Antimicrobial Resistance (AMR) – a Global Health emergency that affects YOU

"A post antibiotic era - in which common infections and minor injuries can kill - far from being an apocalyptic fantasy, is a real possibility." - World Health Organization

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Mould Juice

In 1928, Scottish microbiologist Sir Alexander Fleming left an uncovered petri dish containing the common *Staphylococcus aureus* (staph) bacteria near an open window and it became contaminated with mould [1]. Fleming noticed that a substance excreted by the mould spores was killing the bacteria. He called this substance "mould juice". He then found it to be effective against many types of bacteria responsible for diseases such as scarlet fever, pneumonia, gonorrhoea, meningitis and diphtheria and the world's first bacteria killer, or antibiotic, was born. It was named penicillin since the mould was of the *Penicillium* genus. Antibiotics soon became the wonder drug of the medical world and the dangers of routine surgery and childbirth by caesarean section were vastly reduced, and a small infected cut no longer had the potential to be fatal.

When Sir Fleming accepted the Nobel Prize in Physiology or Medicine in 1945, he made a chilling prediction, that antibiotics will become ubiquitous, that people will underdose themselves and, *"by exposing the microbes to non-lethal quantities of the drug, make them resistant"*. His prediction has come true, and the world is now in a "post-antibiotic" phase that requires other effective antimicrobials [2].

What is antimicrobial resistance (AMR)?

When microbes become resistant to medicines, the options for treating the diseases they cause are reduced.

AMR occurs when microbes such as bacteria, viruses and fungi become exposed to non-lethal doses of antimicrobial agents such as antibiotics, antivirals and antifungals, survive and replicate. Microorganisms that develop antimicrobial resistance are sometimes called "superbugs".

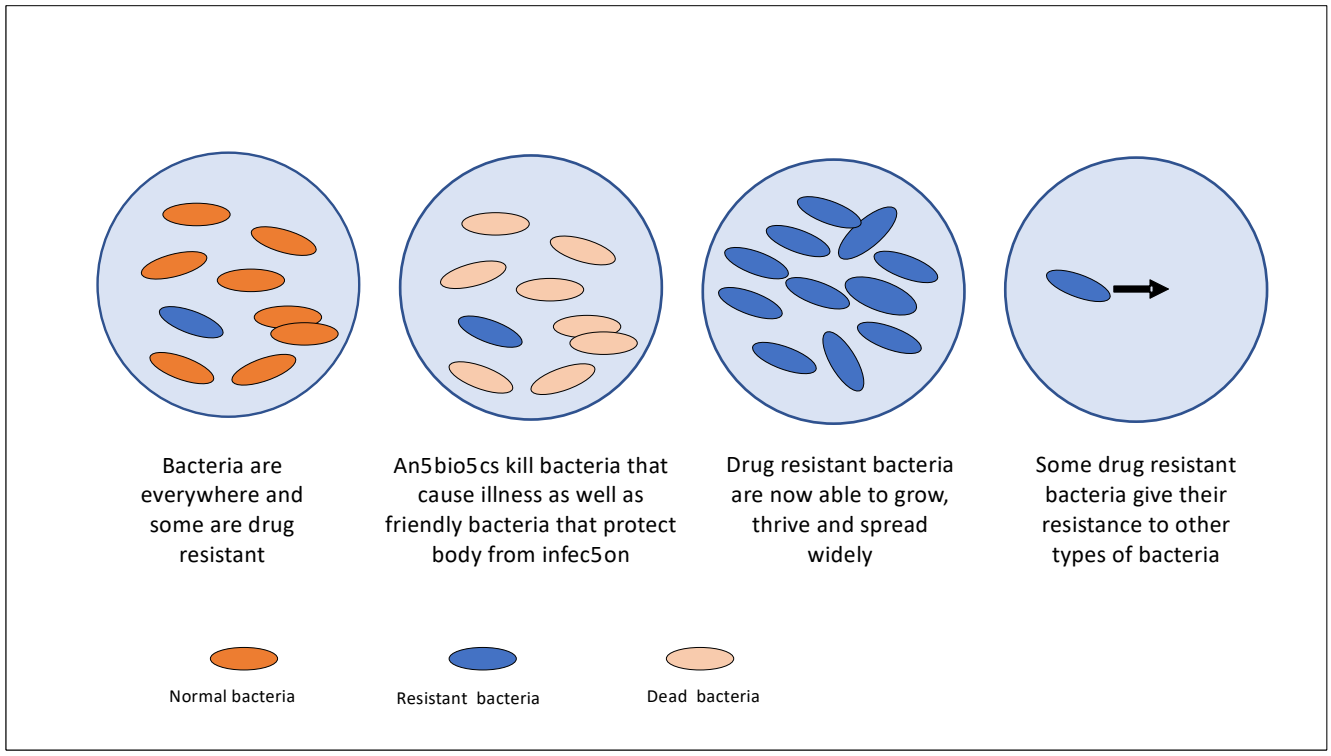
Selected bacteria that exhibit high levels of antibiotic resistance include:

