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Antibiotic Exposure and Dental Health: A Systematic Review

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Abbreviations:

DMFT = Mean number of Decayed, Missing or Filled Teeth
ECC = Early Childhood Caries
TDAs = Tetracycline Derived Antibiotics
MIH = Molar-incisor Hypomineralisation
NOS = Newcastle Ottawa Scale
DDE = Developmental Defects of Enamel

Article Summary

This systematic review investigates the relationship between early childhood antibiotic exposure and dental health including dental caries, tooth staining and enamel defects.

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Contributors Statement Page

Drs David Burgner and Dr Amanda Gwee conceptualized and designed the study, and critically reviewed and revised the manuscript.

Dr Mihiri Silva conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed and revised the manuscript.

Dr Dharini Ravindra conceptualized and designed the study, designed the data collection instruments, collected data, carried out the initial analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript.

Dr Gwendolyn Huang collected data, carried out the initial analyses and critically reviewed and revised the manuscript.

Dr Kerrod Hallett critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Context: The use of antibiotics in young children is widespread and may lead to adverse effects on dental health, including staining, developmental defects, and dental caries.

Objective: To systematically review the effects of early childhood antibiotic exposure on dental health

Data Sources: Medline (Ovid/PubMed), Embase (Ovid) and Cochrane databases. Study bias was assessed using the Newcastle-Ottawa Scale.

Study Selection: English language articles which reported antibiotic exposure prior to 8 years of age and one or more of the relevant outcomes (dental caries, intrinsic tooth staining, or developmental defects of enamel) were included

Data Extraction: Data on study population, design, type of antibiotic, outcome measurement, and results were extracted from the identified studies

Results: The initial search yielded 1003 articles of which 34 studies were included. Five of the 18 studies on tetracycline described a dose response relationship between exposure to tetracycline doses of > 20 mg/kg/day and dental staining. Early childhood exposure to doxycycline (at any dose) was not associated with dental staining. There was no clear association between any early childhood antibiotic exposure and dental caries or enamel defects.

Limitations: In all included studies, the main limitations and sources of bias were the lack of comparison groups, inconsistent outcome measures, and lack of adjustment for relevant confounders.

Conclusions: There was no evidence that newer tetracycline formulations (doxycycline and minocycline) at currently recommended dosages led to adverse effects on dental health. Findings regarding antibiotic exposure and developmental defects of enamel or dental caries were inconsistent. Further prospective studies are warranted.

Introduction

Antibiotics are the most commonly prescribed medications in childhood; in Australia their use has increased by 230% in the ten years between 2000 and 2010.[1] Antibiotics are suggested to have a myriad of effects on dental health, particularly tooth staining, developmental tooth defects (enamel hypoplasia and hypomineralisation), and dental caries.[2] However, data are inconsistent, with both adverse and protective effects reported.[3-7]

The mechanisms underlying these putative associations include direct effects on tooth development and indirect influences via the oral microbiome.[2,8,9] Antibiotics can directly interfere with the highly sensitive process of tooth mineralization, leading to developmental dental defects such as enamel hypoplasia, and hypomineralisation.[10] These defects present clinically as tooth discoloration and breakdown, often necessitating complex dental treatment.[11,12,13] In addition, early life exposure to tetracycline antibiotics can lead to formation of complexes within the tooth structure resulting in characteristic 'tetracycline staining' with dark banding across the tooth.[14-16] However, recent studies suggest that newer formulations of tetracycline antibiotics (e.g., doxycycline) may not cause tooth staining.[17-19]

Dental caries (tooth decay) affects 60-90% of children globally.[20-22] Dental caries is multifactorial disease that occurs as a result of oral microbial dysbiosis driven by dietary sugar and dental plaque. Antibiotic exposure may therefore potentially affect the pathogenesis of dental caries both directly (via the oral microbiome) and indirectly (via contributing to enamel defects).[23] Early studies focused on the inverse relationship between antibiotic exposure and dental caries and subsequent findings indicate a possible relationship between antibiotic exposure and enamel defects.[3,24-26] Data on newer antibiotic

