Episode 100 – Antimicrobial Resistance **January 12, 2024**

Overview

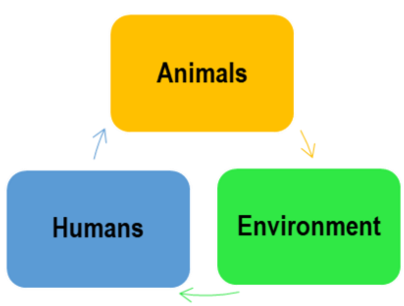
The World Health Organization (WHO) lists antimicrobial resistance (AMR) as one of the top ten threats to global public health. AMR occurs when bacteria, viruses, fungi, and parasites no longer respond to antimicrobial agents. As a result of drug resistance, antimicrobial agents become ineffective, and infections become difficult or impossible to treat, increasing the risk of disease spread, severe illness, disability, side effects from using multiple and stronger medications, and death. [1] [2] [3]

The inability to prevent infections can seriously compromise lifesaving procedures (e.g., chemotherapy, organ transplantation, cesarian section). Drug-resistant infections also impact animal and plant health, farm productivity, and food security. [1] [4]

AMR has significant costs for both healthcare systems and national economies. For example, AMR creates the need for more expensive and intensive healthcare, affects the productivity of affected individuals and their caregivers through prolonged hospital stays, and decreases agricultural productivity. AMR is a problem for all countries at all income levels. Individuals living in low-resource settings and vulnerable populations are especially impacted by both the drivers and consequences of AMR. [4]

AMR is not a new phenomenon. For example, after penicillin was introduced in 1943 for treating often fatal bacterial infections, resistance was observed for *Staphylococcus aureus* by 1948. In 1961, methicillin-resistant *S. aureus* (MRSA) was observed approximately one year after its first clinical use. MRSA infection rates increased rapidly between the 1990s and early 2000s. [5] [6]

Combatting AMR is a global endeavour and must be addressed through a One Health approach. One Health is a multifaceted approach to achieving optimal health for humans, animals, and the environment and recognizing these three sectors are intimately interconnected. [7]



Examples of antimicrobial-resistant pathogens [4] [8] [9] [10] [11] [12] [13]

Pathogen*	Main diseases caused	Reported antimicrobial resistance*
Bacteria		
Clostridioides difficile	Diarrhea Colitis	Aminoglycosides, β-lactams, tetracyclines, macrolides, glycopeptides and quinolones
Extraintestinal pathogenic *Escherichia coli*	Urinary tract infection Bloodstream infection	β-Lactams (including carbapenems), aminoglycosides, tetracyclines and quinolones
Staphylococcus aureus	Surgical site infection Bloodstream infection Skin and soft tissue infection Pneumonia	β-Lactams (e.g., methicillin), aminoglycosides, tetracyclines, macrolides, glycopeptides (e.g., vancomycin), quinolones, lipopeptide and oxazolidinone
Neisseria gonorrhoeae	Gonorrhea Eye infection and disseminated infection	Tetracyclines, β-lactams (including extended-spectrum cephalosporins), fluoroquinolones, sulfonamides and spectinomycin
Pseudomonas aeruginosa	Pneumonia Urinary tract infection Surgical site infection	β-Lactams, aminoglycosides, quinolones and polymyxins
Klebsiella pneumoniae	Pneumonia Meningitis Urinary tract infection Bloodstream infection	β-Lactams (including carbapenems), aminoglycosides and fluoroquinolones
Salmonella enterica subsp. *enterica* serovar Typhi *Salmonella enterica* subsp. *enterica* serovar Paratyphi A	Enteric fever	*Salmonella* Typhi: β-lactams, sulfonamides, chloramphenicol and fluoroquinolones *Salmonella* Paratyphi A: β-lactams, chloramphenicol and fluoroquinolones
Non-typhoidal *Salmonella*	Gastrointestinal disease in high-income countries Bloodstream infection in sub-Saharan Africa	β-Lactams, sulfonamides, chloramphenicol and fluoroquinolones
Shigella species	Moderate to severe diarrhea	Sulfonamides, fluoroquinolones, macrolides, β-lactams and cephalosporins
Group A *Streptococcus*	Pharyngitis	Tetracycline and macrolides

Pathogen*	Main diseases caused	Reported antimicrobial resistance*
	Skin infections Post-streptococcal glomerulonephritis Acute rheumatic fever Rheumatic heart disease	
Mycobacterium tuberculosis	Predominantly pulmonary disease	β-Lactams, fluoroquinolones, aminoglycosides, macrolides, lincosamides, *p*-aminosalicylic acid and pyrazinamide
Fungus		
Candida auris	Invasive candidiasis of the blood (candidaemia), heart, central nervous system, eyes, bones and internal organs	Azole (e.g., fluconazole)
Aspergillus fumigatus	Invasive aspergillosis in the respiratory system, but can disseminate to other organs, particularly central nervous system (e.g., brain)	Azole
Candida albicans	Invasive candidiasis of the blood (candidaemia), heart, central nervous system, eyes, bones and internal organs	Azole
Parasite		
Plasmodium falciparum *P. vivax*	Malaria	Artemisinin, chloroquine, sulfadoxine/pyrimethamine, mefloquine, halofantrine, and quinine Chloroquine
Virus		
Influenza A (H3N2)	Influenza	Adamantanes (e.g., amantadine and rimantadine)
Human immunodeficiency virus (HIV)	Acquired immunodeficiency syndrome (AIDS)	Non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine, efavirenz)

*Nonexhaustive list

Statistics
AMR contributes to almost 5 million deaths from bacterial infections alone each year. In 2019, bacterial AMR was directly responsible for 1.27 million deaths worldwide. Without intervention, AMR could result in up to 10 million deaths a year globally by 2050. Moreover, this burden falls disproportionately on low- and middle-income countries, exacerbating global health inequities. [14] [15]

Because approximately 26% of bacterial infections are currently resistant to first-line antimicrobials,[1] it was estimated resistant bacterial infections were responsible for the deaths of over 14,000 people in Canada in 2018 (about one in 19 deaths). Of these deaths, 5,400 (almost 15 a day) were directly attributable to AMR itself. [16]

AMR is a critical threat in Ontario, with an estimated six lives lost every day due to AMR infections. Approximately one in four antimicrobial courses prescribed to Ontarians is considered unnecessary. Bloodstream infections caused by AMR bacteria increase the odds of death by 30% compared to antibiotic susceptible bacteria. [17] [18] [19] [20]

In addition to death and disability, AMR has significant economic costs. The World Bank estimated AMR could result in $1 trillion USD in additional healthcare costs by 2050, and $1 to $3.4 trillion USD gross domestic product (GDP) losses per year globally by 2030. [4] [21]

The costs to the Canadian healthcare system and GDP are already significant with an estimated $1.4 billion and $2 billion, respectively, in 2018. [22]

Populations at risk
Certain populations in Canada are at an increased risk for acquiring infections and in turn, are at an increased risk of antibiotic resistance. At risk populations include:

- Infants, especially premature babies, due to underdeveloped immune systems.
- Older adults, particularly those living in long-term care or seniors' residences because they:
    - May be exposed to more infections,
    - Are in close contact with many others, and
    - May have a compromised immune system due to illness or extended antibiotic use.
- People who are homeless or living in crowded or unhygienic conditions where it is easy to contract infections.
- Individuals with compromised immune systems due to illness or injury.