- *Staphylococcus aureus* (staph) that causes a wide range of common skin infections such as impetigo (school sores), boils and cellulitis and well as serious, potentially life threatening conditions such as surgical wound infections and infections of prosthetic devices such as heart valves, pacemakers, catheters and joint replacements;
- *Klebsiella pneumonia* that causes pneumonia, wound infections, meningitis and blood stream infections;
- *Pseudomonas aeruginosa* that causes surgical wound infections, folliculitis and urinary tract infections; and
- *Escher Coli* that causes diarrhoea and possible complications such as kidney failure.

How does antibiotic resistance happen?

Antibiotic resistance begins as soon as a new antibiotic is introduced. For example, penicillin was approved for use in 1941 and penicillin resistant staph was identified in 1942 [3]. Similarly, methicillin, a penicillin-related antibiotic, was introduced in 1960 and in the same year, Methicillin-resistant Staphylococcus aureus (MRSA) emerged.

FIGURE 1:
How antibiotic resistance happens



The following factors play an important role in exacerbating AMR [4]:

- inappropriate prescribing (wrong type, wrong dose, wrong duration, and treating conditions that don't warrant antibiotics with antibiotics);
- overuse of broad-spectrum antibiotics by people and in agriculture;
- poor sanitisation and infection control practices e.g. suboptimal wound care and unsanitary handling of medical equipment such as catheters;
- rising high-risk patient numbers needing antibiotic therapy e.g. people undergoing chemotherapy and dialysis, transplant recipients and war trauma victims;
- increasing bacterial density in health care facilities;
- highly mobile individuals and populations;
- declining vaccination rates for preventable illnesses such as measles and flu.

The largest contributor to AMR is the increase in antibiotic prescribing. From 2010 to 2015, global consumption of antibiotics increased 65% [5]. According to the Centers for Disease Control & Prevention (CDC) in the United States, one out of every three antibiotic prescriptions is unnecessary.

For example, antibiotics are often prescribed to patients with upper respiratory symptoms such as coughs or sore throats, even though less than 1% of upper respiratory infections are caused by bacteria [4].

Role of topical antibiotics in driving AMR

Excessive use of topical antibiotics for skin infections is known to be a key driver of AMR, and is directly responsible for increasing staph resistance to antibiotics. For example, New Zealand research has shown a significant association between increased use of topical antibiotics mupirocin and fusidic acid and rapidly rising staph resistance [6]. Similar findings are reported in the UK and Australia.

Resistance to topical antibiotics is important for three reasons:

- increasing resistance leads to ineffective treatment with these medicines;
- resistance to one antibiotic often means resistance to other antibiotics;
- increasing resistance to topical antibiotics threatens the effectiveness of oral and intravenous formulations of these medicines e.g. oral fusidic acid is used to treat invasive infections of bones and joints.

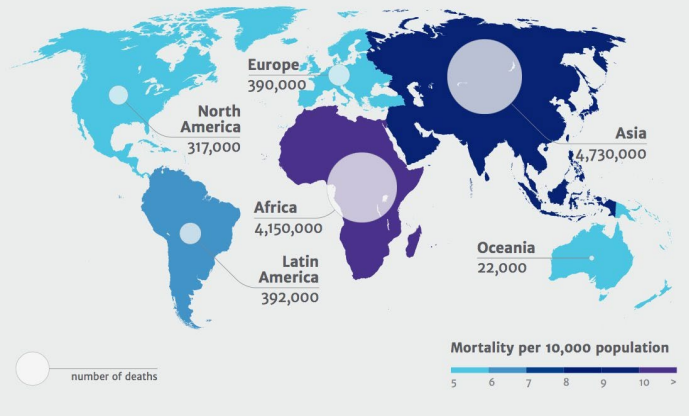
Infectious disease experts believe that there are now few clinical situations in which topical antibiotics are appropriate, and that in the near future they may no longer be recommended at all [6].

Impact of AMR

International health agencies such as the United Nations and the World Health Organisation have declared escalating antimicrobial resistance as one of the gravest and most urgent threats to global public health and patient safety [7].

In the USA alone, nearly 3 million people become infected with antibiotic resistant bacteria every year, and at least 35,000 people die [8]. Globally, antimicrobial-resistant infections kill 700,000 patients every year. By 2050, AMR infections worldwide are projected to cause 10 million deaths and economic (GDP) losses of USD1.2 trillion per annum. FIGURE 2 summarises the projected annual death rate around the world by 2050.