115 formulations and their association with dental caries and enamel defects are
116 inconsistent.[27,28]
117
118 We therefore conducted a systematic review to evaluate the evidence regarding the effect
119 of early childhood antibiotic exposure on dental caries, developmental defects of enamel,
120 and tooth staining
121
122 Methods
123
124 This study followed the Preferred Reporting Items for Systematic Reviews and Meta-
125 analyses (PRISMA) reporting guidelines (Appendix 1. Table 1). The review was registered
126 in the PROSPERO database (CRD42020179098).
127
128 MEDLINE (PubMed/Ovid), Embase (Ovid; 1946-current), and the Cochrane Library
129 databases were searched in September 2021 using the search strategies listed in Appendix
130 1, Methods. All searches were limited to the English language. Reference lists of included
131 articles were checked. In addition, Pro-Quest Dissertation Abstracts and Thesis database
132 and Google Scholar were searched for grey literature.
133
134 Studies were included if they reported antibiotic exposure prior to 8 years of age (the
135 period of tooth development) and one or more of the relevant outcomes (dental caries,
136 intrinsic tooth staining, or developmental defects of enamel) based on visual assessment of
137 the dentition. Developmental defects of enamel with a known etiology such as fluorosis
138 and amelogenesis imperfecta were excluded as outcome measures.[29] For the outcomes of
139 dental caries and developmental defects of enamel, only studies using a validated index
140 were included (Appendix 1. Table 2). As there is no validated tool to measure tetracycline

staining, studies using any clearly described method were included.

Two independent investigators (D.R and G.H.) assessed eligibility of all studies in Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia), in a two-stage screening process; by title and abstract and then by full text. Initial disagreements were resolved by discussion and then by a third independent reviewer (M.S.).

Data on study population, design, type of antibiotic, outcome measurement, and results were extracted from the identified studies by a sole investigator (D.R.) using a standardized extraction form. All data extraction was audited by a second reviewer (G.H.). Odds Ratios, p-values and 95% confidence intervals were extracted from studies that quantified the risk of caries, developmental defects of enamel and dental staining with the exposure, antibiotics. If not reported and when possible, the odds ratios and confidence intervals were calculated. All analyses were performed using STATA 16 software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). Due to heterogeneity and lack of data on covariates, meta-analysis was not considered appropriate.

The studies were assessed for risk of bias according to both the Newcastle Ottawa Scale (NOS) and ROBINS-E tool by a sole investigator (D.R) (Appendix 1. Tables 3 and 4) and audited by a second reviewer (M.S.).[30,31] The NOS was modified to suit the research question (Appendix 1. Table 5). No studies were excluded on the basis of the bias assessment.

Results

Study Characteristics

The initial search yielded 1003 articles with 756 articles screened by title and abstract after duplicates had been removed. Overall, 34 were found to be eligible for qualitative analysis (Figure 1). All 34 studies were retrospective cohort studies. A total of 18 studies investigated tetracyclines and/or tetracycline derived antibiotics, seven investigated amoxicillin only, and nine did not specify the antibiotic class.

Exposure ascertainment was based on hospital/pharmacy records or patient/parent recall of medication use. The median age at the time of antibiotic exposure was 6 years (range 0-8 years). Outcomes were measured between 24 months to 18 years of age. Sample size varied from 25 to 29485 participants (Table 1).[3,32]

The methods used to measure and quantify the three outcomes (dental caries, enamel defects and dental staining) varied considerably. A total of 3 different measures were used for caries, 10 for dental staining, and 7 for enamel defects (Appendix 1. Table 2).[33-35] In addition to detection of tetracycline staining from visual and laboratory analyses, general intrinsic staining was determined by measuring tooth color using a shade guide or spectrometer and applying an arbitrary threshold. The seven indices used to measure developmental defects of enamel were variations of two core validated indices (European Academy of Paediatric Dentistry Criteria for MIH (Molar-Incisor hypomineralisation) and DDE (Developmental Defects of Enamel) Index) (Appendix 1. Table 2).[36,37]

Tetracycline & Tetracycline Derived Antibiotics

Tetracycline and Intrinsic Staining

Eighteen studies investigated tetracyclines and tetracycline derived antibiotics, most of

which (n=16) included dental staining as an outcome. Eleven studies investigated older formulations (e.g., tetracyclines), often at relatively higher doses (from 10 to 38mg/kg/day) whereas 5 studies investigated the newer formulations (e.g., doxycycline), often at lower dosages (from 2.3 to 6.25mg/kg/day) (Table 2). Dosage was not reported in three studies.[38-40]

Three studies assessed the presence of the characteristic pattern of tetracycline staining from visual inspection and four studies used fluorescence of exfoliated or extracted teeth. Four studies used tooth color and shade as a marker of tetracycline staining. The five remaining studies used a combination of the above methods or study specific outcome measures based on inherent tooth shade (intrinsic staining).

