Policy Document

Antimicrobial Resistance (2021)

Position Statement

The Australian Medical Students Association (AMSA) believes that:

1. Antimicrobial resistance (AMR) is a global health crisis, requiring an international and collaborative multi-targeted One-Health approach in order to prevent catastrophe.
2. Australia should be an international leader in tackling AMR, working internationally to address AMR by developing and fostering global collaborations, as well as by funding research into treatments, surveillance, and education.
3. Australian medical professionals must take it upon themselves to enact antimicrobial stewardship and minimise inappropriate use of antimicrobials.
4. Australia must take steps to implement the actions outlined in the National Antimicrobial Resistance Strategy 2020 and beyond.

Policy

AMSA calls upon:

1. The World Health Organisation (WHO) to:
    a. Promote enrolment in and continue development of the Global Antimicrobial Resistance and Use Surveillance System (GLASS) project;
    b. Create additional programs and strategies within GLASS that account for the technological and surveillance deficiencies in poorer countries in order to better facilitate the contribution of data;
2. The Australian Government to:
    a. Uphold, implement and review the strategies detailed in 'Australia's National Antimicrobial Resistance Strategy 2020 and beyond';
    b. Continue to endorse and maintain a 'One Health' focus in all facets of AMR policy and strategy;
    c. Facilitate appropriate and evidence-based antibiotic use across all sectors through:
        i. Infection prevention measures including but not limited to vaccination, effective sanitation, hygiene;
        ii. Public education campaigns about infection control and the appropriate/inappropriate use of antibiotics;
        iii. Continually reviewing and updating antimicrobial usage policies in non-human sectors, including the agricultural and veterinary industries, according to the One Health framework; and
        iv. Developing, providing, and implementing tailored, evidence-based resources and approaches to antimicrobial stewardship across all sectors, including regular assessment and appraisal of certification and skills;

AUSTRALIAN MEDICAL STUDENTS' ASSOCIATION

Head Office
42 Macquarie Street,
Barton ACT 2600

Postal Address
PO Box 6099
Kingston ACT 2604

ABN 67 079 544 513

Email info@amsa.org.au
Web www.amsa.org.au
Twitter @yourAMSA

d. Contribute actively to surveillance and to the monitoring of AMR through:
    i. Involving in worldwide surveillance of AMR by continuing and expanding upon Australia's contribution to WHO's GLASS initiative;
    ii. Establishing a comprehensive national surveillance system for AMR in non-human sectors, including the agricultural and veterinary industries, according to the One Health framework;
    iii. Continuing regular reporting on AMR via the Antimicrobial Use and Resistance in Australia (AURA) Surveillance Strategy;
e. Implement a range of measures to minimise the spread of AMR including but not limited to:
    i. education campaigns for the general public about antimicrobial use and AMR; and
    ii. prescribing guidelines universally across clinical settings;
f. Expand Australia's National AMR Strategy to include strategies addressing risks associated with the use of biocides and biofilms, and expand AMR stewardship guidelines accordingly;
g. Expand AMR surveillance within the agricultural and food production industry;
h. Support research into AMR through:
    i. Recognising the lack of research into the treatment and prevention of AMR, especially in optimising existing strategies and developing novel technologies;
    ii. Expanding research into the mechanisms of AMR, including:
        1. Resistance to vaccination
        2. Zoonotic transmission, specifically its prevalence, the microorganisms involved, and its routes of transmission
    iii. Allocating funding for research into new antimicrobial drugs as a research priority, including antiprotozoals, antiparasitics, antifungals, antivirals, and antibiotics;
    iv. Prioritising research for treatments based on their global burden, particularly on Malaria, and pan-resistant organisms, especially Human Immunodeficiency Virus (HIV) and tuberculosis (TB);
    v. Prioritising research for treatment based on the risk to Australians, particularly *S. aureus, S. pneumoniae, E.coli* and *N gonorrhoeae*;
    vi. Encouraging the development of new antimicrobial treatments through:
        1. Supporting and creating public-private partnerships
        2. Allocating more funding to academia & non-profit
        3. Recognising the emerging role of the private sector in developing new antimicrobial treatments, and:
            a. Engaging with the private sector to develop new antimicrobial treatments, ensuring that priorities such as universal access and quality are upheld
    vii. Broadening the scope of AMR treatment research beyond traditional antimicrobials e.g. antibiotics, to include:

1. Novel technologies, such as bacteriophage therapy and CRISPR;
2. Other treatments, including herbal medicine, vaccination, and monoclonal antibody use;
3. Biocides, cleaning products, pesticides, and biofilms, especially the risk they pose in industrial, agricultural, and medical settings;

i. Direct the Therapeutic Goods Administration (TGA) to:
   i. Regulate medical and industrial products that risk biofilm formation and biocide resistance development;
   ii. Regulate the use of biocides in household products;
j. To take steps to further prevent bioaccumulations of low-concentration biocides in the environment.
k. Expand data collection locally to organisms of concern
l. Respond to the AMR threat by creating a nationally, and globally standard scientific framework providing clarity on AMR and ease of measurement

3. The State Departments of Health to:
   a. Address the differences in resistant infections in remote and regional areas compared to urban regions;
   b. Continually review notifiable conditions and consider adding AMR conditions of concern;
4. The Federal Department of Health to:
   a. Address the differences in resistant infections in remote and regional areas compared to urban regions;
   b. Continually review notifiable conditions and consider adding AMR conditions of concern;
   c. Make MRSA a public health notifiable condition regardless of the type and severity of infection it causes when detected within and outside of hospitals;
   d. Regularly review the screening protocols for AMR-prone or pan-resistant organisms for foreign visa applicants who already have to undergo health screening, such as formal medical examinations;
   e. Implement a national database with compulsory participation and reporting by all health providers around the country, noting the lack of committed and detailed timelines for its creation to date;
5. Australian Medical Regulatory Bodies and Colleges to:
   a. Develop and maintain contemporary, evidence-based guidelines on AMR
   b. Provide sufficient support and encouragement to doctors and hospitals to participate in AMR stewardship, including but not limited to:
      i. Free access to therapeutic guidelines
      ii. Continual education and recertification on AMR protocols
      iii. Implement clinical and therapeutic guidelines in prescribing software
      iv. Make available evidence based information toolkits regarding antimicrobial use and prescribing
   c. Emphasise clinical skills and practices in medical school related to prescription of antimicrobials

    d. Expand current AMR stewardship policies to incorporate biocides and biofilms including but not limited to;
        i. Targeted biofilm cleaning initiatives; and
        ii. Appropriate use of biocides according to the risk of biofilm formation
6. The Royal Australian College of General Practitioners to:
    a. Provide a timeline of when their AMR action plans will be implemented, and how they will be rolled out;
    b. Introduce targets to reduce unnecessarily prescribed and misused antimicrobials;
    c. Monitor and audit adherence of general practitioners to antibiotic therapeutic guidelines;
    d. Make a strong commitment to AMR education campaigns and provide a detailed timeline for doing so;
    e. Address the differences in rates and types of resistant infections in remote and regional areas compared to urban regions;
7. Australian Medical Professionals to:
    a. Make antimicrobial stewardship an integral part of their practice through:
        i. Recognising AMR as a significant health and economic burden in Australia and around the world;
        ii. Utilising appropriate, evidence-based antimicrobial prescription practices;
        iii. Better educate patients to properly use prescribed antimicrobial regimens
        iv. Promoting preventative methods, such as vaccination, and other means to control the spread of infection; and
        v. Engaging with public health policies regarding AMR;
8. Hospitals and Health Services to:
    a. Develop and maintain contemporary, evidence-based guidelines on AMR;
    b. Expand current AMR stewardship policies to incorporate biocides and biofilms including;
        i. Targeted biofilm cleaning initiatives;
        ii. Appropriate use of biocides according to the risk of biofilm formation;
9. Agricultural, food preparation, veterinary, and manufacturing industries to:
    a. Commit to antimicrobial resistance strategies, including but not limited to:
        i. Ensuring adequate ventilation and decreasing livestock living density in barns, feedlots, and slaughterhouses;
        ii. Improving hygiene and sanitation measures on farms;
        iii. Contributing to AMR surveillance initiatives;
    b. Review regulation regarding the use of biocides in food preparation and production to prevent bioaccumulations of low-concentration biocides in the environment;
    c. Review regulation of cleaning processes to limit the formation of biofilms;

10. Australian Medical Universities to:
    a. Provide adequate training for medical students in appropriate antimicrobial use involving a longitudinal and integrative approach to AMR teaching, including:
        i. Training on current prescription guidelines;
        ii. Interactive and realistic mock-clinical scenarios for students to practice antimicrobial stewardship, as per WHO curricula guidelines; and
        iii. Emphasising that AMR encompasses antiviral, antiprotozoan and antifungal resistance as well as antibiotic resistance, and communicating the importance of these issues in terms of local and global health.
    b. Liaise with student bodies to run think-tanks and provide information on AMR and proper prescription practices;
11. Australian Medical Students to:
    a. Recognise that AMR is a significant health and economic burden in Australia and around the world;
    b. Consider how they will contribute to antibiotic stewardship in the future including challenging situations where they may feel pressured to prescribe antibiotics inappropriately;
    c. Recognise that AMR encompasses antibacterial, antiviral, antiprotozoal and antifungal resistance, and raise awareness of this among colleagues;
12. General society to:
    a. To gain a deeper understanding of antimicrobial resistance and the risks posed;
    b. Practice antimicrobial stewardship in regards to use of antimicrobials as directed by health practitioners;
    c. Use household products such as antimicrobial cleaning agents appropriately, especially in public settings including but not limited to:
        i. Schools;
        ii. Local Councils;
        iii. Community groups.

Background

The Australian Medical Students' Association (AMSA) is the peak representative body of all Australian medical students. AMSA believes that all communities have the right to the best attainable health, and accordingly advocates on issues which impact health outcomes of communities in Australia and globally. In particular, the emergence of antimicrobial resistance (AMR) is a global health crisis. The World Health Organisation (WHO) defines antimicrobial resistance (AMR) as when "microorganisms such as bacteria, viruses, fungi and parasites change in ways that render the medications used to cure the infections they cause ineffective" [1].

One estimate has determined that the current total lives lost due to AMR every year is 700,000 people worldwide [2]. However, the current trajectory is indicating that the severity of the situation is greatly worsening. The urgency of the antimicrobial crisis is most effectively demonstrated by the fact that we have now begun to enter the post-antimicrobial era, with the emergence of pan-resistant microorganisms; that is,

microbes resistant to all available forms of treatment. To date, at least ten pan-resistant organisms have been tracked across the globe [3-11]. With this in mind, worst case scenarios have predicted as many as 10 million deaths every year due to AMR by 2050 [2].

AMR poses issues in a number of different ways. There is evidence that microbes that are drug-resistant may have considerably higher mortality rates than drug-susceptible infections. For example, mortality rates amongst those with drug-resistant K. pneumoniae have been found to be as high as 50%, which may be more than four times those of drug-susceptible cases [12]. In addition to increased morbidity and mortality, AMR increases the length of hospital stays, the length of time on mechanical ventilation, a need for intensive care and invasive devices as well as excess surgeries performed [13]. In addition to all of this, AMR burdens hospitals through the need for additional and more complex care, support services, diagnostic tests and imaging, risks for deadlier nosocomial infections, usage of isolation rooms, and the use of consumables such as gloves [13].

It is crucial to denote that the AMR crisis is also an equity issue. AMR is an issue that disproportionately affects those living in poverty, and is also a major cause of poverty [14]. Economically impoverished people are least able to afford effective antimicrobials that can treat drug-resistant infections, tend to lack the educational resources to facilitate their proper use, and reside in settings that lack infection control and proper hygiene measures [2].

Financial Costs

Though tools to understand the financial costs of AMR are still in the phases of development, [14-19] there is reason to believe that the overall cost is enormous. The financial costs accrue due to factors such as increased hospitalizations and longer lengths of stay, increased complexity of treatments with more infection control measures required, and higher levels of sickness and death, which lead to a loss of work by members of the workforce who would have otherwise been productive for the economy [14-19]. One estimate has stated that, by 2050, the cumulative cost of this complex issue may be as high as 100 trillion USD [15].

A World Bank report has also warned that by 2050, due to this issue, more than 28 million additional individuals may move into extreme poverty, a fall of gross domestic product of up to 3.8% per year, and a tripling of healthcare costs globally [14].

Recent analyses in Australia have considered the costs of AMR to be about 500 million AUD per year [17]. Looking to the future, one estimation has predicted that the overall cost to Australia's economy may be as high as 142 to 283 billion AUD by 2050 [20]. However, even these numbers may serve as underestimates due to how difficult it is to quantify the economic costs of lost productivity, and because Australia's limited surveillance measures do not fully track the extent of AMR in the country [17].

Types of Resistance

<u>Antibiotic Resistance</u>

Antibiotic resistance is the highest priority AMR worldwide and in Australia, due to the importance of antibiotic use in many routine therapies including surgery, cancer management and organ transplantation. Drug resistance to all available antibiotics has been detected in clinical bacteria, threatening all advances achieved within the antibiotic era and urging for alternative treatments [20]. Alarmingly high levels of

antibiotic-resistance have been seen in a wide array of highly deadly microbial infections, including Tuberculosis, Klebsiella pneumoniae, Escheria coli, Streptococcus pneumoniae, and Staphylococcus aureus; all of these organisms pose threats both globally, and in Australia [21-27].

Antivirals Resistance

Antiviral drug resistance is an important component of AMR, especially relevant in the treatment of chronic viral diseases. AMR has been identified as a key concern in the treatment of Hepatitis C, where the profiles of various resistant mutations against direct-acting antivirals (DAAs) is well-known [28], despite the use of various class combination DAA therapy to minimise the occurrence of resistant mutations. Moreover, mutations have been identified in human cytomegalovirus (HCMV), which has called for the development of novel HCMV drugs, [29] reflecting the broader need for research in new drug treatment areas. Resistance towards numerous antiviral HIV drugs [30,31] have also been identified, and these studies have consistently highlighted the need for more research into their implications.

