Risk of Adverse Reactions to Oral Antibiotics Prescribed by Dentists

Brief Title – Adverse Reactions to Dental Antibiotics

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Abstract

Background:

Dentists prescribe a large portion of all oral antibiotics and these are associated with a risk of adverse drug reactions (ADRs).

Objective:

The aim of this study was to quantify the risk of ADRs associated with oral antibiotics commonly prescribed by dentists.

Methods:

NHS Digital Prescribing data and Yellow Card Drug Analysis data for 2010-2017 were abstracted to quantify dental antibiotic prescribing in England, and the rate and types of ADR associated with them.

Results:

During the period of study, the mean number of actively practicing dentists in England was 23,624. Amoxicillin accounted for 64.8% of dental antibiotic prescribing and had the lowest reported rate of fatal (0.1/million prescriptions) and overall (21.5/million prescriptions) ADRs. Indeed, amoxicillin was respectively 6 and 3 times less-likely to cause an ADR than the other penicillins, penicillin V and amoxicillin + clavulanic acid, and appears to be very safe in patients with no history of penicillin allergy. In contrast, clindamycin, which is often used in penicillin allergic patients, had the highest rate of fatal (2.9/million prescriptions) and overall (337.3/million prescriptions) ADRs with *Clostridiodes* [formerly *Clostridium*] *difficile* infections pivotal to its ADR profile. Other amoxicillin alternatives e.g. clarithromycin or metronidazole, while significantly worse than amoxicillin, were respectively 3 and nearly 5 times less likely to cause an ADR than clindamycin. Ranked from least to most likely to cause an ADR, antibiotics most commonly prescribed were: amoxicillin<cephalosporins<erythromycin<tetracyclines<azithromycin<metronidazole<amoxicillin + clavulanic acid<clarithromycin<penicillin V<clindamycin.

Conclusions:

This study confirmed the high level of safety associated with use of amoxicillin by dentists and the significantly worse rates of both fatal and non-fatal ADR associated with other penicillins and alternatives to amoxicillin for those who are penicillin allergic. In particular, clindamycin had the highest rate of both fatal and non-fatal ADR of any of the antibiotics commonly prescribed by dentists.

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Antibiotics, dentistry, adverse drug reaction, allergy, *Clostridiodes difficile, Clostridium difficile*, infection

Abbreviations:
Adverse drug reaction (ADR)
National Health Service (NHS)
Medical Dictionary for Regulatory Activities (MedDRA)
Medicines and Healthcare Products Regulatory Agency (MHRA)

Introduction

Dental prescribing accounts for approximately 10% of all antibiotic prescriptions dispensed in primary care (Durkin et al. 2017; Hicks et al. 2015). Although antibiotics are invaluable therapeutic and prophylactic agents, like any medication, they are associated with a risk of adverse drug reactions (ADRs). It is important, therefore, that dentists are aware of the potential risks associated with the antibiotics they prescribe. The aim of this study was to evaluate the antibiotic prescribing practices of dentists in England over the period 2010-2017 and to quantify the ADR risk associated with the antibiotics they commonly prescribe.

Methods

Prescription Cost Analysis data held by NHS Digital (https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis) was abstracted to detect all oral antibiotics prescribed in primary care by general medical practitioners, nurse practitioners and other health care providers including dentists in England from 2010-2017. In addition, we were able to separately extract data on all oral antibiotics prescribed by general dental practitioners in England over the same period. Hospital and private prescribing of antibiotics was not included. Private dental prescribing in the UK is uncommon and is primarily for those ineligible for NHS prescriptions e.g. foreign nationals.

National Yellow Card Interactive Drug Analysis Profile data from the Medicines and Healthcare Products Regulatory Agency (MHRA) (http://yellowcard.mhra.gov.uk/iDAP/) were interrogated for those antibiotics most frequently prescribed by dentists in primary care and data extracted for all prescriptions of oral antibiotics, or prescriptions where the route of administration was not stated but reactions to drugs administered parenterally, topically or by other routes were excluded. The ADR rate/million prescriptions issued in primary care was calculated for those antibiotics commonly prescribed by dentists over the period of study. The Yellow Card system has been in place for over 50 years and allows patients and healthcare professionals to report ADRs to the MHRA, either online or by postage free mail-in. Although ADRs are subdivided into those that are non-serious, serious and fatal, the distinction between serious and non-serious

