Antibiotic resistance and relevance to general dental practice in Australia

Leanne Teoh,* Kay Stewart,† Rodrigo Marino,* Michael McCullough*

**Melbourne Dental School, University of Melbourne, Carlton, Victoria, Australia.*

†Centre for Medicine Use and Safety, Monash University, Parkville, Victoria, Australia.

ACKNOWLEDGEMENTS

This work was supported by the Australian Government Research Training Program Scholarship. The authors have no conflict of interest.

Address for correspondence:

Professor Michael McCullough

Melbourne Dental School

The University of Melbourne

720 Swanston Street

Carlton VIC 3010

Australia

Email: m.mccullough@unimelb.edu.au

DR. LEANNE TEOH (Orcid ID : 0000-0002-9138-813X)

Article type : Review Article (non-solicited)

ABSTRACT

Antibiotic resistance is a well-established global public health crisis, with the use and misuse of antibiotics being the principal cause of bacterial resistance. Studies in both Australia and overseas have demonstrated that the dental prescribing of antibiotics is increasing, and that dentists tend to prescribe antibiotics unnecessarily and for incorrect clinical indications. Dental practitioners in Australia also prefer to prescribe moderate to broad spectrum antibacterial agents and make some inappropriate antibiotic prescribing choices. This review aims to inform dentists about the overall scope and development of bacterial resistance, approaches and challenges to reducing resistance and, ultimately, the role of dental prescribers in practising with optimal antibiotic stewardship.

Keywords: antibiotic resistance, dental, prescribing, Australia, stewardship

Introduction

In 1928, the first antibiotic, penicillin, was discovered by Sir Alexander Fleming and represented a breakthrough in medicine to treat infectious diseases. Sir Howard Florey and Ernst Chain subsequently succeeded in developing a pure, stable form of penicillin for pharmaceutical use and developed the large-scale production of penicillin more than a decade later.[1] The discovery of several other antibiotics occurred over the following decades. Interestingly, with considerable foresight, in 1945, Fleming expressed his concern about the overuse of antibiotics: "The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out… In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism."[2] Fleming was one of the first people to identify the concept of what we refer to today as antibiotic resistance. Over time, the emergence of resistant strains of bacteria to penicillin and other antibacterials has been such that some bacterial species are now resistant to nearly all antibiotics.[3] The most well-known bacterium with extensive resistance is methicillin-resistant Staphylococcus aureus (MRSA).[4] Resistance by other species, such as vancomycin-resistant Enterococcus (VRE), is also increasing,[3] with Australia having one of the highest rates of vancomycin resistant E. faecium in the world.[5] Other bacteria that have developed resistance to multiple antibiotics also include strains of E. faecalis (a bacteria which is predominately a normal commensal of the gut flora but also is one of the common bacteria isolated from obturated root canal systems with failed endodontic treatment),[6] Mycobacterium tuberculosis and Pseudomonas aeruginosa.[3] Infections caused by drug resistant bacteria were responsible for an estimated 50,000 deaths in the European Union and the United States (US) in 2015,[7] and in the US alone, infections due to the bacterial resistance of antibiotics is evaluated to cost between US$21 and US$34 billion annually.[8] The economic burden of antimicrobial resistance is currently unknown in Australia, although a previous study published in 2006 prepared for the National Health and Medical Research Council estimate it to be AUD $250 million per year.[9]The number of resistant organisms, the spectrum of resistance of individual organisms, and the geographic regions with antibacterial resistance are all increasing, making this an unprecedented global public health problem.[10]

Multiple studies have shown that antibiotic consumption from dental prescribing is increasing worldwide.[11-13] The proportion of antibiotics prescribed by dental practitioners comprises around 3-11% of all prescribed antibiotics,[11, 14-17] making the contribution of dentists to antibiotic consumption significant. Surveys have also indicated that the awareness of antibiotic resistance and the impact of antibiotic prescribing by dentists is low. Only 20% of South Australian dentists surveyed correctly knew the term MRSA.[18] Almost two-thirds (64.6%) of Belgian dentists who responded to a survey on their antibiotic prescribing habits in dentistry felt that they were responsible for the contribution towards antibiotic resistance, but despite this knowledge, 61.8% of these respondents did not feel the need to change their prescribing practices.[19]

This review aims to inform dentists about the scope and factors that contribute to antibiotic resistance, and the practical relevance of this to general dentistry.