Antifungal Resistance

Resistance to antifungal drugs are a major concern, particularly due to the very limited total of existing antifungal drugs. Candida auris (C. auris) is a hospital-acquired fungus that is becoming increasingly resistant. Its antifungal resistance has been steadily rising to as high as 90% in certain contexts [32]. Of the three classes of antifungal drugs, all are increasingly becoming ineffective [23, 33]. Crucially, studies have indicated that high usage of antibiotics may contribute to C. auris resistance, possibly due to C. auris proliferation when the host microbiome is disturbed [34].

Antiprotozoals & Antiparasitics

Resistance to antiprotozoals and antiparasitics is yet another complex aspect of the antimicrobial crisis that cannot be ignored. The most significant form of parasite resistance is from malaria. Malaria, a cause of more than 400,000 deaths in 2019, is a disease by parasites that predominantly affect young children in sub-Saharan Africa [35]. Anti-malarial drug-resistance has greatly impacted malaria eradication efforts over the past few years and decades, and has led to malaria resurgence [36,37], as well as mortality rates increasing as much as threefold [37,38].

Vaccination Resistance

Little research has quantified the potential for microbial resistance to vaccinations, but modelling has indicated that there is some possibility it can develop. Generally, vaccines provide overall positive impacts even when moderate resistance develops, but there are some scenarios where its benefits are cancelled out due to resistance. [39] Potential for harm has been highlighted, namely through increasing a pathogen's prevalence via strain replacement or influencing virulence in unvaccinated hosts [39]. Ultimately, there is a significant lack of research into the implications of vaccine resistance, and its place in antimicrobial resistance.

Organisms of concern globally

Across the globe, widespread drug-resistance has been developing in the deadliest infectious diseases, such as tuberculosis, HIV/AIDS, and malaria, as well as in many other major infections.

Pan-resistant Microorganisms

The emergence of pan-resistant microorganisms - that is, microbes resistant to all available forms of treatment - epitomizes just how dire the issue of AMR truly is.To date, at least ten pan-resistant organisms have been tracked across the globe [3-11]. These include Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella enteria, and Achromobacter spp. One of the most concerning elements of this trend has been

the emergence of strains of TB [7,9] and HIV [6] that are pan-resistant. The enormity of the burden of TB, HIV, and these other deadly microbes indicate that there is a clear need to take decisive action to address, and prevent, the potentially catastrophic rise of pan-resistance.

Tuberculosis

Tuberculosis is a disease that was attributed to 1.4 million deaths in 2019 [22]. Drug-resistant TB, with classifications depending on the levels of resistance (such as multi-drug resistant tuberculosis [MDR-TB], and extensively drug-resistant tuberculosis [XDR-TB]) is an enormous problem that serves as a major barrier to the elimination of this deadly disease [40]. Critically, there was an approximate 10% increase in the number of reported cases of drug-resistant TB in 2019, compared to 2018 [22]. However, it is also important to recognize that the worldwide burden of drug-resistant TB is greatly underreported [23].

HIV/AIDS

HIV/AIDS, an infection found in every country across the globe, was a cause of approximately 700,000 deaths in 2020 [41]. HIV is greatly influenced by antiviral resistance; this is partially due to how rapidly the virus can mutate [42], as well as how certain drugs are prone to resistance [43]. About 1 in 4 cases of HIV infection is resistant to treatment, and as many as 69% cases of HIV in babies born from infected mothers are drug-resistant [43].

Organisms of Concern in Australia

Antimicrobial resistance is becoming an increasingly larger issue over time across Australia. In addition to HIV and E. coli, there are several major organisms of concern. Three noteworthy examples are Staphylococcus aureus (S. aureus), Neisseria gonorrhoeae (N. gonorrhoeae), and Streptococcus pneumonaie (S. pneumoniae)

Staphylococcus aureus

Methicillin resistant Staph Aureus is a deadly microbe that is often spread by hospital-acquired infection. Compared to non-resistant strains, methicillin-resistant S. aureus (MRSA) have increased rates of hospitalization, increased lengths of stay, and higher mortality [44-51]; there is a death rate by MRSA of approximately 34.2% among patients with bacteremia [52]. Vancomycin-resistant S. aureus (VRSA), a strain resistant to the last line treatments that has emerged in other contexts [53], while not having yet emerged in the country, is nonetheless a significant concern for Australia.

Neisseria gonorrhoeae

N. gonorrhoeae, a sexually transmitted infection, has seen continual increases in overall resistance over the past few decades in Australia [25, 54]. In 2019, 22.1% of tested isolates were found to be resistant to penicillin [54]. While still treatable with several different drug regimens [25, 54], N. gonorrhoeae resistance must be controlled and prevented, particularly for vulnerable populations that face the highest risk. It is especially concerning that resistant forms of this disease predominantly affect vulnerable groups – men who have sex with men (MSM) and heterosexual Indigenous men [55].

Streptococcus pneumoniae

S. pneumonaie is an organism of concern in Australia as it causes significant disease. Despite varied and relatively low resistance to antibiotics, S. pneumoniae remains a major issue because even mild/moderate resistance can have serious consequences depending on the type of infection and clinical setting [56]. The main concern is strains with reduced susceptibility causing meningitis. This further complicates treatment as benzylpenicillin has poor penetration into the brain [56]. There are

varying levels of resistance across Australia; the reasons for these differences are not known and require further exploration [56].

One Health Response - WHO and Australia

The One Health approach, originally envisioned by the Centers for Disease Control and Prevention (CDC), aims to confront health from a collaborative, multisectoral, and transdisciplinary perspective through engaging with stakeholders on a local, regional, national, and global level. In order to achieve optimum health outcomes, One Health recognises the significance of the interconnection between people, animals, plants, and their shared environment [57].

A One Health approach is necessary in responding to the global threat of antimicrobial resistance. In reflection of this the World Health Organization (WHO) 'Global Action Plan on Antimicrobial Resistance' [126] recognises the need for an effective 'One Health' approach, incorporating this strategy into the plan. Additional initiatives developed by the WHO to tackle AMR includes the Global Antimicrobial Resistance and Use Surveillance System (GLASS), which was launched in 2015. The aim of GLASS is to provide a standardised framework for the global collection, analysis, interpretation and sharing of data in the tracking and management of AMR [127].

In respect to Australia specifically, the National Government has created 'Australia's National Antimicrobial Resistance Strategy – 2020 and beyond' [128], which also endorses a 'One Health' approach, and outlines Australia's aims in contributing to the global effort to stem AMR. This strategy outlines the Australian Federal Government vision for antimicrobial resistance, identifying seven objectives and priority areas for action in tackling antimicrobial resistance in humans, animals, food and the environment.

These objectives include:

- Clear governance for antimicrobial resistance initiatives
- Prevention and control of infection and the spread of resistance
- Greater engagement in the combat against resistance
- Appropriate usage and stewardship practices
- Integrated surveillance and response to resistance and usage
- A strong collaborative research agenda across all sectors
- Strengthen global collaboration and partnerships

This strategy further calls upon the need for a synchronised response between the public sector, private sector and industry, professionals, research community, and society.

Classification and inclusion of notifiable diseases

The Australian Government Department of Health, considers the following several factors for inclusion on the list of notifiable diseases [57]: (1) Burden of ill health (2) Socioeconomic impact of disease (3) Potential threat of disease over the next 5-10 years (4) Health gain opportunity (5) Public concern and confidence (6) WHO/EU interest/Networks/Food Safety Authority interest (7) Professional interest in notification [see Appendix 1].

The Australian States and Territories reserve the right to create their own criteria regarding notifiable diseases [59]. Of the three organisms of concern that are developing rapid AMR (Neisseria Gonorrhoea, Staphylococcus Aureus, and Streptococcus Pneumoniae) [60], only Western Australia requires public health

notification of MRSA [59], whilst Gonorrhoea is nationally notifiable [61]. Victoria has a vague clause for 'diseases of urgent public health concern or emergency', however, it seems that many antibiotic resistant bacteria are not assessed using this clause [59]. No other states have considered the majorly resistant bacterial infections a notifiable disease despite fulfilling the criteria stated above in the guidelines [59].

The list of notifiable diseases in Australia closely mimics that of the USA designed by CDC [62]. The main notable exception regarding our organisms of concern is the inclusion of Vancomycin intermediate/resistant Staphylococcus Aureus (VISA,VRSA) in the CDC document – a disease that has not been detected in Australia, yet [62].
There is potential for adding organisms of concern to the public health notification list. However, there is an extensive process involved for developing and reviewing case definitions. Requests for developing new case definitions must come from Communicable Diseases Network Australia (CDNA) who delegate the development process to the Case Definitions Working Group (CDWG). If there is rapid response needed in exceptional circumstances, the CDWG can be bypassed [63].

Preventing Infections from Arrivals

Australia relies on the following several methods from reducing influx of infectious diseases [64]:

- Vaccinations and proof of vaccinations
- Declarations before coming into the country
- Smartraveller recommendations
- Quarantine measures for contact, airborne and droplet diseases
- General medical examination for migrants
- Infectious disease screening for those aiming to work in healthcare, i.e. Hep B, HIV, Syphilis
- Specific focus on testing for certain diseases from endemic areas, i.e. chest x-rays for TB

To date, Australia has largely avoided the influx of infectious agents that may be resistant to treatment from other countries due to its remoteness and low rate of foreign citizens seeking medical treatments in Australia [64]. However, management of patients with a history of resistant organisms has the potential to rapidly become a reality in Australia due to increased rates of medical tourism, military conflicts, natural disasters, humanitarian support, and increased rates of migration from a diverse range of regions [65]. Adding to the issue of inadequate screening for incoming travellers into Australia, most vaccines are recommended, and never actually audited regarding many diseases unless it is an agent of extreme concern, or from an endemic area, i.e. yellow fever [66-67].

Surveillance of AMR in Australia

Australia's National AMR Strategy – 2020 and beyond, recognises the vital importance for Australia to significantly increase surveillance of AMR. The Antimicrobial Use and Resistance in Australia (AURA) Surveillance System monitors AMR at a national level, obtaining data from across healthcare settings. Organisms under surveillance in community and hospital settings are listed in Appendices 2 and 3. The 2020 strategy recognises the importance of increasing the magnitude of AURA as well as expanding surveillance and developing a One Health system that incorporates data from across environmental and agricultural sectors [68].

The Australian government currently has several stakeholders (the Australian Group on Antimicrobial Resistance (AGAR), the Australian Gonococcal Surveillance Programme, the Australian Meningococcal Surveillance Programme, the Australian

Mycobacterium Reference Laboratory Network (AMRLN) and the National Enteric Pathogen Surveillance Scheme (NEPSS) involved in surveying AMR in community, hospital, and animal settings. Most of this data collected remains at local level and there is no coordination of these programs or utilisation of data at national level [69].

There are plans to create a national database system on collating local level data with the goals to evaluate data quality and identify deficiencies, create links between AMR in human pathogens, detect emergence of new AMR and prevalence of current resistant pathogens [70]. The Australian government understands a comprehensive surveillance system cannot be implemented immediately and a staged approach is needed. A central coordinating unit (CCU) at DoHA (Department of health and aging) is created as a result [71].

Antimicrobial stewardship [AMS] is not a clinical requirement for general practice in Australia, though the RACGP has made commitments to adopt AMR education programs and to implement AMS principles [72; see Appendix 4]. However, there is limited information on whether any of the following are implemented, how strongly these are followed, and if there are any audits and progress on such policies.

Before targets can be set for reduction in prescribing in the community, there is a need to accurately measure the extent of current prescribing and its impacts by GPs. Antibiotic use in Australian hospitals is monitored through AURA, but there is no equivalent system in primary care. Community prescribing rates are estimated using composite data drawn from a variety of sources. General practice prescribing rates reported in AURA may be adulterated by non-GP prescribing (ie, by nurse practitioners or hospital-based GPs). Clean data is required on GP and non-GP prescribing rates for better implementation of action plans [72].

Agricultural industry & AMR

Antimicrobial agents are used in a variety of contexts within the agricultural sector, including as growth supplements for livestock and prophylaxis against infectious diseases [73]. Globally, 73% of all antimicrobial usage occurs in the food industry, particularly in pork and chicken production [74,75]. Although antimicrobial usage has ostensibly improved food quality, yield, and cost, there is a growing evidence base suggesting this has been accompanied by a rise in antimicrobial resistance [73-83]. Resistance has typically been against the most commonly used antibiotics in the agricultural industry - penicillins, tetracyclines, and sulfonamides - although resistance to other antibiotics is also well documented [73,74,77,79,80]. For example, colistin resistance has been attributed to its use as a growth promoter in livestock due to a higher prevalence of colistin antimicrobial resistance genes originating from animals compared to humans [73].

Prominent in food and water sources, drug-resistance to E. coli, through the usage of antibiotics in agriculture, is a major cause of concern [84]. Drug-resistance of E. coli poses a unique threat, considering how common this infection is. In differing contexts, studies have shown rates of E. coli resistance to be as high as 70% from human sources, and as high as 96% in animal sources [85]. Drug-resistance of this bacteria has been shown to greatly increase the rate of sepsis and mortality compared to those with non-resistant E. coli [85,86].

<u>Reasons for Resistance</u>
Given the general paucity of regulations in most countries, subtherapeutic antibiotic doses are often provided to livestock, and usually under unnecessary and unindicated circumstances (e.g. minimal risk of infection and therefore need for prophylaxis; e.g. prescribing antibiotics for viral infections) [73,74,76,78]. This leads to ineffective

clearance and overgrowth of resistant microorganisms, especially enteric bacteria, which then enter the environment in the animal's faeces and are further dispersed throughout the farm in manure used as fertiliser [83]. There is evidence to suggest that these resistant microorganisms can then be transmitted either directly to farm workers and veterinarians working with farm animals, or indirectly to human consumers from the animal meat itself or from food crops exposed to this manure [73,75,76].

Under circumstances in which excessive amounts of antibiotics are prescribed, some may remain unmetabolised upon excretion and continue to act in the environment, furthering AMR [73]. Moreover, intensive farming operations with high livestock density indices bring animals in close proximity to each other under unsanitary conditions, drastically increasing the likelihood of horizontal gene transfer and spread of resistance [73,76]. Inadequate ventilation in such slaughterhouses, feedlots, and barns poses a risk of zoonotic transfer of resistant microorganisms in aerosols from livestock to human operators [73,76].