is left for the person reporting to determine. All ADR reports are categorized using the Medical Dictionary for Regulatory Activities (MedDRA) (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2019). The MedDRA hierarchy of terms has five levels. There are more than 70,000 individual descriptive 'lowest level terms' and these are matched to terms used in the ADR report. e.g. feeling queasy. These are grouped into 'preferred terms' e.g. nausea, and then through three further levels of hierarchy, 'high level terms' e.g. nausea and vomiting symptoms, 'high level group terms' e.g. gastrointestinal signs and symptoms, and finally 'system organ class' e.g. gastrointestinal disorders. There are 27 'system organ class' categories. However, no, or very few antibiotic ADRs are reported for approximately one-half of the 'system organ class' categories. To avoid reporting negative 'system organ class' data, we excluded any categories that did not appear among the top 5 reported for at least one of the antibiotics being studied. This reduced the number of categories to 14. ADRs that fell under any other 'system organ class' categories were grouped under a 15th category 'Other'. Even though data were reported by 'system organ class', we were able to delve deeper into the hierarchical structure where necessary (down to 'preferred term' level) to gain better insight into the precise cause of ADRs.

Because of the small numbers of prescriptions for individual cephalosporin or tetracycline preparations, all cephalosporin class or tetracycline class prescriptions were respectively grouped. For the purposes of this investigation, the azalide, azithromycin, was included under the antibiotic class of macrolides that included erythromycin and clarithromycin. Aminoglycosides were excluded from this investigation since they accounted for only 0.002% of overall oral antibiotic prescribing and zero dental prescribing. Fosfomycin was not included due to limited use, and linezolid and tedizolid were not included since these agents were only prescribed in secondary care. Fluoroquinolone data was included in the overall analysis of oral antibiotic use, although there was no dental prescribing of fluoroquinolones. Further details regarding oral fluoroquinolone use were published elsewhere (Baddour et al. 2019). Oral antibiotics (isoniazid, rifampin, ethambutol, para-aminosalicylic acid, pyrazinamide, clofazimine, bedaquiline, rifabutin, rifapentine, dapsone, ethionamide, cycloserine, prothionamide, and delamanid) used primarily to treat mycobacterial infections, including tuberculosis, were excluded.

Because all data reported herein was obtained from national data resources and completely anonymised, ethics approval was not required.

Results

Dental Antibiotic Prescribing Trends

Between 2010 and 2017, there were 28,825,698 oral antibiotic prescriptions issued by dentists in England and the mean number of actively practicing dentists was 23,624. On average, this amounted to 3,603,212 prescriptions per annum (67 prescriptions per 1,000 of the English population). Amoxicillin was the most frequently prescribed (18,667,126 prescriptions) and accounted for 64.8% of all dental oral antibiotic prescriptions. Metronidazole was the next most frequently prescribed antibiotic (8,082,568), accounting for 28.0% of all dental antibiotic prescribing. These were followed by erythromycin (1,255,878; 4.4% of dental antibiotics), penicillin V (phenoxymethylpenicillin) (270,782, 0.9%), clindamycin (167,426; 0.6%), amoxicillin + clavulanic acid (co-amoxiclave) (132,134, 0.5%), cephalosporins (121,234; 0.4%), tetracyclines (81,983; 0.3%), clarithromycin (33,519, 0.1%) and azithromycin (12,503, <0.1%).

Incidence of Adverse Drug Reactions

The ADR rates were slightly lower for oral antibiotics prescribed by dentists than for those prescribed in primary care overall. This was true for all ADRs (50.9 *v* 57.9/million prescriptions), fatal reactions (0.5 *v* 0.7/million prescriptions) and severe reactions (30.5 *v* 36.8/million prescriptions) (Table 1). However, the differences were not clinically significant.

Among oral antibiotics commonly prescribed by dentists, clindamycin had the highest fatal (2.9/million prescriptions), serious (233.2/million prescriptions) and overall ADR rate (337.3/million prescriptions). This was more than twice that of any other commonly used dental antibiotic (Table 1, Figure 1) and more than 15 times higher than amoxicillin, the most widely used antibiotic, which had the lowest fatal (0.1/million prescriptions), serious (11.9/million prescriptions) and overall (21.5/million prescriptions) ADR rate.