Antibiotics and dental practice

It is well established that most infections of odontogenic origin that are managed by dentists usually require some form of dental treatment, and that removal of the source of infection is the most effective method of managing these conditions.[20] Antibiotics are often only an adjunct to local treatment. In fact, treatment of an acute odontogenic infection with antibiotics alone and without local treatment to target the source of the infection can lead to worsening of the infection with a risk of airway compromise.[20] However, in some cases the prescription of antibiotics is essential, but factors such as the risk of antibiotic toxicity, allergy and contribution to the emergence of antibiotic resistance should be considered.[21]

Antibiotic use in dentistry is most commonly empirical, where the clinician prescribes based on the likely pathogens from previous studies and not on the microbiological investigation of bacteria from the specific lesion.[20, 22] The most commonly used class of drugs in dentistry is the penicillins, and as such this article will focus on resistance to penicillins with respect to bacteria in the oral cavity. Bacteria commonly isolated from endodontic abscesses have demonstrated resistance to penicillin at a frequency of around 5-20%,[23, 24] and this figure is increasing.[3]

The oral flora comprises a wide range of microbes in a complex ecosystem inhabited by around 300-500 species of bacteria, fungi and protozoa.[25] Orofacial odontogenic infections are polymicrobial in composition and can involve both commensal and opportunistic organisms. Gram-positive aerobic cocci and strict or facultative anaerobes are bacteria that are predominately isolated from dentoalveolar infections, which include species such as viridans streptococci, Peptostreptococcus, Prevotella, Porphyromonas and Fusobacterium.[26] Subgingival bacteria in the oral cavity are present within a biofilm. This highly organised, multilayed complex consisting of bacterial cells and extracellular matrix serves to protect the bacteria from antibiotics and host defence mechanisms, and acts as a physical barrier.[3] Bacteria that exist in the biofilm have the potential to be 1000-fold more resistant to antibiotics compared to free-floating bacterial cells.[27] The complexity of the biofilm structure, nutrient and oxygen limitation, and altered growth rates have all been identified as factors that contribute to the protection of bacteria against antibiotics.[28, 29] In addition to physiological resistance from the biofilm, bacteria also develop internal mechanisms to resist the effect of antibiotics.

Mechanisms of resistance

Resistance to antibiotics can be divided into two categories, either natural (intrinsic) resistance, or acquired resistance, and are summarised in Table 1. Intrinsic resistance is a characteristic property of the microorganism, where the entire species of bacteria will be resistant to the antibiotic. For example, the target site of beta-lactam antibiotics is the bacterial cell wall, and so bacteria that lack a cell wall (such as Mycoplasma species) will not be affected by these antibiotics.[30]

Acquired resistance, by comparison, does not affect the entire species of bacteria and will be seen in only some strains.[30] This can occur by two methods. The first is by chromosomal mutation, where changes to the bacterial DNA occur as a spontaneous event, independent of the presence of antibiotics.[3] For example, chromosomal mutations can be seen in the bacterial genome that codes the penicillin-binding proteins (PBPs), which are the site of action for penicillin antibiotics on bacteria, causing an alteration of the target site and therefore conferring resistance to this antibiotic.[3, 30]

The second mechanism of acquired resistance is by the horizontal acquisition of resistance by gene transfer. This is the most problematic mode of resistance developed as it allows resistant genes to be spread within different strains of the same species and also between different bacterial species.[30] There are three methods by which horizontal gene transfer can happen: transformation, transduction and conjugation.[30, 31] During transformation, bacteria that contain antibiotic resistance genes excrete segments of their DNA into the environment when they die, and other nearby competent bacteria acquire these genes.[3, 30] Transduction has a similar mechanism to transformation, but the segment of the DNA with resistance genes is incorporated into a phage particle before being introduced into the recipient organism.[30, 32] The last method, conjugation, is where a plasmid is transferred from the donor to the recipient bacteria and requires physical contact of two bacterial cells.[3] Plasmids are mobile, self-replicating segments of DNA which can contain antibiotic resistance genes (and can be resistant to one, or multiple antibiotics).[3]

Horizontal acquisition of genes conferring antibiotic resistance occurs at a faster rate than chromosomal mutation,[30] as the rate of spread of resistant bacteria for the latter is dependent on the life cycle of the respective bacterium. With horizontal gene transfer, resistance can be conferred to other bacteria independent of the multiplication rates of the organism.

