Incidence and Nature of Adverse Reactions to Antibiotics Used as Endocarditis Prophylaxis

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Synopsis

Objectives: Antibiotic-prophylaxis administration prior to invasive dental procedures has been a leading focus of infective endocarditis prevention. However, there have been long-standing concerns about the risk of adverse drug reactions as a result of this practice. The objective of this study was to identify the incidence and nature of adverse reactions to amoxicillin and clindamycin prophylaxis used to prevent infective endocarditis.

Methods: We obtained antibiotic-prophylaxis prescribing data for England from January 2004 to March 2014 from the NHS Business Services Authority, and adverse drug reaction data from the Medicine and Health products Regulatory Agency 'Yellow Card' reporting scheme for prescriptions of the standard antibiotic-prophylaxis protocol of a single 3g oral dose of amoxicillin or a single 600mg oral dose of clindamycin for those allergic to penicillin.

Results: The reported adverse drug reaction rate for amoxicillin antibiotic-prophylaxis was 0 fatal reactions for nearly 3 million prescriptions and 22.62 non-fatal reactions/million prescriptions. For clindamycin, it was 13 fatal and 149 non-fatal reactions/million prescriptions. Most clindamycin adverse drug reactions were Clostridium difficile infections.

Conclusions: Antibiotic-prophylaxis adverse drug reaction reporting rates in England were low, particularly for amoxicillin, and lower than previous estimates. This suggests that amoxicillin antibiotic-prophylaxis is comparatively safe for patients without a history of amoxicillin allergy. The use of clindamycin antibiotic-prophylaxis was, however, associated with significant rates of fatal and non-fatal adverse drug reactions associated with C. difficile infections. These were higher than expected and similar to those for other doses, durations and routes of clindamycin administration.

Introduction

Infective endocarditis (IE) is an infection of the endocardium that is associated with high morbidity and mortality.[1] Bacteria from the oral cavity, particularly oral viridans group streptococci, are implicated as the causal organisms in approximately 35-45% of cases.[2-6] Consequently, dentists have historically given antibiotic prophylaxis (AP) to patients at risk of developing IE prior to performing invasive dental procedures.

The aim of AP is to reduce or eliminate bacteremia caused by procedures[7-11] that may lead to IE in susceptible individuals. However, there has never been a randomized clinical trial to demonstrate the effectiveness of AP,[12] and there is little evidence to support it's effectiveness.[3, 5, 9] Furthermore, concerns have been expressed that the cost and potential adverse effects of AP may outweigh its benefits.[13-16]

Until recently, it was the standard of care in most parts of the world to provide AP to patients at 'high-risk' (previous IE, prosthetic heart valves or valves repaired with prosthetic material, unrepaired cyanotic congenital heart disease, or certain repaired congenital heart defects) or 'moderate-risk' (previous rheumatic fever, heart murmur, or evidence of native valve disease) of IE.

However, in March 2008, the UK National Institute for Health and Care Excellence (NICE) produced guidance recommending cessation of AP for preventing IE.[17] In contrast, the American Heart Association (AHA)[18] and the European Society for Cardiology (ESC)[19] produced guidelines in 2007 and 2009, respectively, that recommended cessation of AP only for individuals at 'moderate-risk' of IE.

The move to reduce AP prescribing was driven not just by lack of evidence for efficacy, but also by concerns about the risk of adverse drug reactions, the risk of increasing antibiotic resistance, and cost. The aim of this study was to quantify the risk and nature of adverse events associated with AP in England.

Methods

Prior to introduction of the NICE guidelines, a single 3g oral dose of amoxicillin (or a 600mg oral dose of clindamycin in penicillin-allergic individuals) was prescribed before invasive dental procedures as AP to those at 'moderate-risk' or 'high-risk' of developing IE. This dosage schedule and route of administration for amoxicillin and clindamycin are almost exclusively used for AP purposes.[20, 21] Data on their prescribing between January 2004 and January 2014 were obtained from the National Health Service Business Services Authority (http://www.nhsbsa.nhs.uk/prescriptions). We have previously published data on AP prescribing for earlier periods.[20, 21]

The Medicines and Healthcare Products Regulatory Agency (MHRA) provide adverse drug reaction (ADR) data using the 'Yellow Card' reporting scheme (http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/index.htm). ADR data were available for any dose, duration or route of administration of amoxicillin for the period July 1st 1963 until August 29th 2014, and for clindamycin from July 1st 1963 until August 20th 2014. For a single 3g oral dose of amoxicillin, however, it was only possible to extract data for the period from January 13th 1980 until January 15th 2014, and for a single 600mg oral dose of clindamycin from December 18th 1969 until January 15th 2014. To estimate the ADR incidence for a single 3g oral dose of amoxicillin or a single 600mg oral dose of clindamycin, monthly prescribing data for the period January 2004 to March 2013 were used. For earlier periods, the mean number of prescriptions per month during the period January 2004 – March 2008 was used to extrapolate the data.

