


Prevalence of antibiotic resistance genes in the oral cavity and mobile genetic elements that disseminate antimicrobial resistance: A systematic review

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Abstract

The objective of this review was to assess the prevalence of antibiotic resistance genes in the oral cavity and identify mobile genetic elements (MGEs) important in disseminating them. Additionally, to assess if age, geographic location, oral site, bacterial strains and oral disease influence the prevalence of these genes. Three electronic databases (Medline, Embase and the Cochrane Library) were used to search the literature. Journals and the grey literature were also hand searched. English language studies from January 2000 to November 2020 were selected. Primary screening was performed on the titles and abstracts of 1509 articles generated. One hundred and forty-seven full texts were obtained to conduct the second screening with strict inclusion and exclusion criteria. Forty-four final articles agreed with the inclusion criteria. Half of the studies were classed as low quality. *tet(M)* was the most prevalent gene overall and the conjugative transposon Tn916 the most common MGE associated with antibiotic resistance genes in the oral cavity. In babies delivered vaginally, *tet(M)* was more prevalent, whilst *tet(Q)* was more prevalent in those delivered by C-section. Generally, countries with higher consumption of antibiotics had higher numbers of antibiotic resistance genes. Agricultural as well as medical use of antibiotics in a country should always be considered. Between healthy, periodontitis and peri-implantitis subjects, there was no difference in the prevalence of *tet(M)*; however, *erm(B)*, *tet(M)* and *tet(O)* were higher in carious active children than the non-carious group. Subjects with poor oral hygiene have more pathogenic bacteria that carry resistance genes compared to those with good oral hygiene. *Enterococcus faecalis* isolates demonstrated significant tetracycline resistance (*tet(M)* up to 60% prevalence in samples) and erythromycin resistance (*erm(B)* up to 61.9% prevalence in samples), periodontal pathogens showed significant beta-lactam resistance with *blaZ* and *cfxA* present in up to 90%–97% of samples and the normal oral flora had a high level of erythromycin resistance with *mef(A/E)* present

Abbreviations: DDD, defined daily doses; HICs, high-income countries; MGE, mobile genetic element; PCR, polymerase chain reaction; WGS, whole-genome sequencing.

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in 65% of *Streptococcus salivarius* isolates. The most common resistance gene was *tet(M)* in root canals, *cfxA* in subgingival plaque, *erm(B)* in supragingival plaque and *tet(W)* in 100% of whole saliva samples. The review highlights that although many studies in this area have been performed, 50% were classed as low quality. We advise the following recommendations to allow firm conclusions to be drawn from future work: the use of large sample sizes, investigate a broad range of antibiotic resistance genes, improved methodologies and reporting to improve the quality of genetic testing in microbiology and randomisation of subject selection.

KEYWORDS

antibiotic resistance genes, antimicrobial resistance, mobile genetic elements, oral cavity

1 | INTRODUCTION

Penicillin was the first commercially available antibiotic and this began the golden era of antibiotic discovery from 1945 to 1960 (Wright, 2007) which has enabled many advancements in medicine. In 2015 in the United Kingdom, however, there were 2172 deaths due to antibiotic-resistant bacteria and across Europe this was 33,110 (Cassini et al., 2019). National Health Service dentists in primary care across England are responsible for 10% of all prescriptions of antimicrobials (Marra et al., 2016; Sweeney et al., 2004) and so have a role to play in responsible and appropriate prescribing to limit the development and spread of antimicrobial resistance. Only 19% of antibiotics in the United Kingdom are used as recommended by clinical guidelines (Cope et al., 2016).

Dental plaque can harbour bacteria carrying antibiotic-resistant genes (Villedieu et al., 2003) and is an important reservoir of resistance (Xu & Gunsolley, 2014). The complete genomic composition of plaque microbiota remains unknown (Kim et al., 2013), but genetic techniques such as polymerase chain reaction (PCR) (Conrads, 2002) and whole-genome sequencing (WGS) (Koser et al., 2012) are enabling a more complete picture of the number of antibiotic resistance genes (Diaz-Torres et al., 2003).

The oral cavity is a ready environment for horizontal gene transfer because of the close proximity of bacteria in plaque and the availability of exogenous DNA passing through the oral cavity (Lamont & Bryers, 2001).

Genes encoding resistance to tetracycline (*tet*) and macrolides (*erm* or *mef*) are the most common in the oral cavity (Kouidhi et al., 2011; Roberts, 2002; Villedieu et al., 2003). *tet* genes are divided into groups based on their mode of action and genetic relatedness; all of them confer resistance to tetracycline and some also to related antibiotics (Aminov et al., 2002; Diaz-Torres et al., 2006; Villedieu et al., 2003). Resistance to macrolides can be by methylation of the ribosome commonly encoded by genes termed erythromycin ribosomal methylase (*erm*) or by macrolide efflux (encoded by *mef*) (King et al., 2002; Villedieu et al., 2004). There are many different *erm* and *mef* genes

contained on a variety of different mobile genetic elements (MGEs) (Chancey et al., 2015).

tet(M) is the most widespread *tet* gene and is normally found on conjugative transposons (also called integrate conjugative elements) of the Tn916/Tn1545 family (Sun et al., 2012). The most common erythromycin resistance gene is *mef* with its common variants *mef(A)* and *mef(E)* (Amezaga et al., 2002) followed by *erm(B)* (Villedieu et al., 2004).

A previous systematic review has been completed investigating antibiotic resistance genes in the oral cavity; however, this only focused on three intraoral sites: saliva, supragingival biofilm and endodontic infections (Moraes et al., 2015). Here, we aim to determine the prevalence of all known antibiotic resistance genes in the oral cavity and in addition to review what MGEs are important in disseminating them.

2 | MATERIALS AND METHODS

Studies describing the prevalence and presence of antibiotic resistance genes in the oral cavity and the methods of spread of antimicrobial resistance were identified in the electronic databases Embase, Medline and the Cochrane Library using 'free text' and 'MeSH' terms, limited to the English language from January 2000 to November 2020. The following search terms were used alone or in combination: 'tetracycline', 'penicillin', 'metronidazole', 'erythromycin', 'penicillin resistance', 'tetracycline resistance', 'drug resistance', 'antibiotic resistance', 'antibacterial resistance', 'antibacterial susceptibility', 'antimicrobial resistance', 'antimicrobial susceptibility', 'mouth', 'dentistry', 'oral cavity', 'oral flora', 'biofilms', 'dental plaque', 'saliva', 'genes' and 'genetics'.

The *Journal of Clinical Periodontology*, *Oral Microbiology and Immunology*, *Journal of Antimicrobial Chemotherapy* and *Journal of Endodontics* were hand searched and the grey literature identified in Open Grey (www.opengrey.eu) to minimise the effect of publication bias.

The first screening process was completed by title screening and abstract analysis independently by two reviewers (L.B. and U.N.). The inclusion and exclusion criteria for the initial and secondary screening can be seen in Table 1.

TABLE 1 Inclusion and exclusion criteria for primary and secondary screening

Inclusion criteria	Exclusion criteria
Healthy patients or patients with oral disease only.	Literature reviews, letters to editors and poster presentations.
Detected antibiotic resistance genes by suitable modern molecular techniques such as PCR, whole genome sequencing, DNA sequencing or next-generation sequencing.	Did not use modern and suitable molecular methods for detection of presence of resistance genes. Older and low-quality methods like microarray and labelling of dinucleotide probes were excluded.
Collected samples from saliva, supra and subgingival plaque, periodontal pockets, gingival sulcus, root canals and oral mucosa only. Studies that detected genes in additional locations to the oral cavity were included but had data listed separately to the oral cavity samples.	Detected antibiotic resistance genes in other environments from the oral cavity or pooled samples from other locations with samples from the oral cavity or pooled samples within the oral cavity.
In vitro studies	The objective of the study was not the detection of resistance genes or the methods of dissemination of antibiotic resistance.
Studies from January 2000 to November 2020 and English language only.	
Detected antibiotic resistance genes either before and/or after antibiotic treatment.	
Studies that detected methods of dissemination of antibiotic resistance.	

Disagreements on study inclusion were resolved by discussion after the full texts were obtained and with a third reviewer (P.M.). For articles that met the above criteria, the full texts were read and a second screening was completed.

Inter-reviewer agreement for the second screening was determined using Cohen's kappa coefficient.

Most of the studies included in the systematic review were cross sectional and no scale could be found to score such studies in the field of microbiology, so we designed quality criteria for this study. A high-quality study was defined as one that satisfied all four of the requirements below:

1. Used PCR or WGS;
2. Used sequencing or restriction digest, DNA hybridisation or Southern blot hybridisation to verify the genes that were identified;
3. Controls stated;
4. Triplicate results, in the case of PCR, stated.

Studies that did not meet all four requirements were classed as low quality.