Conjugation in particular, can result in the wide promulgation of antibiotic resistance genes and development of multidrug-resistant bacteria and it is believed to be the most frequent method by which bacteria transfer genetic elements in both humans and ecosystems.[3]

Types of resistance

There are four principal methods by which bacteria are able to resist antibiotics as a result of modified gene expression (Table 2).[33] The first method involves the bacteria's active binding site for the antibiotic becoming conformationally altered so the antibiotic molecule can no longer adhere to this binding site,[33] such as that which occurs with spontaneous mutation of genes that encode forPBPs as previously described. The second method is where alterations to the bacterial genome result in the restriction of antibiotics from the cell. An example is the alteration of to porin channels, which are pore-forming proteins that cross bacterial membranes, often occurring in Gram negative bacteria. Several antibiotics enter bacteria through these protein channels to the periplasmic space. Structural modification or changes to the expression levels of these proteins therefore results in restricted uptake or inability of the antibiotic to diffuse through the porin channel, thereby rendering the antibiotic inactive.[34] The third method occurs when antibiotics are actively extruded out of a bacterial cell by a transport protein known as an efflux pump.[33] The last mechanism involves antibiotic destruction via enzymatic inactivation such that which occurs with beta-lactam antibiotics in the presence of bacteria producing beta-lactamase enzymes.[30] All beta-lactam antibiotics have a four-membered beta-lactam ring, and their mode of action is to interfere with the synthesis of the peptidoglycan layer in the bacterial cell wall.[3] They bind to the PBPs on the external surface of the cytoplasmic membrane, with the eventual outcome being lysis of the bacterium.[35] The enzyme beta-lactamase catalyses the cleavage of the beta-lactam ring by the process of hydrolysis, thereby rendering the antibiotic ineffective.[30, 35]

Resistance mechanisms of bacteria

Oral beta-lactamases

The first beta-lactamases (then called penicillinases) were identified in 1940,[36] and with the increased use of broad spectrum penicillins and the related cephalosporin antibiotics, over 200 to 300 types of beta-lactamase enzymes have now been identified.[3, 30] Several classification systems exist and the enzymes vary in their substrate and inhibitor profiles, as well as physiological properties.[30] The first clinical failures with penicillin therapy of orofacial infections were described in 1980,[37] where strains of the Bacteroides species that produced beta-lactamase were isolated from each case of the five cases of ineffective penicillin treatment. The presence of beta-lactamase producing bacteria in the subgingival microbiota of patients with periodontitis was demonstrated in 1986,[38] and also showed that there was a greater recovery of beta-lactamase producing bacteria in a person who had recently taken penicillin. Over time, many studies confirmed the presence of bacteria resistant to penicillin and other antibiotics in the subgingival flora of subjects with chronic and refractory periodontitis,[39-41] as well as from odontogenic abscesses.[23, 24, 42]

Ecology of resistance

The ability of bacteria to develop resistance is a natural biological consequence of antibiotic use and is an evolutionary property of bacteria for the purposes of survival.[30] It has been established that the main cause of the development of resistant bacteria is selective pressure. By inhibiting the bacteria that are susceptible to the given antibiotic, the environment then allows the resistant bacteria to multiply and so causes selective pressure on the emergence of resistant strains.[10, 30] It is the density of antibiotic usage, and so total consumption of antibiotics, that will determine the degree of selection pressure, and thus the magnitude of the formation of resistant bacteria.[10, 30] The more antimicrobials are ingested, the more frequently bacteria are exposed to the medicine, thus having an increased chance to develop or acquire resistance to the medicine. The Antimicrobial Use and Resistance in Australia (AURA) 2016 report revealed that broad spectrum antibiotics are more likely to contribute to antimicrobial resistance than narrow spectrum antibiotics,[5] since they target a wider range of bacteria.

The ecology of resistance is such that resistant commensals form after an individual takes an antibiotic. If there is little usage of the same antibiotic, the resistant strains will eventually be "diluted out", and will be superseded by the antibiotic-susceptible bacteria.[10] However, with increased and more widespread usage of the antibiotic, the equilibrium between the relative proportion of resistant and susceptible bacteria will shift in favour of resistant bacteria. This equilibrium is determined by factors such as the strength and health of the susceptible and resistant strains, the genetic method of resistance and total antibiotic consumption.[30]

Worldwide approaches and challenges to reduce bacterial resistance

Most developed countries have now developed national plans and policies to address antibiotic resistance. Resistant bacteria spread between people by direct contact, air-borne particles, contaminated surfaces, food and water.[3, 43] Strategies that are generally adopted include preventing infections and the spread of resistance through measures such as immunisation, safe food preparation and appropriate infection control protocols.[44] At a national level, measures such as monitoring the consumption of antibiotics and the spread of antibiotic-resistant infections are employed. The development of new antibiotics is also another strategy, as bacterial resistance can be slowed, but not ceased since it is a natural biological outcome of antibiotic use.[44, 45]