Of the penicillins, penicillin V had an overall (137.0/million prescriptions), serious (61.7/million prescriptions) and fatal ADR rate (0.4/million prescriptions) more than 4 times that of amoxicillin. Amoxicillin + clavulanic acid had an overall (71.2/million prescriptions) and serious ADR rate (51.4/million prescriptions) more than 3 times that of amoxicillin. Perhaps most concerning however, amoxicillin + clavulanic acid had the highest fatal ADR rate (1.5/million prescriptions) among the penicillins, which was second only to clindamycin.

Cephalosporins and tetracyclines had relatively low overall ADR rates. Indeed, the cephalosporin overall ADR rates were similar to those of amoxicillin, and the tetracycline overall ADR rates were close to the average for all antibiotics (Table 1, Figure 1). Among the macrolide antibiotics (erythromycin, azithromycin and clarithromycin), erythromycin had the lowest overall ADR rate, azithromycin overall ADR rates were only marginally higher, while overall ADR rates for clarithromycin were almost twice those for erythromycin (overall 98.0/million prescriptions, serious 65.5/million prescriptions and fatal 1.3/million prescriptions, see Table 1); clarithromycin had the third highest fatal ADR rate among those oral antibiotics commonly prescribed by dentists.

Metronidazole was the second most commonly prescribed antibiotic by dentists in England and was associated with overall (70.6/million prescriptions), serious (51.4/million prescriptions) and fatal (0.7/million prescriptions) ADR rates that were greater than the average and more than 3 times that of amoxicillin but nearly a fifth of those of clindamycin.

Types of adverse drug reaction (ADR)

Clindamycin had the highest fatal ADR rate (2.9/million prescriptions). All fatal reactions were related to infection or gastrointestinal problems, mostly related to *C. difficile* infection (Table 2). These also accounted for a significant proportion of all clindamycin-related ADRs (Table 2). Skin reactions, however, accounted for a majority of non-fatal clindamycin ADRs and of them, the vast majority were allergic rashes or pruritis.

Gastrointestinal disturbances accounted for a significant proportion of the ADRs recorded for all antibiotics examined, although clindamycin had the highest rate of gastrointestinal disturbance reactions reported,

followed by clarithromycin, metronidazole and erythromycin (Table 2). The most frequent gastrointestinal disturbances reported for all antibiotics were nausea or diarrhoea.

Skin reactions, mainly allergic in nature, were also a feature of all antibiotics studied. The rate of skin reactions was considerably higher for clindamycin than for any other antibiotic, although none of these were fatal. Penicillin V had the next highest rate of skin reactions, followed by amoxicillin + clavulanic acid, clarithromycin and metronidazole. Fatal skin reactions, however, were only seen with amoxicillin, amoxicillin + clavulanic acid, tetracyclines, erythromycin and clarithromycin.

Immune system ADRs were reported most frequently with penicillin V. These were all due to allergic reactions and more than one-fifth were reported as anaphylactic or anaphylactoid reactions. These included 0.15 deaths/million prescriptions. Immune system ADRs also occurred with amoxicillin and amoxicillin + clavulanic acid, but to a lesser degree than with penicillin V. All of these reactions were allergic in nature and a significant proportion were anaphylactic or anaphylactoid. However, no fatal anaphylactic or anaphylactoid reactions were recorded with oral amoxicillin and only 0.12 fatal reactions/million prescriptions with amoxicillin + clavulanic acid. Cephalosporins and erythromycin were also associated with a considerable number of allergic reactions including a small number of fatal anaphylactic reactions.

Nervous system ADRs accounted for a significant proportion of ADRs seen with metronidazole, clindamycin and the macrolide antibiotics clarithromycin and azithromycin. Nervous system ADRs were not a significant feature of the penicillins. With metronidazole, nervous system ADRs presented mainly as headaches, dizziness, altered taste or paraesthesia. Clindamycin was associated with headaches and neurological disorders, particularly altered taste. For macrolides, nervous system ADRs presented mainly as dizziness, altered taste, somnolence or paraesthesia.

Psychiatric disorder ADRs were also a feature with clarithromycin and metronidazole but were not seen with penicillins. For clarithromycin and metronidazole, psychiatric disorder ADRs largely presented as anxiety disorders, confusion, hallucinations or sleep disturbance. For metronidazole, some psychiatric ADRs also presented as depressive mood disorders.