Additionally, the provision of cationic heavy metals in fertilisers and as dietary supplements in animal feed has been shown to select for heavy metal resistance and co-select for AMR in bacteria by inducing an adaptive stress response in which resistance can spread more easily, possibly by the formation of biofilms [77, 78]. The coexistence of both antibiotic and heavy metal resistance is known to complicate treatments. Finally, antimicrobial usage in pesticides and the use of biocides in antiseptics, disinfectants, and preservatives, may also contribute to AMR [77].

Restrictions in Agriculture

Despite marked increases in resistance worldwide, AMR due to agricultural practices in both the animals themselves and in the humans that have contact with them is reduced in countries that have adopted bans or have restricted the usage of antimicrobials [73,75]. Since its adoption of the recommendations of the UK's Swann Report, Australia has since banned multiple classes of antibiotics for non-therapeutic use in livestock. Consequently, lower rates of resistance in Campylobacter, Salmonella, and Escherichia species have been observed compared to in countries where antimicrobial usage is unregulated [75]. Moreover, numerous Western European studies have found that although there is a minor increase in the incidence of diarrhoeal diseases in farm animals following such bans, this is only transient and is able to be controlled by improving animal housing and hygiene measures [73]. There is some evidence to indicate that such measures lead to rates of diarrhoeal disease lower than pre-ban levels too, making bans more efficient and cost-effective [73].

Research Gaps

There are still major gaps in the research. Some studies have shown there to be a complex and non-linear correlation between antimicrobial usage and the development of antimicrobial resistance genes, suggesting that antimicrobial exposure is not the only important factor in selecting for resistance [77]. Several studies have found no or insignificant links with transmission of AMR between animals and humans [73,77,79-81]. In cases where resistance to clinically important antibiotics was observed, the animal strains were often phylogenetically distinct from those typically causing disease in humans, suggesting the human strains did not originate from livestock [73,79]. In addition, an Australian study of enterococci from Australian finisher pigs found resistance to the streptogramin antibiotic class, despite streptogramins having not been previously used in the agricultural industry, possibly suggesting horizontal gene transfer [79]. Also, the impact of pesticides and biocides used in agriculture on AMR is poorly understood [77]. Finally, AMR surveillance in certain middle-income countries, especially in South America, is lacking despite these

countries possessing more resources than lower-income African countries in which surveillance is relatively better [74]. More research must be conducted in all these areas to better inform future resistance-control measures.

AMR in household and hospital products

Biocides

Biocides are antimicrobial agents which have found prolific use in products not limited to household cleaners and disinfectants [87] through to lunchboxes, shower gels, wood preservation, and water treatment [88]. Important examples of biocides include alcohol, hydrogen peroxide, surfactants, and other chemicals such as triclosan, quaternary ammonium compounds, and chlorhexidine [88]. Notably, disinfection and medical use contribute the major portion of biocide use [89]. A biocide may have multiple target sites within a bacterial cell, including inhibition of membrane enzymes, action as alkylating agents, cross-linkage of DNA, and via efflux pumps [90].

The widespread use of biocides in countless consumer and medical products has led to biocide accumulations in a number of natural and human environments. Biocides used in household products, and those utilised in food processing and production can be washed into drains and enter waterways, become concentrated in waste-water, and ultimately enter the environment [91–94].

Theoretical and in vitro evidence of biocide resistance exists in several bacterial strains. There is concern that this resistance could coselect for AMR through;

1. cross-resistance, where a bacterial resistance mechanism can act liberally against other structurally and functionally different agents;
2. co-resistance, where gene(s) that confer reduced susceptibility to a biocide is selected with anti-microbial resistant gene(s) [95].

Given biocide targets are not particularly specific, these resistance methods are also non-specific, and can have cross-resistance to antibiotics [96]. In particular, efflux pumps are an important contributor to multi-drug resistance due to their ability to expel a wide range of functionally and structurally distinct antibiotics [97], and have been identified as an important mechanism underlying biocide resistance [98].

A growing body of literature has identified biocide resistance in vitro in a range of bacterium including Salmonella enterica [99], Escheria coli [100], Klebsiella Pneumoniae [101] and Pseudomonas aeruginosa where cross-resistance to other antimicrobial agents was seen after sublethal exposure to benzalkonium chloride disinfectants [102]. There are several other in vitro studies which demonstrate similar biocide resistance in other organisms [103,104]. Chlorhexidine is a biocide that has wide use in clinical applications requiring decolonisation and infection control. Some in vitro studies have demonstrated resistance to chlorhexidine in some pan-resistant gram-negatives, including Pseudomonas Aeruginosa and Klebsiella Pneumoniae [101,105,106], however resistance is yet to be demonstrated in gram-positive organisms [107]. Given the prolific medical use of biocides, resistance would have dire consequences for infection control.

However, most studies describing biocide resistance are limited to laboratory conditions, and there is a dearth of empirical evidence supporting biocide resistance promoting AMR in real-world scenarios. Additionally, in food preparation and disinfection applications, biocides are typically used at much higher concentrations above the thresholds shown to drive resistance in laboratory studies [96]. Several recent meta-analyses also identify the lack of strong causal evidence linking biocide exposure with increased AMR [108,109]. Accordingly, biocide resistance is considered

a potential threat to AMR. Nonetheless, a recent Joint Food and Agriculture Organization/World Health Organization Expert Committee concluded the need for application of 'precautionary measures' to limit the ongoing and future potential of biocide resistance and its contribution to AMR [110], particularly in view of environmental accumulations of low-concentration biocides [111,112].

Biofilms

Bacteria naturally and preferentially live as colonies attached to surfaces within self-produced extracellular polymeric substances (EPS), forming a matrix that protects from environmental threats and promotes long-term residence. Biofilms have been reported in food processing environments [113], and are thought to be implicated in an important proportion of hospital acquired infections [114]. The EPS matrix allows organisms contained within to withstand robust chemical challenges, thus favouring coselection [100]. This may also pose challenges to current use of biocides in sanitation practises [96]. Furthermore, bacteria within a biofilm are known to live in close proximity, facilitating genetic exchanges [115]. This has the potential to promote the spread of AMR. Indeed, efficient transfer of extended spectrum ß-lactamase-encoding plasmid to bacteria within a biofilm was identified in antibiotic resistant strains of Klebsiella Pneumoniae in a hospital environment [116]. Whilst biofilms typically thrive in moist environments, the perceived threat has escalated with the recent discovery of 'dry surface biofilms' [117]. A recent study demonstrated biofilms containing multi-drug resistant organisms could persist for up to 12 months on equipment within an intensive care unit despite cleansing involving detergent and bleach [118]. This is a growing field of research, with novel interventions such as electromechanical vibration[119], and non-pathogenic probiotic sanitising agents [120] under investigation. The potential for biofilms to contribute to the continuing issue of AMR is significant, and should not be overlooked in future efforts to contain AMR [121-125].

Preventative Solutions

As the WHO has directly related AMR to poverty, low education levels, hygiene protocols, and inappropriate practice, it is important to address these issues systematically and step-by-step. As an overall approach, the need to address socio-economic issues that lead to poor education and hygiene is of utter importance [126].

Increased education

The primary goal would be to increase education levels on the need, inappropriate and incomplete use of antimicrobials, and the concept of AMR. This can be aided by increasing education in health workers regarding AMR, and inappropriate prescriptions. Health workers are central to delivering good quality primary care services. In one study overseas, over 80% of medical and pharmacy students incorrectly believed that antibiotics could treat influenza, and that giving antibiotics if requested by a patient constituted good patient care [129]. Health workers would benefit from more training about antimicrobial resistance and good antibiotic prescribing practice – in both their preservice and in-service training. Recertification on this topic should be implemented at least every few years [126].

Continuing on the theme of educating health care workers, GPs who essentially work as private entities and businesses must be targeted with mandates on the use of therapeutic guidelines with regular audits in place. Most GPs and other primary care settings get their education and guidelines from pharmacy representatives who have sales targets to meet; while this does not automatically indicate that such providers are unjustly receiving reimbursement from private actors, there is nonetheless a need to remain vigilant for this to be taking place [126].

Better availability of technologies

Rapid diagnostic technologies need to be brought into primary care settings to improve diagnostic accuracy and prevent use of incorrect or empirical antimicrobials. This would assist healthcare workers in their goals to combat AMR and complement the educational efforts stated above [130]. Technology and mobile applications can then be used to support health education, case detection, case management, and diagnosis of people in remote and regional areas without direct and frequent access to health care [131,132]. It will also ensure adequately trained health care workers in remote and disadvantaged communities. This can also be aided by general enhancement of primary care in all regions to a certain standard to ensure quality care, and better trust by the users [126].

Hygiene protocols

It must be recommended to apply the same hygiene and infection control measure employed in hospitals to primary care and GP practices to reduce community onset infections – over 60% of countries have a national action plan for AMR in tertiary centres. Extension of these actions plans to primary care setting is imperative [133].
Focusing on multiple factors such as hygiene protocols, and educating the public on dangers of microbes that lead to eventual AMR would help. Utilising public campaigns on preventing and managing common health problems, improving water quality, sanitation and hygiene practices, and raising awareness about appropriate antibiotic consumption are also paramount [134,135]. This is shown to have been effective in countries with low hygiene measures and public health concerns. Awareness needs to be raised about dangers of self-dosing with antimicrobials as seen in regular URTIs, recent use of antivirals and antiparasitics in COVID-19 [136].

Awareness of agricultural issues

The public also needs to be aware of AMR from agricultural and food practices. The general populace needs to be empowered and engaged in understanding where their food comes from, and to ensure they understand the consequences of antibiotic use as growth promoters in animals. A method that has shown some success is to focus on consumption of meat from animals that have not been subject to antimicrobial growth promoters – this has been deployed in the USA [137].

Calling on industry

Calling on the pharmaceutical and medical industries to remove irrational fixed doses that create drug resistance – to apply evidence based medicine – has shown delay in resistance rates in India, and can be implemented globally. There also needs to be better protocols in place, in case of drug shortages, or allergy to specific antimicrobials to ensure the right drug is used. This will prevent dosage with the incorrect antimicrobial providing no therapeutic benefit and leading to AMR [137, 138].

Involvement in GLASS

The aim of GLASS on a global level is to assist countries, territories, and areas, to establish effective AMR surveillance systems and maintain and develop a centralised database for the analysis and tracking of AMR in order to inform strategy and policy. Current activities of GLASS include routine data surveillance of resistance (GLASS-AMR) and consumption (GLASS-AMC) of antimicrobials. GLASS-AMR aims to optimise the use of data available in the form of routinely collected patient specimens (e.g. bloods) and encourages the additional screening and documentation of these specimens for the purpose of AMR [142]. Pathogens under surveillance include Acinetobacter spp., E. coli, Klebsiella pneumoniae, Neisseria gonorrhoeae, Salmonella spp., Shigella spp., Staphylococcus aureus, and Streptococcus pneumoniae. Furthermore, GLASS-AMC aims to assess the use of antimicrobial agents through

monitoring of import and distribution of products in addition to documentation of prescriptions and insurance [140].

92 countries have enrolled in GLASS as of 2020; however, the contribution of data from these enrolled countries is still in the preliminary phases as country-based surveillance systems are established. Furthermore, most of the focus up to now has been in tertiary care; therefore, it will be crucial to strengthen the GLASS system in primary care [139].

Australia made minimal contributions to GLASS so far, despite being one of the first world countries signed up to the program [141,142]. In the GLASS report of Early Implementation 2020, Australia contributed data from 1 laboratory and 8 surveillance sites [140], reporting on a single pathogen (N, gonorrhoea). Most of the focus has been on tertiary care up until now.

Monitoring of MRSA

MRSA is currently not public health notifiable in Australia. There is no definite answer as to why this is the case, but there are a myriad of contributing factors that make it appear less of a risk than it is [143].

The distinction between hospital acquired MRSA (HA-MRSA) and community onset MRSA (CO-MRSA) has not helped, as a distinction does not need to be made. The confusion comes from the criteria for CO-MRSA which states 'any MRSA infection within 72hrs of admission'. Not all infections are monitored or picked up timely, and the reporting time also changes the definition of the infection. As a result, CO-MRSA is not adequately recorded or reported [143,144].

The other contributing factor is that MRSA can cause several different types of infection, including lower respiratory tract infections, skin and soft tissue infections, or bloodstream infections. Each of these types of infection are considered differently due to their risk profiles despite the same causative agent. This further results in reduced concern for certain infections caused by MRSA in the community [143].

Hospital acquired MRSA infections have been considered a health risk since the 1960's [144, 192]. However, recent improved hygiene and infection control measures have either kept the rates steady, or decreased its levels overall resulting in HA-MRSA being considered less of a risk, and 'well controlled' [144]. There is also a ten-step public health response to MRSA infections which help control its outbreak [144]. It warrants further investigation only if there are 'clusters' of infections. This leads to reduced concern for MRSA if no 'clusters' are detected for whatever reason, and reduced reporting [144].

HA-MRSA has the potential to become a more serious pathogen as seen in USA and Europe in cases of VISA (vancomycin-intermediate S. aureus), h-VISA (heterogeneous vancomycin-intermediate S. aureus) or VRSA (vancomycin-resistant S. aureus). However, these resistant organisms have not emerged in Australia as of yet [145,147]. Our lack of proximal neighbours and reduced travel with the rest of the world helps protect us from arrival of such organisms at our shores. There is no tradition of foreign citizens seeking medical treatments in Australia as is common in 'free cross border treatments' in Europe. This prevents HA-MRSA infections from crossing borders into Australia [145,146].

CO-MRSA reporting is inadequate and most infections are unrepresented by the data available. Multiple pathology and community care centres exist that either do not report the infections, or do not often catch them in a timely and appropriate manner

[143]. Not all cases treated in the ED are captured in study data either, creating a lack of resources and information regarding the seriousness of CO-MRSA when most of the focus has been on HA-MRSA. The lack of a central reporting system does not help [143]. Each state and territory is allowed to report at their own discretion and the collection of data varies wildly among states and territories. States with the least amount of CO-MRSA mandate reporting (Tasmania) compared to every other state where prevalence is much higher. Incidence rates are as high as 40% in some rural and remote areas compared to urban regions [147,148]. Rates of methicillin resistance in S. aureus are higher and increasing in remote and very remote areas of Australia, reflecting the growing problem of MRSA in some communities [147].