Antibiotic stewardship, which is the appropriate, safe and discriminate use of antimicrobials, is one principal method utilised globally to try to shift the equilibrium in favour of susceptible bacteria. It is well established that use and misuse of antimicrobials are the main drivers of the development of resistance. Inappropriate use includes the unnecessary prescribing of antimicrobials, use for incorrect indications, or inappropriate dosing, duration and/or route of administration.[30] The Antimicrobial Use and Resistance in Australia Surveillance System has been established since 2013 and is a national collaborative and multidisciplinary approach for the monitoring of antimicrobial resistance and use of antibiotics for human health.[5] They target clinicians, researchers and policy makers to promote antimicrobial stewardship and implement changes around antimicrobial use.[5]

Several studies have demonstrated a decrease in bacterial resistance following a reduction in antibiotic use. In the UK, a reduction in the incidence of antibiotic resistance was shown in the local community following a decline in antibiotic prescribing for urinary tract infections at the level of general medical practice.[4] In Finland, there was a decrease observed in the levels of resistance of group A streptococci to erythromycin following a nationwide decrease in the consumption of macrolide antibiotics.[46] Australia has the seventh lowest rate of E. coli resistance to fluoroquinolones compared to European countries which is much higher, mostly due to pharmaceutical benefits scheme (PBS) restrictions limiting prescribing of these medicines.[5] These findings are significant, as they show that clinicians have the collective ability to alter patterns of antibiotic resistance.[4]

In addition to the overprescribing of antimicrobials within the health care system, other factors such as the utilisation of antibiotics in the food industry contribute greatly to the development of antibiotic resistance. Antibiotic use in agriculture and aquaculture contributes to 80% of the annual antibiotic consumption in the US,[7] and the long term use of sub-therapeutic doses of antibiotics for growth promotion in food animals still causes selective pressure on resistant strains.[10] While Australia has one of the lowest levels of antibiotic use in food producing animals,[43] it had the sixth highest community antibiotic consumption in 2014 compared to European countries.[5]

Pharmaceutical development of new antimicrobials has slowed in recent years, with several socioeconomic and non-medical factors affecting the research and development of new antibiotics. Drug companies usually generate more profit from therapeutic agents that are used long term to treat chronic illnesses such as diabetes or hypertension.[8] The development of a new antibiotic has more limitations and hence a narrow sales potential, as it would usually be reserved as a last-resort treatment option, would normally be used for short courses, and bacteria will eventually develop resistance to it.[8, 47] The net return of a new antibiotic has been estimated to be negative US$50 million, after taking into account development costs, clinical trials and profit, compared to a therapeutic agent used to treat a neuromuscular disease, which would be worth positive US$1 billion.[45, 47] The lack of financial incentive, in addition to the regulatory barriers, make the investment into the development of new antibiotic unattractive for pharmaceutical companies and this is reflected in the slowing of the development of new antibiotic agents.[47] It is therefore important not to rely on new drugs as an ‘only solution’ to this problem, but rather to use the current therapeutic agents correctly and judiciously.

Another factor that directly influences antibiotic resistance and indirectly affects resistance in neighbouring countries include financial incentives for the sale and prescribing of drugs. For example, In China, until 2010, a physician’s salary was linked with profits from the sale of prescription drugs,[8, 48] sales from drugs still form a part of a Chinese hospital’s income,[48] and studies have shown high and unnecessary prescribing of antibiotics.[8]

The impacts of antibacterial resistance will likely be greatest in poorer countries with fewer alternative agents to use;[8] however, with an increase in the volume of international travel[3] and trade, antibacterial resistance is a global problem. Some other socioeconomic and behavioural factors that tend to be observed in, but are not exclusive to, developing countries that contribute to the selection of bacterial resistance include lack of patient compliance with the advised antibiotic regimen,[30] the availability of antibiotics without prescription and being sold by non-medically trained people, substandard quality of antibiotics, expired antibiotics being repackaged, and inappropriate storage conditions leading to degraded antibiotics.[49] Other contributing factors include unreliable water supplies, overcrowding in urban areas, many immune-compromised people due to malnutrition, and poor infection control regimens and hygiene standards in healthcare facilities.[8, 49, 50] High burdens of infectious disease exist concurrently with high levels of antibiotic usage in these countries, and together with the other compounding factors, facilitate the spread of resistant commensals.[30]