The greatest risk factor for acquiring a resistant infection is previous antimicrobial treatment.

At risk groups based on behaviours and settings include those:

- In healthcare facilities, day care centres, or other settings where infections can easily spread, especially if infection prevention and control measures are not followed.

[1] First-line therapy refers to the initial recommended antimicrobial to treat a disease or infection.

- Who do not practice good infection prevention and control behaviours, (e.g., proper hand hygiene).
- Who do not store, handle, or prepare food safely.
- With substance use disorder.
- In occupations with increased exposure risk to bacteria or infectious diseases (e.g., healthcare providers, veterinarians, slaughter house and meat processing plants workers, farmers). [3] [16]

Mechanisms of resistance
AMR is a natural process that occurs over time through adaptive evolutionary genetic changes in pathogens that enable them to withstand antimicrobials. These genetic mechanisms give rise to resistance because they result in biochemical modifications that alter certain bacterial cell properties that normally render the cell sensitive to an antibiotic.

Examples of biochemical modifications include:
- Production of enzymes that inactivate the drug.
- Activation of drug efflux pumps that deliberately remove a drug from the cell.
- Alteration of the protein, enzyme, or receptor targeted by the drug.
- Alteration of cell wall proteins that inhibit drug uptake into the cell. [23]

Genetic mechanisms that can give rise to antibiotic resistance are mutation and acquisition of new genetic material.
- <u>Mutation</u> occurs naturally when cells divide. The rate at which resistance develops can be attributed to the rate at which bacteria mutate. Bacteria are especially prone to mutation because their genome consists of a single chromosome and because they have a high rate of replication. The more replications a cell undergoes, the higher the chance it has to mutate.
- <u>Acquisition</u> of new genetic material appears to be the most common mechanism by which resistance develops. It is facilitated because bacteria are prokaryotic organisms (i.e., they do not have a nucleus protecting the genome) and by the presence of plasmids, small pieces of DNA that exist in a bacterial cell separate from the chromosome. Thus, the genetic material of bacteria is free-floating within the cell, making it open to gene transfer (i.e., movement of a segment of genetic material from one bacterial cell to another), which often involves the transmission of plasmids. [23]

In nature, the primary mechanisms of bacterial gene transfer are transduction and conjugation.
- <u>Transduction</u> occurs when a bacterial virus, called a bacteriophage, detaches from one bacterial cell, carrying with it some of that bacterium's genome, and then infects another cell. When the bacteriophage inserts its genetic content into the genome of the next bacterium, the previous bacterium's DNA also is incorporated into the genome.

- Conjugation occurs when two bacteria come into physical contact with each other and a plasmid is transferred from the donor cell to the recipient cell. Plasmids often carry genes encoding enzymes capable of inactivating certain antibiotics. [23]

Drivers of AMR

Emergence and spread of AMR are accelerated by human activity, mainly the misuse and overuse of antimicrobials to treat, prevent, or control infections in humans, animals (especially those used for food production), and plants. [1] [4]

Examples of antibiotic misuse include:

- Giving antibiotics to people and animals when they are not needed.
- Taking antibiotics in ways other than how they were prescribed.
- Self-medicating or antibiotic sharing.
- Taking antibiotics for an infection not caused by bacteria. [24]

Other contributing factors include:

- Inadequate access to clean water, sanitation, and hygiene for both humans and animals.
- Poor infection prevention and control practices in healthcare, residences, and farms.
- Limited availability to quality, affordable vaccines, medications, and diagnostics.
- Inadequate awareness and knowledge among healthcare providers and the public.
- Inadequate enforcement of legislation to regulate antimicrobial use. [4]

A systematic review and meta-analysis by Auta et al. (2019) on global access to antibiotics without a prescription reported that, across 38 studies from 24 countries, the pooled proportion of nonprescription supply of antibiotics was 62%. Nonprescription supply of antibiotics was highest in South America. The study demonstrate antibiotics are frequently supplied without prescription in many countries. This overuse of antibiotics can facilitate the development and spread of antibiotic resistance. [25]

According to a 2022 survey by the WHO's European Region, a third of individuals in 14 countries (mostly in Eastern Europe and Central Asia) used antibiotics without a prescription. In some of these countries, more than 40% of the antibiotics were obtained without medical advice. In contrast, the equivalent survey conducted across the European Union in 2022 revealed only 8% of participants consumed antibiotics without a prescription.

The survey involved 8,221 participants, half of whom reported taking oral antibiotics in the past 12 months. The reasons cited for taking the antibiotics included colds (24%), sore throat (21%), cough (18%), and flu-like symptoms (16%). These are often caused by viruses unaffected by antibiotics.

Overall, 84% of participants showed a lack of knowledge about appropriate antibiotic use. Only 37% reported receiving any information in the past year about the importance of avoiding unnecessary antibiotic use. A notable proportion (22%) held the misconception that antibiotics can be stopped once they start feeling better. Among respondents who reported having COVID-19, 28% took antibiotics with a prescription, while 8% took antibiotics without a prescription.

Medical expertise is essential to make a correct diagnosis and determine whether antibiotics are the right course of treatment. The research clearly highlights the need for education and raising awareness about antibiotics. All countries in the region have regulations to protect antibiotics from misuse (e.g., preventing over-the-counter sales without a prescription). Enforcing these regulations would help prevent antibiotic misuse. Proactively addressing these challenges can foster a culture of responsible antibiotic use and make major strides in global efforts to combat AMR. [15] [26]

Leftover antibiotics

Personal beliefs and healthcare system barriers contribute to inappropriate antibiotic use, reported researchers who presented at the IDWeek 2023 Annual Meeting.[2]

Shah and colleagues conducted a cross-sectional survey of 564 patients at six primary care clinics and two emergency departments in Houston, Texas to identify motivations to use antibiotics without a prescription. Nonprescription antibiotic use among participants included using antibiotics leftover from a prior prescribed course, obtained from social networks, and purchased over-the-counter in other countries or illegally in United States-based stores and markets.

