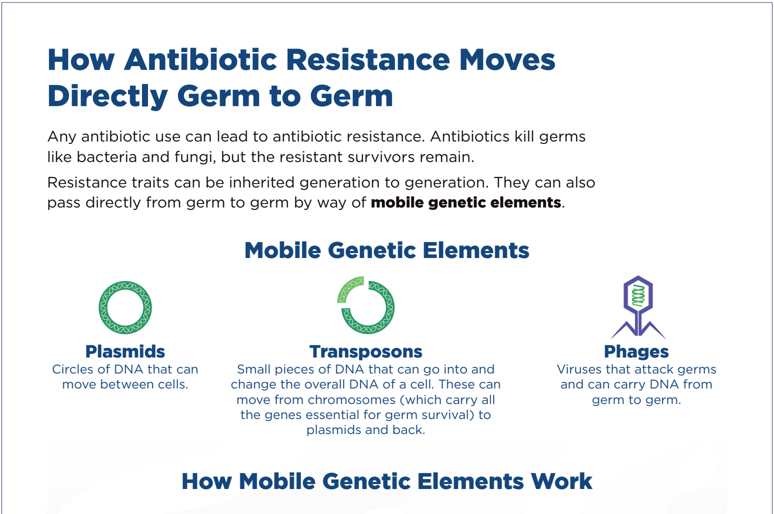
antibiotics which can be taken orally, without admission to hospital.

Examples of Gram-positive beta-lactamase-producing bacteria include:

- **MRSA** (methicillin-resistant *Staphylococcus aureus*): causes wound and bloodstream infections, pneumonia (hospital strains), skin abscesses and pneumonia (community strains)
- **MRSE** (methicillin-resistant *Staphylococcus epidermidis*): deep wound infection after joint replacement, and central venous catheter-associated bloodstream infections

Gram-negative pathogens such as ***E. coli, Klebsiella*** and ***Serratia*** species also produce *carbapenemase* enzymes, which hydrolyse the molecular structure of the **carbapenem** group of antibiotics (ertapenem, imipenem, meropenem, etc.), rendering them ineffective. **These deadly bacteria are collectively described as** ‘**CRE organisms**’ (carbapenem-resistant Enterobacterales).

‘**Acquired antimicrobial resistance**’ occurs when microbes acquire new genetic material via processes known as ‘**transformation**’, ‘**transduction**’ **and** ‘**conjugation**’ (all forms of ‘*horizontal gene transfer*’).



How Antibiotic Resistance Moves Directly Germ to Germ

Any antibiotic use can lead to antibiotic resistance. Antibiotics kill germs like bacteria and fungi, but the resistant survivors remain.

Resistance traits can be inherited generation to generation. They can also pass directly from germ to germ by way of **mobile genetic elements**.

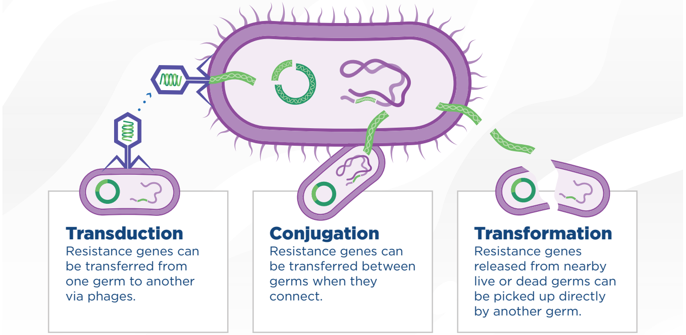
Mobile Genetic Elements

Plasmids
Circles of DNA that can move between cells.

Transposons
Small pieces of DNA that can go into and change the overall DNA of a cell. These can move from chromosomes (which carry all the genes essential for germ survival) to plasmids and back.

Phages
Viruses that attack germs and can carry DNA from germ to germ.