FIGURE 2:
Global AMR related deaths per annum, by 2050



Source: [9]

AMR is reducing the pool of effective antibiotics and other antimicrobials which is the core of modern medicine. These drugs are needed in the treatment of potentially fatal infectious diseases and to ensure that complex medical procedures such as surgery such as joint replacements and organ transplants, kidney dialysis and chemotherapy can be provided with little risk.

The problem of AMR is exacerbated by the fact that the number of new antibiotics being developed remains at an all-time low since pharmaceutical companies are disincentivised by regulatory issues, technical challenges, and unfavourable marketing conditions. If resistance overtakes currently available antibiotics, it will spell the "end of modern medicine" as we know it [10].

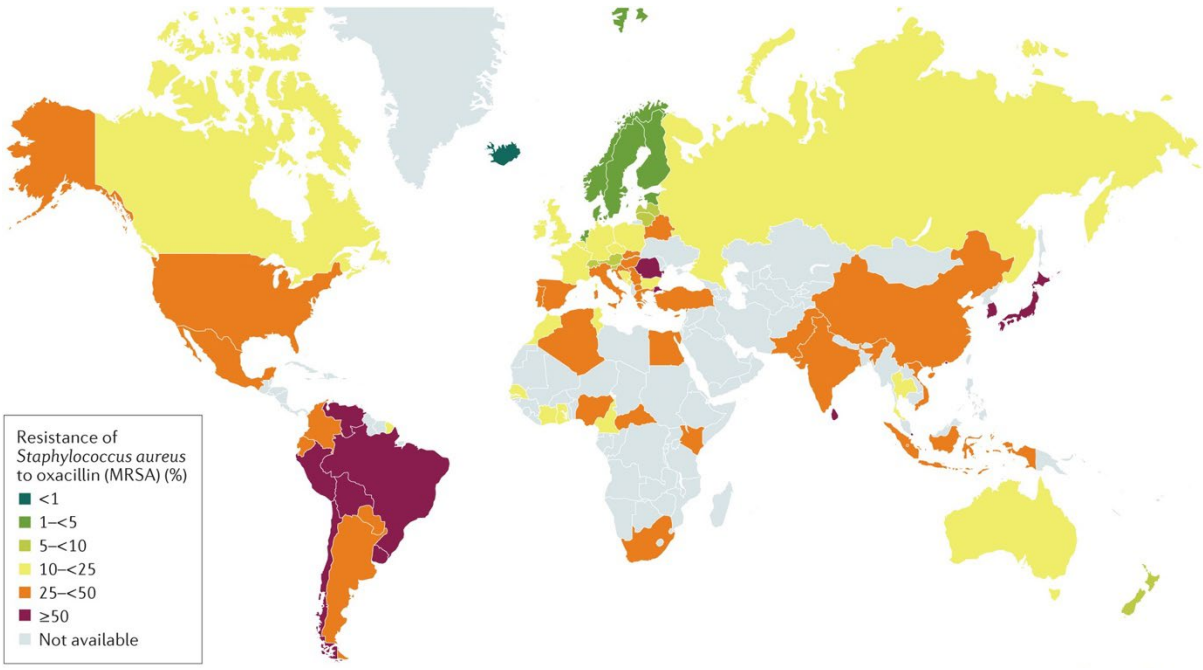
Methicillin resistant *Staphylococcus aureus* (MRSA)

MRSA is a leading cause of bacterial infections in both health-care and community settings [11].

When the skin microbiome is disrupted by chronic skin conditions such as eczema, wounds or surgical intervention, MRSA can gain access to the underlying tissues or the bloodstream and cause infection. MRSA infections range from relatively mild skin and soft tissue infections to rapidly escalating invasive disease with high mortality. People with chronic diseases such as diabetes or compromised immune systems and those with invasive medical devices such as replacement valves, pacemakers and catheters, are particularly vulnerable.

The geographic variation of MRSA is noteworthy. Figure 3 provides an overview of global MRSA infections (where data is available).

FIGURE 3:
Worldwide prevalence of MRSA



Source: [11]

MRSA is widespread in most Asian hospitals. In Japan, South Korea and Sri Lanka, up to 70% of staph infections are MRSA related. These high rates of AMR are a result of widespread inappropriate antimicrobial use, for example, self-medication and over-the-counter use exacerbated by high population density facilitating rapid transmission of multidrug-resistant infections.

In the United States, around 53% of *S. aureus* infections were MRSA related in 2005. Improved MRSA screening and hygiene practices have resulted in halving of this rate by 2017.
MRSA prevalence ranges from less than 5% in Northern Europe e.g. Denmark, Netherlands Norway and Sweden, to 25-50% in Southern Europe e.g. Italy, Greece, Portugal and Spain. These variations are attributed to varying infection control practices and antimicrobial usage.