Lack of consistent terminology for the same infection has caused further confusion and decreased coordination in data collection and compilation. Different terms such as 'Community associated MRSA', 'Community acquired MRSA' and 'Community onset MRSA' are used. Not all of these infections are reported despite being the same organism of concern [143].

Major groups such as the WHO have not issued specific guidelines for MRSA. However, a comprehensive review on MRSA by Cameron et al. has suggested [143]:

- A national reporting system
- Consistent terminology
- Available and reportable data for all type of infection caused by CO-MRSA, and not just bloodstream infections
- All cases treated in primary care to be captured and reported
- Consider CO-MRSA the same level of threat as HA-MRSA and make it notifiable allowing for data to be accessible for better clarity of information on the true threat of CO-MRSA

AMR Education

Education in both medical school and clinical practice is an effective strategy in combating antimicrobial resistance (AMR) [149]. Effective communication and education are crucial in strengthening consumer awareness on antimicrobial, addressing commonly held erroneous beliefs, and providing a framework for sustainable prescription practices [149].

Existing AMR education is primarily achieved through antimicrobial stewardships (AMS), which are post-graduate programs that are accredited and mandated through hospitals [150]. Stewardship reinforces AMR practices and is based on evidence-based best-practice information attained through surveillance data and research findings, representing the best available antibiotic treatment practices nationally. AMS is tailored to meet the needs and challenges of all relevant sectors, including agriculture and veterinary medicine [151].

Antibiotic prescription practices and attitudes are developed in the formative years of medical education; hence greater emphasis on sustainable antibiotic prescription and AMR education is needed earlier in medical training [152]. A cross-sectional study of final-year medical students found knowledge of antimicrobial use was unsatisfactory, especially when compared to clinical knowledge of other diseases regularly taught in the curriculum, such as cardiovascular disease [153]. Specifically, students noted a need for further training in clinical placement settings in addition to being taught basic concepts [153].

The WHO curricula guide on AMR training provides suggestions for teaching methods including interactive small group learning activities, continuous appraisal, and assessment of AMR training [154]. Moreover, as patient care is multi-disciplinary, all

professions involved in patient management should be involved in stewardship and education.

Adherence to prescription policies

There are also existing issues with current antimicrobial stewardship programs. Lack of adherence to antibiotic prescription practices is a major barrier to reducing AMR [155]. This can be combated through effective communication strategies and regular monitoring of prescription behaviours.

Currently, antimicrobial stewardship is not a mandatory requirement for practicing GPs. In 2017, General Practitioners in the top 30% of prescribers were asked directly to seek assistance in reducing unnecessary antibiotic prescribing. This resulted in a 12% reduction in antibiotic prescriptions filled or approximately 126,000 fewer scripts over an initial six-month period [155].

Community Education

Further work is also needed to alter the public perception on antimicrobials as community setting prescription is influenced by the expectations and demands of patients. Public campaigning consisting of clear, consistent, simple messaging is key in educating and changing societal views and expectations on AMR use, as well as providing a space for organic social change on antimicrobial use [156].

Creating/developing new drugs

Aside from prevention, one of the most important ways to address the rising scourge of AMR directly will be by the research, and creation, of new classes of drugs that can be effective against resistant organisms. This will entail the creation of new antibiotics, but also antivirals, antifungals, antiparasitics, and antiprotozoals, particularly for the organisms of concern globally and in Australia.

Australia's current funding to research has taken a diverse approach to understanding and developing new solutions to address the AMR crisis. While funding has already been allocated towards creating new classes of antimicrobial drugs [157], there is a clear need to expand the amount of current funding in order to have more drugs to address this rapidly worsening issue.

Engaging with Stakeholders

Need for funding

While it is clear that the development of new antimicrobials will be necessary to treat microbes for which current drugs are ineffective, such endeavours have been limited. One reason for this is the minimal financial motivations for pharmaceutical companies to create new drugs for this problem. This is largely based on how profits from new medications are linked to the number of people who buy and use them, but if antimicrobial drugs are used frequently, then resistance occurs. These drugs therefore need to be used minimally, and this limits the potential for profit for companies; limited prospects for profits have meant that very few private companies pursue the creation of new antimicrobials [158, 193, 194]. This helps to explain why no new class of antibiotics has been created since 1987 [158].

In order to address this issue, a diverse array of solutions are needed in many different domains, as explained below.

Academia & Non-Profit

Funding directly allocated towards academic research, and non-profit involvement, must remain a priority. Increasing funding in the forms of grants will be a simple and decisive way to ensure that more research on antimicrobial treatments is conducted

in university settings. The non-profit sector can also potentially have a major impact in antimicrobial drug development. One such non-profit is the Global Antibiotic Research and Development Partnership (GARPD), which is collaborating with WHO to conduct antimicrobial drug research and address gaps which neither academia, nor industry, have focused on [194]. Australia can contribute to non-profit research of antimicrobials by funding groups such as GARPD, as well as by encouraging the creation of new non-profits within Australia.

Engaging with the Private Sector

The WHO, Australian government and Australian non-profits clearly call for an engagement of the private sector [197, 198] in addressing AMR. Ways to engage them include, public-private partnerships, adopting international models, market incentives & priority review vouchers.

Public-Private Partnerships

An important way to establish and encourage the development of new treatments will be via the partnership of members of both the private and public sectors. In recent years and decades, numerous such partnerships have emerged globally; these include the Innovative Medicines Initiative's (IMI's) New Drugs for Bad Bugs (ND4BB) program and the Biomedical Advanced Research and Development Authority's (BARDA) Broad Spectrum Antimicrobials Program. [195]. These collaborative efforts allow for the directed usage of public resources to drive and accelerate further innovation in the private sphere so that new drugs can be developed as rapidly as possible. An array of different countries across the globe have been involved in such partnerships [194], and Australia can do more to be involved in order to contribute to the innovations; as well more partnerships can be developed locally.

De-linked funding approaches

Trials of a de-linked funding system for novel and priority antimicrobials have been conducted in the United Kingdom and Sweden [198]. These systems involve the government paying pharmaceutical companies an annual subscription fee on the premise they will provide a suitable supply of antimicrobials based on local need. Such a system ensures that novel drugs are paid for based on their expected value to the health system, determined by the prevalence, severity, and resistance of the infections they treat among other things, rather than being paid for by the actual volume of drugs used [199]. When the actual income a company makes is less than expected, the government will pay the difference. This approach ensures the availability of vital treatments and reduces the financial burden on hospitals, which may resort to using less effective, generic drugs due to budgeting constraints [198].

Market Entry Rewards

Market entry rewards, which are among the most commonly proposed incentive policies, simply involve providing groups financial reimbursement for the creation of new drugs; reimbursement would be based on the overall need of the drug, and it would be mandatory to limit the sales and marketing of the new drug to prevent the rapid occurrence of resistance [159]. Rewards that are spread out over several years would allow for proper enforcement of these requirements, but a delayed reward would typically be less desirable for drug manufacturers. It has therefore been recommended that a balance be attained between upfront and delayed payments [160]. Numerous scholars have therefore called for the usage of market entry rewards, though it has been recommended that a balance be attained between upfront and delayed payments [160, 193, 196]. Piloting of market entry rewards have recently begun in the United Kingdom and Sweden [193]; ongoing monitoring of the effects of these policies can dictate whether they should also be applied in an Australian context.

Priority Review Vouchers

Priority review vouchers are transferable vouchers which would be given to a company when a new antimicrobial is created and would expedite the process of review for other drugs that are also in the creation process, saving about four months [162]. This incentive would ultimately cost significantly less to the public compared to the other solutions. However, it also needs to be recognized that the overall benefits for many pharmaceutical manufacturers would also be considerably lower because of this policy [160,163]. Evidence from this comes from previously implemented voucher programs for neglected tropical diseases. The most expensive voucher from the program ended up being worth 350 million USD [163], which is considerably less than what is offered by both the market entry rewards.

Combined Approaches

All of these approaches, in some way or another, have the capability to increase the likelihood that new antimicrobial drugs will be created. An effective approach for Australia to apply these solutions would be for the policies and actions to be enacted in combination with each other.

Vaccines as a Solution

Expanding Existing Vaccine Technology

With rising challenges in developing new antibiotics, prevention of primary and secondary bacterial infections is an increasingly more viable approach in tackling AMR. This may come in the form of vaccinations either directly targeting antimicrobial resistant pathogens, or preventing secondary resistance [164].

Currently, there are already vaccines targeting bacterial pathogens, including haemophilus influenzae type B and a pneumococcal conjugate vaccine [165]. Modelling has demonstrated there is significant potential to expand these into other problematic pathogens in clinical settings, where targeted vaccination can offer short-term protection for patients and long-term benefits by counterbalancing positive selection of resistance in particular clones or strains [165]. The spread of methicillin-resistant staphylococcus aureus (MRSA) has been identified through such modelling as having potential to be significantly reduced using vaccination, with an efficacy between 78-91% after 10 days post-inoculation (assuming full protection after 10 days) [165].

The prevention of secondary infection through vaccination has also been identified as a means of preventing AMR. This may be either through reducing antibiotic use in treating secondary infection, or preventing viral diseases prone to bacterial co-infection or superinfection [164,166]. Modelling of a hypothetical dengue vaccine has suggested that there is potential in curbing evolved antibiotic resistance through reducing inappropriate antibiotic administration in dengue patients, with significant economic savings as a result [167].

However, vaccinations alone are limited in their effectiveness in combating AMR. They should be focused on bacteria which can develop AMR quickly, and be used in combination with other approaches to manage infection or reduce demand for antibiotics [168]. Additionally, vaccines with shorter-term immunity present the risk of transforming individuals as reservoirs for infection in vulnerable populations, which offers the opportunity for resistant strains to circulate [169]. Furthermore, much research is either hypothetical or based on modelling, highlighting the need for significantly more research and the establishment of clinical trials into their effectiveness.

New Vaccine Technology

New developments in vaccination techniques show potential to improve the use of vaccination in targeting AMR. Emerging technologies include improved reverse vaccinology techniques, nanoparticle-based vaccination and RNA vaccines, and their application for several organisms of interest have already been flagged. Vaccinations have already been developed through reverse vaccinology e.g. vaccines against meningococcus [170], and 'reverse vaccinology 2.0' has been proposed to diversify vaccination development techniques, with organisms including Neisseria meningitidis already identified as potential targets [170]. Additionally, nanoparticle-based vaccination has potential to overcome the limitations of conventional vaccines through prompting highly-specific immune responses, and have already been identified as a means of targeting Hepatitis B [170]. Furthermore, RNA vaccines have been shown to be effective in viral pathogens, and have had success against bacteria. Major benefits include low cost and being capable of inducing rapid expression of large quantities of antigens [170], highlighting them as an effective and efficient vaccine solution to AMR.

Other New Technologies & Treatments

Monoclonal Antibodies

Monoclonal antibody use is another possible strategy tackling AMR organisms, already showing strong promise against bacterial toxins [170]. Moreover, they offer additional benefits through existing as an alternative antimicrobial treatment option, and their development facilitating an increased understanding of antimicrobial activity and the immune system [170]. Agents already in use include Bezlotoxumab [171], which was approved by the FDA for use in prevention of recurrent clostridium difficile infections in high-risk patients [170]. Further studies show promise in the neutralisation of Staph Aureus infection and the prevention of S. aureus associated pneumonia [172]. Whilst these therapies have not been shown as cures, monoclonal antibodies provide a promising starting point in the development of new therapies against microbes.

Bacteriophage Therapy

Bacteriophage therapy has been identified as a very promising treatment option for multi-drug resistant organisms [173-176]. Having already been proven to kill antimicrobial resistant species of E. coli [174], they offer another means of targeting pathogenic microbes and confer many benefits over traditional antibiotic use. Bacteriophages are highly specific to particular bacterial antigens and are overwhelmingly incapable of infecting eukaryotic mammalian cells [175,176], therefore offering potent efficacy in attacking a narrow spectrum of bacteria with minimal toxic side effects [176]. Moreover, they are able to target bacterial populations poorly treated with antibiotics, being shown to be highly effective in destroying bacterial biofilm, for which antibiotic treatment options are extremely limited [175]. In addition, the development of phage resistance may lead to increased antibiotic susceptibility in targeted bacteria [174,176]. Research has shown that bacteriophages targeting drug-resistant E.coli also exerted selective pressure in their populations to develop characteristics increasing antibiotic susceptibility [174], and that there is evidence that virulence may be reduced as well [176]. Furthermore, their natural ability to self-replicate removes the need for frequent dosage seen in antibiotic use [175], and preliminary studies have suggested that bacteriophage therapy may be more cost-effective than antibiotic regimes [175].

However, whilst showing extremely promising signs of being a highly effective treatment, limitations exist within bacteriophage therapy. Their highly specific nature may diminish their effectiveness in multi-microbial infection e.g. those found in burn wounds [175], developed resistance to phages has been documented [176], and their

unique pharmacological therapies may limit administration options [175]. Thus, bacteriophage therapy is a treatment option with significant potential, held back only by the infancy of its research.

CRISPR

CRISPR is another emerging solution in fighting multi-drug resistant pathogens, with existing research showing strong potential for its use. This has focused in particular as a treatment option for ESKAPE (Enterococcus spp., Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp.) infections, which are the leading causes of nosocomial infections worldwide [177]. CRISPR-Cas9 has been shown to have the ability modify antibiotic resistant properties in bacterial populations, successfully re-establishing antibiotic-sensitive phenotypes in beta-lactam resistant E.coli to several beta-lactam antibiotics [178]. Additionally, the success of CRISPR in carbapenem resistant organisms [178] is particularly significant, given third-generation cephalosporins are last resort treatments. Moreover, in cases where complete resistance reversal is not achieved, even moderate or intermediate sensitivity to antibiotic therapy may still offer therapeutic success [178,179]. Furthermore, there have been proposals to use phage-mediated CRISPR-Cas9 systems as a preventative measure via administration on surfaces, supplementing preventative disinfection and cleansing procedures [178]. As with other emerging technologies, limitations exist in the current state of CRISPR. Studies on its use against ESKAPE organisms are limited, especially in its ability to modify virulence factors or antibiotic resistance [180]. Moreover, its delivery to target bacteria, and the impacts of off-target genome modifications [180] are also key issues which constrain its practicality in current healthcare settings. Thus, with more research, CRISPR technology has significant potential to become an effective tool in addressing AMR.