Participants primarily reported using antibiotics for symptoms of COVID-19, influenza, and the common cold, as well as for pain management, allergies and wounds. Participants used antibiotics to treat symptoms they previously had or because they believed they understood their illnesses and which medications would be the most effective for their bodies. Some participants used antibiotics as an alternative to over-the-counter medications they perceived as ineffective.

Participants documented barriers to healthcare and treatment access, including long wait times to schedule appointments and wait times to see the doctor while at their appointments. Participants struggled with getting transportation to appointments, paying for parking, and affording the associated costs of doctor visits. Many participants opted to use nonprescription antibiotics because they were more convenient than visiting a clinician and were easier to obtain and afford.

The study highlights the importance of providing education on safe antibiotic use, providing alternative treatment options for everyday symptoms, and working to improve access to healthcare and related services. [27]

[2] IDWeek is the joint annual meeting of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. IDWeek is recognized for peer-reviewed presentations of new research on scientific advances and bench-to-bedside approaches in prevention, diagnosis, treatment and epidemiology of infectious diseases. [27]

COVID-19 pandemic
The COVID-19 pandemic may have exacerbated AMR. A rapid review and meta-analysis by Langford et al. (2021) found unnecessary antibiotic use was high in individuals with COVID-19. The results showed the proportion of individuals with COVID-19 receiving an antibiotic was approximately 75%, despite the viral etiology of COVID-19 and low bacterial coinfection (3.5%) and secondary infection (14%) rates in COVID-19. [28]

Antibiotic overuse was common when initial etiology was uncertain while waiting test results and when there were concerns about possible coinfection even once SARS-CoV-2 was identified. Further, the pandemic disrupted antimicrobial stewardship programs due to redeployed staff and competing tasks such as addressing drug shortages, acquiring therapeutic agents, and developing COVID-19 guidelines. [29]

A systematic review and meta-analysis by Langford et al. (2023) indicated as many as 60% of individuals that had bacterial infections and COVID-19 harbour an antibiotic resistant organism. [30]

A 2022 special report from the US Centers for Disease Control and Prevention found a 15% increase in AMR in a number of microorganism species, including carbapenem-resistant *Acinetobacter*, MRSA, carbapenem-resistant Enterobacterales (CRE), multidrug-resistant *P. aeruginosa*, and antifungal-resistant *Candida auris* associated with the pandemic. Overall, research demonstrates antimicrobial stewardship efforts are urgently needed to help mitigate the impact of COVID-19 on AMR. [31]

Oral healthcare
It is important to consider the role dentistry plays in AMR, since dentists prescribe 10% of all antibiotics dispensed worldwide, and research has shown up to 80% of antibiotics prescribed by dentists may be unnecessary. [32] [33]

A scoping review by Stein et al. (2018) found dentists regularly prescribed antibiotics for inappropriate purposes, such as:

- Administering prophylactic doses to healthy clients.
- Treating oral infections with systemic antibiotics when localized treatment would suffice.
- Prescribing antibiotic prophylaxis for cardiac conditions no longer included in the guidelines.[3]
- Prescribing antibiotics to clients who were underinsured rather than completing recommended surgical treatment because of affordability issues.

The study provides insight into the importance of antibiotic stewardship in the oral health setting, and encourages dentists to reflect on their antibiotic prescription practices. [34]

[3] Refer to Episodes 23 and 37 for antibiotic prophylaxis for the prevention of infective endocarditis or prosthetic joint infection.

Ramanathan et al. (2023) found no change in US dental antibiotic prescribing rates from 2012 to 2019, despite changes in guidelines and decreases in national medical antibiotic prescribing. During the study period, 216 million antibiotics were prescribed by 241,106 dentists, with a majority going to male clients (55%) and those aged 40 to 64 years (42%). Amoxicillin and clindamycin were the most frequently prescribed antibiotics, making up 63% and 14% of prescriptions, respectively.

The average provider-based prescribing rate for all antibiotics was 142,155 prescriptions per 1,000 dentists per year. Dental specialties, especially oral and maxillofacial surgeons, had the highest prescribing rate with increases over time. The authors concluded antibiotic stewardship efforts to improve unnecessary prescribing by dentists, particularly targeting dental specialists, may decrease overall dental antibiotic prescribing rates. [35]

Data from British Columbia, Canada indicated during a ten-year period, antibiotic prescriptions by physicians decreased by 18%, while prescriptions by dentists increased by 62%. Explanatory themes for dental antibiotic prescribing included:

- Unnecessary prescriptions for periapical abscess and irreversible pulpitis.
- Increased prescribing associated with dental implants and their complications.
- Slow or incomplete adoption of guidelines calling for less perioperative antibiotic coverage for clients with valvular heart disease and prosthetic joints.
- Emphasis on cosmetic practices reducing the surgical skill set of average dentists.
- Underinsurance practices driving antibiotics to be a substitute for clinical dentistry.
- Aging population. [36]

Data from a 2017 survey of Canadian dentists indicated there was misunderstanding by dentists on both the cardiac conditions and the dental procedures requiring antibiotic prophylaxis to prevent infective endocarditis. There was also:

- A lack of awareness of changes to antibiotic guidelines for total joint replacement;
- Variation in prescribing practices among dentists for antibiotic prophylaxis for the prevention of surgical site infections;
- Use of antibiotics for conditions where antibiotics were not necessary; and
- General overuse of clindamycin and underuse of penicillin V. More than 80% prescribed clindamycin for clients who reported a penicillin allergy. Note: Overuse of clindamycin (a broad-spectrum antibiotic) can promote AMR and *C. difficile* infection. To minimize use of clindamycin, clients should be encouraged to receive testing for penicillin allergy considering a true penicillin allergy is rare. [37] [38] [39]

Recent data show more than 80% of antibiotics prescribed for prophylaxis before oral health visits were unnecessary despite guidelines limiting antibiotic prophylaxis to high-risk individuals. [40]

Inappropriate antibiotic prescribing for oral health appointments costs millions annually according to a modelling study by Gong et al. (2023). The researchers estimated the costs associated with this practice and assessed its impact from a healthcare payer perspective. The researchers used 2018 US Census data on adults aged ≥18 years who had a dental visit with an antibiotic prescribed.