The studies investigating older formulations of tetracyclines, were published between 1962 and 1980, and had a moderate to critical risk of bias, often failing to clearly report the method for measurement of outcomes. Higher doses of tetracyclines were associated with increased presence of dental staining. In five studies, doses of ≥ 20 mg/kg/day with a duration from 5 to 11 days were associated with dental staining whereas only one study of the same dose reported no association.[41-46] The study that reported the strongest association (OR: 11.62, 95% CI 5.96, 24.32) evaluated the highest dose for the longest consecutive duration (26.7mg/kg/day for a mean of 11 days).[41]

All five studies evaluating the relationship between newer formulations of tetracycline (minocycline and doxycycline) and dental staining showed no association. The studies were published between 1998 to 2017 and average dosage ranged from 2.3 to 25 mg/kg/day with a mean duration of 10.7 days.[17,19,47-49] Notably no cases of tetracycline staining were observed in 58 and 78 children at average doses of 2.3 mg/kg/day and 6.25 mg/kg/day,

respectively. Although the overall risk of bias varied, there was evidence from 3 low bias studies that doxycycline did not cause intrinsic staining, including tetracycline staining.[17,19,47]

Developmental Defects of Enamel

Five studies investigated the relationship between childhood use of tetracycline derived antibiotics and developmental defects of enamel.[17,40,42,43,50] Four of these papers provided details regarding dosage (Table 2). Two papers reported contradictory results for tetracycline at doses of 20 mg/kg/day.[42,43] One study with a critical level of bias investigated 40 premature infants with an average treatment duration of 4 days and found higher odds of enamel defects (OR 5.83, 95% CI 0.42, 314.48). However, the study did not address the role of prematurity on the relationship.[43] In contrast, the other study with a moderate level of bias investigated 160 participants aged 6 to 12 years with an average of 6 days of medication and found no cases of enamel hypoplasia.[42]

The two studies of newer formulations (doxycycline at 5 mg/kg/day and minocycline at 2.3 mg/kg/day) did not report an increased odds of enamel hypoplasia (OR 0.89, 95% CI 0.38, 2.11; OR 0.92, 95% CI 0.2, 4.2).[17,50] The findings from these five studies are contradictory and preclude clear conclusions but suggest that newer formulations at lower dosages likely do not have an association with developmental defects of enamel.[17,40,42,43,50]

Dental Caries

Three of the four studies of dental caries used the total number of decayed, missing, filled teeth or surfaces based on visual inspection as a measure of caries prevalence or severity; a single study used radiographic evaluation in addition to a clinical criterion. Tetracycline use at 20mg/kg/day had no association with the presence of dental caries (OR 1.42, 95% CI

0.34, 7.06).[51] A study of 100 participants found fewer carious tooth surfaces (0.099 +/- 0.088) in the exposed group compared to the comparison group (0.146 +/- 0.087), however, this study had a serious level of bias due to lack of confirmation of exposure. [38] A similar association was also reported in a study of 86 patients that found a mean of 7.5 (+/- 1.0) carious surfaces in the exposed group compared a mean of 13.5 (+/- 1.3) in the comparison group.[40] All four studies had high levels of bias, with one lacking a comparator group and another reliant upon parent recall for exposure ascertainment and all failing to adjust for confounders, such as socioeconomic status (a major social determinant of dental caries risk).

Amoxicillin

Seven of the included studies evaluated the effect of amoxicillin on enamel defects and/or dental caries whilst effects on intrinsic staining were not evaluated (Table 3).