Herbal Medicines

The antimicrobial potential of herbal extracts have been repeatedly demonstrated in the literature, showing microbe fighting traits not only when used alone but also in combination with conventional antimicrobial drugs. Given the integration of traditional plant-based medicine in mainstream healthcare in many parts of the world [185], their use has the potential to be a widely available and effective means of combating drug-resistant microorganisms.

Whilst most research has focused on the antibacterial properties of these compounds, they have also been shown to be effective against viruses [183], parasites [191] and potential against fungi [183]. Of note is the 2015 Nobel Prize winning development of the antimalarial drug Artemisinin [191], derived from the sweet wormwood plant of China [189], where Artemisinin-based combination therapy is currently recommended by the WHO for the treatment of uncomplicated malaria [190]. Other herbs with antimicrobial properties that are used in traditional Chinese medicine have been identified [182], as well as hundreds of other plant genuses worldwide [185].

The main mechanism of herbal antimicrobial action comes from the presence of secondary metabolites, such as alkaloids and polyphenols [186]. Postulated antibacterial mechanisms include interference with intracellular processes and structures [183, 186], inhibiting bacterial growth [182, 183, 186], reducing virulence [182, 183], destroying biofilm creation [182, 183, 186] and decreasing adhesion ability [182]. Additionally, they may also enhance the efficacy of conventional antimicrobial treatments [173, 183-186], through optimising drug pharmacodynamics and pharmacokinetics [184]. Moreover, some have been identified to have broad-spectrum antibiotic potential with greater efficacy than traditional antibiotics [181], and can target different bacterial strains depending on the part of the plant used [181, 182].

Furthermore, there may also be plant compounds that are effective against already multi-drug resistant bacteria, with one already identified as having positive results against mycobacterium tuberculosis [188].

Extracted compounds from plants are also postulated to hinder a pathogen's ability to develop resistance to them [183, 184]. This may be due to the presence of a multitude of secondary metabolites, presenting challenges to resistance development arising from the high number and chemical complexity of these substances [183]. In addition they may also enhance cellular processes such as immune responses to infection [183, 184], further diminishing the ability of pathogens to develop within a host.

There is much promising research into the use of herbal medicines as a tool against AMR, and there is an overwhelming call for more research into this area [173, 181-188]. This includes more in vitro examination [184-186], given most available research is conducted in vivo, and to identify the more complex antimicrobial mechanisms of these compounds [182]. Moreover, other challenges include difficulty obtaining high-purity extracts [182], and the limited evidence of bacterial resistance to herbal antimicrobials [187].

References

[1] World Health Organization. What is antimicrobial resistance [Internet]. World Health Organization; 2017 July. Available from: http://www.who.int/features/qa/75/en/

[2] Review on Antimicrobial Resistance. Antimicrobial Resistance: tackling a crisis for the future health and wealth of nations. London: Review on Antimicrobial Resistance; 2014 Dec 11. 20 p. Report no.: 1.

[3] Jackson BR, Chow N, Forsberg K, et al. On the Origins of a Species: What Might Explain the Rise of Candida auris?. J Fungi (Basel). 2019;5(3):58. Published 2019 Jul 6. doi:10.3390/jof5030058

[4] Theriault N, Tillotson G. Pan-resistant, Currently Untreatable Gram-Negative Infections Come Closer to Home. Paper presented at: ASM Microbe Conference; 2019 Jul 2. Available from: https://www.contagionlive.com/view/panresistant-currently-untreatable-gramnegative-infections-come-closer-to-home

[5] Zhi-Wen Y, Yan-Li Z, Man Y, Wei-Jun F. Clinical treatment of pandrug-resistant bacterial infection consulted by clinical pharmacist. Saudi Pharm J. 2015;23(4):377-80. Available from: 10.1016/j.jsps.2015.01.001

[6] Puertas MC, Ploumidis G, Ploumidis M, Fumero E, Clotet B, Walworth CM, et al. Pan-resistant HIV-1 emergence in the era of integrase strand-transfer inhibitors: a case report. The Lancet Microbe. 2020;1(3):e130-e5. Available from: https://doi.org/10.1016/S2666-5247(20)30006-9

[7] Rowland, K. Totally drug-resistant TB emerges in India. Nature (2012). https://doi.org/10.1038/nature.2012.9797

[8] Jaloot AS, Owaid MN. Antibiotic Resistance Pattern and Prevalence of Multi-Drug and Extensive Resistant Acinetobacter Baumannii Isolates from Clinical Specimens after Military Operations Western Iraq. GMJ. 2021;32:381-8.

[9] Varshney, K, Frasso, R, Leader, A., Risk Factors for Incurable Drug-Resistant Tuberculosis (2020). Master of Public Health Capstone Presentations. Presentation 355. https://jdc.jefferson.edu/mphcapstone_presentation/355

[10] Belcher R, Zobell JT. Optimization of antibiotics for cystic fibrosis pulmonary exacerbations due to highly resistant nonlactose fermenting Gram negative bacilli: Meropenem-vaborbactam and cefiderocol. Pediatric Pulmonology. 2021;56(9):3059-61. Available from: https://doi.org/10.1002/ppul.25552

[11] Elshebrawy HA, Mahros MA, Abd-Elghany SM, Elgazzar MM, Hayashidani H, Sallam KI. Prevalence and molecular characterization of multidrug-resistant and β-lactamase producing Salmonella enterica serovars isolated from duck, pigeon, and quail carcasses in Mansoura, Egypt. LWT. 2021;149:111834. Available from: https://doi.org/10.1016/j.lwt.2021.111834

[12] Xu L, Sun X, Ma X. Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant Klebsiella pneumoniae. Annals of Clinical Microbiology and Antimicrobials. 2017;16(1):18. Available from: https://doi.org/10.1186/s12941-017-0191-3

[13] Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. Clin Infect Dis. 2003;36(11):1433-7

[14] The World Bank. Drug-resistant infections: A threat to our economic future [Internet]. The World Bank; 2017. Available from: https://www.worldbank.org/en/topic/health/publication/drug-resistant-infections-a-threat-to-our-economic-future

[15] Wozniak TM, Graves N, Barnett AG. How much do superbugs cost Australian hospitals? An evidence-based open-access tool. Infection, Disease & Health. 2018;23(1):54-6. Available from: https://doi.org/10.1016/j.idh.2017.11.002

[16] Jit M, Ng DHL, Luangasanatip N, Sandmann F, Atkins KE, Robotham JV, et al. Quantifying the economic cost of antibiotic resistance and the impact of related interventions: rapid methodological review, conceptual framework and recommendations for future studies. BMC Med. 2020;18(1):38-. Available from: 10.1186/s12916-020-1507-2

[17] Outbreak. A One Health antimicrobial resistance economic perspective.[Internet]. University of Technology Sydney; 2020. Available from: https://outbreakproject.com.au/wp-content/uploads/2020/12/OUTBREAK_REPORT_2020_economics_ERRATUM.pdf

[18] O'Neill J et al. Review on Antimicrobial Resistance. 2016 [Internet] Available from: https://amr-review.org/

[19] Wozniak TM, Barnsbee L, Lee XJ, Pacella RE. Using the best available data to estimate the cost of antimicrobial resistance: a systematic review. Antimicrobial Resistance & Infection Control. 2019;8(1):26. Available from: https://doi.org/10.1186/s13756-019-0472-z

[20] Superbugs to trigger our next global financial crisis', OUTBREAK consortium (2020) Available from: https://outbreakproject.com.au/wp-content/uploads/2020/12/OUTBREAK_REPORT_2020_economics_ERRATUM.pdf)

[21] CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA:U.S. Department of Health and Human Services, CDC; 2019.

[22] World Health Organisation. Tuberculosis, 2020; WHO; [Internet] Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis

[23] World Health Organisation. Antimicrobial resistance, 2020; WHO; [Internet] Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance

[24] Cong Y, Yang S, Rao X. Vancomycin resistant Staphylococcus aureus infections: A review of case updating and clinical features. Journal of Advanced Research. 2020;21:169-76. Available from: https://doi.org/10.1016/j.jare.2019.10.005

[25] Fletcher-Lartey S, Dronavalli M, Alexander K, Ghosh S, Boonwaat L, Thomas J, et al. Trends in Antimicrobial Resistance Patterns in Neisseria Gonorrhoeae in Australia and New Zealand: A Meta-analysis and Systematic Review. Antibiotics (Basel). 2019;8(4):191. Available from: 10.3390/antibiotics8040191

[26] Australian Commission on Safety and Quality in Health Care (ACSQHC). AURA 2019: third Australian report on antimicrobial use and resistance in human health. Sydney: ACSQHC; 2019

[27] Aworh MK, Kwaga J, Okolocha E, Mba N, Thakur S. Prevalence and risk factors for multi-drug resistant Escherichia coli among poultry workers in the Federal Capital Territory, Abuja, Nigeria. PloS one. 2019 Nov 21;14(11):e0225379 Available from: https://doi.org/10.1371/journal.pone.0225379

[28] Kovacikova K, van Hemert MJ. Small-Molecule Inhibitors of Chikungunya Virus: Mechanisms of Action and Antiviral Drug Resistance. Antimicrob Agents Chemother. 2020;64(12):e01788-20. Published 2020 Nov 17. doi:10.1128/AAC.01788-20

[29] Kim S, Han KH, Ahn SH. Hepatitis C Virus and Antiviral Drug Resistance. Gut Liver. 2016;10(6):890-895. doi:10.5009/gnl15573

[30] Anstett K, Brenner B, Mesplede T, Wainberg MA. HIV drug resistance against strand transfer integrase inhibitors. Retrovirology. 2017;14(1):36. Published 2017 Jun 5. doi:10.1186/s12977-017-0360-7

[31] Charpentier C, Descamps D. Resistance to HIV Integrase Inhibitors: About R263K and E157Q Mutations. Viruses. 2018;10(1):41. Published 2018 Jan 18. doi:10.3390/v10010041

[32] Chaabane F, Graf A, Jequier L, Coste AT. Review on antifungal resistance mechanisms in the emerging pathogen Candida auris. Frontiers in microbiology. 2019 Nov 29;10:2788.Available from: https://doi.org/10.3389/fmicb.2019.02788

[33] Centres for Disease Control and Prevention. Candida auris; 2021;CDC [Internet] Available from: https://www.cdc.gov/fungal/candida-auris/index.html

[34] Jackson BR, Chow N, Forsberg K, et al. On the Origins of a Species: What Might Explain the Rise of Candida auris?. J Fungi (Basel). 2019;5(3):58. Published 2019 Jul 6. doi:10.3390/jof5030058

[35] World Health Organisation. Malaria, 2021; WHO; [Internet] Available from: https://www.who.int/news-room/fact-sheets/detail/malaria

[36] Ippolito MM, Moser KA, Kabuya J-BB, Cunningham C, Juliano JJ. Antimalarial Drug Resistance and Implications for the WHO Global Technical Strategy. Current Epidemiology Reports. 2021;8(2):46-62. Available from: https://doi.org/10.1007/s40471-021-00266-5

[37] Bosman A, Mendis KN. A major transition in malaria treatment: the adoption and deployment of artemisinin-based combination therapies. Am J Trop Med Hyg. 2007;77(6 Suppl):193–7.

[38] Trape JF. The public health impact of chloroquine resistance in Africa. Am J Trop Med Hyg. 2001;64(1-2 Suppl):12–7.

[39] Reid MC, Peebles K, Stansfield SE, et al. Models to predict the public health impact of vaccine resistance: A systematic review. Vaccine. 2019;37(35):4886-4895. doi:10.1016/j.vaccine.2019.07.013

[40] Global tuberculosis report 2020. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO

[41] UNAIDS. Global HIV & Aids statistics; 2021; UNAIDS [Internet] Available from: https://www.unaids.org/en/resources/fact-sheet

[42] Cuevas, J. M., Geller, R., Garijo, R., López-Aldeguer, J., & Sanjuán, R. (2015). Extremely high mutation rate of HIV-1 in vivo. PLoS biology, 13(9), e1002251.

[43] World Health Organisation. HIV drug resistance, 2020; WHO; [Internet] Available from: https://www.who.int/news-room/fact-sheets/detail/hiv-drug-resistance

[44] Turnidge JD, Kotsanas D, Munckhof W, Roberts S, Bennett CM, Nimmo GR, et al. Staphylococcus aureus bacteraemia: a major cause of mortality in Australia and New Zealand. Med J Aust. 2009;191(7):368–73.

[45] Munckhof WJ, Nimmo GR, Carney J, Schooneveldt JM, Huygens F, Inman-Bamber J, et al. Methicillin-susceptible, non-multiresistant methicillin-resistant and multiresistant methicillin-resistant Staphylococcus aureus infections: a clinical, epidemiological and microbiological comparative study. Eur J Clin Microbiol Infect Dis. 2008;27(5):355–64.

[46] Nimmo GR, Coombs GW. Community-associated methicillin-resistant Staphylococcus aureus (MRSA) in Australia. Int J Antimicrob Agents. 2008;31(5):401–10.

[47] Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest. 2000;118(1):146–55.

[48] Khatib R, Saeed S, Sharma M, Riederer K, Fakih MG, Johnson LB. Impact of initial antibiotic choice and delayed appropriate treatment on the outcome of Staphylococcus aureus bacteremia. Eur J Clin Microbiol Infect Dis. 2006;25(3):181–5.

[49] Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD, et al. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J Int Med. 1998;244(5):379–86.

[50] Lodise TP, McKinnon PS, Swiderski L, Rybak MJ. Outcomes analysis of delayed antibiotic treatment for hospital-acquired Staphylococcus aureus bacteremia. Clin Infect Dis. 2003;36(11):1418–23.