Inappropriate dental antibiotic prescriptions to prevent infective endocarditis resulted in approximately $31 million in excess costs to the healthcare system and clients annually. This included out-of-pocket costs ($20.5 million), drug costs ($2.69 million), and adverse event costs (e.g., *C. difficile* and hypersensitivity) of $5.82 million for amoxicillin, $1.99 million for clindamycin,[4] and $380,849 for cephalexin. Addressing the issue of inappropriate antibiotic use in dentistry is crucial to reduce the burden of preventable adverse effects, healthcare costs, and antibiotic resistance. [41]

Client pressure

Antibiotic prescribing by dentists can be influenced by client pressure. Al-Khatib and AlMohammad (2022) evaluated dentists' antibiotic prescribing habits and the frequency of facing client pressure for prescriptions. One third of participants reported being pressured by clients to prescribe unnecessary antibiotics more than once per week, while 22% reported parents pressuring them to prescribe unnecessary antibiotics for their children. The authors recommended educating dentists on how to respond to clients' requests for antibiotic prescriptions to minimize unnecessary antibiotic use. [42]

Ineffective usage of the healthcare system for nontraumatic dental conditions

Research has shown a significant number of people in Canada, including Ontario, visit physicians' offices and emergency departments for their dental concerns. Individuals seeking care for nontraumatic dental conditions from these settings usually receive only prescription medications, including antibiotics and opioid pain killers, which most often do not address the cause of the problem. The clinical situation may worsen from delayed treatment and repeated antimicrobial usage, requiring more specialized care. Individuals are also at risk of developing resistance to antimicrobials and dependence on pain medications. [43]

Oral healthcare and COVID-19

The COVID-19 pandemic had a profound impact on oral healthcare worldwide. Deferred care during the early months of the pandemic created a huge backlog of needed oral health treatment. During the months of virtual triage or office closures, with only very urgent care provided in person, antibiotics were often prescribed more readily and for longer duration. Data have demonstrated dentist-driven prescriptions added to the global increase in antibiotic prescribing as a result of the pandemic.

Antibiotic prescribing in UK oral healthcare practices had been slowly declining in the years before the COVID-19 pandemic, but restricted access to oral healthcare led to increased levels of prescribing. Reasons for increased prescribing were probably multifactorial, adding that swelling and pain were the most common primary reasons for

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[4] Note: Clindamycin was removed from the 2021 update to the American Heart Association infective endocarditis prophylaxis guidelines. Clindamycin may cause more frequent and severe reactions than other antibiotics used for antibiotic prophylaxis. Clindamycin substantially increases the risk of developing *C. difficile* infection even after a single dose. [95]
Symptoms of *C. difficile* include watery diarrhea, fever, loss of appetite, nausea, and abdominal pain/tenderness. It can also cause life-threatening pseudomembranous colitis, bowel perforation, sepsis, and death. [94]

antibiotic dispensing and that dentists may have felt less confident diagnosing and treating acute pain remotely. [44]

During the first wave of the COVID-19 pandemic in Alberta, Canada, reduced provision of oral health procedures was accompanied by an increase in drug prescribing. The leading drug prescription increases occurred during April-May 2020, when access to care was most restricted, with antibiotics at 300% and nonopioid analgesics at 738% higher than the same time in 2019. [45]

Mian et al. (2021) investigated prescribing trends for dental medications in Australia over the COVID-19 pandemic. Total prescriptions during the lockdown period fell, reflecting a reduction in total oral healthcare visits. Use of antibiotics and opioid analgesics during this period remained relatively high, consistent with an increased use of these medications as an alternative to routine clinical treatment to reduce COVID-19 transmission. Following easing of service restrictions, prescriptions for broad-spectrum antibiotics and opioid analgesics increased, which may reflect clinical deterioration from delayed treatment during the lockdown period. [46]

Oral impact

Meinen et al. (2021) isolated bacterial pathogens from individuals with odontogenic infections and analyzed their resistance to antibiotics. It was observed that the most frequently found microorganisms, *Streptococcus spp* (36%) and *Staphylococcus spp* (12%), were resistant to penicillin and aminopenicillin in 6.9% and 5.8% of strains, respectively. In addition, more than 17% showed resistance to clindamycin and macrolide antibiotics. The substantial antibiotic resistance observed in isolates from odontogenic infections calls for strengthened efforts in antibiotic stewardship and infection prevention and control measures in oral healthcare. [47]

Clindamycin has been used in dentistry for decades to treat *Porphyromonas gingivalis* related conditions, from periodontitis to periodontal abscesses. However, evidence collected over 20 years shows *P. gingivalis* may be developing resistance to this antibiotic. Rams et al. (2023) evaluated pretreatment subgingival biofilm samples from three sets of US participants with severe periodontitis from three different time periods: 1999–2000, 2009–2010, and 2019–2020.

The results indicated:

- Clindamycin-resistant *P. gingivalis* increased significantly from 0.6% of participants in 1999–2000 to 9.3% (15-fold increase) in 2019–2020.
- *P. gingivalis* resistance to amoxicillin also significantly increased from 0.1% of participants in 1999–2000 to 2.8% (28-fold increase) in 2019–2020.
- *P. gingivalis* resistance to metronidazole, metronidazole plus amoxicillin, and doxycycline was low (≤0.5% prevalence), and statistically unchanged, over the 20-year period.

The authors noted the prevalence of antibiotic-resistant *P. gingivalis* and other periodontal pathogens varies considerably between countries and geographic regions, underscoring the need for region-specific monitoring of antibiotic resistance trends among periodontopathic bacterial species. The authors concluded increased antibiotic resistance of *P. gingivalis* and other periodontitis-associated bacteria threatens the efficacy of periodontal antimicrobial therapy. [48]

D'Ambrosio et al. (2022) evaluated adherence to oral antibiotic therapy and AMR awareness among oral healthcare clients. Clients generally showed a low (52%) adherence to oral antibiotic therapy, and medium and high adherence was reported only by 29% and 19% of participants, respectively. Level of adherence to antibiotic therapy was positively associated with a higher education level. AMR awareness was higher in younger (56%) participants (18-36 years) and was positively associated with higher education.

Given that adherence to antibiotic treatment is necessary to make the therapy effective and reduce the impact of AMR, interventions to increase clients' knowledge of antibiotic therapy and AMR may improve their adherence to treatment. [49]

However, the term "antimicrobial resistance" held little meaning to the public and may need to be renamed according to a recent study by Krockow et al. (2023). The study looked at word memorability and risk association for six most frequently used terms to describe AMR, including:

- Antimicrobial resistance,
- AMR,
- Antibiotic resistance,
- Bacterial resistance,
- Drug-resistant infections, and
- Superbugs.