Developmental Defects of Enamel

Four studies investigated the relationship between amoxicillin and developmental defects of enamel. [9,52-54] One study found a positive association (OR 7.88, 95% CI 2.43, 25.12) between penicillin and developmental defects of enamel in a cohort of 433 with a median age of 7.8 years.[52] This study had a low level of bias, and adjusted for relevant confounders fluoride exposure, tooth wear and age. Conversely two studies, with a low to moderate risk of bias in populations of 120 and 367 showed a protective association between penicillin (dosage not reported) and developmental defects of enamel with ORs 0.44 (95% CI 0.25, 0.77) and 0.07 (95% CI 0.02, 0.28).[9,53]

Dental Caries

There were four studies that investigated the relationship between amoxicillin and dental

caries all with a moderate level of bias.[3,52,55,56] Only two studies reported dosage with one being an average of 16mg/kg/day and the other of 125mg/day.[55,56] One study with an exposure group of 433 in a population of 7 to 9 year olds found a higher number of carious surfaces in the exposed group (mean 1.46, SD: 0.99) than in the comparison group (0.76, SD: 1.33).[52] Contrastingly, another study of penicillin (125mg/day) found a lower number of carious surfaces in the exposed group of 6 to 13 year olds (mean 3.55, SD: 0.58) compared with the control group (mean 4.84, SD: 0.32).[55] A birth cohort study of 29 485 participants found that the number of teeth affected by caries at 2 years of age was on average lower in children who had taken amoxicillin ($p<0.0001$). However, dosage was not provided and odds ratios unable to be calculated from the data provided limiting conclusions about effect size.[3] This was consistent with a cohort study of 393 participants where amoxycillin doses of 5 to 29 mg/kg/day were found to be protective for dental caries with a mean 0.47 (+/- 0.6) carious surfaces in the exposed group, compared to 1.50 (+/- 0.32) in the comparison group.[56] Overall, a clear association could not be identified due to the heterogeneity in outcome measures across the studies.

Unspecified Classes of Antibiotics

Nine studies (Table 4) evaluated the dental effects of any antibiotic exposure by either combining several antibiotics into a single exposure group, or without specifying the antibiotic formulations.[2,57-64] Four studies, all with low to moderate bias focused on molar-incisor hypomineralisation (MIH), a common developmental defect, three of these found a positive association with MIH prevalence, In contrast, none of the three studies with low to moderate risk of bias that investigated developmental defects of enamel in general (as opposed to MIH specifically) reported an association.[58,62,65]

Discussion

To our knowledge, this is the first systematic review to investigate early childhood antibiotics and three dental outcomes (caries, enamel defects and dental staining). We included evidence from 34 studies. Tetracyclines at higher dosages (≥ 20mg/kg/day) were associated with dental staining; these doses are not currently recommended. There were conflicting results both between early childhood antibiotics and dental caries and between early childhood antibiotic use and MIH.

There was no evidence that newer tetracycline-related formulations (doxycycline, minocycline), nor other antibiotic classes, were associated with adverse dental outcomes. Our findings are in keeping with other systematic reviews of doxycycline that concluded that median treatment durations up to 10 days had negligible effects on tooth staining. [18,28,66,67] The change in formulation from tetracycline to doxycycline included removal of the hydroxyl group at C-6.[68] This resulted in an inherent change on calcium binding capacity (doxycycline 19% vs tetracycline 39.5%) with doxycycline therefore less likely to result in the ion complexes that cause intrinsic staining.[27] This change combined with more recent studies on safety of doxycycline has also prompted the American Academy of Pediatrics 2021 Red Book to recommend use of doxycycline for less than 21 days regardless of age.[69]

A previous systematic review reported an association between antibiotic use and developmental defects of enamel (MIH) but lacked data on dosage and the age of antibiotic administration, so it was not possible to ascertain if exposure occurred during tooth calcification.[70] Notwithstanding, the findings are in keeping with the current study. No studies evaluating enamel defects have determined if the effect on dentition is due to the

antibiotic itself or the underlying illness.[58,71-73] Therefore, until any risk of MIH has been quantified through prospective studies with data on any dose response relationship, the treatment of infections with antibiotics outweighs any putative MIH risk.