3 | RESULTS AND DISCUSSION

3.1 | Overview of the included studies

Figure 1 shows the 1509 articles identified from the databases, hand searching and grey literature after duplicates were removed. After initial screening, the full texts of 147 studies were analysed according to the selection criteria, leaving 44 to be included. Table S1 shows why

103 of the articles were excluded at second screening. During the primary screening, many studies were excluded because they investigated the presence of antibiotic resistance genes in soil, rivers and animals, especially livestock, and with hospital patients, samples tended to be taken from blood, urinary tract infections and wound swabs, not from the oral cavity. During the second screening, many papers were excluded because some combined samples from the oral cavity with other body sites; we wanted to focus on the oral cavity only. Papers that included subjects with health problems other than oral disease were excluded as this could have influenced the results. The Kappa score for the inter-reviewer agreement was 0.925. Table 2, which lists studies showing the prevalence of antibiotic-resistant genes, and Table 3, which lists studies showing different MGEs in the oral cavity, demonstrate the final 44 papers included.

From these studies, half were classed as low quality (Table S2) since they did not satisfy the four criteria for quality. One recommendation is that improved methodologies and reporting need to be achieved allowing easier comparisons between studies. (Table S3 shows additional information regarding the final studies not shown in Tables 2 and 3).

The studies were very varied making comparisons difficult. In some, samples were pooled (Villedieu et al., 2003), some investigated antibiotic resistance genes in all of the bacteria present (Lancaster et al., 2005) and some focused on specific species (Nakayama & Takao, 2003). Sample sizes were often small and so reliable conclusions could not be made; therefore, larger scale experiments would be useful to make correlations between factors rather than just identifying which antibiotic resistance genes and MGEs are present at a specific time point.

Antibiotic resistance genes encoding resistance for tetracycline, erythromycin and beta-lactams were mainly studied. Fifteen tetracy-

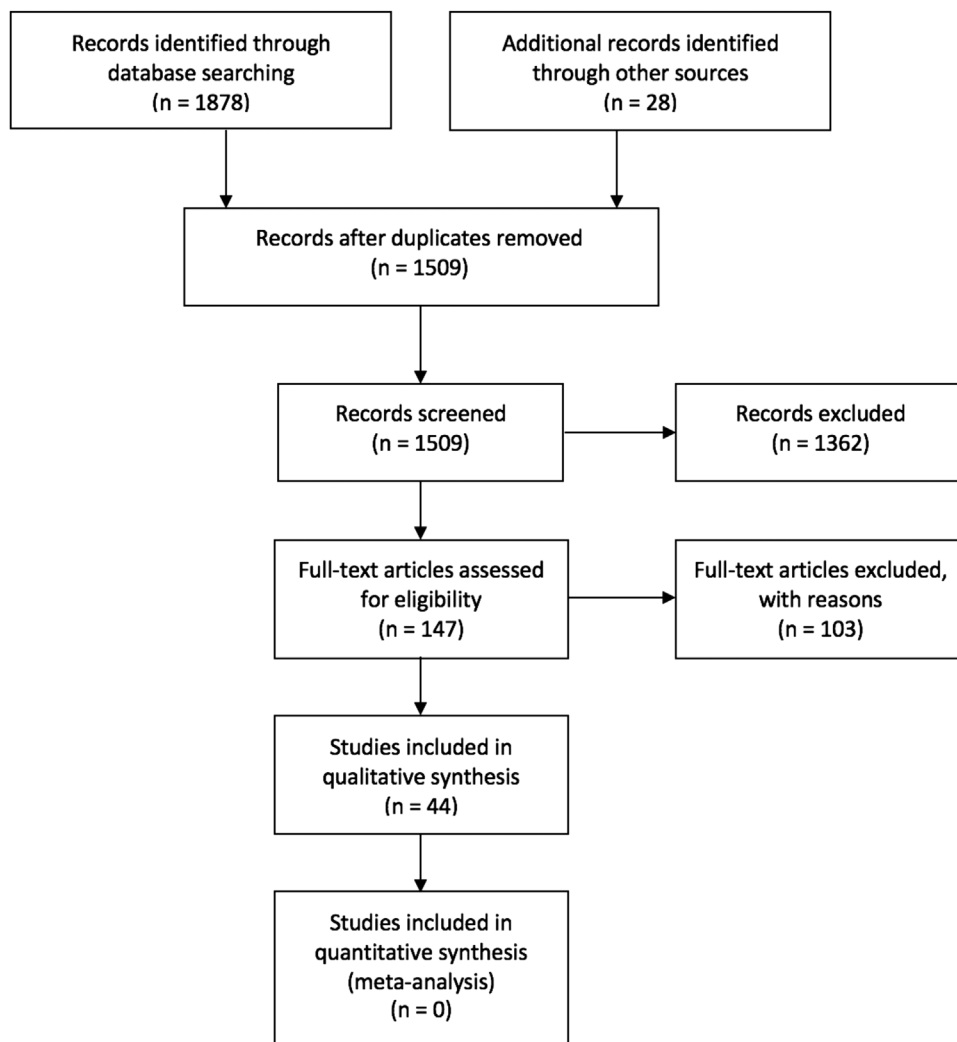


FIGURE 1 Flow diagram to show results of search strategy

cline, six erythromycin and nine beta-lactam resistance genes were detected but zero *nim* genes, which encode resistance to metronidazole, an antibiotic commonly used in dentistry. They have been associated with the following plasmids: pIP417, pIP419, pIP421 and pBF388c (Sóki et al., 2006). Further research is required into the prevalence of *nim* genes as only two studies searched for them (Ioannidis et al., 2009; Koukos et al., 2014). In addition, some studies investigated one or a small number of antibiotic resistance genes, whilst others detected a wide variety. As a result, a meta-analysis was not possible.

The time varied as to when the subjects had their last course of antibiotics from 0 to 9 months before samples were taken and no information about the antibiotics taken was provided. Such information is required to determine the effect of different antibiotics on the microbiome. Research investigating the desirable time period before a subject's sample is taken and their last course of antibiotics would be useful.

Not all bacteria can be grown in the laboratory and those studies that relied on culturing bacteria risked introducing bias into their

findings as well as those where there was no proper randomisation of subject selection.

A statistician was consulted and only a small number of studies were sufficiently similar to be pooled. Three studies obtained samples from primary endodontic infections (Jungermann et al., 2011; Rocas & Siqueira, 2012, 2013) and another three from subgingival plaque (Collins et al., 2016; Ioannidis et al., 2009; Manch-Citron et al., 2000), which all had *tet(M)*. These were able to be pooled to answer the question: Is there a difference in the prevalence of antibiotic resistance genes between primary endodontic infections and subgingival plaque samples, the latter from subjects with periodontal disease? (See Table S4.) The *p*-value was calculated using Pearson Chi-square test, which showed a significant difference between the groups ($p < 0.001$). Subgingival plaque samples showed a higher prevalence of *tet(M)* with 31%–80% of samples containing *tet(M)* compared to 5%–60% from primary endodontic infections. Only two studies (Collins et al., 2016; Ioannidis et al., 2009) tested for the presence of *tet(M)* in subjects from subgingival plaque samples in healthy, gingivitis and periodontal groups. These were pooled to answer the question: Is there a