A total of 237 US and 924 UK participants were tested on memory for and the risk they associated with each term on a scale ranging from very safe to very risky. Results showed "AMR" and "antimicrobial resistance" were among the lowest-scoring terms for both risk association and memorability and therefore unsuitable for public health communication. However, the terms "antibiotic resistance" and to a lesser extent "drug-resistant infections" performed better.

Participants generally found it difficult to remember words associated with AMR and did not think they sounded risky compared to other health risk words. Future risk communication might benefit from renaming AMR to better signal the severity of the problem and motivate behaviour change. [50]

Chlorhexidine and AMR

Chlorhexidine (CHX) is a widely used biocide in clinical and household settings.
It is a bisbiguanide agent with broad-spectrum antimicrobial activity against gram-positive and gram-negative bacteria, plus fungi and certain viruses. The antimicrobial effect of chlorhexidine is dose-dependent, being bacteriostatic (inhibits bacterial growth) at low concentrations (0.02%-0.06%) and bactericidal (kills bacteria) at high concentrations (>0.1%). [51] [52] [53] [54]

CHX is used in medicine for preoperative skin disinfection, decontamination of skin and mucous membranes in intensive care units, impregnation of medical devices (e.g., catheters), and disinfection of inanimate surfaces. In addition. CHX is used in oral care in mouthrinses (0.12% and 0.2%), toothpastes, gels, varnishes, and sprays. [51] [52]

CHX mouthrinse is one of the most used mouthrinses in oral care to reduce the bacterial load in the oral cavity to control or prevent oral infections. CHX exerts its bactericidal properties through an increase in cell membrane permeability, which causes lysis, loss of intracellular material, and bacterial cell death. [55]

Research has shown no significant changes in bacterial sensitivity, overgrowth of potentially opportunistic organisms, or other adverse changes in the oral microbial flora following the use of chlorhexidine gluconate mouthrinse 0.12% for six months. Three months after use was discontinued, the number of bacteria in plaque had returned to pretreatment levels, and sensitivity of plaque bacteria to chlorhexidine gluconate remained unchanged. [56]

However, studies over the last few decades have reported CHX resistance in different bacterial species, but at concentrations well below those used in the clinical setting. Meanwhile, studies of *in vitro* CHX-adapted bacteria have reported cross-resistance between CHX and other antimicrobials. While clinical studies to support the hypothesis of CHX cross-resistance with antibiotics are currently lacking, it is important oral health practitioners understand that appropriate clinical use of CHX should be oral disease specific. [51] [54]

Triclosan and AMR

Triclosan is a broad-spectrum antimicrobial additive in a wide range of consumer products, such as:

- Hand sanitizers
- Fragrances, deodorants, face makeup
- Natural health products
- Toothpaste and mouthwash
- Soaps, skin cleansers, lotions, and shampoos [57]

It is added to products to:

- Act as a preservative
- Help prevent odours
- Kill bacteria
- Stop the growth of bacteria and fungus [57]

Canada regulates cosmetics, nonprescription drugs, and natural health products. The maximum amount of triclosan allowed is:

- 0.03% in mouthwashes
- 1.0% in nonprescription drugs
- 0.3% in cosmetics and natural health products [57]

In 2016, Health Canada assessed the potential health and environmental risks of triclosan. From the assessment, they found triclosan poses a risk to the environment when products containing triclosan (e.g., toothpaste, soap) are washed down the drain. The amount of triclosan that is released can pose a risk to plants, fish, and animals in lakes, streams, and rivers, affecting growth, reproduction, and survival. The government found no clear link between use of products containing triclosan and antibacterial resistance. [57] [58]

However, a study by University of Toronto researchers Barrett et al. (2022) found triclosan maybe contributing to antibiotic resistance in Canada. The study investigated sewage sludge from Ontario's sewage treatment plants and found triclosan was the predominant antibacterial compound impacting *E. coli*.

Sewage treatment plants are a breeding ground for antibiotic resistant bacteria due to the diverse set of antibiotics found there. Products containing antibiotic ingredients are rinsed down the drain and transported to sewage treatment plants where they accumulate and may interact with bacteria and cause the development of antibiotic resistance.

In 2016, the US Food and Drug Association banned triclosan use in antibacterial liquid soaps, and, a year later, from being used in topical antiseptics found in healthcare settings. Currently, there are limited regulations on triclosan in Canada, and Health Canada deemed triclosan safe for use in a variety of consumer products at specified levels. The results of the Ontario study demonstrate an urgent need for regulatory agencies in Canada to reevaluate the use of triclosan. [59] [60]

Staphylococcus aureus

Staphylococci are gram-positive aerobic organisms. The *Staphylococcus* genus consists of 70 species and subspecies, from which the majority are common colonizers of the human skin and mucous membranes of the nose and mouth. *Staphylococcus aureus* is the most pathogenic staphylococci bacteria. It is considered a High Priority Pathogen by the WHO in which new antibiotics are urgently needed due to causing severe infections worldwide and to the rise and emergence of strains resistant to clinically relevant antibiotics. [61] [62] [63]

S. aureus typically causes skin infections, such as folliculitis, impetigo, and often causing abscesses. *S. aureus* can also cause pneumonia, endocarditis, osteomyelitis (bone infection), septicemia (bloodstream infection), sepsis, and death. The bacteria also tend to accumulate on medical devices in the body, such as artificial heart valves or joints, heart pacemakers, and catheters inserted through the skin into blood vessels.

Treatment is usually with penicillinase-resistant β-lactams, but because antibiotic resistance is common, vancomycin or other newer antibiotics may be required. Usually, infected bone and foreign material (e.g., pacemaker, artificial joint) have to be removed surgically to cure the infection. Abscesses, if present, are usually drained.

A carrier state is common. Carriers are individuals who have the bacteria but do not have signs of infection. The bacteria are carried in the anterior nares (nose) of about 30% of people and on the skin of about 20%. From these locations, staphylococci can cause infection in the host and others. Carriage rates are higher in hospitalized patients and hospital personnel. *S. aureus* infections are more prevalent in carriers than in noncarriers. *S. aureus* recurs in up to 50% of carriers and frequently becomes resistant. [64] [65] [66]

Many *S. aureus* strains have developed resistance to antibiotics. If carriers take antibiotics, the antibiotics kill the strains that are not resistant, leaving mainly the resistant strains. Methicillin-resistant *Staphylococcus aureus* (MRSA) is used to describe strains of *S. aureus* that have acquired resistance to β-lactam antibiotics (e.g., methicillin, penicillin, amoxicillin, cephalosporins, etc.). About 2% of people carry MRSA.