We were unable to draw clear conclusions regarding the effect of early childhood antibiotics on dental caries due to the heterogeneity of outcome measures. Previous studies have reported an increase in risk of dental caries from early childhood antibiotic use.[3] This is in contrast to data from patients with cystic fibrosis, who have prolonged cumulative antibiotic exposure from early childhood and in whom there is a lower risk of dental caries.[2,5,6]

Strengths and Limitations

This study has a number of strengths including assessment of three different dental outcomes for the first time. Two bias tools were used to assess all papers, which was done in duplicate using a number of databases and at several time points. Most of the studies in this systematic review have methodological limitations. All rely on retrospective data, and several did not adjust for potential confounders such as socioeconomic status and age. The previous data on tetracycline-derived antibiotics and dental staining is largely from the 1960s and 1970s, and data quality is limited. The introduction of standardised reporting guidelines (such as STROBE) has improved the quality and reduced bias.[74]

Limitations include the lack of standardized and validated outcome measures (for tooth staining in particular) that made comparison between studies difficult. While validated outcome measures were used for both developmental defects of enamel and caries, several

different indices were used (Appendix 1. Table 2). A validated index for tetracycline staining is hard to develop because of the low prevalence of staining. This systematic review applied causal inference using observational data to evaluate the effect of early childhood antibiotic use on dental outcomes. Such analyses are powerful and increasingly common, there are inherent biases and challenges to answering causal questions from observational research.[75] General associations between any exposures to antibiotics and dental health without specific doses may provide a signal of an association but are limited in providing causal insights. Further studies with prospective longitudinal cohorts of patients with quantification of dosages would provide more complete evidence to inform clinical practice.

Conclusions

Despite the limitations of the existing, largely retrospective data, we found no evidence that currently used antibiotics at currently recommended doses prior to 8 years of age was associated with later dental effects of tooth staining, developmental defects of enamel, or caries. Newer formulation tetracyclines (doxycycline and minocycline) at currently recommended doses do not cause long term dental effects. There is conflicting evidence for the relationship between antibiotic use and other dental outcomes (caries and enamel defects). Further well-designed prospective longitudinal cohort studies are needed to determine this relationship using standardized outcomes with adjustment for confounders, together with biological sampling and microbiome analysis, are warranted.

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Tables

Table 1. Study Characteristics and Risk of Bias for Included Studies

Study Descriptors					**Antibiotic**			**Outcome Measures**			**Newcastle-Ottawa Bias Analysis**		
Journal Article	Level of Evidence	Number of Subjects	Subject Characteristics	Study Design	Type of Antibiotic	Dosage	Length of Medication	Caries	Dental Staining	Developmental Defects of Enamel	Selection	Comparability	Outcomes
Ahmadi, 2012	Cohort Study	433	7–9-year old's	Cross-Sectional Study	Amoxicillin	Unknown	Unknown	DMFT[a]		DDE index	****		***
Alaki, 2009	Cohort Study	29485	13-24 months	Cross-Sectional Study	Penicillin	Unknown	Unknown	ECC[b] - restoration, SCC, sedative filling, pulp treatment or			***		**

								extraction of primary dentition SEC C - any smooth surface caries less than 3yo				
Allazzam, 2014	Cohort Study	267	8–12-year old's	Cross-Sectional Study	Not specified	Unknown	Unknown		EAPD Judgement for MIH	***		***
Arrow, 2009	Cohort Study	550	5–6-year old's	Cross-Sectional Study	Medication Amoxicillin Other medication	Unknown	Unknown	WHO Criteria	Modified DDE Index	***	*	***

					Other antibiotic								
Brearley, 1973	Cohort Study	100	3–12-year old's	Cross-Sectional Study	Tetracycline	Unknown	Unknown	DMFT	Dental Staining as the following criteria - pale yellow, bright yellow, brown or grey-brown, yellow-brown, grey, grey-yellow or orange		*	*	***
Cascio, 2004	Cohort Study	41	10.1 to 13 years	Cross-Sectional Study	Minocycline	5mg/kg/day	21 days			Developmental Defects of Enamel Index	***	*	***

Conchie, 1970	Cohort Study	238	8 to 11 years	Cross-Sectional Study	Tetracycline	26.7mg/kg/day	11 days	Staining via fluorescence		****		***
Frankel, 1964	Cohort Study	25	4 to 55 days	retrospective Cohort	Doxycycline	2mg/kg on first day and then 1mg/kg every day after	6 to 17 days	Fluorescence		***		***
Forti, 1969	Cohort Study	1724	5 to 10 years	Cross-Sectional Study	Tetracycline	20mg/kg/day	Unknown	Staining as colors and fluorescence		*	*	**
Gluca, 2018	Cohort Study	120	9.8 +/- 1.8 years 10.2 +/- 2 years	Cross-Sectional Study	Antibiotics	Unknown	Unknown		Weerheijm (MIH Index)	***	*	***
Grossman, 1971	Cohort Study	160	6 to 12 years	Cross-Sectional Study	Demethylchlortetracycline Tetracycline	20mg/kg/day	6 days	Staining against tooth shade guide and under UV light		***		***