Amoxicillin + clavulanic acid was the only antibiotic associated with hepatobiliary ADRs, that presented almost entirely with features of cholestatic jaundice, a rare but well recognised reaction.

Cardiac arrhythmia ADRs were the most common cause of death for the macrolides, erythromycin and clarithromycin, and accounted for two-thirds of deaths associated with azithromycin. Macrolides are known to prolong the QT interval which can predispose to the development of *torsades de pointes* (Hancox et al. 2013).

Discussion

Although all antibiotics are associated with ADRs, our study quantifies which antibiotics are safer for patients. Penicillins, the antibiotic class most commonly prescribed by dentists, are well known for their capacity to induce hypersensitivity reactions, usually manifesting as skin-rashes, which can include serious and fatal skin reactions e.g. Steven's Johnson syndrome or toxic epidermal necrolysis, and more rarely, anaphylaxis. In the current investigation, skin and immune reactions accounted for a considerable proportion of ADRs reported for penicillins. However, gastrointestinal disturbances, which were less frequently reported by healthcare providers, were also prominent. Nevertheless, fatal, serious, and overall ADR rates for amoxicillin were lower than for any other antibiotic. Indeed, amoxicillin appeared to be the safest, particularly for those with no history of penicillin allergy. It is important to point out that during the period of the study, i.e. 2010-2017, national guidance recommended against all use of antibiotic prophylaxis in patients at risk of infective endocarditis (IE) in the UK (National Institute for Health and Care Excellence (NICE) 2008). Unlike in the US, there has never been guidance recommending antibiotic prophylaxis for those with prosthetic joints or organ transplants in the UK. Nor is antibiotic prophylaxis recommended for those at risk of medication- or radiotherapy-related osteonecrosis of the jaw or for patients with underlying medical conditions such as diabetes mellitus or immunosuppression (https://bnf.nice.org.uk/guidance/prescribing-in-dental-practice.html). Thus, it is likely that the vast majority of antibiotic prescribing identified in this study was for treating dental infections. None-the-less, in an earlier study, using data from a period when antibiotic prophylaxis was still recommended to prevent IE, we demonstrated that a single 3-gram dose of amoxicillin was also safe and had an extremely low incidence of ADRs (Thornhill et al. 2015). The results of the current

investigation suggest that amoxicillin is a safe antibiotic for both treatment and prophylaxis and may be safer than penicillin V and amoxicillin + clavulanic acid. Perhaps not surprisingly, the risk of a skin or immune reaction was roughly twice as high with amoxicillin + clavulanic acid (amoxicillin plus clavulanic acid) than with amoxicillin alone. Penicillin V harbored a risk of skin or immune reaction that was respectively 6 and 11 times higher than that of amoxicillin. The reason for this is unclear, but may relate to the subtly different chemical structures of amoxicillin and penicillin V.

Although skin and immune reactions are most commonly associated with penicillins, it is noteworthy that non-penicillin-based antibiotics also can cause skin and immune reactions. This is exemplified by macrolide antibiotics (erythromycin, clarithromycin and azithromycin), and metronidazole and clindamycin. Indeed, for clindamycin, the immune system ADR rate was second only to penicillin V and the rate of skin and subcutaneous reactions more than twice that of any other antibiotic. These results serve as a reminder that metronidazole and clindamycin are not necessarily a safer alternative to penicillin.

Ideally, although often difficult to achieve in primary care dental practice, amoxicillin should not be replaced with alternatives without confirmatory evidence of penicillin allergy (Shenoy et al. 2019). 90% of patients who report a history of penicillin allergy are not confirmed to be penicillin allergic by skin testing combined with an oral amoxicillin challenge (Shenoy et al. 2019). If further evaluation is not done for those reporting penicillin sensitivity, then this could result in exposure to antibiotics with potentially worse ADR profiles, in particular clindamycin, an increased risk of causing antibiotic resistance, suboptimal antibiotic therapy and higher healthcare costs ((CDC) ; Drug and Therapeutics Bulletin 2017; Har and Solensky 2017; Macy and Contreras 2014; Shenoy et al. 2019; Trubiano et al. 2017). Better screening of patients with self-reported penicillin allergy could significantly reduce the number of individuals unnecessarily denied penicillins and improve antimicrobial stewardship and patient safety ((CDC) ; Drug and Therapeutics Bulletin 2017; Gonzalez-Estrada and Radojicic 2015; Har and Solensky 2017; Macy 2014; Macy and Contreras 2014; Macy and Ngor 2013; Macy et al. 2009; National Institute for Health and Care Excellence (NICE) 2014; Shenoy et al. 2019; Trubiano et al. 2017).