MRSA strains are common in healthcare-acquired (nosocomial) infections. Some strains of MRSA cause community-acquired infections, including mild abscesses and skin infections that may look like a pimple or boil, which can be red, swollen, painful, or have pus or other drainage. Community-acquired infections are becoming more common. [64] [66] [67]

MRSA can spread by direct contact with an infected person or via contaminated objects (e.g., gym equipment, towels, phones, door knobs, television remote controls, elevator buttons), or, less often, by inhaling infected droplets dispersed by sneezing or coughing.

In healthcare settings, MRSA is typically spread from patient to patient on unclean hands of healthcare personnel or through the improper use or reuse of equipment.

Risk factors for MRSA include:

- History of MRSA infection or colonization
- Recent and/or frequent antibiotic use
- Sports participants who have skin-to-skin contact, skin damage, shared clothing or equipment
- Living in crowded or unsanitary conditions
- Men who have sex with men
- Injection drug use
- Hospitalization
- Having an invasive medical device (e.g., intravenous line, urinary catheter)
- Residing in a long-term care facility
- Close contact with someone known to be infected or colonized with MRSA
- Recurrent skin disease [68] [69] [70]

Preventing healthcare-associated MRSA

- Ensure appropriate hand hygiene (soap and water or alcohol-based hand sanitizer) along with other appropriate infection prevention and control practices.
- In some healthcare facilities, people are routinely screened for MRSA when they are admitted. Some facilities only screen those at increased risk of MRSA infection (e.g.,

prior to certain operations). Screening involves testing a nasal swab sample. If MRSA strains are detected, the person is isolated to prevent spread of the bacteria until the infection is cured. [65] [71]

Preventing community-associated MRSA includes:
- Practising thorough hand hygiene.
- Avoid sharing personal items (e.g., towels, razors, etc.).
- Showering after exercising or participating in sports.
- Keeping cuts, scrapes, and wounds clean and covered until healed.
- Seeing a medical provider for early diagnosis and treatment if an infection is suspected. [67] [68] [69]

Oral MSRA
S. aureus is considered a commensal as well as pathogen. As a commensal, *S. aureus* is principally isolated from the anterior nares, although it colonizes other anatomical sites, including the oral cavity and tonsillar crypts. Oral *S. aureus* may originate in the oral cavity or they could transit to the mouth from the nares via the oropharynx. Prevalence of oral *S. aureus* tends to vary by population. Reports indicate a prevalence of 24-84% in healthy dentate adults, and 48% in denture wearers. [72] [73]

Reports indicate high *S. aureus* and MRSA carriage rates in the oral cavity. Although it is unclear whether these reported high rates are due to increased focus on *S. aureus* and MRSA. MRSA oral carriage may constitute a reservoir for subsequent colonization of other body sites or for cross-infection to other people. Evidence from several studies indicate MRSA appears to preferentially colonize denture surfaces, which then may act as a source of infection to distant sites (e.g., aspiration pneumonia), cross-infection, or recolonization. MRSA organisms are sometimes very difficult to eradicate from dentures, requiring certain antimicrobial agents (e.g., 2% chlorhexidine, 1% sodium hypochlorite), microwave irradiation, or fabrication of new prostheses. [72] [74] [75] [76]

Research involving an elderly veteran population in an extended care facility demonstrated that 19% had MRSA oral carriage, whereas 20% were nasal carriers. Of interest, 4% of the proven MRSA oral carriers were culture negative for nasal carriage. This observation partly explains why decolonization exercises that target nasal carriage alone may fail. [72] [77]

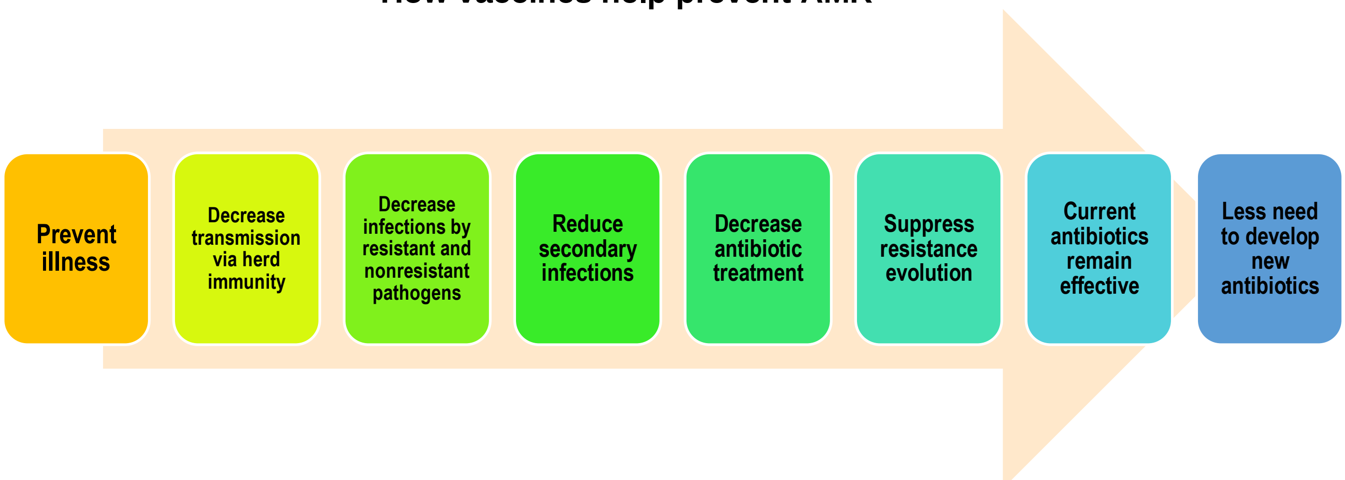
S. aureus is implicated in several infective oral pathologies, including angular cheilitis, parotitis, and mucositis (with erythema, swelling, pain or burning of the oral mucosa), and also in dental implant failure. Generally, very few studies have reported on MRSA clinical infections in the oral cavity, and were inconclusive as to whether the isolation of MRSA reflected disease or carriage. [72] [75] [78]

Role of vaccines in AMR
Addressing AMR begins with preventing infections. Vaccines are important in the fight against AMR. Vaccines directly block the transmission of pathogens that cause infections. Decreasing transmission decreases the number of infections and reduces the chance of a pathogen mutating to a drug resistant form. In addition, individuals

protected by vaccines are less likely to get sick as often, which helps reduce the overall consumption of antibiotics. Since antibiotics are often inappropriately prescribed for viral infections (e.g., influenza), vaccines against these viral infections could reduce inappropriate antibiotic use and help prevent AMR. [79]