Antibiotic resistance and dental practice

Dental antibiotic prescribing has been studied with greater interest in recent decades, with multiple studies showing that the consumption of dental prescribed antibiotics is increasing in both Australia and worldwide.[11-13, 51] In addition, many surveys of dentists worldwide reveal that a significant proportion of dentists prescribe antibiotics unnecessarily and for incorrect clinical indications.[19, 52, 53] The only survey[18] of dentists in Australia regarding prescribing choices revealed that 49% of respondents would prescribe antibiotics for a patient with an odontogenic infection with cellulitis,[20] prior to doing dental treatment. In addition, 39% of respondents indicated that they would prescribe antibiotics for a localised periapical abscess without any systemic involvement. A recent cross-sectional study in Wales that assessed the prescribing habits of dentists, found that 65.6% of the prescribed antibiotics were given in situations where there was no evidence of systemic involvement, and 70.6% of antibiotics were prescribed without undertaking concurrent dental treatment.[54] Several surveys reveal non-clinical factors where dentists feel compelled to prescribe antibiotics despite knowing it may not be necessary, such as clinical time pressure, patients who are unwilling to accept operative treatment,[54] and a patient's social history, demands and expectations.[19, 55, 56] In the UK, a survey of dentists revealed that nearly one third (30.3%) would prescribe antimicrobials due to time pressure.[55] These findings were in parallel with the study of Welsh dentists, which found that when the dentist had insufficient time to perform dental treatment, the odds of a patient being prescribed an antibiotic (without any signs or symptoms of an infection) were 10.21 times more likely compared to when the dentist had adequate clinical time.[54] A national survey of American endodontists affirms that antibiotics continue to be prescribed unnecessarily, with the most common reason being patient expectations.[57] Further research is required if dentists in Australia also experience similar non-clinical pressures to prescribe antibiotics, but it has been established that antibiotic prescribing decisions by dentists are multi-factorial and complex, with non-clinical factors also affecting prescribing choices.

Multiple studies have also shown that dentists tend to not prescribe according to recommended guidelines and prescribe antibiotics unnecessarily. A prospective study showed that 81% of Welsh dentists did not prescribe in accordance with recommended guidelines,[54] and a clinical audit of dental practitioners in the UK found that approximately 50% of antibiotics were prescribed inappropriately.[51] Two studies that addressed dental antibiotic prescribing in Australia found that dental practitioners did not adhere to prescribing guidelines for some antibiotics, and there were some inappropriate prescribing choices.[12, 17] Amoxicillin accounted for around 65% of all antibiotics dispensed from 2013 to 2016 by dentists,[17] and it is the preferred antibiotic by dentists for odontogenic infections in Australia.[12, 17] This is not an ideal first choice as it is a moderate spectrum antibiotic and while phenoxymethylpenicillin (narrow spectrum) is recommended as first line for odontogenic infections, it only accounted for 1.4% of dispensed antibacterials by dentists in 2016.[17]

For the individual practising clinician, 'Therapeutic Guidelines: Oral and Dental' was established in 2007, and the second version published in 2012 is the current recommended guideline for prescribing in Australia. For an antibiotic to be prescribed appropriately and prudently, the recommendations are shown below in Table 3.

Employing the MINDME protocol in dental practice involves choosing antibiotics with the narrowest spectrum required, at the appropriate dose and specified length of time to target the bacteria that have been shown to be commonly isolated from odontogenic infections. For this reason, phenoxymethylpenicillin is a preferred first choice for odontogenic infections as it has a narrow spectrum but been shown to have efficacy against approximately 85% of the bacteria that are commonly isolated from odontogenic infections, with amoxicillin only being slightly more effective against odontogenic infections, having 91% efficacy.[23] Of concern, studies have shown that the dispensed use of the broad spectrum antibiotic amoxicillin with clavulanic acid is increasing in Australia,[17] and elsewhere.[11, 13] Indeed, Ford et al showed that there was a staggering increase of nearly 200% in the dental dispensed use of amoxicillin/clavulanic acid to concessional beneficiaries in Australia from 2001 to 2012.[12] This preference for moderate to broad spectrum antibiotics by dentists are inappropriate as first line choices as broad -spectrum antibiotics are more likely to contribute to the development of antibiotic resistance than those with a narrow spectrum.[5] A recent study on dental prescribing in Australia has shown that dentists also prescribe antibiotics which are not recommended in the current guidelines.[17] For example, there were approximately 11,000 dispensed dental prescriptions for the broad spectrum antibiotic erythromycin in 2016, which is not recommended as it has poor activity against Fusobacterium and viridians streptococci, both of which are common isolates from odontogenic infections.[17, 26] There were also small but significant numbers of other antibiotics prescribed by dentists which were inappropriate, such as trimethoprim with sulfamethoxazole which has no dental indication and has not been shown to be efficacious against orofacial infections.[17] These are some examples of inappropriate dental prescribing choices in Australia.