Gastrointestinal disturbance, not unexpectedly, occurs frequently with oral antibiotics, but disturbances differ considerably in severity, from mild nausea to severe *C. difficile* infection. The more severe *C. difficile* infection cases, which can be complicated by mortality, were reported in either the 'Gastrointestinal' or 'Infections & Infestations' organ systems categories. In both categories, amoxicillin had the lowest rate of ADRs of all oral antibiotics used by dentists, including other penicillins.

Historically, the macrolides, particularly erythromycin, have been characterized by gastrointestinal disturbance. However, our study revealed that the newer macrolides, which have superior pharmacokinetic properties, had higher ADR rates within the Yellow Card database. Specifically, clarithromycin was more likely than erythromycin to cause gastrointestinal upset; azithromycin also had one of the highest rates of ADR. It is possible however that this reflects a greater likelihood for clinicians to report ADRs associated with newer drugs (see Limitations section).

Clindamycin was clearly the worst of the oral antibiotics prescribed by dentists for risk of both 'Gastrointestinal' (155.5/million prescriptions) or 'Infections' (343.7/million prescriptions) related ADRs, including fatal ADRs (1.5/million prescriptions each). Although, clindamycin was likely prescribed to treat dental infections, the data are consistent with the results of an earlier investigation that examined the risk of ADRs following a single oral dose of clindamycin for dental IE prophylaxis. This investigation also demonstrated a much higher risk of gastrointestinal and infection-related ADRs, including fatal ADRs, with a single 600mg oral dose of clindamycin, than with other antibiotics used for IE prophylaxis (Thornhill et al. 2015). Our findings are also consistent with the results of a systematic review of the risk of *C. difficile* infection following use of different antibiotics in the community setting; the risk of *C. difficile* infection was highest with clindamycin followed by macrolides; penicillins and tetracyclines had little to no risk (Brown et al. 2013). Given that clindamycin is recommended as an alternative to amoxicillin for antibiotic prophylaxis globally, this underscores the importance of performing penicillin skin testing and, if negative, subsequent oral amoxicillin challenge to confirm that amoxicillin can be used as AP with avoidance of clindamycin.

Metronidazole was the second most frequently prescribed antibiotic by dentists in the UK. Moreover, dental prescribing accounted for 57% of all metronidazole prescribing in primary care. In England, metronidazole

has been the primary alternative to amoxicillin for treating dental infections in those who are penicillin allergic and accounts for 28% of all dental oral antibiotic prescribing. In contrast, clindamycin accounted for only 0.6% of prescribing. Metronidazole has also been the preferred alternative to amoxicillin in many parts of Europe (Al-Haroni and Skaug 2007; Palmer et al. 2000), Africa (Fadare et al. 2017), the Middle East (Dar-Odeh et al. 2008), the Indian Subcontinent (Konde et al. 2016; Tanwir et al. 2015) and Australasia (Ford et al. 2017; Teoh et al. 2018). In the USA, however, metronidazole has accounted for less than 0.9% of dental antibiotic prescribing and clindamycin is regarded as the primary alternative to amoxicillin, accounting for 15% of dental antibiotic prescribing (Durkin et al. 2017).

There are scant published data regarding the risk and types of ADRs associated with oral metronidazole other than the well-known 'Antabuse' reaction that can occur in patients who ingest alcohol while taking metronidazole. Metronidazole was the third most likely oral antibiotic to cause an ADR. Of these, gastrointestinal ADRs, including nausea and vomiting, were common. However, nervous system ADRs, including dizziness, altered taste and somnolence, were more frequent than with any other dental antibiotic. Psychiatric disturbance, including confusion, depression, altered perception and sleep disturbance, were also more common than with any other antibiotic except clarithromycin. Skin reactions were not uncommon.

The newer macrolides, azithromycin and clarithromycin, generally had a higher frequency of ADRs than erythromycin. In particular, they were associated with higher rates of nervous system ADRs, including altered taste, dizziness and somnolence and psychiatric ADRs, including anxiety symptoms, sleep disturbance, confusion and altered perception. Azithromycin and clarithromycin also had a higher rate of cardiac ADRs, mainly rhythm disturbances, than any other antibiotics prescribed by dentists, and a significant proportion of these (10-20%) were associated with a fatal outcome.