TABLE 2 Prevalence of antibiotic resistance genes

Author	Age	Geographic location	Oral site	Healthy/diseased patients	Bacteria	Presence and prevalence of genes
Alicea-Serrano et al., 2013	Adult mothers: 21–33 years New born babies	Venezuela	Oral mucosa	Healthy	No bacterial strains stated in relation to presence of antibiotic resistance genes.	Percentage of mothers who have tet genes: tet(M), 67%; tet(O), 56%; tet(Q), 0%; tet(W), 22%. Percentage of vaginally delivered babies who have tet genes: tet(M), 50%; tet(O), 50%; tet(Q), 0%; tet(W), 0%. Percentage of C-section-delivered babies who have tet genes: tet(M), 0%; tet(O), 17%; tet(Q), 0%; tet(W), 33%.
Arredondo et al., 2019	Not stated	Spain	Subgingival plaque	Healthy	<i>Streptococcus oralis</i>	First time presence of tet(B) has been confirmed in Gram-positive bacteria normally found in Gram-negative bacteria.
Card et al., 2014	Adults	Finland, France, Italy, Norway, Scotland	Saliva samples	Healthy	For saliva samples, predominant taxa belonged to Firmicutes, Proteobacteria, Bacteroidetes and Fusobacteria.	Types of antibiotic resistance genes detected in human saliva: Finland— <i>aadb</i> , <i>blaTEM</i> , <i>erm(B)</i> and <i>tet(B)</i> ; France— <i>aac6'-aph2'</i> , <i>aadb</i> , <i>blaTEM</i> , <i>erm(B)</i> ; <i>vatE</i> , <i>sul2</i> , <i>tet(B)</i> and <i>tet(X)</i> ; Italy— <i>blaTEM</i> , <i>erm(B)</i> and <i>sul2</i> ; Norway— <i>blaTEM</i> , <i>erm(B)</i> , <i>sul2</i> and <i>tet(B)</i> ; Scotland— <i>aac6'-aph2'</i> , <i>aac6'-Ib</i> and <i>erm(B)</i> .
Chaffanel et al., 2015	One 38-year-old adult, four children between 15 and 33 months.	France	Saliva	Healthy	<i>Streptococcus salivarius</i>	Percentages of antibiotic resistance genes in 20 isolates of <i>Streptococcus salivarius</i> from saliva samples: <i>erm(B)</i> , 10%; <i>mef(A/E)</i> , 65%; <i>tet(M)</i> , 20%; <i>cat(Q)</i> , 0%; <i>erm(B) + tet(M)</i> , 10%; <i>erm(B) + mef(A/E)</i> , 0%; <i>erm(B) + tet(M) + mef(A/E)</i> , 0%; <i>mef(A/E) + cat(Q)</i> , 0%.
Chung et al., 2002	All patients more than 65 years old.	USA	Supra and subgingival plaque	Samples from patients with gingivitis or periodontitis.	<i>Porphyromonas gingivalis</i> , <i>Prevotella intermedia</i> , <i>Prevotella nigrescens</i>	Percentages of tet(Q) in the following bacteria from plaque samples: <i>P. gingivalis</i> , 33%; <i>P. intermedia</i> , 40%; <i>P. nigrescens</i> , 8%.
Collins et al., 2016	18–65 years	Dominican Republic	Subgingival samples	Healthy	<i>P. gingivalis</i> , <i>T. denticola</i> , <i>T. forsythia</i> , <i>A. actinomycetemcomitans</i> , <i>P. intermedia</i> , <i>F. nucleatum</i> , <i>P. micra</i> , <i>D. pneumosintes</i> , <i>E. corrodens</i> .	Percentages of tet genes in subgingival samples: Healthy/chronic periodontitis patient groups: <i>tet(32)</i> , 9.09%/72.4%; <i>tet(M)</i> , 45.5%/31%; <i>tet(O)</i> , 11.1%/31%; <i>tet(Q)</i> , 45.5%/82.8%; <i>tet(W)</i> , 36.4%/62.1%; <i>tet(L)</i> , 0%/3.45%; <i>tet(B)</i> , 0%/5.88%; <i>tet(K)</i> , 0%/0%; <i>tet(S)</i> , 0%/0%; <i>tet(31)</i> , 0%/0%; <i>tet(37)</i> , 0%/0%.

(Continues)

TABLE 2 (Continued)

Author	Age	Geographic location	Oral site	Healthy/diseased patients	Bacteria	Presence and prevalence of genes
Diaz-Mejia et al., 2002	Not stated	Mexico and Cuba	Swabs from periodontal area	Healthy	Oral commensal <i>streptococci</i> .	Presence of <i>erm</i> genes isolated from erythromycin-resistant oral <i>streptococci</i> : Mexico, 6; Cuba, 1. Presence of <i>erm</i> genes isolated from erythromycin intermediate-resistant oral <i>streptococci</i> : Mexico, 5; Cuba, 5.
Ehrmann et al., 2014	Healthy patients: 20–70 years Haematology patients: 7–62 years Periodontitis patients: 30–59 years	France	Subgingival plaque	Healthy, periodontitis patients, haematology patients	<i>Capnocytophaga</i> species	Percentage of antibiotic resistance genes in 48 <i>Capnocytophaga</i> species: <i>blacfxA</i> , 31%; <i>blacsp-1</i> , 12.5%; <i>ermF</i> , 27%; <i>ermC</i> , 2%.
Fernandez-Canigia et al., 2015	35–60 years olds	Argentina	Subgingival plaque	Periodontal disease	<i>Prevotella intermedia</i> , <i>Prevotella nigrescens</i>	Percentage of beta-lactamase production in <i>Prevotella</i> species from subgingival plaque in periodontal patients: <i>P. intermedia</i> , 50%; <i>P. nigrescens</i> , 11.1%. <i>CfxA</i> more frequent in <i>P. intermedia</i> than <i>P. nigrescens</i> .
Fosse et al., 2002	Not stated	France	Subgingival plaque	Periodontal patients	<i>Prevotella</i> species	Percentages of antibiotic resistance genes in aminopenicillin-resistant <i>Prevotella</i> : 97% were positive for <i>cfxA</i> and 2.9% were positive for <i>CepA/cbIA</i> .
Hirose et al., 2019	Age 3–6 years	Japan	Saliva	Healthy	20 methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)/methicillin susceptible <i>Staphylococcus aureus</i> (MSSA) isolates. 15 methicillin-resistant coagulase-negative <i>Staphylococcus</i> (MR-CNS) isolates	Presence/percentages of ARGs in following isolates: MRSA— <i>blaZ</i> , 9/9 (100%); <i>aac(6′)-le-aph(2′′)-la</i> , 3/9 (33%); <i>ant(4′)-la</i> , 2/9 (22%); <i>ant(6)-la</i> , 0/9 (0%); <i>msrA</i> , 0/9 (0%); <i>ermA</i> , 4/9 (44%); <i>ermB</i> , 0/9 (0%); <i>ermC</i> , 1/9 (11%); <i>tet(K)</i> , 0/9 (0%); <i>tet(L)</i> , 0/9 (0%); <i>tet(M)</i> , 0/9 (0%); <i>aph(3′)IIIa</i> , 0/9 (0%); MR-CNS— <i>blaZ</i> , 15/15 (100%); <i>aac(6′)-le-aph(2′′)-la</i> , 5/15 (33%); <i>ant(4′)-la</i> , 1/15 (7%); <i>ant(6)-la</i> , 2/15 (13%); <i>msrA</i> , 6/15 (40%); <i>ermA</i> , 0/15 (0%); <i>ermB</i> , 0/15 (0%); <i>ermC</i> , 0/15 (0%); <i>tet(K)</i> , 0/15 (0%); <i>tet(L)</i> , 0/15 (0%); <i>tet(M)</i> , 0/15 (0%); <i>aph(3′)IIIa</i> , 0/15 (0%).
Ioannidis et al., 2009	19–76 years	Greece	Subgingival plaque	Healthy	Not stated	Percentages of antibiotic resistance genes in subgingival samples in the following patient groups: Healthy/gingivitis/periodontitis— <i>tet(Q)</i> , 76.5%, 69.2% and 66.7%; <i>tet(M)</i> , 82.4%, 76.9% and 70.8%; <i>blaTEM</i> , 47.1%, 46.2% and 50%; <i>nim</i> , 0%, 0% and 0%.

(Continues)

TABLE 2 (Continued)

Author	Age	Geographic location	Oral site	Healthy/diseased patients	Bacteria	Presence and prevalence of genes
Jungermann et al., 2011	Adults 19–94 years old	USA	Root canals	Systemically healthy but patients had primary or persistent root canal infection.	Bacterial strains not stated in relation to antibiotic resistance genes.	Percentages of antibiotic resistance genes in samples from primary endodontic infection (pre-op/pre-obturation): <i>bla</i> TEM-1, 43% and 10%; <i>cfxA</i> , 17% and 0%; <i>bla</i> Z, 0% and 0%; <i>tet</i> (M), 17% and 30%; <i>tet</i> (W), 20% and 0%; <i>tet</i> (Q), 30% and 0%. Percentages of antibiotic resistance genes in samples from persistent endodontic infection (pre-op/pre-obturation): <i>bla</i> TEM-1, 13% and 7%; <i>cfxA</i> , 0% and 0%; <i>bla</i> Z, 7% and 0%; <i>tet</i> (M), 20% and 7%; <i>tet</i> (W), 13% and 7%; <i>tet</i> (Q), 7% and 0%.
Kadhem, 2018	Not stated	Not stated	Root canals	Not stated	<i>E. faecalis</i>	Out of seven <i>E. faecalis</i> isolates, 57% had <i>van</i> (A) present and 28.6% had <i>van</i> (B) present.
Kim & Lee, 2015	Not stated	Korea	Saliva	Periodontal patients	<i>Staphylococcus aureus</i>	Percentage of <i>bla</i> Z gene in <i>S. aureus</i> isolates from periodontal patients: 90%
Kouidhi et al., 2011	4–12 years old	Tunisia	Supragingival plaque	Healthy	21 Twenty-one species isolated. Most isolated strains were <i>S. mutans</i> , <i>S. oralis</i> , <i>E. faecalis</i> and <i>S. constellatus</i> .	Percentages of antibiotic resistance genes in 21 bacterial isolates from plaque samples in caries group/caries free group: <i>erm</i> (B)—12.84% and 0.092%; <i>tet</i> (M)—9.17% and 3.67%; <i>tet</i> (O)—27.52% and 3.67%.
Koukos et al., 2014	Adults >30 years old	Greece	Oral sulcus	Systemically healthy	No bacterial strains stated in relation to presence of antibiotic resistance genes.	Percentages of antibiotic resistance genes in samples from the gingival sulcus in the following groups: Healthy implant patients/peri-implantitis patients— <i>tet</i> (M), 30% and 40%; <i>tet</i> (Q), 65% and 75%; <i>bla</i> TEM, 15% and 5%; <i>nim</i> , 0% and 0%; <i>mec</i> (A), 0% and 0%.
Kulik et al., 2019	Not stated	Switzerland	Subgingival samples	Periodontal patients	57 Fifty-seven strains of <i>A. actinomycetemcomitans</i> (AA) 56 strains of <i>P. gingivalis</i> (Pg).	<i>cfxA</i> not detected in either Pg/AA strains. <i>tet</i> Q detected in two Pg strains (2/56) 4%. <i>erm</i> F detected in one AA strain (1/56) 2%.
Lancaster et al., 2005	4–6 years old	UK	Plaque	Healthy	Bacterial strains not stated in relation to antibiotic resistance genes.	Presence of antibiotic resistance genes in tetracycline-resistant oral bacteria: <i>tet</i> (M) (most prevalent gene) found to persist within the oral bacteria at all three time points (0, 6 and 12 months) in 14 of 18 children. <i>Tet</i> (B), (K), (O), (Q), (S) and (W) only detected at one time point. <i>Tet</i> (32) found in two children in the same class.