In Australia, the majority of medicines, including antibiotic prescribing for dentists, are subsidised by the PBS.[58] Antibiotics are packaged as standard pack sizes that correlate with PBS-specified quantities. Depending on the frequency of the drug prescribed, the pack size does not always correlate with the specified length of time an antibiotic should be given for according to current guidelines. Dentists should specify the time frame on prescriptions, rather than tell the patient to "finish the course", as completing the antibiotic to the PBS specified pack size may mean the patient will be taking the antibiotic for longer than guidelines indicate is necessary. Studies have shown that shorter courses are effective for dentoalveolar infections provided that drainage of the source of the infection has been established.[59] Another possible strategy which is widely used in medical practice and would minimise the inappropriate use of antibiotics is to consider pathology testing for unresolved infections.

Other recommendations for appropriate dental prescribing include:

1. Manage dental infections appropriately by addressing the source of the infection, using active local treatment and employing the use of antibiotics only as an adjunct to treatment if indicated.
2. Prescribe antibiotics only when necessary according to recommended guidelines and for the correct indications, selecting the correct antibiotic with the narrowest spectrum as appropriate.
3. Prescribe in accordance with the recommended dose, frequency and duration, and not according to the PBS pack size.
4. Patients should be given counselling on how to take the antibiotic, to avoid errors of administration.
5. The education of patients is critical for those who expect or request antibiotics for incorrect indications or who are unwilling to accept local treatment.

Conclusions

It has been well established that high antibiotic usage within a community is correlated to higher levels of antibiotic resistance, which is a worldwide, multi-faceted problem. The use and misuse of antibiotics is a significant driver of antimicrobial resistance. Given the increasing use of antibiotics by dental practitioners in Australia and worldwide, the significant incidence of unnecessary prescribing, inappropriate prescribing choices and the increasing preference for moderate to broad spectrum antibacterials, dentists are likely contributing to the global public health problem of antibiotic resistance. Dentists should prescribe antibiotics judiciously and when necessary in adjunct with local treatment, for evidence-based indications according to guidelines which are established to minimise the use and inappropriate use of antibiotics. Appropriate prescribing is a professional responsibility of all dentists, as antibiotics are a unique class of drugs that have the potential to affect the individual patient as well as the community and entire populations.[3]

References

1. Kyle RA, Steensma DP, Shampo MA. Howard Walter Florey-Production of Penicillin. Mayo Clin Proc. 2015;90(6):e63-4.

2. Penicillin's finder assays its future. New York Times. June 26, 1945;21.

3. Handal T, Olsen I. Antimicrobial resistance with focus on oral beta-lactamases. Eur J Oral Sci. 2000;108(3):163-74.

4. Lewis MA. Why we must reduce dental prescription of antibiotics: European Union Antibiotic Awareness Day. Br Dent J. 2008;205(10):537-8.

5. Australian Commission on Safety and Quality in Health Care (ACSQHC) . AURA 2016: first Australian report on antimicrobial use and resistance in human health - consumer summary. Sydney: ACSQHC; 2016.

6. Love RM. Enterococcus faecalis--a mechanism for its role in endodontic failure. Int Endod J. 2001;34(5):399-405.

7. Glick M. Antibiotics: The good, the bad, and the ugly. Journal of the American Dental Association (1939). 2016;147(10):771-3.

8. World Economic Forum.. Global Risks 2013, Eighth Edition, Insight Report.

9. Wozniak TM GN, Barnett AG. How much do superbugs cost Australian hospitals? An evidence-based, open-access tool. Infection, Disease and Health. 2017;23(1):54-6.

10. Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. Nat Med. 2004;10(12 Suppl):S122-9.

11. Marra F, George D, Chong M, Sutherland S, Patrick DM. Antibiotic prescribing by dentists has increased: Why? Journal of the American Dental Association (1939). 2016;147(5):320-7.

12. Ford PJ, Saladine C, Zhang K, Hollingworth SA. Prescribing patterns of dental practitioners in Australia from 2001 to 2012. Antimicrobials. Aust Dent J. 2017;62(1):52-7.

13. Pipalova R, Vlcek J, Slezak R. The trends in antibiotic use by general dental practitioners in the Czech Republic (2006-2012). Int Dent J. 2014;64(3):138-43.

14. Prescribing and Primary Care Services. Prescribing by dentists: England 2012. London; 2013.

15. Al-Haroni M, Skaug N. Incidence of antibiotic prescribing in dental practice in Norway and its contribution to national consumption. J Antimicrob Chemother. 2007;59(6):1161-6.