Limitations

This study has several limitations. The Yellow Card reporting scheme is dependent on clinicians and patients reporting ADRs. This is likely to result in underreporting, particularly of non-serious ADRs. It may also result in higher reporting rates for newer drugs and under reporting for older drugs where the ADR profile is well recognized and associated mechanisms responsible for ADRs better understood. Reporting rates are not,

therefore, the same as incidence rates and are likely to underestimate the true incidence. A further limitation is that categorisation of ADR severity is not defined and is decided by the individual reporting an ADR. Although there should be no error in the reporting of fatal ADRs, the distinction between serious and non-serious ADRs is arbitrary. The Medical Dictionary of Regulatory Activities (MedDRA) (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2019) is helpful in categorizing the diverse terminology used by individuals reporting ADRs into the different organ systems affected. However, with 5 terminological hierarchies encompassing >70,000 individual descriptors, it is impossible to express the vast array of data available with the full depth of detail contained within the Interactive Drug Analysis Profile data included for each antibiotic by the MHRA.

An advantage of the data evaluated in this study is that it was abstracted from a large dataset that represented all available ADR data for oral antibiotics prescribed in primary care in England during the period 2010-2017.

Conclusions

The current investigation demonstrated that amoxicillin, the most commonly prescribed antibiotic in dental practice, is remarkably safe, particularly in those with no history of penicillin allergy. Other penicillins, including amoxicillin + clavulanic acid and penicillin V, had significantly worse ADR profiles than amoxicillin. Of the antibiotics commonly used as alternatives to penicillins, particularly in those with a history of penicillin allergy, clindamycin has the worst ADR profile of any of the oral antibiotics prescribed by dentists. Overall, clindamycin was 15 time more likely to cause an ADR than amoxicillin and nearly 30 times more likely to cause a fatal ADR. This underscores the importance of assessing patients with a purported history of pencillin allergy with penicillin skin testing and amoxicillin oral challenge. Clarithromycin and metronidazole had the next worst ADR profiles amongst the penicillin alternatives, but were respectively still 3 times and nearly 5 times less likely than clindamycin to cause an ADR. Ranked from least to most likely to cause an ADR, antibiotics most commonly prescribed by dentists were: amoxicillin<cephalosporins<erythromycin<tetracyclines<azithromycin<metronidazole<amoxicillin + clavulanic acid<clarithromycin<penicillin V<clindamycin.

Author Contributions:

Professor Martin Thornhill contributed to the conception and design of the paper, acquisition of the data and it's analysis and interpretation, drafted the manuscript and gave final approval. Dr Mark Dayer and Professor Larry Baddour contributed to the conception and design of the paper, the analysis and interpretation of the data, critically revised the manuscript and gave final approval. Professor Michael Durkin and Peter Lockhart contributed to the interpretation of the data, critically revised the manuscript and gave final approval.

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Figure legends:

Figure 1.

The number of adverse drug reactions per million prescriptions of each oral antibiotic type