In Australia, among health-care-associated staph infections, MRSA has accounted for 20–33% of cases since 2001.

FIGURE 4 depicts a scanning electron micrograph of the MRSA bacteria and examples of infections it causes.

FIGURE 4:
MRSA bacteria and resulting infections

Source: various

The parallel health emergencies of COVID-19 and AMR

The COVID-19 pandemic and AMR are parallel and intersecting health emergencies [8], but there are some key differences. TABLE 1 compares these two emergencies.

Since the sequential loss of effective antibiotics has occurred gradually over the last 80 years, AMR has been aptly described as a subtle, "slow moving catastrophe" [4]. In contrast, the fast moving, highly infectious COVID-19 pandemic has produced a more immediate and tangible threat. For these reasons, AMR has received far less public and media attention and funding.

Furthermore, certain actions to alleviate COVID-19 suffering might represent a rapid and far-reaching risk to AMR, which will continue to affect the health of global citizens well beyond the COVID-19 crisis [8]. For example, existing antimicrobials are being used to treat critically ill COVID-19 patients in the absence of COVID-19 specific treatments. This is highly likely to contribute to AMR.

TABLE 1:
Comparison of COVID-19 and AMR

#	COVID-19	AMR
Characteristics		
Worldwide cases	18 million as of 3/8/20 [12]	64.5 million annually
Knowledge of problem	Developing	Established
Spread	Fast	Gradual
Mechanism	New transfer from non-human host	Natural selection[1] in humans, animals, environment
Behaviour Changes Required		
Handwashing	Continuously needed	Continuously needed
Physical Distancing	Urgent, possibly recurrent	Probably recurrent
Travel Restrictions	Urgent, possibly recurrent	Probably recurrent
Quarantine	Confirmed & suspected cases	Confirmed & suspected cases
Impacts		
Deaths worldwide	524,750 as of 3/7/20 [12]	812,000 annually
Economic impact	Unknown	USD 400 billion
Health inequity	Increased	Increased
Management Needs		
Vaccine	In development	Not available for resistant microbes
Increased testing	Realtime picture of spread	Surveillance of the problem
Rapid diagnostics	In development	Some useful tests
New drugs	In development	Few in development
Stewardship	In time	Continuously & internationally

Source: [8]

[1] Natural Selection is the process by which organisms with favourable traits (such as the ability of some bacteria to resist the killing effect of antibiotics) reproduce and pass these traits on to the next generation.

Some solutions

All people and healthcare providers have a role in reducing the incidence of AMR [3].

Everybody

- Learn about AMR and its effect on you, your community and rest of the world.
- Lower expectations about needing antibiotics. (For example, many minor skin conditions are self-limiting and don't usually need antibiotics).
- If you are given antibiotics, take the full course. Don't stop when you begin to feel better.
- Get vaccinated e.g. viral infections such as measles, flu shots and when travelling.
- If you think you are allergic to penicillin, get formally tested. Most antibiotic allergy labels are inaccurate and 90% of such cases are able to tolerate common antibiotics such as amoxillin and augmentin [4].
- Be aware of changes in your health. Catch infections early.
- Wash hands, maintain good health and hygiene practices in the home, office, public transport and in caring for pets.
- Prevent sexually transmitted diseases.
- Stay safe and healthy when travelling abroad. Learn the risks of medical tourism.
- Explore natural options to keep your skin microbiome healthy.
- Use evidence-based natural skincare and topical products containing antimicrobial essential oils such as German chamomile, manuka, and thyme to keep the skin microbiome healthy and to treat minor skin infections such as acne, eczema, impetigo or herpes.

Medical professionals

- Learn about AMR and help educate patients. It is a problem of TODAY, not the future.
- Track and improve appropriate antibiotic usage.
- Be well informed of resistant infections in your patients, facility and community.
- Topical antiseptics are generally recommended for minor skin infections. If an antibiotic is required, oral treatment is likely to be more effective than a topical antibiotic cream.
- Study and recommend clinically proven topical treatments that contain essential oils with powerful broad-spectrum antimicrobial properties that may be as effective as antibiotics and far less likely to contribute to AMR.
- Develop personalised infection treatment methodologies where genomic blueprints can determine an individual's susceptibility to diseases so that therapies can be customised [13].
- Practice scrupulous infection control practices e.g. e.g. disposable gloves and gowns, surface disinfection.

- Hand sanitisation of healthcare workers and patients while protecting the skin microbiome is vital. This can be achieved through the use of sanitisers and emollients that contain soothing, antimicrobial essential oils such as manuka oil.

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