[51] Cameron JK, Hall L, Tong SYC, Paterson DL, Halton K. Incidence of community onset MRSA in Australia: least reported where it is Most prevalent. Antimicrobial Resistance & Infection Control. 2019;8(1):33. Available from: https://doi.org/10.1186/s13756-019-0485-7

[52] Collignon, P., Nimmo, G. R., Gottlieb, T., Gosbell, I. B., & Australian Group on Antimicrobial Resistance (2005). Staphylococcus aureus bacteremia, Australia. Emerging infectious diseases, 11(4), 554–561. https://doi.org/10.3201/eid1104.040772

[53] Cong Y, Yang S, Rao X. Vancomycin resistant Staphylococcus aureus infections: A review of case updating and clinical features. Journal of Advanced Research. 2020;21:169-76. Available from: https://doi.org/10.1016/j.jare.2019.10.005

[54] Australian Gonococcal Surveillance Programme Annual Report, 2019. Monica M Lahra, Masoud Shoushtari, CR Robert George, Benjamin H Armstrong and Tiffany R Hogan for the National Neisseria Network, Australia

[55] Trembizki E, Wand H, Donovan B, Chen M, Fairley CK, Freeman K, et al. The Molecular Epidemiology and Antimicrobial Resistance of Neisseria gonorrhoeae in Australia: A Nationwide Cross-Sectional Study, 2012. Clinical Infectious Diseases. 2016;63(12):1591-8. Available from: https://doi.org/10.1093/cid/ciw648

[56] Australian Commission on Safety and Quality in Health Care (ACSQHC). AURA 2019: third Australian report on antimicrobial use and resistance in human health. Sydney: ACSQHC; 2019.

[57] Centers for Disease Control and Prevention. One Health [Internet]. U.S: Department of Health and Human Services; 2021 [updated 2021 Aug 26; cited 2021 Sep 5]. Available from: https://www.cdc.gov/onehealth/index.html

[58] Igoe D; Criteria for Inclusion on list of notifiable disease; Health Protection Surveillance Centre [Internet] Available from: https://www.hpsc.ie/abouthpsc/sslproa/sphmoncall/documentarea/documentsandreferences/File,12428,en.pdf

[59] "Australian National Notifiable DISEASES CASE Definitions - Appendix B: Australian State and Territory Notifiable Diseases." Department of Health, 24 Apr. 2019, www1.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-statedis.htm.

[60] Australian Commission on Safety and Quality in Health Care. AURA 2016: first Australian report on antimicrobial use and resistance in human health. Sydney, Australia: ACSQHC, 2016.

[61] Communicable Diseases Network Australia. "Australian National Notifiable Diseases and CASE DEFINITIONS." Department of Health, Australian Government Department of Health, 30 June 2021, www1.health.gov.au/internet/main/publishing.nsf/Content/cdna-casedefinitions.htm.

[62] Adams, Deborah, et al. "Summary of Notifiable Infectious Diseases and Conditions - United STATES, 2013." Centers for Disease Control and Prevention, Division of Health Informatics and Surveillance, 23 Oct. 2013, www.cdc.gov/mmwr/preview/mmwrhtml/mm6253a1.htm.

[63] "Process for Developing and Reviewing Case Definitions." Department of Health, CDNA, 20 Apr. 2018, www1.health.gov.au/internet/main/publishing.nsf/Content/ohp-process-dev-case-def.htm.

[64] Dickmann P, Keeping S, Döring N, Schmidt AE, Binder C, Ariño-Blasco S, et al. Communicating the risk of MRSA: The role of clinical PRACTICE, regulation and other policies in Five European countries. Frontiers in Public Health. 2017;5.

[65] Rogers BA, Aminzadeh Z, Hayashi Y, Paterson DL. Country-to-Country Transfer of Patients and the Risk of Multi-Resistant Bacterial Infection. Clinical Infectious Diseases. 2011;53(1):49-56. Available from: https://doi.org/10.1093/cid/cir273

[66] "Infectious Diseases." Smartraveller, Department of Foreign Affairs and Trade , 2021, www.smartraveller.gov.au/before-you-go/health/diseases.

[67] “Infectious and Communicable Diseases.” Australian Institute of Health and Welfare, 23 July 2020, www.aihw.gov.au/reports/australias-health/infectious-and-communicable-diseases.

[68] Rogers BA, Aminzadeh Z, Hayashi Y, Paterson DL. Country-to-Country Transfer of Patients and the Risk of Multi-Resistant Bacterial Infection. Clinical Infectious Diseases. 2011;53(1):49-56. Available from: https://doi.org/10.1093/cid/cir273

[69] Department of Home Affairs. “Immigration and Citizenship.” What Health Examinations You Need, The Australian Government, 17 Mar. 2020, immi.homeaffairs.gov.au/help-support/meeting-our-requirements/health/what-health-examinations-you-need.

[70] Department of Health; Australia’s National Antimicrobial Resistance Strategy - 2020 and Beyond; 2020; Australian Government [Internet] Available from: https://www.amr.gov.au/resources/australias-national-antimicrobial-resistance-strategy-2020-and-beyond

[71] Department of Health; Strategy for antimicrobial resistance surveillance in Australia; Australian Government; 2003 [Internet] Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-pubs-cdi-2003-cdi2704-htm-cdi2704c.htm

[72] Australian Government; Objective 5: Integrated surveillance and response to resistance and usage; Australian Government; 2020 [Internet] Available from: https://www.amr.gov.au/australias-response/objective-5-integrated-surveillance-and-response-resistance-and-usage

[73] Vidovic N, Vidovic S. Antimicrobial Resistance and Food Animals: Influence of Livestock Environment on the Emergence and Dissemination of Antimicrobial Resistance. Antibiotics. 2020;9(2).

[74] Van Boeckel TP, Pires J, Silvester R, Zhao C, Song J, Criscuolo NG, et al. Global trends in antimicrobial resistance in animals in low- and middle-income countries. Science. 2019;365(6459):eaaw1944.

[75] Hill-Cawthorne G, Negin J, Capon T, Gilbert GL, Nind L, Nunn M, et al. Advancing Planetary Health in Australia: focus on emerging infections and antimicrobial resistance. BMJ Global Health. 2019;4(2):e001283.

[76] Caruso G. Antibiotic Resistance in Escherichia coli from Farm Livestock and Related Analytical Methods: A Review. J AOAC Int. 2018;101(4):916-22.

[77] Cheng G, Ning J, Ahmed S, Huang J, Ullah R, An B, et al. Selection and dissemination of antimicrobial resistance in Agri-food production. Antimicrob Resist Infect Control. 2019;8:158.

[78] Dweba CC, Zishiri OT, El Zowalaty ME. Methicillin-resistant Staphylococcus aureus: livestock-associated, antimicrobial, and heavy metal resistance. Infect Drug Resist. 2018;11:2497-509.

[79] Lee T, Jordan D, Sahibzada S, Abraham R, Pang S, Coombs GW, et al. Antimicrobial Resistance in Porcine Enterococci in Australia and the Ramifications for Human Health. Appl Environ Microbiol. 2021;87(10).

[80] Smith MG, Jordan D, Gibson JS, Cobbold RN, Chapman TA, Abraham S, et al. Phenotypic and genotypic profiling of antimicrobial resistance in enteric Escherichia coli communities isolated from finisher pigs in Australia. Aust Vet J. 2016;94(10):371-6.

[81] Sodagari HR, Mohammed AB, Wang P, O'Dea M, Abraham S, Robertson I, et al. Non-typhoidal Salmonella contamination in egg shells and contents from retail in Western Australia: Serovar diversity, multilocus sequence types, and phenotypic and genomic characterizations of antimicrobial resistance. Int J Food Microbiol. 2019;308:108305.

[82] Tyrrell C, Burgess CM, Brennan FP, Walsh F. Antibiotic resistance in grass and soil. Biochem Soc Trans. 2019;47(1):477-86.

[83] Aworh MK, Kwaga J, Okolocha E, Mba N, Thakur S. Prevalence and risk factors for multi-drug resistant Escherichia coli among poultry workers in the Federal Capital Territory, Abuja, Nigeria. PloS one. 2019 Nov 21;14(11):e0225379. Available from: https://doi.org/10.1371/journal.pone.0225379

[84] Pormohammad A, Nasiri MJ, Azimi T. Prevalence of antibiotic resistance in Escherichia coli strains simultaneously isolated from humans, animals, food, and the environment: a systematic review and meta-analysis. Infect Drug Resist. 2019;12:1181-1197. Published 2019 May 8. doi:10.2147/IDR.S201324

[85] Goldstein, E., MacFadden, D. R., Karaca, Z., Steiner, C. A., Viboud, C., & Lipsitch, M. (2019). Antimicrobial resistance prevalence, rates of hospitalization with septicemia and rates of mortality with sepsis in adults in different US states. International journal of antimicrobial agents, 54(1), 23–34. https://doi.org/10.1016/j.ijantimicag.2019.03.004

[86] Mortality following bacteraemic infection caused by extended spectrum beta-lactamase (ESBL) producing E. coli compared to non-ESBL producing E. coli

[87] Buffet-Bataillon S, Tattevin P, Bonnaure-Mallet M, Jolivet-Gougeon A. Emergence of resistance to antibacterial agents: the role of quaternary ammonium compounds—a critical review. Int J Antimicrob Agents. 2012 May 1;39(5):381–9.

[88] Aiello AE, Larson EL, Levy SB. Consumer Antibacterial Soaps: Effective or Just Risky? [Internet]. Vol. 45, Clinical Infectious Diseases. 2007. p. S137–47. Available from: http://dx.doi.org/10.1086/519255

[89] Gnanadhas DP, Marathe SA, Chakravortty D. Biocides--resistance, cross-resistance mechanisms and assessment. Expert Opin Investig Drugs. 2013 Feb;22(2):191–206.

[90] Neale M. The Biocide products directive - industry concerns. Pestic Outlook. 2003;14(2):71–3.

[91] Denyer SP, Stewart GSAB. Mechanisms of action of disinfectants. Int Biodeterior Biodegradation. 1998 Jan 1;41(3):261–8.

[92] Cahill JD, Furlong ET, Burkhardt MR, Kolpin D, Anderson LG. Determination of pharmaceutical compounds in surface- and ground-water samples by solid-phase extraction and high-performance liquid chromatography-electrospray ionization mass spectrometry. J Chromatogr A. 2004 Jul 2;1041(1-2):171–80.

[93] Blair BD, Crago JP, Hedman CJ, Klaper RD. Pharmaceuticals and personal care products found in the Great Lakes above concentrations of environmental concern. Chemosphere. 2013 Nov;93(9):2116–23.

[94] Bedoux G, Roig B, Thomas O, Dupont V, Le Bot B. Occurrence and toxicity of antimicrobial triclosan and by-products in the environment. Environ Sci Pollut Res Int. 2012 May;19(4):1044–65.

[95] Wu X, Ernst F, Conkle JL, Gan J. Comparative uptake and translocation of pharmaceutical and personal care products (PPCPs) by common vegetables. Environ Int. 2013 Oct;60:15–22.

[96] Donaghy JA, Jagadeesan B, Goodburn K, Grunwald L, Jensen ON, Jespers AD, et al. Relationship of Sanitizers, Disinfectants, and Cleaning Agents with Antimicrobial Resistance. J Food Prot. 2019 May;82(5):889–902.

[97] Amsalu A, Sapula SA, De Barros Lopes M, Hart BJ, Nguyen AH, Drigo B, et al. Efflux Pump-Driven Antibiotic and Biocide Cross-Resistance in Pseudomonas aeruginosa Isolated from Different Ecological Niches: A Case Study in the Development of Multidrug Resistance in Environmental Hotspots. Microorganisms [Internet]. 2020 Oct 24;8(11). Available from: http://dx.doi.org/10.3390/microorganisms8111647

[98] Levy SB. Active efflux, a common mechanism for biocide and antibiotic resistance. Symp Ser Soc Appl Microbiol. 2002;(31):65S – 71S.

[99] Blanco P, Hernando-Amado S, Reales-Calderon JA, Corona F, Lira F, Alcalde-Rico M, et al. Bacterial Multidrug Efflux Pumps: Much More Than Antibiotic Resistance Determinants. Microorganisms [Internet]. 2016 Feb 16;4(1). Available from: http://dx.doi.org/10.3390/microorganisms4010014

[100] Condell O, Iversen C, Cooney S, Power KA, Walsh C, Burgess C, et al. Efficacy of biocides used in the modern food industry to control salmonella enterica, and links between biocide tolerance and resistance to clinically relevant antimicrobial compounds. Appl Environ Microbiol. 2012 May;78(9):3087–97.

[101] Soumet C, Méheust D, Pissavin C, Le Grandois P, Frémaux B, Feurer C, et al. Reduced susceptibilities to biocides and resistance to antibiotics in food-associated

bacteria following exposure to quaternary ammonium compounds. J Appl Microbiol. 2016 Nov;121(5):1275–81.

[102] Amsalu A, Sapula SA, De Barros Lopes M, Hart BJ, Nguyen AH, Drigo B, et al. Efflux Pump-Driven Antibiotic and Biocide Cross-Resistance in Pseudomonas aeruginosa Isolated from Different Ecological Niches: A Case Study in the Development of Multidrug Resistance in Environmental Hotspots. Microorganisms [Internet]. 2020 Oct 24;8(11). Available from: http://dx.doi.org/10.3390/microorganisms8111647

[103] Levy SB. Active efflux, a common mechanism for biocide and antibiotic resistance. Symp Ser Soc Appl Microbiol. 2002;(31):65S – 71S.

[104] Blanco P, Hernando-Amado S, Reales-Calderon JA, Corona F, Lira F, Alcalde-Rico M, et al. Bacterial Multidrug Efflux Pumps: Much More Than Antibiotic Resistance Determinants. Microorganisms [Internet]. 2016 Feb 16;4(1). Available from: http://dx.doi.org/10.3390/microorganisms4010014

[105] Condell O, Iversen C, Cooney S, Power KA, Walsh C, Burgess C, et al. Efficacy of biocides used in the modern food industry to control salmonella enterica, and links between biocide tolerance and resistance to clinically relevant antimicrobial compounds. Appl Environ Microbiol. 2012 May;78(9):3087–97.

[106] Soumet C, Méheust D, Pissavin C, Le Grandois P, Frémaux B, Feurer C, et al. Reduced susceptibilities to biocides and resistance to antibiotics in food-associated bacteria following exposure to quaternary ammonium compounds. J Appl Microbiol. 2016 Nov;121(5):1275–81.

[107] Wand ME, Bock LJ, Bonney LC, Sutton JM. Mechanisms of Increased Resistance to Chlorhexidine and Cross-Resistance to Colistin following Exposure of Klebsiella pneumoniae Clinical Isolates to Chlorhexidine. Antimicrob Agents Chemother [Internet]. 2017 Jan;61(1). Available from: http://dx.doi.org/10.1128/AAC.01162-16

[108] Muñoz M del CC, Benomar N, Ennahar S, Horvatovich P, Lerma LL, Knapp CW, et al. Comparative proteomic analysis of a potentially probiotic Lactobacillus pentosus MP-10 for the identification of key proteins involved in antibiotic resistance and biocide tolerance. Int J Food Microbiol. 2016;222:8–15.