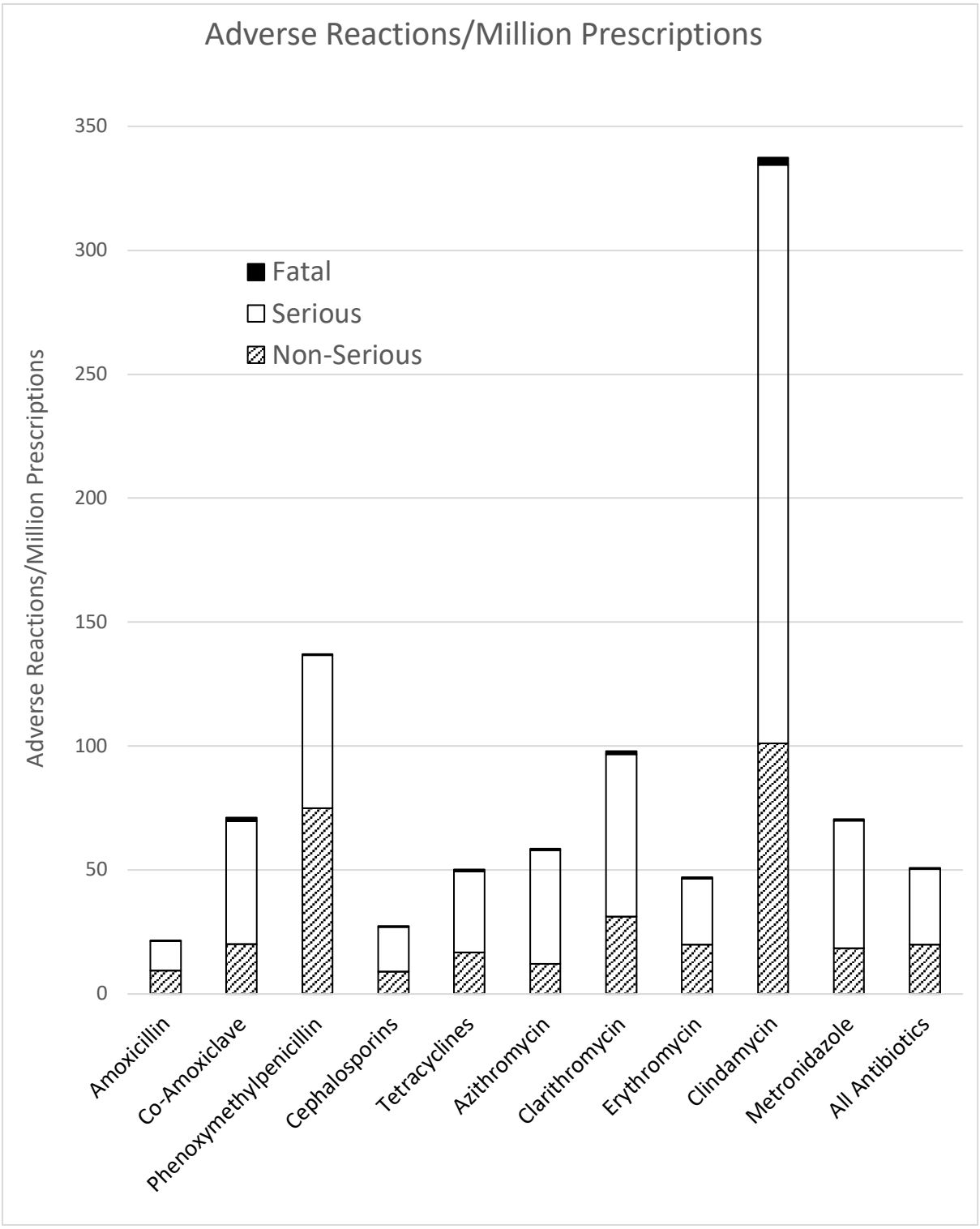
Table 1. Adverse drug reaction data for 2010-2017.

Drug Name	Adverse Reactions/Million Prescriptions (2010-17)			
	Non-Serious	Serious	Fatal	Total
Amoxicillin	9.4	11.9	0.1	21.5
Amoxicillin + Clavulanic Acid	20.2	49.5	1.5	71.2
Penicillin V	75.0	61.7	0.4	137.0
Cephalosporins	9.0	17.9	0.5	27.4
Tetracyclines	16.8	32.6	0.9	50.2
Azithromycin	12.1	45.8	0.8	58.7
Clarithromycin	31.2	65.5	1.3	98.0
Erythromycin	19.8	26.7	0.7	47.2
Clindamycin	101.2	233.2	2.9	337.3
Metronidazole	18.5	51.4	0.7	70.6
All Antibiotics Rx by Dentists	**19.9**	**30.5**	**0.5**	**50.9**
All Antibiotics	**20.4**	**36.8**	**0.7**	**57.9**

Table 2. Types of Adverse Reaction/Million Prescriptions Between 2010-17 by Organ System Affected