Vaccines as tools to reduce AMR have been well established. For example, *Haemophilus influenzae* type B (Hib) and *Streptococcus pneumoniae* (pneumococcal) conjugate vaccines not only prevent life threatening diseases caused by these bacteria, but also reduce antibiotic use and AMR. [5]

How vaccines help prevent AMR



Vaccine hesitancy

The WHO recognizes vaccine hesitancy as one of the ten major global public health threats. Vaccine hesitancy, the reluctance or refusal to vaccinate despite the availability of vaccines, threatens to reverse progress made in tackling vaccine-preventable diseases. Vaccination is one of the most cost-effective ways of avoiding disease. Vaccination currently prevents 2-3 million deaths a year, and a further 1.5 million could be avoided if global coverage of vaccinations improved. [1]

Reasons why individuals choose not to vaccinate are complex. Complacency, inconvenience in accessing vaccines, and lack of confidence are key reasons underlying hesitancy. Healthcare workers remain the most trusted advisor and influencer of vaccination decisions. [1]

Role of oral health practitioners

Oral health practitioners have the potential to assist with vaccination education. A study by Steinbaum et al. (2023) assessed clients' attitudes toward oral health practitioners' roles in HPV and vaccinations. This study verified client willingness to consider education, recommendations, and administrations of vaccines from oral health practitioners, including those for COVID-19 and HPV. [80]

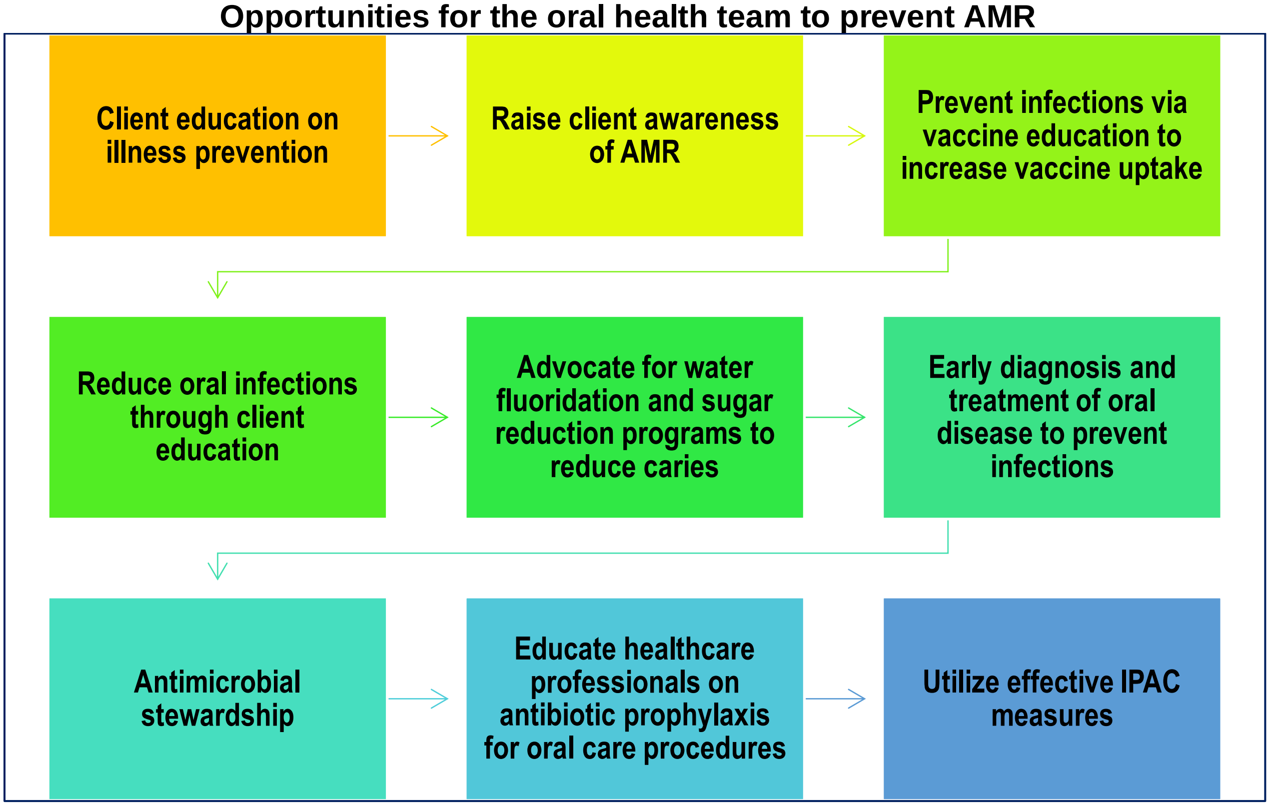
Research has also shown parents are comfortable discussing vaccines available for their children with both their child's dentist and dental hygienist. Oral health practitioners are trusted healthcare professionals poised to make a positive impact on youth vaccination programs. Overall, oral health practitioners have the opportunity to support clients and provide a larger platform for vaccine education. [81] [82]

Tackling AMR in oral healthcare

Opportunities for the oral health team to tackle AMR include:

- Educating clients, family, and friends on how to reduce risk of becoming ill (e.g., hand hygiene, safe food practices, etc.).
- Raising client and public awareness and understanding about AMR, including responsible use of antibiotics.
- Preventing infections by increasing vaccine uptake through client education.
- Reducing the incidence of oral infections through client education on oral self-care, healthy eating, and oral disease prevention.
- Advocating for reduced sugar consumption (e.g., through sugar taxes) and water fluoridation programs to help reduce dental caries.
- Early diagnosis and treatment of oral disease to prevent infections and reduce the need for antibiotics.
- Optimizing antibiotic use through effective stewardship (e.g., following evidence-based guidelines on antibiotic use in oral healthcare).
- Educating medical professionals on antibiotic prophylaxis for oral care procedures.
- Utilizing effective infection prevention and control (IPAC) measures in oral healthcare (e.g., hand hygiene, personal protective equipment, equipment sterilization, appropriate handling of contaminated equipment, materials, and surfaces; safe injection practices; and safe handling of sharps). [33] [70] [83] [84]

Opportunities for the oral health team to prevent AMR



Responsible use of antibiotics
Remind clients not all illnesses can or should be treated with antibiotics. If antibiotics are prescribed, recommend they use them responsibly. For example,