How Mobile Genetic Elements Work

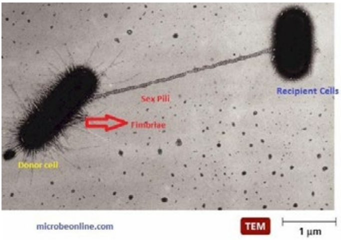


Transduction
Resistance genes can be transferred from one germ to another via phages.

Conjugation
Resistance genes can be transferred between germs when they connect.

Transformation
Resistance genes released from nearby live or dead germs can be picked up directly by another germ.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention



Bacterial conjugation: two live bacteria come together – a special fimbria on the cell wall (called a '*sex pilus*') extends from one bacterial cell and adheres to another bacterium. At the area of contact, a channel or '*conjugation bridge*' is formed; and **DNA** is transferred from the donor to the recipient cell.

THE ROLE OF BIOFILM IN AMR [6]

Biofilms are complex **polymicrobial communities** containing bacteria and fungi. These microorganisms synthesise and secrete a protective slimy barrier of sugars and proteins which attaches the biofilm firmly to a surface.

The 'biofilm barrier' protects the microorganisms contained within it and increases their tolerance to external threats such as phagocytic neutrophils, antibodies and antimicrobial substances.
A survival strategy that many bacteria in biofilms have developed is for a subpopulation to become metabolically 'quiescent'. **Bacteria need to be metabolically active for antibiotics to act, so quiescent (hibernating) bacteria in biofilms are unaffected by antibiotics that would normally kill them. Research has shown that the lowest concentration required to kill or eliminate bacterial biofilm for most antibiotics**

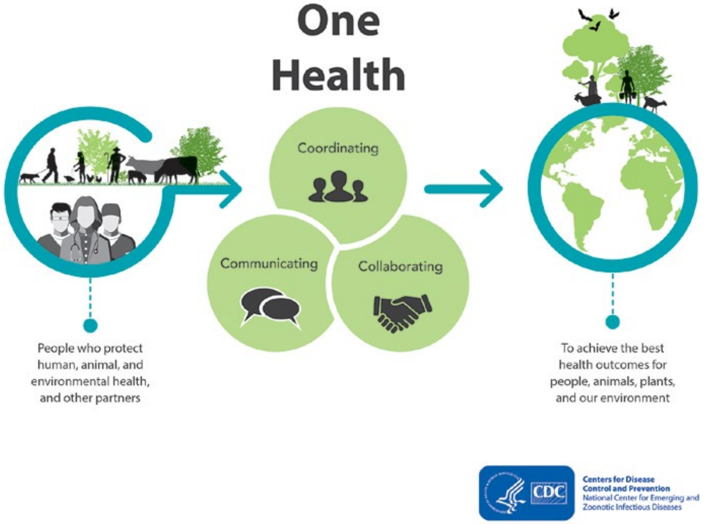
exceeds the maximum prescribed levels for the antibiotic many times over!

Therefore, standard oral doses of an antibiotic, which would effectively kill the normally susceptible bacteria when grown planktonically in a clinical laboratory, may have little or no antimicrobial effect on the same type of bacteria when in biofilm form in a patient!

THE HUMAN - ANIMAL CONNECTION [1,3,4,5]

Antimicrobial agents have been used for treating or preventing disease in raising food animals for decades. The animal feed often contains drugs in amounts that range from below therapeutic levels to full therapeutic levels, and they are mostly from the antimicrobial classes used in humans.