Hamp, 1967	Cohort Study	40		Cross-Sectional Study	Tetracycline	20mg/kg/day	7 days	Caries presence	Color	Hypoplasia	*	*
Handelman, 1966	Cohort Study	393	6 to 19 years	Cross-Sectional Study	2 groups: Penicillin and Penicillin + Tetracycline	5mg/kg/day to 29mg/kg/day	2.5 years	Ability to be able to penetrate the surface with an explorer and evidence of deterioration of enamel walls or			**	***

								softened cavity floor				
Hysi, 2016	Cohort Study	1575	8-10 years	Cross-Sectional Study	Not specified	Unknown	Unknown		MIH - Weerheijm	***		***
Jalevik, 2001	Cohort Study	516	8-year old’s	Cross-Sectional Study	Not specified	Unknown	Unknown		Modified DDE Index	***	*	***
Kinirons, 1992	Cohort Study	164	4 to 18 years	Cross-Sectional Study	Not specified	Unknown	Unknown	DMFT		*	*	**

Lahdesmaki, 2016	cohort Study	39	13.5 years average	Retrospective Cohort	Doxycycline	6.25mg/kg/day	12 days		Not specified		*	***
Laisi, 2009	Cohort Study	141	10.7 years average with SD 1.3 and range from 7.8-12.7 years	Cross-Sectional Study	Penicillin V Amoxicillin	Unknown	Unknown			Developmental Defects of Enamel Index	***	***
Littleton, 1964	Cohort Study	435	6 to 13 years	Cross-Sectional Study	Penicillin	200 000 units/day	Unknown	DMF Index			****	***
Lochary, 1998	Cohort Study		Mean age of 13.7 years with 11 to 19 years	Retrospective Cohort	Doxycycline	Range from 25mg/kg to 100mg/kg[c]	Range from 1 to 10 days		Ordinal number scale Researchers own method		****	***
Mariri, 2003	Cohort Study	39	4-7 years	Case-Control	Antibiotics	Unknown	Unknown	Pitts et al criteria			***	* ***
Martin, 1969	Cohort Study	4690	4 to 17 years	Retrospective	Tetracycline	Unknown	Unknown		Researchers own method	Barnard Index 1967	***	***

				Cohort									
Poyhonen, 2017	Cohort Study	38	4.7 average 0.6 to 7.9 years	Retrospective Cohort	Doxycycline	6.25 mg/kg/day	12.5 days		Diffuse discolored bands of tooth crown	Enamel Hypoplasia	**		***
Primosch, 1980	Cohort Study	86	3 to 24 years	retrospective Cohort	Tetracycline	Unknown	Unknown	Clinical and radiographic criteria from Davies and Cadell	Discoloration	Weinmann And Associates Criteria	**	*	**
Souza, 2012	Cohort Study	903	6-12 years old	Cross Sectional Study	Antibiotics	Unknown	Unknown			EAPD MIH Judgement	****		*

Swallow, 1967	Cohort Study	63	1-15 years	Retrospective Cohort	Tetracycline, Oxytetracycline, Chlortetracycline	20mg/kg/day	Unknown	Authors own severity index - compared to 30 artificial teeth		**		***
Tariq, 2014	Cohort Study	367	7-14 years	Cross-Sectional Study	Penicillin, Cephalosporin	Unknown	Unknown		DDE Index	***		***
Todd, 2015	Cohort Study	58	8 to 16 years	Cross-Sectional Study	Doxycycline	2.3mg/kg/day	7.3 days	Own methods Assessed against a spectrophotometer		***	*	***
Volovitz, 2007	Cohort Study	61	10.4 +/- 2.1 years	Cross Sectional Study	Doxycycline	4mg/kg/day	11 days	Measured against a shade guide		**		***
Wallman, 1962	Cohort Study	67	Premature babies	Cross Sectional Study	Oxytetracycline Tetracycline	38/mg/kg/day	5 days	Not mentioned		***		**