(Continues)

TABLE 2 (Continued)

Author	Age	Geographic location	Oral site	Healthy/diseased patients	Bacteria	Presence and prevalence of genes
Lins et al., 2013	Not stated	Brazil	Root canals	Systemically healthy but with primary endodontic infection.	20 <i>E. faecalis</i> isolates.	Percentage of resistant genes in <i>E. faecalis</i> from primary endodontic infection: <i>tet</i> (M)—60%; <i>tet</i> (L)—20%; <i>erm</i> (A)—0%; <i>erm</i> (B)—0%; <i>van</i> (A)—0%; <i>van</i> (B)—0%; <i>van</i> (C1)—0%; <i>van</i> (C2/3)—0%.
Manch-Citron et al., 2000	Adult >26 years old	USA	Subgingival plaque samples before and 6 months after tetracycline fibres placed in periodontal pocket.	Systemically healthy but with generalised moderate-severe adult periodontitis.	<i>P. gingivalis</i> , <i>E. corrodens</i> , <i>F. nucleatum</i> , <i>C. rectus</i> , <i>B. forsythus</i> , <i>T. denticola</i> .	Percentages of antibiotic resistance genes in subgingival samples from periodontal patients before and 6 months after tetracycline fibres were placed in periodontal pockets: <i>tet</i> (M)—80% and 50%; <i>tet</i> (O)—0% and 20%; <i>tet</i> (Q)—20% and 30%.
Menon et al., 2019	18–45 years	Hong Kong	Saliva	Healthy	Not stated	From five patients following ARGs present: TEM-1 most common; <i>mtr</i> 2, <i>tet</i> A, <i>cfxA</i> , PBP2x, <i>saa</i> , <i>lmrD</i> , <i>lmrC</i> , <i>ng3</i> , <i>nacB</i> -1, <i>sar</i> , PBP1b, <i>mtr</i> , <i>ecf</i> , <i>acrF</i> , <i>mtrC</i> , <i>macA</i> , <i>ng2</i> , <i>macB</i> , <i>ermF</i> , <i>mexQ</i> , <i>mtrE</i> , <i>ng1</i> and <i>emrY</i> .
Milanovic et al., 2020	18–59 years	Italy	Saliva	Healthy	Not stated	Presence/percentage of ARGs from 144 individuals: <i>erm</i> (A)—1 (1%); <i>erm</i> (B)—140 (97%); <i>erm</i> (C)—39 (27%); <i>van</i> A—15 (10%); <i>van</i> B—0 (0%); <i>tet</i> (O)—22 (15%); <i>tet</i> (M)—135 (94%); <i>tet</i> (W)—144 (100%); <i>tet</i> (S)—70 (49%); <i>tet</i> (K)—58 (40%); <i>mecA</i> —0 (0%); <i>blaZ</i> —68 (47%).
Montagner et al., 2014	Not stated	Brazil	Root canals	Systemically healthy but patients presented with spontaneous pain and pulp necrosis.	<i>Prevotella intermedia/nigrescens</i> , <i>Prevotella buccae</i> , <i>Prevotella oralis</i> , <i>Prevotella disiens</i> , <i>Parvimonas micra</i> , <i>Porphyromonas endodontalis</i> and <i>Porphyromonas gingivalis</i> .	Percentage of <i>cfxA/cfxA2</i> detected in <i>Porphyromonas</i> , <i>Prevotella</i> and <i>Parvimonas</i> species from acute endodontic infections was 6.9%.
Okamoto et al., 2001	3 groups - Young: 6–11 years; Middle: 11–40 years; Older: 70 years.	Japan	Gingival sulcus	Healthy	<i>P. nigrescens</i> , <i>P. intermedia</i> and <i>P. gingivalis</i> .	Percentages of <i>tet</i> (Q) gene in black-pigmented anaerobe-positive subjects in three age groups: Young (6–10 years), 29.4%; Middle (11–40 years), 32.1%; Elder (70 years), 30%. Total percentage of <i>tet</i> (Q)-positive isolates in <i>P. nigrescens</i> 27.5%, <i>P. intermedia</i> 6.4% and <i>P. gingivalis</i> 0%.

(Continues)

TABLE 2 (Continued)

Author	Age	Geographic location	Oral site	Healthy/diseased patients	Bacteria	Presence and prevalence of genes
Palma et al., 2016	2–16 months	Brazil	Oral mucosa	Healthy	<i>Streptococcus salivarius</i>	Percentage of antibiotic resistance genes in the genome of 21 <i>Streptococcus salivarius</i> strains: <i>tet(M)</i> , 47.6%; <i>tet(O)</i> , 14.3%.
Patterson et al., 2007	Not stated	Scotland, Norway, France, Finland, Italy, England	Saliva	Healthy	Bacterial strains not stated in relation to antibiotic resistance genes.	Presence of antibiotic resistance genes in saliva samples in the following countries: Scotland— <i>tet(O)</i> ; Norway— <i>tet(O)</i> ; France— <i>tet(O)</i> ; Finland— <i>tet(O)</i> ; Italy— <i>tet(O)</i> and <i>tet(W)</i> ; England—nil.
Penas et al., 2013	Not stated	Brazil	Root canals	Not stated	<i>E. faecalis</i>	Percentages of antibiotic resistance genes in <i>E. faecalis</i> isolated from failed root canal treatment: <i>tet(M)</i> —57.1%; <i>erm(B)</i> —61.9%; <i>erm(B)</i> + <i>tet(M)</i> —47.6%; <i>aac6'-aph2''</i> —4.8%; <i>van(A)</i> —0%.
Poeta et al., 2009	11–61 years: No fixed appliance group 13–55 years: Fixed appliance group	Portugal	Supragingival dental plaque	Systemically healthy	<i>E. faecium</i> , <i>E. faecalis</i> , <i>E. coli</i>	Presence of antibiotic resistance genes in different bacteria from supragingival plaque in fixed appliance group: <i>E. coli</i> — <i>tet(A)</i> , <i>tet(B)</i> , <i>aadA</i> , <i>sul1</i> , <i>sul2</i> , <i>int1</i> , <i>int2</i> and <i>cmlA</i> ; <i>E. faecium</i> — <i>erm(B)</i> , <i>aph(3')-IIIa</i> and <i>tet(L)</i> ; <i>E. faecalis</i> — <i>erm(B)</i> , <i>tet(M)</i> , <i>tet(L)</i> , <i>aph(3')-IIIa</i> , <i>ant(6)-Ia</i> and <i>cat(A)</i> . Patients who did not wear a fixed appliance had none of the above bacteria present.
Ready et al., 2006	Not stated	UK	Dental plaque	Healthy	<i>Veillonella</i> species.	Percentages of antibiotic resistance genes from 96 <i>Veillonella</i> species: <i>tet(M)</i> —8.3%; <i>tet(S)</i> —5.2%; <i>tet(O)</i> —1.04%; <i>tet(A)</i> —1.04%; <i>tet(L)</i> —1.04%.
Reynolds et al., 2016	Not stated	Not stated	Saliva	Not stated	Not stated	Identification of novel tetracycline resistance determinants, <i>tetAB(60)</i> . This is a heterodimeric ABC transporter which specifically exports tetracycline and tigecycline, conferring high levels of resistance to these antibiotics.
Rocas & Siqueira, 2012	Not stated	Brazil	Root canals	Not stated	Multiple bacterial strains noted.	Percentages of antibiotic resistance genes detected in all bacterial strains isolated from root canals with primary infection: <i>blaTEM</i> , 17%; <i>cfxA</i> , 2%; <i>blaCMY-Z</i> , 0%; <i>blaZ</i> , 0%; <i>amp(C)</i> , 0%; <i>mec(A)</i> , 0%; <i>tet(M)</i> , 5%; <i>tet(O)</i> , 0%; <i>tet(Q)</i> , 0%; <i>tet(S)</i> , 2%; <i>tet(W)</i> , 10%; <i>erm(A)</i> , 0%; <i>erm(B)</i> , 0%; <i>erm(C)</i> , 10%.