16. Hicks LA, Bartoces MG, Roberts RM, Suda KJ, Hunkler RJ, Taylor TH, Jr., et al. US outpatient antibiotic prescribing variation according to geography, patient population, and provider specialty in 2011. Clin Infect Dis. 2015;60(9):1308-16.

17. Teoh L SK, Marino R, McCullough M. Part 1. Current prescribing trends of antibiotics by dentists in Australia from 2012 to 2016. Australian Dental Journal. 2018.

18. Jaunay T, Sambrook P, Goss A. Antibiotic prescribing practices by South Australian general dental practitioners. Aust Dent J. 2000;45(3):179-86; quiz 214.

19. Mainjot A, D'Hoore W, Vanheusden A, Van Nieuwenhuysen JP. Antibiotic prescribing in dental practice in Belgium. Int Endod J. 2009;42(12):1112-7.

20. Oral and Dental Expert Group. Therapeutic guidelines: oral and dental. Version 2 ed. Melbourne: Therapeutic Guidelines Limited; 2012.

21. American Dental Association Council on Scientific A. Combating antibiotic resistance. Journal of the American Dental Association (1939). 2004;135(4):484-7.

22. Kuriyama T, Absi EG, Williams DW, Lewis MA. An outcome audit of the treatment of acute dentoalveolar infection: impact of penicillin resistance. Br Dent J. 2005;198(12):759-63; discussion 4; quiz 78.

23. Baumgartner JC, Xia T. Antibiotic susceptibility of bacteria associated with endodontic abscesses. J Endod. 2003;29(1):44-7.

24. Khemaleelakul S, Baumgartner JC, Pruksakorn S. Identification of bacteria in acute endodontic infections and their antimicrobial susceptibility. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;94(6):746-55.

25. Sweeney LC, Dave J, Chambers PA, Heritage J. Antibiotic resistance in general dental practice--a cause for concern? J Antimicrob Chemother. 2004;53(4):567-76.

26. Kuriyama T, Karasawa T, Nakagawa K, Saiki Y, Yamamoto E, Nakamura S. Bacteriologic features and antimicrobial susceptibility in isolates from orofacial odontogenic infections. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;90(5):600-8.

27. Neelakantan P, Romero M, Vera J, Daood U, Khan AU, Yan A, et al. Biofilms in Endodontics-Current Status and Future Directions. Int J Mol Sci. 2017;18(8).

28. Gander S. Bacterial biofilms: resistance to antimicrobial agents. J Antimicrob Chemother. 1996;37(6):1047-50.

29. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science. 1999;284(5418):1318-22.

30. Al-Haroni M. Bacterial resistance and the dental professionals' role to halt the problem. J Dent. 2008;36(2):95-103.

31. Munita JM, Arias CA. Mechanisms of Antibiotic Resistance. Microbiol Spectr. 2016;4(2).

32. Hewitt LF. Bacteriophage as a factor in epidemiology and bacterial evolution; lysis of diphtheria Bacilli by Staphylococcal bacteriophage. Lancet. 1952;2(6728):272-3.

33. Anderson D. The ways in which bacteria resist antibiotics. Sweden; 2004.

34. Scorciapino MA, Acosta-Gutierrez S, Benkerrou D, D'Agostino T, Malloci G, Samanta S, et al. Rationalizing the permeation of polar antibiotics into Gram-negative bacteria. J Phys Condens Matter. 2017;29(11):113001.

35. Rang HP, Dale MM, Ritter JM. Pharmacology. 4th ed. Edinburgh ; New York: Churchill Livingstone; 1999. x, 830 p. p.

36. Abraham EP, Chain E. An enzyme from bacteria able to destroy penicillin. 1940. Rev Infect Dis. 1988;10(4):677-8.

37. Heimdahl A, von Konow L, Nord CE. Isolation of beta-lactamase-producing Bacteroides strains associated with clinical failures with penicillin treatment of human orofacial infections. Arch Oral Biol. 1980;25(10):689-92.

38. Kinder SA, Holt SC, Korman KS. Penicillin resistance in the subgingival microbiota associated with adult periodontitis. J Clin Microbiol. 1986;23(6):1127-33.

39. Rams TE, Degener JE, van Winkelhoff AJ. Antibiotic resistance in human chronic periodontitis microbiota. J Periodontol. 2014;85(1):160-9.

40. Handal T, Olsen I, Walker CB, Caugant DA. Beta-lactamase production and antimicrobial susceptibility of subgingival bacteria from refractory periodontitis. Oral Microbiol Immunol. 2004;19(5):303-8.

41. Handal T, Olsen I, Walker CB, Caugant DA. Detection and characterization of beta-lactamase genes in subgingival bacteria from patients with refractory periodontitis. FEMS Microbiol Lett. 2005;242(2):319-24.