[109] Curiao T, Marchi E, Grandgirard D, León-Sampedro R, Viti C, Leib SL, et al. Multiple adaptive routes of Salmonella enterica Typhimurium to biocide and antibiotic exposure. BMC Genomics. 2016 Jul 13;17:491.

[110] Techaruvichit P, Takahashi H, Kuda T, Miya S, Keeratipibul S, Kimura B. Adaptation of Campylobacter jejuni to biocides used in the food industry affects biofilm structure, adhesion strength, and cross-resistance to clinical antimicrobial compounds. Biofouling. 2016 Aug;32(7):827–39.

[111] Zhang Y, Zhao Y, Xu C, Zhang X, Li J, Dong G, et al. Chlorhexidine exposure of clinical Klebsiella pneumoniae strains leads to acquired resistance to this disinfectant

and to colistin [Internet]. Vol. 53, International Journal of Antimicrobial Agents. 2019. p. 864–7. Available from: http://dx.doi.org/10.1016/j.ijantimicag.2019.02.012

[112] Saleem HGM, Seers CA, Sabri AN, Reynolds EC. Dental plaque bacteria with reduced susceptibility to chlorhexidine are multidrug resistant. BMC Microbiol. 2016 Sep 15;16:214.

[113] Venter H, Henningsen ML, Begg SL. Antimicrobial resistance in healthcare, agriculture and the environment: the biochemistry behind the headlines. Essays Biochem. 2017 Feb 28;61(1):1–10.

[114] Wales AD, Davies RH. Co-Selection of Resistance to Antibiotics, Biocides and Heavy Metals, and Its Relevance to Foodborne Pathogens. Antibiotics (Basel). 2015 Nov 13;4(4):567–604.

[115] Ortega Morente E, Fernández-Fuentes MA, Grande Burgos MJ, Abriouel H, Pérez Pulido R, Gález A. Biocide tolerance in bacteria. Int J Food Microbiol. 2013 Mar 1;162(1):13–25.

[116] Food and Agriculture Organization of the United Nations, World Health Organization. Joint FAO/WHO Expert Meeting in collaboration with OIE on Foodborne Antimicrobial Resistance: Role of the Environment, Crops and Biocides: Meeting report. Food & Agriculture Org.; 2019. 62 p.

[117] Giuliano CA, Rybak MJ. Efficacy of triclosan as an antimicrobial hand soap and its potential impact on antimicrobial resistance: a focused review. Pharmacotherapy. 2015 Mar;35(3):328–36.

[118] Coughlan LM, Cotter PD, Hill C, Alvarez-Ordóñez A. New Weapons to Fight Old Enemies: Novel Strategies for the (Bio)control of Bacterial Biofilms in the Food Industry. Front Microbiol. 2016 Oct 18;7:1641.

[119] Bowler P, Murphy C, Wolcott R. Biofilm exacerbates antibiotic resistance: Is this a current oversight in antimicrobial stewardship? Antimicrob Resist Infect Control. 2020 Oct 20;9(1):162.

[120] Gilbert P, Allison DG, McBain AJ. Biofilms in vitro and in vivo: do singular mechanisms imply cross-resistance? Symp Ser Soc Appl Microbiol. 2002;(31):98S – 110S.

[121] Hennequin C, Aumeran C, Robin F, Traore O, Forestier C. Antibiotic resistance and plasmid transfer capacity in biofilm formed with a CTX-M-15-producing Klebsiella pneumoniae isolate. J Antimicrob Chemother. 2012 Sep;67(9):2123–30.

[122] Ledwoch K, Dancer SJ, Otter JA, Kerr K, Roposte D, Rushton L, et al. Beware biofilm! Dry biofilms containing bacterial pathogens on multiple healthcare surfaces; a multi-centre study. J Hosp Infect. 2018 Nov;100(3):e47–56.

[123] Hu H, Johani K, Gosbell IB, Jacombs ASW, Almatroudi A, Whiteley GS, et al. Intensive care unit environmental surfaces are contaminated by multidrug-resistant

bacteria in biofilms: combined results of conventional culture, pyrosequencing, scanning electron microscopy, and confocal laser microscopy. J Hosp Infect. 2015 Sep;91(1):35–44.

[124] Jonge E de, de Jonge E, de Boer MGJ, van Essen EHR, Dogterom-Ballering HCM, Veldkamp KE. Effects of a disinfection device on colonization of sink drains and patients during a prolonged outbreak of multidrug-resistant Pseudomonas aeruginosa in an intensive care unit [Internet]. Vol. 102, Journal of Hospital Infection. 2019. p. 70–4. Available from: http://dx.doi.org/10.1016/j.jhin.2019.01.003

[125] D'Accolti M, Soffritti I, Mazzacane S, Caselli E. Fighting AMR in the Healthcare Environment: Microbiome-Based Sanitation Approaches and Monitoring Tools. Int J Mol Sci [Internet]. 2019 Mar 27;20(7). Available from: http://dx.doi.org/10.3390/ijms20071535

[126] Technical Series; Antimicrobial Resistance and Primary Health Care WHO; 2018 [Internet] Available from: https://www.who.int/docs/default-source/primary-health-care-conference/amr.pdf?sfvrsn=8817d5ba_2

[127] RACGP; Response to antimicrobial resistance in primary care; RACGP; 2017 [Internet] Available from: https://www.racgp.org.au/download/Documents/Reports/RACGP-Response-to-antimicrobial-resistance-in-primary-care.pdf

[128] Australian Government; Objective 5: Integrated surveillance and response to resistance and usage; Australian Government; 2020 [Internet] Available from: https://www.amr.gov.au/australias-response/objective-5-integrated-surveillance-and-response-resistance-and-usage

[129] Jamshed SQ, Elkalmi R, Rajiah K, Al-Shami AK, Shamsudin SH, Siddiqui MJA, et al. Understanding of antibiotic use and resistance among final-year pharmacy and medical students: a pilot study. J Infect Dev Ctries. 2014;8(6):780–5. doi: 10.3855/jidc.383

[130] World Malaria Report 2017. Geneva: World Health Organization; 2017 [Internet] Available from: http://www.who.int/malaria/publications/world-malaria-report-2017/report/en/

[131] PharmaDynamics; BugWise [Internet] Available from: http://bugwise.co.za/

[132] WHO Collaborating Centre on Patient Safety, Geneva. Evaluation of antibiotic awareness campaigns. World Health Organization; 2016 [Internet] Available from: http://www.who.int/selection_medicines/committees/expert/21/applications/antibacterials-ccps_rev/en/

[133] Sharland M, Pulcini C, Harbarth S, Zeng M, Gandra S, Mathur S, et al. Classifying antibiotics in the WHO Essential Medicines List for optimal use—be aRe. Lancet Infect Dis. 2018;18(1):18–20. doi: 10.1016/S1473-3099(17)30724-7

[134] Meadley T. Community design of hygiene promotion IEC materials. Water Week. Washington(DC):WorldBank;2003. http://siteresources.worldbank.org/EXTWAT/Resources/4602122-1213366294492/5106220-1213366309673/9.5LaoPDRExperience-CommunityDesign_San_Hygiene.p

[135] Sabuncu E,David J, Bernede-Bauduin C, Pepin S, Leroy M, Boelle P-Y, et al. Significant reduction of antibiotic use in the community after a nationwide campaign i France, 2002–2007. PLoS Med. 2009;6(6): e1000084. Doi: 10.1371/journal.pmed.100008

[136] Evidence for action on antimicrobial resistance. London: Wellcome Trust; 2016 [Internet] Available from: https://wellcome.ac.uk/sites/default/files/evidence-for-action-on-antimicrobial-resistance-wellcome-sep16.pdf

[137] The FAO action plan on antimicrobial resistance 2016–2020. Rome: Food and Agriculture Organization; 2016 [Internet] Available from: http://www.fao.org/3/a-i5996e.pdf

[138] Jensen US,Muller A, Brandt CT, Frimodt-Møller N, Hammerum AM, Monnet DL. Effect of generics on price and consumption of ciprofloxacin in primary healthcare: The relationship to increasing resistance. J Antimicrob Chemother. 2010;65(6):1286–91. doi: 10.1093/jac/dkq0

[139] Situational analysis on antimicrobial resistance in the South-East Asia Region: report 2016. New Delhi: World Health Organization, Regional Office for South-East Asia;2016

[140] Global antimicrobial resistance surveillance system (GLASS) report: early implementation 2020. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

[141] Schnall J, Rajkhowa A, Ikuta K, Rao P, Moore CE. Surveillance and monitoring of antimicrobial resistance: limitations and lessons from the GRAM project; BMC Medicine; 2019 17:176 https://doi.org/10.1186/s12916-019-1412-8

[142] Department of Health; Australia's National Antimicrobial Resistance Strategy - 2020 and Beyond; 2020; Australian Government [Internet] Available from: https://www.amr.gov.au/resources/australias-national-antimicrobial-resistance-strategy-2020-and-beyond

[143] Cameron, J.K., Hall, L., Tong, S.Y.C. et al. Incidence of community onset MRSA in Australia: least reported where it is Most prevalent. Antimicrob Resist Infect Control 8, 33 (2019). https://doi.org/10.1186/s13756-019-0485-7

[144] Department of Health NSW. MRSA in the community control guideline. NSW DoH. [Internet] Available from: https://www.health.nsw.gov.au/Infectious/controlguideline/Pages/methicillin_res_stap.aspx

[145] Department of Health Vic. Staphylococcal infections. Vic DoH [Internet] Available from: https://www2.health.vic.gov.au/public-health/infectious-diseases/disease-information-advice/staphylococcal-infections

[146] Dickmann P, Keeping S, Döring N, Schmidt AE, Binder C, Ariño-Blasco S, et al. Communicating the risk Of MRSA: The role of clinical PRACTICE, regulation and other policies in Five European countries. Frontiers in Public Health. 2017;5.

[147] Australian Commission on Safety and Quality in Health Care. Australian passive antimicrobial resistance surveillance. First report: multi-resistant organisms. Sydney:ACSQHC, 2018.

[148] Australia. Parliament. Australian Government response to the Senate Finance and Public Administration References Committee report on Progress in the implementation of the recommendations of the 1999 Joint Expert Technical Advisory Committee on Antimicrobial Resistance: Commonwealth of Australia, 2019.

[149] Pereira, N. R., Castro-Sanchez, E., & Nathwani, D. (2017). How can Multi-Professional Education Support Better Stewardship?. Infectious disease reports, 9(1), 6917. https://doi.org/10.4081/idr.2017.6917

[150] Australian Commision on Safety and Quality in Health Care (2020). Antimicrobial Stewardship Clinical care standard [Online]. https://www.safetyandquality.gov.au/sites/default/files/2020-11/Antimicrobial%20Stewardship%20Clinical%20Care%20Standard%20%20Consumer%20guide.pdf

[151] Department of Health; Australia's National Antimicrobial Resistance Strategy - 2020 and Beyond; 2020; Australian Government [Internet] Available from: https://www.amr.gov.au/resources/australias-national-antimicrobial-resistance-strategy-2020-and-beyond

[152] Md Anwarul Azim Majumder, Keerti Singh, Marquita Gittens-St Hilaire, Sayeeda Rahman, Bidyadhar Sa & Mainul Haque (2020) Tackling Antimicrobial Resistance by promoting Antimicrobial stewardship in Medical and Allied Health Professional Curricula, Expert Review of Anti-infective Therapy, 18:12, 1245-1258, DOI: 10.1080/14787210.2020.1796638

[153] Weier N, Thursky K, Zaidi STR (2017) Antimicrobial knowledge and confidence amongst final year medical students in Australia. PLoS ONE 12(8): e0182460. https://doi.org/10.1371/journal. pone.0182460

[154] World Health Organisation (2019). Health Workers' Education And Training On Antimicrobial Resistance [Online]. Licence: CC BY-NC-SA 3.0 IGO https://apps.who.int/iris/bitstream/handle/10665/329380/9789241516358-eng.pdf

[155] Australian Government Department of Health and Department of Agriculture (2019). Consultation Paper: Australia's Antimicrobial Resistance Strategy - 2020 and Beyond [Online].

https://consultations.health.gov.au/ohpd-health-protection-policy-branch/consultation-on-next-amr-strategy/user_uploads/amr-report-accessible-version.pdf

[156] Garau, J., & Bassetti, M. (2018). Role of pharmacists in antimicrobial stewardship programmes. International journal of clinical pharmacy, 40(5), 948–952. https://doi.org/10.1007/s11096-018-0675-z

[157] https://www.amr.gov.au/australias-response/objective-6-strong-collaborative-research-agenda-across-all-sectors

[158] Nawrat, A., & Kent, C. (2019). In the age of AMR, does a nationalised drug company make sense? The case for and against. Pharmaceutical Technology. Retrieved from: https://www.pharmaceutical-technology.com/features/nationalised-drug-company-future-of-pharma/

[159] Daniel, G. W., Schneider, M., Lopez, M. H., & McClellan, M. B. (2018). Implementation of a market entry reward within the united states. The Journal of Law, Medicine & Ethics, 46(1_suppl), 50-58. doi:10.1177/1073110518782915

[160] Seabury, S. & Sood, N. (2017). Toward a new model for promoting the development of antimicrobial drugs. HealthAffairs. Retrieved from: https://www.healthaffairs.org/do/10.1377/hblog20170518.060144/full/

[161] Renwick, M. J., Brogan, D. M., & Mossialos, E. (2016). A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. The Journal of Antibiotics, 69(2), 73-88. doi:10.1038/ja.2015.98

[162] Outterson, K., & McDonnell, A. (2016). Funding antibiotic innovation with vouchers: Recommendations on how to strengthen A flawed incentive policy. Health Affairs (Project Hope), 35(5), 784-790. doi:10.1377/hlthaff.2015.1139

[163] Kesselheim, A. S., Rome, B. N., Sarpatwari, A., & Avorn, J. (2017). Six-month market exclusivity extensions to promote research offer substantial returns for many drug makers. Health Affairs (Project Hope), 36(2), 362-370. doi:10.1377/hlthaff.2016.1340

[164] Buchy P, Ascioglu S, Buisson Y, et al. Impact of vaccines on antimicrobial resistance. Int J Infect Dis. 2020;90:188-196. doi:10.1016/j.ijid.2019.10.005

[165] Tekle YI, Nielsen KM, Liu J, et al. Controlling antimicrobial resistance through targeted, vaccine-induced replacement of strains. PLoS One. 2012;7(12):e50688. doi:10.1371/journal.pone.0050688

[166] Jansen KU, Anderson AS. The role of vaccines in fighting antimicrobial resistance (AMR). Hum Vaccin Immunother. 2018;14(9):2142-2149. doi:10.1080/21645515.2018.1476814

[167] Kurauchi A, Struchiner CJ, Wilder-Smith A, Massad E. Modelling the effect of a dengue vaccine on reducing the evolution of resistance against antibiotic due to misuse in dengue cases. Theor Biol Med Model. 2020;17(1):7. Published 2020 May 13. doi:10.1186/s12976-020-00125-8

[168] O'Neill J. Tackling drug resistant infections globally: Final report and recommendations - The Review on Antibiotic Resistance. United Kingdom 2016.