(Continues)

TABLE 2 (Continued)

Author	Age	Geographic location	Oral site	Healthy/diseased patients	Bacteria	Presence and prevalence of genes
Rocas & Siqueira, 2013	19–64 years	Brazil	Single root canals before and after instrumentation.	Not stated	No bacterial strains stated in relation to the presence of antibiotic resistance genes.	Percentages of antibiotic resistance genes in root canal samples from asymptomatic apical periodontitis patients before/after instrumentation: <i>bla</i> TEM—0%/0%; <i>cfxA</i> —0%/0%; <i>erm</i> (C)—25%/8%; <i>tet</i> (M)—42%/13%; <i>tet</i> (Q)—0%/0%; <i>tet</i> (W)—29%/8%.
Rossi-Fedele et al., 2006	Not stated	UK	Root canals	Not stated but all had radiographically detectable periapical lesions.	<i>Tet</i> (M) containing bacteria: <i>Streptococcus mitis</i> , <i>Neisseria</i> sp., <i>Mycobacterium</i> sp. and <i>Amycolatopsis</i> sp.	53% of the tetracycline-resistant bacteria isolated from root canal samples possessed the <i>tet</i> (M) gene.
Sun et al., 2012	36–72 years Average age of 53 years	Norway	Subgingival plaque samples from periodontal pockets	Systemically healthy but periodontal patients.	<i>E. faecalis</i>	Percentages of antibiotic resistance genes from 24 <i>E. faecalis</i> bacterial strains from subgingival plaque samples in chronic periodontitis patients: <i>tet</i> (K)—0%; <i>tet</i> (L)—4%; <i>tet</i> (M)—42%; <i>tet</i> (O)—4%; <i>tet</i> (S)—0%; <i>erm</i> (B)—12.5%; <i>int</i> —42%.
Tang et al., 2020	20–30 years	China	Supragingival dental plaque	Healthy	Methicillin-resistant <i>Staphylococcus epidermidis</i> (MRSE).	From 35 MRSE isolates: <i>aacA-aphD</i> —7/35 (20%); <i>aadD</i> —10/35 (29%); <i>aphA3</i> —8/35 (23%); <i>dfrG</i> —27/35 (77%); <i>dfrK</i> —0/35 (0%); <i>dfrA</i> —35/35 (100%); <i>ermA</i> —0/35 (0%); <i>ermB</i> —0/35 (0%); <i>ermC</i> —5/35 (14%); <i>ileS2</i> —0/35 (0%); <i>msrA</i> —2/35 (6%); <i>vgb</i> —0/35 (0%); <i>tetK</i> —6/35 (17%); <i>tetM</i> —0/35 (0%); <i>sul1</i> —0/35 (0%); <i>sul2</i> —0/35 (0%); <i>sul3</i> —0/35 (0%); <i>qnrA</i> —0/35 (0%); <i>norA</i> —3/35 (9%).
Warburton et al., 2013	Adults	France	Saliva	Healthy	<i>S. australis</i>	Identification of a novel tetracycline resistance determinant, <i>tetAB</i> (46), in an oral viridans <i>Streptococcus</i> species. <i>TetAB</i> (46) is related to known MDR-type ABC transporters in both gram-positive and gram-negative bacteria but confers resistance only to tetracyclines.

(Continues)

TABLE 2 (Continued)

Author	Age	Geographic location	Oral site	Healthy/diseased patients	Bacteria	Presence and prevalence of genes
Zhang & Zhang, 2019	Not stated	China	Saliva	Caries active patients	<i>Lactobacillus fermentum</i> (17 clinical strains), <i>Lactobacillus rhamnosus</i> (seven clinical strains), <i>Lactobacillus plantarum</i> (seven clinical strains)	Tetracycline resistance genes detected in following clinical isolates: <i>L. fermentum</i> — <i>tetPB</i> , <i>tetT</i> , <i>otrA2</i> , <i>tetW1</i> , <i>tetW2</i> and <i>tcr3</i> ; <i>L. rhamnosus</i> — <i>tetW</i> , <i>tetO</i> , <i>tetT</i> and <i>tcr3</i> ; <i>L. plantarum</i> — <i>tetT</i> , <i>tetO</i> , <i>tetL</i> , <i>tcr3</i> and <i>tetPB</i> ; most common— <i>tetT</i> , <i>tetW</i> , <i>tetO</i> and <i>tetL</i> .
Zhu et al., 2017	Not stated	China	Plaque samples	Healthy but periodontal patients	Viridans group <i>Streptococci</i>	Percentages of resistance genes from 42 Viridans group <i>Streptococci</i> isolates: 85% <i>mef(A)</i> , 14.3% <i>erm(B)</i> .

difference between the prevalence of *tet(M)* in subgingival plaque samples between healthy, gingivitis and periodontitis subjects? (See Table S5.) Using the Pearson Chi-square test, no significant difference was found between the groups ($p = 0.198$).

Comparing only two to three studies will limit any conclusions that can be drawn. The method of pooling the samples was crude with no weighting used, so the results are not conclusive. A greater number of studies are needed to draw definite conclusions and research is unquestionably needed in this area.

3.2 | Age

Five studies investigated the prevalence of antibiotic resistance genes from plaque, plaque and teeth with carious lesions, the oral mucosa and the gingival sulcus in children (Alicea-Serrano et al., 2013; Kouidhi et al., 2011; Lancaster et al., 2005; Okamoto et al., 2001; Palma et al., 2016) (Table 2). These were only able to be compared with two adult studies (Collins et al., 2016; Ioannidis et al., 2009), which took samples from these sites and were from healthy adults. Tetracycline resistance genes were predominantly investigated, so only these were discussed. One study found that age was not a factor in the prevalence of antibiotic resistance genes, for example *tet(Q)* in black-pigmented anaerobe-positive subjects from whole subgingival plaque samples was similar between 6–10-year-olds (29.4%), 11–40-year-olds (32.1%) and 70-year-olds (30%) (Okamoto et al., 2001).

Another study showed, however, the mode of birth and the child's environment in the early stages of life can influence which genes are obtained. In this study, *tet(M)* was present in 50% of samples from the oral mucosa and was the most prevalent gene in babies delivered vaginally and *tet(W)* (present in 33% of samples) for babies delivered by C-section; however, tests to see if this relationship was statistically significant were not completed (Alicea-Serrano et al., 2013). Antibiotic resistance genes transferred at the time of birth depended on the different bacteria present. For example, *Lactobacillus* and *Prevotella* are vaginal dominant bacteria and can carry the *tet(M)* gene (Dominguez-

Bello et al., 2010), whilst *Staphylococcus* and *Corynebacterium* carry the *tet(W)* gene and are commonly from the skin (Dominguez-Bello et al., 2010), which can be acquired during a C-section. The C-section babies did not obtain any *tet(M)* genes; however, later in life these genes can disseminate by other means. This can start in the hours after birth when the oral cavity is exposed to many microorganisms through breathing, breastfeeding and contact with parents and medical staff (Sampaio-Maia & Monteiro-Silva, 2014).

Palma et al. (2016) documented the presence of *tet(M)* and *tet(O)* in infants and discussed the mother–child transmission relationship. Genes can disseminate through contact with other children, for example at day care centres or school (Palma et al., 2016).

3.3 | Geographic location

Twelve studies were able to be compared to look at the presence of antibiotic resistance genes between different countries (Table 2) (Card et al., 2014; Collins et al., 2016; Diaz-Mejia et al., 2002; Ioannidis et al., 2009; Jungermann et al., 2011; Manch-Citron et al., 2000; Milanovic et al., 2020; Patterson et al., 2007; Rocas & Siqueira, 2012, 2013; Sun et al., 2012; Tang et al., 2020).

From studies looking at antibiotic resistance genes in saliva samples in Europe, the most prevalent gene was *erm(B)* which was present in up to 97% of individuals (Milanovic et al., 2020). *tet(B)*, *tet(O)* and *tet(W)* were all found to be the most common tetracycline resistance genes with *tet(W)* present in 100% of saliva samples in Italy (Milanovic et al., 2020).

Although antibiotic resistance genes have been detected in humans where there is little or no evidence of antibiotic use (Bhullar et al., 2012; Pallecchi et al., 2007), from our findings, countries with higher consumption of antibiotics generally had higher numbers of antibiotic resistance genes. On a global scale, high-income countries (HICs) have the highest antibiotic consumptions with an average 25 DDD (defined daily doses) per 1000 inhabitants per day (Antoñanzas & Goossens, 2019). The United States, France and Italy are the HICs that were

the leading consumers of antibiotics in 2015 (Klein et al., 2018). Low- and middle-income countries such as Brazil average around 15 DDD per 1000 inhabitants per day (Antoñanzas & Goossens, 2019). Three studies compared antibiotic resistance genes in root canals from the United States and Brazil (Jungermann et al., 2011; Rocas & Siqueira, 2012, 2013). Three genes (*bla*TEM-1, *cfxA* and *tet(Q)*) out of the five genes that could be compared were all lower in the Brazilian samples than the U.S. samples, which may reflect this difference in antibiotic consumption rates.