42. Eick S, Pfister W, Straube E. Antimicrobial susceptibility of anaerobic and capnophilic bacteria isolated from odontogenic abscesses and rapidly progressive periodontitis. Int J Antimicrob Agents. 1999;12(1):41-6.

43. Australian Government Department of Health. Antimicrobial resistance [Available from: https://www.amr.gov.au/about-amr/amr-australia/amr-and-animal-health-australia. Accessed 1 February 2018.

44. Centres of Disease Control and Prevention . About Antimicrobial Resistance [updated 6 April 2017. Available from: https://www.cdc.gov/drugresistance/about.html. Accessed 1 August 2017.

45. Bartlett JG, Gilbert DN, Spellberg B. Seven ways to preserve the miracle of antibiotics. Clin Infect Dis. 2013;56(10):1445-50.

46. Seppala H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. N Engl J Med. 1997;337(7):441-6.

47. Shaban RZ SG, Trott DJ, Turnidge J, Jordan J. Surveillance and reporting of antimicrobial resistance and antibiotic usage in animals and agriculture in Australia. 2014.

48. Yezli S, Li H. Antibiotic resistance amongst healthcare-associated pathogens in China. Int J Antimicrob Agents. 2012;40(5):389-97.

49. Okeke IN, Lamikanra A, Edelman R. Socioeconomic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. Emerg Infect Dis. 1999;5(1):18-27.

50. Laxminarayan R, Heymann DL. Challenges of drug resistance in the developing world. BMJ. 2012;344:e1567.

51. Guidance Development Group.. Drug Prescribing for Dentistry: Scottish Dental Clinical Effectiveness Programe; 2016, January.

52. Al-Haroni M SN. Knowledge of prescribing antimicrobials among Yemeni general dentists. Acta Odontologica Scandinavica. 2006;64:274-80.

53. Segura-Egea JJ, Velasco-Ortega E, Torres-Lagares D, Velasco-Ponferrada MC, Monsalve-Guil L, Llamas-Carreras JM. Pattern of antibiotic prescription in the management of endodontic infections amongst Spanish oral surgeons. Int Endod J. 2010;43(4):342-50.

54. Cope AL, Francis NA, Wood F, Chestnutt IG. Antibiotic prescribing in UK general dental practice: a cross-sectional study. Community Dent Oral Epidemiol. 2016;44(2):145-53.

55. Palmer NA, Pealing R, Ireland RS, Martin MV. A study of therapeutic antibiotic prescribing in National Health Service general dental practice in England. Br Dent J. 2000;188(10):554-8.

56. Kohler M, Meyer J, Linder M, Lambrecht JT, Filippi A, Kulik Kunz EM. Prescription of antibiotics in the dental practice: a survey of dentists in Switzerland. Schweiz Monatsschr Zahnmed. 2013;123(9):748-59.

57. Germack M, Sedgley CM, Sabbah W, Whitten B. Antibiotic Use in 2016 by Members of the American Association of Endodontists: Report of a National Survey. J Endod. 2017;43(10):1615-22.
58. Australian Government Department of Health. About the PBS 2017 [Available from: http://www.pbs.gov.au/info/about-the-pbs. Accessed 1 December 2017.
59. Martin MV, Longman LP, Hill JB, Hardy P. Acute dentoalveolar infections: an investigation of the duration of antibiotic therapy. Br Dent J. 1997;183(4):135-7.

Tables

Table 1: (Adapted from Handal and Olsen, 2000)3

Type of resistance	**Features**
Natural/intrinsic	• **Characteristic property of the microorganism that renders the antibiotic resistant** • **Entire species will be resistant**
Acquired	• **Does not affect the entire species and will only be seen in some strains, can occur by 2 methods** **<u>1. Chromosomal mutation</u>**

	- changes to the DNA occur as a spontaneous event **<u>2. Horizontal acquisition of resistance by gene transfer</u>** **- Transformation** **- Transduction** **- Conjugation**

Table 2: Resistance Mechanisms of Bacteria (Adapted from Andersson, 2004)33

1. Alteration of the active binding site of the antibiotic
2. Restriction of antibiotic entry into the cell
3. Active extrusion of the antibiotics by an efflux pump
4. Enzymatic inactivation of antibiotics

Table 3: (reproduced from Therapeutic Guidelines: Oral and Dental Version 2)20

The antimicrobial creed
M microbiology guides therapy wherever possible
I indications should be evidence-based
N narrowest spectrum required
D dosage appropriate to the site and type of infection
M minimise duration of therapy
E ensure monotherapy in most situations