Weyman, 1966	Cohort Study	41		Case-Control	Tetracycline	Unknown	Unknown	DMF Index		**		***
Whatling, 2008	Cohort Study	109	8.7 years (6-13 years)	Cross-Sectional Study	Mixed, Penicillin, Amoxicillin, Erythromycin, Trimethoprim	10mg/kg/day	Unknown		Not specified	****		***
Wuollet, 2016	Cohort Study	287	7-12 years	Retrospective Cohort	Penicillin Amoxicillin Cephalosporin Sulphonamide-Trimethoprim Macrolide	Unknown	Unknown		EAPD MIH Judgement	****	**	**
Zegarelli, 1966	Cohort Study	28	6 to 8 years	Retrospective Cohort	Oxytetracycline	10mg/kg/day	5 days	Mean intensity, visual examination		***		*

Footnotes for Table 1:

a. DMFT = Mean number of Decayed, Missing or Filled Teeth
b. ECC = Early Childhood Caries
c. The antibiotic dose for each patient was not given and no length of administration so unable to convert dosage to mg/kg/day

Table 2. Exposure to Tetracycline antibiotics in early childhood and reported effects on later dental health

Article	Antibiotic	Outcome Measure	Dosage (mean)	Duration (mean)	Results OR (95% CI)[a]	RoB
Brearley, 1973	Tetracycline	Tooth Staining	Unknown	Unknown	19/100 with staining	Serious
Conchie, 1970	Tetracycline	Tooth Staining	26.7mg/kg/day	11 days	11.62 (5.96, 24.32)	Moderate
Frankel, 1964	Tetracycline	Tooth Staining	20mg/kg/day		0.49 (0.02, 0.27)	Critical
Grossman, 1971	Tetracycline, Demethylchlortetracycline	Tooth Staining	20mg/kg/day	6 days	Mean of affected group: 2.57 (-1 to 8) Mean of unaffected group: 0.86 (-1 to 6.5) *Mean refers to average colour of teeth	Moderate
Hamp, 1967	Tetracycline	Tooth Staining	20mg/kg/day	7 days	20.25 (1.55, 983.05)	Critical
Lahdesmaki, 2016	Doxycycline	Tooth Staining	6.25mg/kg/day	12 days	0.03 (0.01, 0.76)	Serious
Lochary, 1998	Doxycycline	Tooth Staining	Range from 25mg/kg to 100mg/kg	Range from 1 to 10 days	p=0.38	Moderate
Martin, 1969	Tetracycline	Tooth Staining			145.18 (58.79, 358.54)	Serious
Poyhonen,	Doxycycline	Tooth	6.25 mg/kg/day	12.5days	0.03 (0.01, 0.78)	Moderate

2017		Staining				
Swallow, 1967	Tetracycline	Tooth Staining	20mg/kg/day		5.77 (0.73, 260.60)	Serious
Todd, 2007	Doxycycline	Tooth Staining	2.3mg/kg/day	7.3 days	No patients with staining	Low
Volovitz, 2007	Doxycycline	Tooth Staining	4mg/kg/day	11 days	0.99 (0.01, 78.46)	Moderate
Wallman, 1962	Tetracycline	Tooth Staining	38/mg/kg/day	5 days	231.00 (19.34, 2759.99)	Critical
Zegarelli, 1966	Oxytetracycline	Tooth Staining	10mg/kg/day	5 days	2.11 (0.02, 174.27)	Serious
Forti, 1969	Tetracycline	Tooth Staining	1st dose: 2mg/kg/day 2nd day: 1mg/kg/day	6 to 17 days	No patients with staining	Critical
Primosch, 1980	Tetracycline	Tooth Staining	Unknown	Unknown	21/86 discolouration	Moderate
Cascio, 2004	Minocycline	DDE	5mg/kg/day	21 days	0.90 (0.38, 2.11)	Serious
Grossman, 1971	Tetracycline, Demethylchlortetracycline	Hypoplasia	20mg/kg/day	N/A	No patients with hypoplasia	Moderate
Hamp, 1967	Tetracycline	Hypoplasia	20mg/kg/day	N/A	5.83 (0.42, 314.48)	Critical
Todd, 2007	Doxycycline	Hypoplasia	2.3mg/kg/day	N/A	0.92 (0.2, 4.2)	Low
Primosch, 1980	Tetracycline	Enamel Defects	Unknown	Unknown	21/86 enamel defects	Moderate
Brearley, 1973	Tetracycline	DMFT	Unknown	Unknown	$p<0.01$[b]	Serious
Swallow, 1967	Tetracycline	DMFT	20mg/kg/day	Unknown	1.42 (0.34, 7.06)	Serious
Weyman, 1966	Tetracycline	DMFT	38/mg/kg/day	Unknown	29/41 had caries	Critical
Primosch, 1980	Tetracycline	DMFT	Unknown	Unknown	Mean carious surfaces of exposed group	Moderate