In Europe, France has the fifth highest antibiotic prescription rate out of 29 European countries, Italy 12th, UK 17th and Finland 22nd (European Centre for Disease Prevention and Control, 2018), and one study showed in saliva samples taken from 20 healthy volunteers in different countries that eight antibiotic resistance genes were present in the French samples compared to three in samples taken from Scotland and Italy (Card et al., 2014). Remaining in Europe, Greece has the highest antimicrobial consumption in Europe with 34 DDD per 1000 inhabitant per day and has a relatively lax antimicrobial policy as antibiotics can be brought easily over the counter (European Centre for Disease Prevention and Control, 2018). This is contrast to Norway which has low consumption of antibiotics at 15.3 DDD per 1000 inhabitant per day which is reflected in our found studies. In Greek subgingival plaque samples, *tet(M)* was present in 70.8% of cases compared to 42% of samples in Norway (Ioannidis et al., 2009; Sun et al., 2012). Further research would need to be completed to confirm this link and to obtain a deeper understanding of the effect of antibiotic consumption on the spread of resistance one needs to follow the antibiotic consumption of individuals over time and correlate that with the antibiotic resistance genes in their resistome.

A country's antibiotic use in the livestock industry is also another factor to consider in the spread of antimicrobial resistance since antibiotic resistance genes can be transferred to bacterial cells in the human oral cavity from food sources (Li et al., 2001). In the Dominican Republic, the livestock industry uses subtherapeutic levels of antibiotics as growth promoters in poultry feed that can select resistant bacterial strains (Silfrany et al., 2013). One study demonstrated the prevalence of *tet(Q)* in all bacteria in subgingival samples to be 82.8% and *tet(O)* 31% (Collins et al., 2016), a higher level than in Norway (prevalence of *tet(O)* in *Enterococcus faecalis* species 4%) (Sun et al., 2012) and the United States (*tet(Q)* 20%, *tet(O)* 0%) (Manch-Citron et al., 2000). Although the EU and Norway banned antibiotic use for growth promotion in 2003 (Centers for Disease Control and Prevention, 2019), the United States did not ban the use of antibiotics in livestock without a veterinary prescription (U.S. Food and Drug Administration, 2012) until after the study of Manch-Citron, so the lower levels of resistance genes in this country cannot be completely explained by the lower use of antibiotics.

3.4 | Health and oral disease

Two studies investigated the prevalence of genes between healthy and periodontal subjects (Collins et al., 2016; Ioannidis et al., 2009).

Collins et al. (2016) showed *tet(Q)* and *tet(32)* were more prevalent in subgingival samples from chronic periodontitis subjects (82.8% and 72.4%, respectively) compared to the healthy group (45.5% and 9.09%, respectively) which was statistically significant ($p = 0.023$ for *tet(Q)* and $p = 0.019$ for *tet(32)*). The studies established that overall there was no difference in the prevalence of the common *tet(M)* gene between healthy (45.5%–82.4%) and chronic periodontitis (31%–70.8%) subjects (Collins et al., 2016; Ioannidis et al., 2009). This supports our statistical analysis, which could not find a statistically significant difference ($p = 0.198$) between the prevalence of *tet(M)* of healthy, gingivitis and periodontitis subjects.

One study compared healthy and peri-implantitis subjects (Koukos et al., 2014). No difference was observed between the healthy implant versus the peri-implantitis group regarding tetracycline resistance genes; however, findings showed high frequencies of detection for both groups concerning *tet(M)* (>30%) and *tet(Q)* (>65%) (Koukos et al., 2014).

Two studies looked at the prevalence of antibiotic resistance genes between carious and non-carious groups (Kouidhi et al., 2011; Zhang & Zhang, 2019). In bacterial isolates of children with active caries, higher frequencies of *ermB* (12.84%), *tet(M)* (9.17%) and *tet(O)* (27.52%) were found compared to the non-carious group (*ermB* [0.092%], *tetM* [3.67%] and *tet(O)* [3.67%]) (Kouidhi et al., 2011). *Lactobacilli* is highly prevalent in patients with caries-active lesions, whilst those who are caries free harbour low levels (Caufield et al., 2015). From 31 *Lactobacilli* clinical strains, isolated from caries-active patients, it was shown the most common tetracycline resistance genes were *tet(T)*, *tet(W)*, *tet(O)* and *tet(L)*.

A final study involved subjects with fixed orthodontic appliances and found subjects with poor oral hygiene select for more pathogenic bacteria that can carry resistance genes (Poeta et al., 2009). Those in the poor oral hygiene group harboured 14 different antibiotic resistance genes in *E. coli* and *Enterococcus* species, which were not present in individuals with good oral hygiene (Poeta et al., 2009). Recognition of oral commensal organisms such as *streptococci* as a reservoir of resistance genes is important since they can transfer to more pathogenic organisms (Bryskier, 2002) that are implicated in systemic disease such as endocarditis, cardiovascular disease and pneumonia (Li et al., 2000). Controlling oral disease with good oral hygiene therefore is imperative. Multiple studies have also shown that improved oral hygiene can decrease the risk of pneumonia as oral colonisation by respiratory pathogens is reduced as well as subsequent aspiration of respiratory pathogens into the lower airway. This is important to consider in the current COVID-19 crisis (Scannapieco, 2006).

3.5 | Bacterial strains

Fourteen studies investigated the prevalence of antibiotic resistance genes in specific bacterial strains (Table 2); four of these were in *E. faecalis*, two of which were from root canals (Lins et al., 2013; Penas et al., 2013) and the others from supra- and subgingival plaque (Poeta et al., 2009; Sun et al., 2012). *Enterococcus faecalis* is not regarded as a normal

TABLE 3 Mobile genetic elements

Author	Age	Geographic location	Oral site	Healthy/diseased patients	Bacteria	Mobile genetic elements
Chaffanel et al., 2015	One 38-year-old adult, four children between 15 and 33 months	France	Saliva	Healthy	<i>Streptococcus salivarius</i>	Number of genetic elements present in 20 isolates of <i>Streptococcus salivarius</i> : ICEst3—integrative and conjugative element—11/20; Tn916—integrative and conjugative element—4/20; Tn3872 [<i>erm</i> (B) in orf9 of Tn916]—0/20; Tn6002 [<i>erm</i> (B) in rel of Tn916]—2/20; Tn2009 [<i>mef</i> (A/E) in orf6 of Tn916]—0/20; The MEGA element which carries a <i>mef</i> (A/E) gene—13/20; IQ like element [<i>mef</i> (A/E) and <i>catQ</i> linkage]—0/20.
Ciric et al., 2011	Not stated	UK	Saliva	Healthy	<i>Streptococcus oralis</i>	Detection of a novel small multidrug resistance gene, <i>qrg</i> , that encodes resistance to CTAB. It is located on a composite transposon consisting two IS1216 elements flanking <i>qrg</i> , inserted in a Tn916-like element (Tn6087) capable of transfer by transformation to another streptococcal strains.
Ciric et al., 2014	No stated	UK	Saliva	Healthy	<i>Streptococcus infantis</i>	Determines the genetic basis of minocycline resistance in a human derived oral <i>S. infantis</i> isolate. Shows that it is due to <i>tet</i> (S) present on a novel low copy number plasmid (pSI01) flanked by IS1216 elements. It is capable of excising, together with orf6 and one of the IS1216 into a free, non-replicative circular form. Authors suspects that this type of recombination between IS1216 elements associated with <i>tet</i> (S) is aiding dissemination of <i>tet</i> (S) amongst different DNA molecules.
Fernandez-Canigia et al., 2015	Subgingival plaque: 35–60 years	Argentina	Subgingival plaque and peritonsillar abscesses	Patients with periodontal disease or tonsillar abscesses	<i>Prevotella intermedia</i> , <i>Prevotella nigrescens</i>	<i>mobA</i> with high level identity to Tn4555, a conjugative transposon that is potentially involved in the horizontal transfer of β -lactamase genes in <i>Bacteroides</i> , <i>Prevotella</i> and <i>Capnocytophaga</i> , was detected downstream of <i>cfxA</i> .
Lancaster et al., 2005	4–6 years old	UK	Plaque	Systemically healthy	Multiple bacterial species included.	Study indicates that <i>tet</i> (M) was contained within a Tn916-like element.