There is evidence to support the idea that feeding antibiotics to animals results in the development of antimicrobial resistant organisms, and that these resistant organisms may be transferred to the humans who consume those animals. **Other common routes include contamination of water sources and direct contact with animals**.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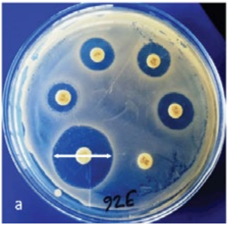
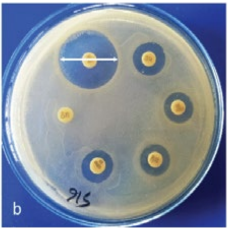
Coordinating
Communicating
Collaborating
People who protect human, animal, and environmental health, and other partners
To achieve the best health outcomes for people, animals, plants, and our environment
CDC
Centers for Disease Control and Prevention
National Center for Emerging and Zoonotic Infectious Diseases

THE ROLE OF THE CLINICAL LABORATORY IN THE DIAGNOSIS OF MULTIDRUG-RESISTANT ORGANISMS (MDRO's)





Accurate diagnosis of infection is key to appropriate prescribing – therefore, laboratory specimens should always be collected before antibiotic therapy is commenced. The results of traditional bacterial cultures and antimicrobial susceptibility testing - which take 2-7 days to obtain - remains one of the major barriers to providing optimal therapy. This is especially important for severe infections and sepsis, for which a delay in initiating effective therapy is a strong predictor of death.[7]

Fortunately, new molecular techniques such as **polymerase chain reaction or 'PCR'** can identify bacterial species and detect the presence of AMR genes independent of culture and are an integral part of antimicrobial stewardship measures. [8,9]

MALDI-TOF ('matrix-assisted laser desorption/ionisation time-of-flight') **mass spectrometry** is a versatile analytical technique to detect and characterise mixtures of organic molecules. In microbiology, it is being used as a rapid, accurate and cost-effective method for the identification of bacteria and fungi. Microbial growth is isolated from plated culture media (or it can be concentrated from broth culture by centrifugation in certain cases) and applied directly onto the MALDI test plate. The plate is analysed by the software system, allowing rapid identification of the microorganism.

Within less than a decade, MALDI-TOF mass spectrometry has become the gold standard for microbial identification in clinical microbiology laboratories. Besides more rapid turnaround times for the identification of pathogens as well as antibiotic resistance, this technology has enabled timeous, more accurately targeted antimicrobial therapy.[10]

Infection Control
healthcare
investigation
health
sterilization
disinfection
setting
isolation
workers
outbreak
spread
infection
common
control
years
surveillance
patients
care
essential
vaccination
prevention
epidemiology
cleaning
hand

THE BOTTOM LINE...[1,3,4,5]

- ✓ The emergence of **AMR** is both a natural and an acquired phenomenon.

- **Stop referring to a coming post-antibiotic era** - it is already here! The time for action is now and we are part of the solution.
- **Complex and interlinking drivers are increasing the prevalence of MDRO's**, arising from the widespread use of antimicrobial agents in human beings, animals, crop farming and the pollution of the environment.
- **Prior use of antimicrobial drugs puts a patient at risk for infection with a drug-resistant organism**; and those patients with the highest exposure to antimicrobials are most often those who are infected with resistant pathogens.
- Strict adherence to **correct specimen collection methods** is crucial to avoid contamination of specimens and inaccurate culture results.
- **Changing how antimicrobials are used** may be the single most important action to combat resistance, since it is estimated that their use is appropriate in only 50% of cases.
- **Stop playing the blame game!** Every person, industry and country can influence the development of AMR and should be held accountable to make meaningful progress against this threat.
- **Stop believing that antibiotic resistance is a problem elsewhere!** AMR has been found in every country across the globe. Take infection prevention action from hand hygiene, environmental cleaning and waste management, to improving antibiotic use.
- **There is no single solution to AMR** - multiple, synergistic, overlapping and complementary approaches are needed; with overarching international political will to ensure and sustain access to MDRO surveillance, up-to-date laboratory technology, a 'One Health' approach to antimicrobial stewardship education, and effective antimicrobial therapies.

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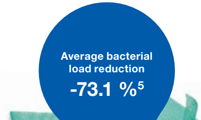
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-73.1 %[5]

- **Effective against the Top 5 WHO (World Health Organisation) pathogens[3]**
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