	Amox	Amox +Clav	Pen V	Ceph	Tetra	Azith	Clarith	Eryth	Clinda	Metro
Type of ADR	Adverse Drug Reactions/million prescriptions									
Cardiac	0.25	2.39	0.26	0.56	1.07	6.3	7.64	2.55	4.4	1.98
Eye	0.65	1.84	1.8	4.47	4.52	4.28	3.39	2.05	2.93	8.12
Gastrointestinal	5.85	32.43	25.28	12.39	26.91	26.7	52.99	37.22	155.46	42.91
General & administration site	4.48	17.25	18.33	7.83	13.39	21.91	33.11	13.69	68.93	31.19
Hepatobiliary	0.64	15.36	0.31	0.75	2.26	2.52	2.82	1.18	10.27	1.98
Immune system	2.64	5.94	28.62	3.17	1.59	1.76	3.97	5.1	20.53	3.74
Infections & infestations	1.51	6.85	2.78	3.63	3.45	18.39	6.78	1.87	33.73	4.66
Injury, poisoning & procedural complications	0.56	2.94	0.72	3.26	1.89	3.02	5.4	1.37	14.67	4.16
Investigations	1.41	11.38	0.98	2.14	3.54	11.84	12.82	3.24	26.4	6.21
Nervous system	2.1	11.14	5.82	6.8	12.54	16.88	42.59	6.1	44	49.4
Psychiatric	1.49	5.69	2.47	3.35	6.5	7.56	35.58	1.68	17.6	20.89
Renal & urinary	0.45	2.88	0.82	1.03	1.34	1.51	5.17	1.18	1.47	6.56
Respiratory, thoracic & mediastinal	1.74	6	9.88	2.7	4.79	7.81	12.24	4.05	19.07	8.47
Skin & subcutaneous	16.42	33.9	93.44	14.91	19.53	11.59	30.46	19.23	217.06	27.74
Other	2.44	12.83	5	6.16	12.4	18.89	27.66	9.42	64.52	26.11
Total Reactions	42.63	168.82	196.51	73.15	115.72	160.96	282.62	109.93	701.04	244.12
Type of ADR	Fatal Adverse Drug Reactions/million prescriptions									
Cardiac	0.01	0.18	0.00	0.00	0.09	0.50	0.40	0.25	0.00	0.00
Eye	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Gastrointestinal	0.00	0.00	0.00	0.09	0.00	0.00	0.06	0.00	1.47	0.00
General & administration site	0.04	0.37	0.15	0.09	0.15	0.25	0.23	0.00	0.00	0.21
Hepatobiliary	0.03	0.18	0.00	0.00	0.09	0.00	0.00	0.06	0.00	0.35
Immune system	0.00	0.12	0.15	0.09	0.00	0.00	0.06	0.12	0.00	0.07
Infections & infestations	0.03	0.18	0.05	0.09	0.09	0.00	0.06	0.12	1.47	0.07
Injury, poisoning & procedural complications	0.00	0.00	0.00	0.09	0.00	0.00	0.11	0.00	0.00	0.00
Investigations	0.00	0.00	0.00	0.00	0.00	0.00	0.06	0.00	0.00	0.00
Nervous system	0.00	0.06	0.00	0.00	0.03	0.00	0.00	0.00	0.00	0.00
Psychiatric	0.00	0.06	0.00	0.00	0.12	0.00	0.06	0.00	0.00	0.00
Renal & urinary	0.01	0.06	0.00	0.00	0.15	0.00	0.00	0.00	0.00	0.00
Respiratory, thoracic & mediastinal	0.00	0.12	0.00	0.00	0.03	0.00	0.06	0.06	0.00	0.00
Skin & subcutaneous	0.02	0.06	0.00	0.00	0.03	0.00	0.11	0.06	0.00	0.00
Other	0.00	0.13	0.00	0.02	0.03	0.00	0.04	0.00	0.00	0.00
Total Fatal Reactions	0.14	1.53	0.36	0.47	0.82	0.76	1.26	0.68	2.93	0.71

NOTES: Amox = Amoxicillin; Amox+Clav = Amoxicillin + Clavulinic Acid; Pen V = Penicillin V; Ceph = Cephalosporins; Tetra = Tetracyclines; Azith = Azithromycin; Clarith = Clarithromycin; Eryth = Erythromycin; Clinda = Clindamycin; Metro = Metronidazole; Individuals may have adverse reactions affecting more than one organ system at any one time. Hence, total number of different organ systems affected (Total Reactions or Total Fatal Reactions) for each antibiotic may exceed the total number of reactions reported in Table 1.


Adverse Reactions/Million Prescriptions
Adverse Reactions/Million Prescriptions
350
300
250
200
150
100
50
0
Fatal
Serious
Non-Serious
Amoxicillin
Co-Amoxiclave
Phenoxymethylpenicillin
Cephalosporins
Tetracyclines
Azithromycin
Clarithromycin
Erythromycin
Clindamycin
Metronidazole
All Antibiotics