(Continues)

TABLE 3 (Continued)

Author	Age	Geographic location	Oral site	Healthy/diseased patients	Bacteria	Mobile genetic elements
Ready et al., 2006	Not stated	UK	Dental plaque	Healthy subjects	<i>Veillonella</i> species.	A <i>tet(M)</i> positive <i>Veillonella dispar</i> strain was shown to transfer a Tn916-like element to four <i>Streptococcus</i> species by conjugation at a frequency of 5.2×10^{-6} to 4.5×10^{-5} per recipient.
Rossi-Fedele et al., 2006	Not stated	UK	Root canals	Not stated but all had radiographically detectable periapical lesions.	<i>Tet(M)</i> containing bacteria: <i>Streptococcus mitis</i> , <i>Neisseria</i> sp., <i>Mycobacterium</i> sp. and <i>Amycolatopsis</i> sp.	Discovered a tetracycline-resistant <i>Neisseria</i> species capable of transferring an unstable Tn916-like element to <i>E. faecalis</i> ; the first time such a transfer has been recorded.
Sedgley et al., 2008	Not stated.	USA	Oral site of bacterial strains not stated. Bacterial strains inserted into root canals of extracted teeth.	Not stated but teeth used were virgin teeth.	<i>S. gordonii</i> and <i>E. faecalis</i>	Bidirectional transfer of an erythromycin resistance determinant on the conjugative plasmid pAM81 between <i>S. gordonii</i> and <i>E. faecalis</i> . Average frequencies for transfer of erythromycin resistance: transfer from <i>S. gordonii</i> to <i>E. faecalis</i> averaged 10^{-3} transconjugants per donor at both 24 and 72 h. Transfer from <i>E. faecalis</i> to <i>S. gordonii</i> averaged 10^{-6} and 10^{-7} transconjugants per donor at 24 and 72 h, respectively. Control teeth yielded no transconjugants.
Sun et al., 2012	36–72 years old	Norway	Subgingival plaque samples from periodontal pockets	Healthy but periodontal patients	<i>E. faecalis</i>	Tn916-like elements harbouring <i>tet(M)</i> and <i>int</i> genes were detected in seven of 24 strains that expressed resistance or intermediate susceptibility to doxycycline. Tn1545-like elements harbouring <i>tet(M)</i> , <i>erm(B)</i> and <i>int</i> genes were detected in three of 24 strains, including two strains with high-level resistance to erythromycin and doxycycline. The study has revealed a direct link between Tn916/Tn1545-like elements and the resistance to doxycycline and/or erythromycin.

(Continues)

TABLE 3 (Continued)

Author	Age	Geographic location	Oral site	Healthy/diseased patients	Bacteria	Mobile genetic elements
Villedieu et al., 2004	Adults: not stated	UK	Saliva and plaque	Healthy	<i>Streptococcus</i> , <i>Veillonella</i> , <i>Prevotella</i> , <i>Neisseria</i> , <i>Lactobacillus</i> and <i>Staphylococcus</i> .	Filter mating study showed four of 12 isolates (mixture of <i>Streptococcus</i> , <i>Neisseria</i> , <i>Staphylococcus</i> , <i>Veillonella</i> and <i>Prevotella</i> species) were able to transfer genes encoding resistance to both erythromycin <i>erm(B)</i> and tetracycline <i>tet(M)</i> to an <i>E. faecalis</i> recipient. These two genes have previously been found on the same conjugative transposon, Tn1545, which belongs to a larger class of conjugative transposons including Tn916.
Warburton et al., 2007	Not stated	UK	Subgingival plaque	Systemic health not stated but patients had generalised severe periodontitis.	<i>Streptococcal</i> species	Study demonstrates transfer of doxycycline resistance mediated by a novel transposon CTn60002. Demonstrates the transfer of antimicrobial resistance from one oral <i>streptococcal</i> species to another during antimicrobial treatment of periodontitis.

inhabitant of the oral cavity (Murray, 2000), yet has been isolated from carious lesions, chronic periodontitis and endodontic infection (Zhu et al., 2010). The prevalence of *tet(M)* from *E. faecalis* isolates is high both from endodontic infections and periodontal subjects, ranging from 42% to 60% (Lins et al., 2013; Penas et al., 2013; Poeta et al., 2009; Sun et al., 2012). This may be explained by selection pressure from the use of tetracycline in periodontal disease and intracanal medicaments such as Ledermix paste, containing tetracycline. There is also a high prevalence of *erm(B)* in *E. faecalis* isolates (0%–61.9%) (Penas et al., 2013; Sun et al., 2012). This suggests *E. faecalis* represents a reservoir of resistance to tetracycline and erythromycin indicating the need to consider alternative approaches to treatment in dentistry such as vaccines (Dagan & Klugman, 2008) and bacteriophage therapy (Soothill, 2013).

Seven studies investigated the prevalence of antibiotic resistance genes in periodontal pathogens. Four studies looked at *Prevotella* (Chung et al., 2002; Fernandez-Canigia et al., 2015; Fosse et al., 2002; Okamoto et al., 2001), one *Capnocytophaga* species (Ehrmann et al., 2014) and another two *Staphylococcus aureus* (Kim & Lee, 2015); (Hirose et al., 2019). Two studies investigated the prevalence of *tet(Q)* in plaque from the following black-pigmented anaerobes: *Porphyromonas gingivalis*, *Prevotella intermedia* and *Prevotella nigrescens* (Chung et al., 2002; Okamoto et al., 2001). In the periodontal group, *tet(Q)* was present in 33% of *P. gingivalis* and 40% *P. intermedia* isolates compared to 0% and 6.4%, respectively, in the healthy periodontal group (subjects with probing depths of 3 mm or less, no bleeding on probing, suppuration or signs of erythema). However, the healthy group had higher levels of

tet(Q) in *P. nigrescens* (27.5% compared to 8% in the periodontal group). *Prevotella nigrescens* is a marker bacterium for periodontally healthy subjects (Okamoto et al., 2001) in contrast to *P. gingivalis* which exists at low levels in the healthy gingival sulcus (Conrads et al., 1996). As the prevalence of these bacteria differs in healthy and diseased states, this may account for the difference in prevalence of *tet(Q)* between the two studies.

Two studies investigated beta-lactam resistance in *Prevotella* species found in subgingival plaque taken from periodontal subjects (Fernandez-Canigia et al., 2015; Fosse et al., 2002). The presence of beta-lactamase gene *cfxA* was high at 97% (Fosse et al., 2002) and it was more frequent in *P. intermedia* than in *P. nigrescens* (Fernandez-Canigia et al., 2015); however, in another study the opposite has also been shown (Bernal et al., 1998).

Capnocytophaga species can be associated with periodontal health or disease (Riep et al., 2009). In one study (Ehrmann et al., 2014), there was a high prevalence of beta-lactam and macrolide resistance genes. From 48 *Capnocytophaga* isolates, 31% had *blaCFxA* present and 27% had *ermF* present demonstrating that *Capnocytophaga* species are the main reservoir of MLS (macrolide–lincosamide–streptogramin) genes in the oral cavity.

Staphylococcus aureus has a role in periodontal disease progression (Kim & Lee, 2015; Passariello et al., 2012) and has high levels of beta lactam resistance. According to the latest antimicrobial guidelines (Palmer, 2020), only those patients less than 40 years old who have rapidly progressing periodontal disease should be prescribed sys-

temic antimicrobials which are usually amoxicillin and metronidazole. For those over 40 years with slow or moderate progression of periodontitis, systemic antimicrobials are not recommended as an adjunct to thorough and effective mechanical debridement (Palmer, 2020). The high presence of beta-lactam resistance genes like *blaZ* could compromise treatment outcomes.

Three studies (Chaffanel et al., 2015; Ready et al., 2006; Zhu et al., 2017) investigated the prevalence of resistance genes in *Streptococcus salivarius*, *Veillonella* and Viridans Group *Streptococci* (VGS), which are all part of the normal oral flora showing that commensal bacteria often have high frequencies of antibiotic resistance genes, for example the erythromycin resistance gene; *mef(A/E)* was present in 65% of *S. salivarius* isolates (Chaffanel et al., 2015).

3.6 | Oral sites

3.6.1 | Root canals

Eight studies investigated the prevalence of antibiotic resistance genes in root canals (Jungermann et al., 2011; Kadhem, 2018; Lins et al., 2013; Montagner et al., 2014; Penas et al., 2013; Rocas & Siqueira, 2012, 2013; Rossi-Fedele et al., 2006). *tet(M)* was the most prevalent tetracycline resistance gene in root canals at 5%–60% (prevalence of the gene in either primary or persistent root canal infections before instrumentation at the first stage of root canal treatment) followed by *tet(Q)* (0%–30%) and *tet(W)* (10%–29%).

tet(M), in one instance after instrumentation of the root canals, increased from 17% to 30% (Jungermann et al., 2011), and another study found that although *tet(M)* reduced after treatment, it still had a prevalence of 13% (Rocas & Siqueira, 2013). Although these studies looked at total bacterial load in root canals, it suggests that *E. faecalis* which often resists treatment survives and harbours this gene. In *E. faecalis* in root canals, the *tet(M)* frequency was much higher at 60% (Lins et al., 2013) and 57.1% (Penas et al., 2013) compared to 5%–42% (Jungermann et al., 2011; Rocas & Siqueira, 2012, 2013) in all bacterial species in root canal sites.

In root canals studies that looked at all bacterial species present in primary endodontic infections, *ermC* was the most prevalent erythromycin resistance gene ranging from 10% to 25% (Rocas & Siqueira, 2012, 2013).

BlaTEM was the most prevalent beta-lactam resistance gene at 0%–43% (Jungermann et al., 2011; Rocas & Siqueira, 2012, 2013) (prevalence of the gene in either primary and persistent root canal infection before instrumentation) followed by *cfxA* (0%–17%) (Jungermann et al., 2011; Rocas & Siqueira, 2012, 2013). This is a concern since beta-lactams are the main antibiotics recommended in the treatment in endodontics (Rocas & Siqueira, 2013).