7.5 ± 1.0
Mean of
unexposed group
13.5 ± 1.3

Footnotes:

a. Where possible odds ratios of the likelihood of having the outcome measure were calculated and presented with 95% confidence interval. In some cases the mean value of the exposed group compared to the control groups is given with respect to that outcome measure. If no comparison group was present, the number of the exposed group with the outcome is given as a nominal value over the entire exposed population
b. Only a p value was reported

Table 3. Exposure to Amoxicillin in early childhood and reported effects on dental health

Article	Antibiotic	Outcome Measures	Dosage (mean)	Duration (mean)	Results (OR, 95% CI)[a]	RoB
Ahmadi, 2012	Amoxicillin	DMFT	Unknown	Unknown	Mean of affected group: 1.46 (SD: 0.99) Mean of unaffected group: 0.76 (SD: 1.33)	Moderate
Alaki, 2009	Penicillin	ECC	Unknown	Unknown	Ab at 13-18 months:; $p<0.0001$[b] Ab at 19-24 months: $p=0.51$[b]	Moderate
Handelman, 1966	Penicillin	DMFT	Range from 5mg/kg/day to 29mg/kg/day	2.5 years	$p=0.004$[b]	Moderate

Littleton, 1964	Penicillin	DMFT	200 000 units of penicillin daily	Unknown	Mean of affected group: 3.55 (+/- 0.58) Mean of unaffected group: 4.84 (+/- 0.32)	Moderate
Ahmadi, 2012	Amoxicillin	DDE	Unknown	Unknown	7.87 (2.43, 25.12)	Moderate
Giuca, 2018	Penicillin	DDE	Unknown	Unknown	0.07 (0.02, 0.27)	Moderate
Laisi, 2009	Penicillin	DDE	Unknown	Unknown	4.14 (1.05, 16.4)	Moderate
Tariq, 2014	Penicillin	DDE	Unknown	Unknown	0.44 (0.25, 0.77)	Low

Footnotes:

a. Where possible odds ratios of the likelihood of having the outcome measure were calculated and presented with 95% confidence interval. In some cases the mean value of the exposed group compared to the control groups is given with respect to that outcome measure. If no comparison group was present, the number of the exposed group with the outcome is given as a nominal value over the entire exposed population
b. Only a p value was reported

Table 4. Results for Unspecified Class of Antibiotics

Article	Dosage	Days	Outcome Measures	Results[a]	RoB
Allazzam, 2014	Unknown	Unknown	EAPD for Judgement MIH	4.822 (1.196, 16.588)	Low
Arrow, 2009	Unknown	Unknown	DDE	0.761 (0.462, 1.271)	Low
Hysi, 2016	Unknown	Unknown	MIH	1.41 (1.06, 1.87)	Low
Jalevik, 2001	Unknown	Unknown	Modified DDE	0.835 (0.640, 1.867)	Low
Whatling, 2008	10mg/kg/day	N/A	DDE	0.61 (0.17-2.22)	Low
Wuollet, 2016	Unknown	Unknown	MIH	1.72 (0.83 to 3.58)	Low
Souza, 2012	Unknown	Unknown	MIH	0.93 (0.63, 1.37)	Moderate

Kinirons, 1992	Unknown	Unknown	DMFT	Mean difference: 1.3 (+/- 1.74) Study group: 3.5 (+/- 2.46) Intervention Group: 4.8 (+/- 3.39)	Serious
Mariri, 2003	Unknown	Unknown	Caries	p=0.057[b]	Low

Footnotes:

a. Where possible odds ratios of the likelihood of having the outcome measure were calculated and presented with 95% confidence interval. In some cases the mean value of the exposed group compared to the control groups is given with respect to that outcome measure. If no comparison group was present, the number of the exposed group with the outcome is given as a nominal value over the entire exposed population
b. Only a p value was reported