[169] Chen Z, He Q. Immune persistence after pertussis vaccination. Human Vaccines & Immunotherapeutics. 2017;13(4):744-756. doi:10.1080/21645515.2016.1259780

[170] Rosini R, Nicchi S, Pizza M, Rappuoli R. Vaccines Against Antimicrobial Resistance [published correction appears in Front Immunol. 2020 Jul 21;11:1578]. Front Immunol. 2020;11:1048. Published 2020 Jun 3. doi:10.3389/fimmu.2020.01048

[171] Motley MP, Banerjee K, Fries BC. Monoclonal antibody-based therapies for bacterial infections. Curr Opin Infect Dis. 2019;32(3):210-216. doi:10.1097/QCO.0000000000000539

[172] Yu XQ, Robbie GJ, Wu Y, et al. Safety, Tolerability, and Pharmacokinetics of MEDI4893, an Investigational, Extended-Half-Life, Anti-Staphylococcus aureus Alpha-Toxin Human Monoclonal Antibody, in Healthy Adults. Antimicrob Agents Chemother. 2016;61(1):e01020-16. Published 2016 Dec 27. doi:10.1128/AAC.01020-16

[173] Shin B, Park W. Antibiotic resistance of pathogenic Acinetobacter species and emerging combination therapy. J Microbiol. 2017;55(11):837-849. doi:10.1007/s12275-017-7288-4

[174] Colom J, Batista D, Baig A, et al. Sex pilus specific bacteriophage to drive bacterial population towards antibiotic sensitivity. Sci Rep. 2019;9(1):12616. Published 2019 Aug 30. doi:10.1038/s41598-019-48483-9

[175] Adesanya O, Oduselu T, Akin-Ajani O, Adewumi OM, Ademowo OG. An exegesis of bacteriophage therapy: An emerging player in the fight against antimicrobial resistance. AIMS Microbiol. 2020;6(3):204-230. Published 2020 Jul 22. doi:10.3934/microbiol.2020014

[176] Aslam S, Schooley RT. What's Old Is New Again: Bacteriophage Therapy in the 21st Century. Antimicrob Agents Chemother. 2019;64(1):e01987-19. Published 2019 Dec 20. doi:10.1128/AAC.01987-19

[177] Santajit S, Indrawattana N. Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens. Biomed Res Int. 2016;2016:2475067. doi:10.1155/2016/2475067

[178] Tagliaferri TL, Guimarães NR, Pereira MPM, et al. Exploring the Potential of CRISPR-Cas9 Under Challenging Conditions: Facing High-Copy Plasmids and Counteracting Beta-Lactam Resistance in Clinical Strains of Enterobacteriaceae. Front Microbiol. 2020;11:578. Published 2020 Apr 30. doi:10.3389/fmicb.2020.00578

[179] The European Committee on Antimicrobial Susceptibility Testing [EUCAST], (2019). New definitions of S, I and R. Available online at: http://www.eucast.org/newsiandr/ (accessed August, 2021).

[180] González de Aledo M, González-Bardanca M, Blasco L, et al. CRISPR-Cas, a Revolution in the Treatment and Study of ESKAPE Infections: Pre-Clinical Studies. Antibiotics (Basel). 2021;10(7):756. Published 2021 Jun 22. doi:10.3390/antibiotics10070756

[181] Dildar Ahmed, Kamal Ahmed Qasim, Chaudhary Muhammad Ashraf & Husnul Maab | (2017) Verbena officinalis a herb with promising broad spectrum antimicrobial potential, Cogent Chemistry, 3:1, 1363342, DOI: 10.1080/23312009.2017.1363342

[182] Chen K, Wu W, Hou X, Yang Q, Li A. A review: antimicrobial properties of several medicinal plants widely used in Traditional Chinese Medicine. Food Quality and Safety 2021;5 doi:10.1093/fqsafe/fyab020

[183] Gupta PD, Birdi TJ. Development of botanicals to combat antibiotic resistance. J Ayurveda Integr Med. 2017;8(4):266-275. doi:10.1016/j.jaim.2017.05.004

[184] Anand U, Jacobo-Herrera N, Altemimi A, Lakhssassi N. A Comprehensive Review on Medicinal Plants as Antimicrobial Therapeutics: Potential Avenues of Biocompatible Drug Discovery. Metabolites. 2019;9(11):258. Published 2019 Nov 1. doi:10.3390/metabo9110258

[185] Chassagne F, Samarakoon T, Porras G, Lyles JT, Dettweiler M, Marquez L, Salam AM, Shabih S, Farrokhi DR, Quave CL. A Systematic Review of Plants With Antibacterial Activities: A Taxonomic and Phylogenetic Perspective. Front. Pharmacol. 2021;11:586548. doi: 10.3389/fphar.2020.586548

[186] Jubair N, Rajagopal M, Chinnappan S, Abdullah NV, Fatima A. Review on the Antibacterial Mechanism of Plant-Derived Compounds against Multidrug-Resistant Bacteria (MDR) Hindawi 2021; doi:10.1155/2021/3663315

[187] Vadhana P., Singh B.R., Bharadwaj M., Singh S.V. Emergence of herbal antimicrobial drug resistance in clinical bacterial isolates. Pharm Anal Acta. 2015;6:434.

[188] Gupta P.D., Bhatter P.D., D'souza D., Tolani M., Daswani P., Tetali P. Evaluating the anti Mycobacterium tuberculosis activity of Alpinia galanga (L.) Willd. Axenically under reducing oxygen conditions and in intracellular assays. BMC Complement Altern Med. 2014;14:84.

[189] Shen Q, Zhang L, Liao Z, Wang S, Yan T, Shi P, Liu M, Fu X, Pan Q, Wang Y, Lv Z, Lu X, Zhang F, Jiang W, Ma Y, Chen M, Hao X, Li L, Tang Y, Lv G, Zhou Y, Sun X, Brodelius PE, Rose JKC, Tang K. The Genome of Artemisia annua Provides Insight into the Evolution of Asteraceae Family and Artemisinin Biosynthesis. Mol Plant. 2018 Jun 4; 11(6):776-788.

[190] WHO. Guidelines for the treatment of malaria third edition. WHO (2015). ISBN: 978 92 4 154912 7

[191] Su XZ, Miller LH. The discovery of artemisinin and the Nobel Prize in Physiology or Medicine. Sci China Life Sci. 2015;58(11):1175-1179. doi:10.1007/s11427-015-4948-7

[192] Enright, Mark C et al. "The evolutionary history of methicillin-resistant Staphylococcus aureus (MRSA)." Proceedings of the National Academy of Sciences of the United States of America vol. 99,11 (2002): 7687-92. doi:10.1073/pnas.122108599

[193] Dutescu, Ilinca A, and Sean A Hillier. "Encouraging the Development of New Antibiotics: Are Financial Incentives the Right Way Forward? A Systematic Review and Case Study." Infection and drug resistance vol. 14 415-434. 5 Feb. 2021, doi:10.2147/IDR.S287792

[194] Simpkin VL, Renwick MJ, Kelly R, Mossialos E. Incentivising innovation in antibiotic drug discovery and development: progress, challenges and next steps. J Antibiot (Tokyo). 2017 Dec;70(12):1087-1096. doi: 10.1038/ja.2017.124. Epub 2017 Nov 1. PMID: 29089600; PMCID: PMC5746591.

[195] Renwick, M. J., Simpkin, V. & Mossialos, E. Targeting innovation in antibiotic drug discovery and development: the need for a one-health, one-Europe, one-world framework. European Observatory on Health Systems and Policies, London, UK, Health Policy Series No. 45, 1–133, ISBN 9789289050401 (2016).

[196] Okhravi, C.. Economics of public antibiotics development. Frontiers in Public Health, 8, 161. 2020. https://doi.org/10.3389/fpubh.2020.00161

[197] Addressing the crisis in antibiotic development [Internet]. WHO. 2020 [cited 9 October 2021]. Available from: https://www.who.int/news/item/09-07-2020-addressing-the-crisis-in-antibiotic-development

[198] Australian Antimicrobial Resistance Network (AAMRNet) 2021-2022 Pre-Budget Submission, January 2021 [Internet]. Treasury.gov.au. 2021 [cited 9 October 2021]. Available from: https://treasury.gov.au/sites/default/files/2021-05/171663_australian_antimicrobial_resistance.pdf

[199] Framework for Value Assessment of New Antimicrobials [Internet]. The University of Sheffield & University of New York; 2018. Available from: http://www.eepru.org.uk/wp-content/uploads/2017/11/eepru-report-amr-oct-2018-059.pdf

Appendicies

Appendix 1: Classification and inclusion of notifiable diseases of the Australia Department of Health

- Burden of ill health
    - Adjustments to years lost
- Socioeconomic impact of disease
    - Considers the cost of infection to individuals, organisations and the health care systems. Assessments are usually subjective as economic impact analysis data does not exist.
- Potential threat of disease over the next 5-10years
    - Considers antimicrobial resistance, gaps/shortages in vaccination coverage, changes in environments, endemic areas, agriculture and animal care, and communicability of the disease.
- Health gain opportunity
    - Assesses preventability by potential and availability of vaccines, and potential scope of disease spread by public health response.
- Public concern and confidence
    - Considers interest from Q&A groups, governments, medial, and special interest groups
- WHO/EU interest/Networks/Food Safety Authority interest
    - Considers mandates on collection of information regarding certain diseases [i.e. Cholera, TB] by WHO/EU, and other international organisations.
- Professional interest in notification
    - Whether a professional group would have an interest in notifying.

Appendix 2: Organisms are under surveillance in community settings:

Organism (community setting)	Passive surveillance	Targeted surveillance (current group)
Streptococcus pneumoniae	Yes	Invasive only i.e. blood/cerebrospinal fluids (none)
Haemophilus influenzae	Yes	Invasive type b only i.e. blood/cerebrospinal fluids (none)
Moraxella catarrhalis	Yes	No
Staphylococcus aureus	Yes	Yes (AGAR)
Streptococcus pyogenes	Yes	No
Escherichia coli	Yes	Yes (AGAR)
Salmonella species	No	Yes (NEPSS)
Campylobacter species	No	Yes (NEPSS)

Neisseria gonorrhoeae	No	Yes (NNN)
Neisseria meningitidis	No	Yes (NNN)
Mycobacterium tuberculosis	No	Yes (AMRLN)

Appendix 3: Organisms are under surveillance in hospital settings:

Organism (hospital setting)	Passive surveillance	Targeted surveillance (current group)
Staphylococcus aureus	Yes	Yes –multi-resistant Staphylococcus aureus (AGAR)
Enterococcus species	Yes	Yes –vancomycin resistant enterococci (AGAR)
Escherichia coli	Yes	Yes (AGAR)
Klebsiella species	Yes	Yes (AGAR)
Enterobacter species	Yes	Yes (AGAR)
Acinetobacter species	Yes	Yes –multi-resistant (SA only at present)
Pseudomonas aeruginosa	No	Yes –multi-resistant (SA only at present)
Clostridium difficile	Yes	No

Appendix 4: RACGP commitments to adopt AMR education programs and to implement AMS principles

Objective	Action plan
Community education	• Strengthen consumer awareness to improve understanding AMR and appropriate antibiotic use • Reinforcing key messages to patients and client, increase support for human and animal health professionals • Create action plan to ensure community wide engagement and awareness regarding AMR • Work with NPS, NPSMedicinewise to develop and promote educational resources for appropriate antibiotic use
Clinical governance	• Utilisation of Medicare funding to improve AMR strategies • Removal of OTC topical antibiotics • Call on clinical softwares to remove automatic repeats for antibiotics • Date limit prescriptions to prevent use of antibiotics for other ailments or 2nd dosing • Authority prescription for antibiotics that need reduction in use

GP education	• Increase and strengthen communication and education initiatives for health care members • Ensure availability of tailored and evidence based guideline • Develop tailored and evidence based support of AMS programs • Implement clinical guidelines into prescribing software • Addressing AMR, and AMS in aged care settings • Plans to employ audit and feedback, delayed prescribing, and nudge behaviour techniques
Infection control	• Ensure availability of evidence based, best practice and nationally consistent standards of infection prevention control across human and animal health sectors
Outcome monitoring	• Improve human health surveillance by monitoring antibiotic prescribing activity in primary care • Monitor rates of AMR organisms in Australia • Monitor hospital and ED presentations that may have been triggered by AMR in the community
Research	• Agree on a national research agenda and promote investment in the discovery and development of new products and approaches to prevent, detect, and contain AMR

Policy Details

Name: Antimicrobial Resistance (2021)

Category: G – Global Health

History: Reviewed and adopted, Council 3, 2021
Karan Varshney, Dennis Shen, Samuel Browning, Imogen Bowden, Reece Ansaar, Mansimran Loyal, Anton Vellnagel, Ashraf Docrat, Sally Boardman
Reviewed and adopted, Council 3, 2018
Milla Mclean, Erica Keller, Isobel Dunbabin, Damien Wu, Jessie Zhang, Jonathan Wirth, Rewena Mahesh
Adopted, Council 3, 2014