3.6.2 | Subgingival plaque

Nine studies (Collins et al., 2016; Ehrmann et al., 2014; Fernandez-Canigia et al., 2015; Fosse et al., 2002; Ioannidis et al., 2009; Kulik

et al., 2019; Manch-Citron et al., 2000; Sun et al., 2012; Zhu et al., 2017) (Table 2) compared the prevalence of antibiotic resistance genes in subgingival plaque from periodontal subjects.

tet(M) was the most found tetracycline resistance gene. *tet(Q)* also had a higher prevalence in subgingival plaque (20%–82.8%) compared to root canal samples (0%–30%). This is likely due to these genes being present in periodontal pathogens *Porphyromonas* and *Capnocytophaga* genera (Manch-Citron et al., 2000). No definitive conclusions can be made regarding if *tet(M)* and *tet(Q)* are more prevalent in subgingival plaque samples compared to root canals due to the small number of studies viewed; therefore, we recommend additional research is needed in this area.

One study recorded an increased prevalence of *tet(O)* after the application of tetracycline fibres in periodontal pockets (Manch-Citron et al., 2000). *tet(M)*, however, decreased from 80% to 50% over a 6-month period but remained high. These findings question the effectiveness of this treatment; however, as only 10 subjects were investigated, the result has to be interpreted with extreme caution as subgingival application of tetracycline fibres is still used today and can result in probing pocket depth reduction (Matesanz-Perez et al., 2013).

Concerning beta-lactamase resistance genes in periodontal subjects, *blaTEM* was present in 50% of all bacterial species in subgingival samples (Ioannidis et al., 2009), which is comparable to its prevalence in root canals with primary endodontic infection before treatment at 43% (Jungermann et al., 2011). One study showed a high prevalence of the *cfxA* gene (97%) taken from aminopenicillin-resistant *Prevotella* isolates from subgingival plaque samples (Fosse et al., 2002), which is much higher than the gene's prevalence in root canal infection (0%–17%) (Jungermann et al., 2011; Montagner et al., 2014; Rocas & Siqueira, 2012, 2013).

3.6.3 | Supragingival plaque

Three studies investigated antibiotic resistance genes in supragingival plaque (Lancaster et al., 2005; Poeta et al., 2009; Ready et al., 2006). Two studies only investigated tetracycline resistance genes and showed *tet(M)* to be the most prevalent gene (Lancaster et al., 2005; Ready et al., 2006); however, in *E. coli*, *E. faecalis* and *E. faecium* isolates, *erm(B)* was the most prevalent resistance gene being in 80% of samples and *tet(L)* the most common tetracycline-resistant gene in 40% of the isolates analysed (Poeta et al., 2009).

3.6.4 | Saliva

Eight studies investigated the prevalence of antibiotic resistance genes in saliva (Card et al., 2014; Chaffanel et al., 2015; Hirose et al., 2019; Kim & Lee, 2015; Menon et al., 2019; Milanovic et al., 2020; Patterson et al., 2007; Zhang & Zhang, 2019). No single tetracycline resistance gene dominated; however, in one study, *tet(M)* and *tet(W)* were present in 94% and 100% of the samples, respectively (Milanovic et al., 2020), which is much higher than in root canals and subgingival plaque.

TEM-1 was the most frequent beta-lactamase resistance gene in healthy individuals which increased 7.32-fold over a 6-month period after amoxicillin was prescribed on a prophylactic basis to those subjects after wisdom tooth removal in contrast to a 2.41-fold increase in those who did not receive antibiotics after the extraction. This difference was not statistically significant; however, the increase in TEM-1 was accompanied by an increase in the levels of gram-negative *Proteobacteria*. Antimicrobials are not recommended to prevent post-operative complications after tooth extractions (Palmer, 2020), especially as a number of systematic reviews have concluded there is no evidence to support their use (Lodi et al., 2012; Marchionni et al., 2017; Singh Gill et al., 2018). These recommendations should be followed as an oral microbiota resistant to future antibiotic use can be produced (Bush, 2013).

3.7 | Mobile genetic elements

Eleven studies discussed MGEs (Table 3). Nine investigated conjugative transposons, particularly Tn916 and its relatives such as CTn60002, Tn1545, Tn4555, Tn6000 and Tn6887 that carry tetracycline, erythromycin or beta-lactam resistance determinants (Chaffanel et al., 2015; Ciric et al., 2011; Fernandez-Canigia et al., 2015; Lancaster et al., 2005; Ready et al., 2006; Rossi-Fedele et al., 2006; Sun et al., 2012; Villedieu et al., 2004; Warburton et al., 2007). Multiple studies demonstrated *tet(M)* to be contained within a Tn916-like element (Lancaster et al., 2005; Ready et al., 2006; Rossi-Fedele et al., 2006). Tn916 was responsible for the transfer of *tet(M)* from *Neisseria* species to *E. faecalis* in root canals (Rossi-Fedele et al., 2006). Since the root canal system is a closed environment with bacterial cells in close proximity, isolation from the oral environment and immune system make ideal conditions for dissemination of antibiotic resistance (Rossi-Fedele et al., 2006). Another study showed the transfer of the same resistance gene but from *Veillonella* to streptococcal species in dental plaque also mediated by Tn916 (Ready et al., 2006). *tet(M)* and *erm(B)* were able to transfer to an *E. faecalis* recipient genetically linked on the same Tn916-like conjugative transposon Tn1545 (Villedieu et al., 2004). Other conjugative transposons that can disseminate resistance are CTn60002 (part of the Tn916 family) that transfers doxycycline resistance (Warburton et al., 2013) and Tn4555, which harbours *cfxA*, a beta-lactam resistance gene (Fernandez-Canigia et al., 2015). Recently one study (Lunde et al., 2021) investigated the presence of Tn916-like elements in the oral cavity of 100 clinical oral samples from Norway. They found that 24% of oral streptococci contained *tet(M)* and that this gene was contained on integrative conjugative elements of the Tn916 family. In addition, they showed that these elements were capable of inter- and intra-genus transfer, further underlying the importance of these MGEs as vectors for spread of resistance in the oral cavity.

Conjugative plasmids are also important vectors of antibiotic resistance (Roberts & Mullany, 2006) and two studies investigated this (Ciric et al., 2014; Sedgley et al., 2008). Sedgley et al. showed bidirectional transfer of erythromycin resistance via the conjugative plasmid,

pAM81, between *S. gordonii* and *E. faecalis* in root canals (Sedgley et al., 2008). There was a higher rate of transfer of pAM81 from *S. gordonii* to *E. faecalis*.

The most common MGEs that transfer antibiotic resistance genes are conjugative transposons and conjugative plasmids. Both are equally important as they transfer resistance determinants, especially the more frequently studied erythromycin and tetracycline resistance genes between different bacterial species in the oral cavity.

4 | CONCLUSION

This systematic review has shown that antibiotic resistance genes are widespread in bacteria from the oral cavity with *tet(M)* being the most prevalent.

In babies delivered vaginally, *tet(M)* was more prevalent, whilst *tet(Q)* was more prevalent in those delivered by C-section. Generally, countries with higher consumption of antibiotics generally had higher numbers of antibiotic resistance genes. Agricultural as well as medical use of antibiotics in a country should always be considered when investigating antibiotic resistance. Studies in this review showed no difference in the prevalence of *tet(M)* between healthy, periodontitis and peri-implantitis subjects; however, *erm(B)*, *tet(M)*, and *tet(O)* were higher in carious active children than the non-carious group. In addition, subjects with poor oral hygiene select for more pathogenic bacteria that carry resistance genes compared to those with good oral hygiene. *Enterococcus faecalis* isolates demonstrated significant tetracycline and erythromycin resistance, periodontal pathogens showed significant beta-lactam resistance with *blaZ* and *cfxA* present in up to 90%–97% of samples and the normal oral flora has a high level of erythromycin resistance with *mef(A/E)* present in 65% of *S. salivarius* isolates. The most common resistance gene was *tet(M)* in root canals, *cfxA* in subgingival plaque, *erm(B)* in supragingival plaque and *tet(W)* in 100% of whole saliva samples. Most of the antibiotic resistance genes are contained on highly promiscuous MGEs of the Tn916 family of conjugative transposons.

The review also highlights that although many studies in this area have been performed, 50% were classed as low quality and the lack of standardisation has prevented firm conclusions about the role of external selective factors such as antibiotic use and disease states on the spread of resistance being drawn. It is hoped that this review will highlight the need for more rigorous approaches in future studies and we make the following recommendations to allow firm conclusions to be drawn from future work:

- the use of much larger sample sizes than found in most studies;
- investigate a broader range of antibiotic resistance genes including the presence of *nim* genes which encode resistance to metronidazole, an antibiotic commonly used in dentistry;
- improve methodologies and reporting to improve the quality of genetic testing in microbiology;
- randomisation of subject selection.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the Supporting Information of this article.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/omi.12375>.

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SUPPORTING INFORMATION

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