- Take antibiotics only as directed by a healthcare provider (e.g., when to take them; correct dosage, and for how long) and complete the antibiotic treatment, even if symptoms improve, to prevent the emergence of resistance.
- If told to stop taking antibiotics by a healthcare provider, return unused antibiotics to a pharmacy for safe disposal.
- Do not use leftover antibiotics; share antibiotics; or use antibiotics prescribed for someone else.
- Tell their healthcare provider if they experience a bad reaction or side effect. [85]

Antimicrobial stewardship
Antimicrobial stewardship is the appropriate use of antimicrobials to optimize clinical outcomes, combat resistant infections, avoid adverse drug events, and minimize costs. It means prescribing the right antimicrobial, only when needed and for only as long as needed. [86]

An accurate diagnosis should be obtained and the specific antibiotic for the bacterium causing the infection should be used, rather than broad-spectrum antibiotics. The appropriate dosage should be used for the shortest possible time required to eliminate the bacteria causing the infection to help lessen AMR, as well as reduce side effects and costs. [55]

Evidence-based guidelines
The American Dental Association (ADA) has developed the ‘Evidence-based clinical practice guideline on antibiotic use for the urgent management of pulpal- and periapical-related dental pain and intraoral swelling.’

Key points of the guideline include:

- Not using antibiotics for most pulpal and periapical conditions and instead recommends only using dental treatment and, if needed, over-the-counter pain relievers (e.g., acetaminophen and ibuprofen).
- Instead of prescribing antibiotics, prioritizing dental treatments (e.g., pulpotomy, pulpectomy, nonsurgical root canal treatment, or incision and drainage) for symptomatic irreversible pulpitis, symptomatic apical periodontitis, and localized acute apical abscess in adult clients who are not severely immunocompromised.
- Prescribing antibiotics if a client’s condition progresses to systemic involvement, showing signs of fever or malaise. [87] [88]

In 2020, the European Federation of Periodontology (EFP) developed an S3-level clinical treatment guideline for stages I to III periodontitis based upon a rigorous standardized process. The guideline states due to concerns about client health and the impact of systemic antibiotic use to public health, the routine use of antibiotics as an adjunct to subgingival debridement in clients with periodontitis is not recommended. However, based on the available evidence, the adjunctive use of specific systemic antibiotics may be considered for certain client categories (e.g. generalized periodontitis stage III in young adults). Importantly, these clients should be referred to a periodontist if systemic antibiotics are being considered.[5] [89] [90]

In order to improve antimicrobial use in humans globally, WHO developed the Access, Watch, Reserve (AWaRe) antibiotic book. The publication contains evidence-based guidance on the optimal treatment for over 30 common infections in children and adults, including oral and dental infections.[6] [4]

Novel research

An integrated strategy is required to combat AMR effectively. This includes developing:

- Novel antibiotics.
- Next generation vaccines (e.g., using novel adjuvants to improve immune response).
- Rapid diagnostic tools to identify the cause of microbial infections and to determine antimicrobial susceptibility to inform treatment strategy.
- Monoclonal antibodies to address bacterial infections by targeting molecules specific only for pathogenic bacteria safeguarding the microbiota, activating the body's immune system resulting in a broader and more effective response, and reducing the toxicity associated with high antibiotic doses.
- Microbiota interventions to establish a healthy microbiome to prevent opportunistic bacteria from causing infections.
- Phage therapy to tackle AMR and emerging infectious disease. Bacteriophages (phages) are highly specific viruses that infect bacteria. Phage therapy uses active phages to kill bacteria that cause human diseases, while leaving other bacteria unaffected. [8] [91] [92]

Barbour et al. (2023) discovered a new biotherapeutic molecule, patented as salivaricin 10 (Sali10), produced by a strain of oral probiotic[7] bacteria called *Streptococcus salivarius*, that kills infectious pathogens while promoting a healthy microbiome. This discovery provides opportunity for an alternative to conventional antibiotic treatments and is a novel solution to prevent infectious diseases. For example, Sali10 exhibited potent antimicrobial activity against a wide range of gram-positive bacteria, including opportunistic pathogens such as multidrug-resistant *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, vancomycin-resistant *Enterococcus faecium*, and multidrug-resistant *Enterococcus faecalis* clinical isolates. Importantly, Sali10 also possessed antibacterial activity against selected gram-negative disease-associated bacteria, including *P. gingivalis*, *Tannerella forsythia,* and *Neisseria gonorrhoeae*.[8] [93]

Take home messages

- AMR threatens the effective prevention and treatment of an increasing range of infections. The inability to treat resistant infections results in increased illness and

[5] Refer to Episode 49 for discussion on the classification of periodontal diseases and Episode 50 for additional information on the *EFP S3 level clinical practice guideline*.
[6] The WHO AWaRe (Access, Watch, Reserve) antibiotic book. Refer to chapter 8 for information on oral and dental infections. https://www.who.int/publications/i/item/9789240062382
[7] Refer to Episode 63 for additional information on probiotics and the oral microbiome.
[8] Refer to Episode 98 for discussion with Dr. Barbour on this novel research.

deaths and makes routine medical procedures riskier. Treating resistant infections also has economic consequences, including increased healthcare costs, prolonged hospital stays, and time off work.

- The potential benefit of antibiotic administration must be weighed against the risk of side effects, such as severe allergic reactions and anaphylaxis, and infections caused by *C. difficile*.
- Exposing clients to antibiotics when not necessary (e.g., “just in case” or to meet client demands) increases the risk antibiotics will fail when they are truly necessary. It also increases the risk bacteria resistant to antibiotics will spread to the client's families, friends, and others. Before every decision to prescribe antibiotics, care must be taken to assess the risk of antibiotic resistance developing for the individual client as well as spreading more widely across society.
- By preventing oral infections, raising awareness about AMR, and optimizing the use of antibiotics through stewardship, oral health professionals can protect individual clients and society in general.

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https://www.canada.ca/en/public-health/services/antibiotic-antimicrobial-resistance/antibiotic-resistance-awareness-materials/help-reduce-antibiotic-resistance.html

Help reduce antibiotic resistance poster, Government of Canada
https://www.canada.ca/en/public-health/services/antibiotic-antimicrobial-resistance/antibiotic-resistance-awareness-materials/help-reduce-antibiotic-resistance.html

Germs and antibiotics, Government of Canada
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Germs and antibiotics poster, Government of Canada
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Antibiotic Quiz
https://antibioticwise.ca/quiz/

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Viruses or Bacteria What's got you sick? Centers for Disease Control and Prevention
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