Unless specifically stated otherwise, the data presented are for England only.

Results

Prescribing of amoxicillin antibiotic prophylaxis

Monthly prescribing data for all prescriptions of a single 3g oral dose of amoxicillin are shown in Figure 1(a) with breakdown according to prescriber status in Figure 1(b).

Before the introduction of the NICE guidelines, 93·4% of all prescriptions for a single 3g oral dose of amoxicillin were written by dentists and 6·3% were written by general practitioners. Prescribing by hospitals (0·2%) and nurses (<0·1%) was infrequent.

Following introduction of the NICE guidelines, there was a dramatic (87·8%) fall in the prescribing of amoxicillin AP from a mean of 8,395 prescriptions per month before NICE, to a mean of 1,026 prescriptions per month in the 6 months from July 2013 until January 2014 ($p<0·001$). Following the NICE guidelines, there was a small reduction in the proportion of prescriptions written by dentists (from 93·4% to 89·3%) and a compensatory rise in the proportion written by general practitioners (from 6·3% to 10·2%).

Prescribing of clindamycin antibiotic prophylaxis

Data are shown for prescriptions for a single 600mg dose of oral clindamycin (Figures 1(a) and 1(c)). Before the introduction of the NICE guidelines, 88·8% of all prescriptions for clindamycin AP were written by dentists and 10·9% by general practitioners. Prescribing by hospitals (0·2%) and nurses (<0·1%) was infrequent.

Following introduction of the NICE guidelines, there was a marked decline (95·2%) in prescribing of clindamycin AP from a mean of 2,504 prescriptions per month before NICE, to a mean of 120 prescriptions per month in the 6 months from July 2013 until January 2014 ($p<0·001$). Following the NICE guidelines, there was a substantial reduction in the proportion of prescriptions written by dentists (from 88·8% to 66·6%) and a compensatory rise in the proportion written by general practitioners (from 10·9% to 32·5%).

Taken together, there was an 89·5% reduction in the number of courses of AP prescribed (amoxicillin or clindamycin) following introduction of the NICE guidelines, from a mean of 10,900 per month in the period January 2004 to March 2008 to a mean of 1,146 in the last 6 months of study ($p<0·001$) (Figure 1(a)).

Incidence of amoxicillin related adverse events

Analysis of ADR reports for all doses, duration and routes of administration of amoxicillin (as a single active constituent) during the period July 1963 to August 2014 revealed 73 fatal reports, 5 of which were recorded as immune system and 13 as allergy-related skin disorders. There were also 3072 non-fatal reports, including 304 immune system and 2063 allergy-related skin reports. Analysis of amoxicillin prescribing data for all purposes between 2004-2007 demonstrated an average of 12,896,805 courses per annum. Assuming a constant prescribing rate over the 51 years of data availability, this allows a crude estimate of 0·11 fatal and 4·67 non-fatal reactions per million courses of amoxicillin prescribed. Since amoxicillin prescribing has gradually increased over the period of ADR reporting, this probably represents an underestimate of the current frequency of reported adverse events for amoxicillin.

In contrast, analysis of ADR reports (where relevant data were available concerning dose and route of administration) revealed no fatal reaction reports following a single 3g oral dose of amoxicillin during the data-recording period from January 1980 to January 2014. There were, however, 67 non-fatal reaction reports in the same period, 16 of which were recorded as immune system disorders (anaphylactic/allergic reactions) and 38 as allergy-related skin disorders (rashes, angioedema, pruritis and urticaria). Over the same period, we estimate that 2,961,900 courses of a single 3g oral dose of amoxicillin were prescribed. Using these figures, a crude estimate of the adverse reaction reporting rate was 0 fatal and 22·62 non-fatal reports per million courses of prescribed amoxicillin AP, (of which 18 could be allergy-related). For the period before introduction of the NICE guidelines, this equates to 0 fatal and 2·28 non-fatal (but reportable) reactions per annum. For the level of AP prescribing during the most recent 6 months of the post-NICE guidelines period, this equates to 0 fatal and 0·28 non-fatal reports per annum.

Incidence of clindamycin related adverse events

The association of clindamycin with C. difficile infection is well documented and accounted for 41 (77.4%) of 53 fatalities reported for clindamycin between July 1963 and August 2014 (32 reported as C. difficile infections and 9 as gastrointestinal disorders). Only 2 fatalities were reported as immune- (1) or allergy-related skin (1) disorders. During the same period, 1273 non-fatal reactions were reported (including 410 gastrointestinal, 102 infections, 19 immune system and 366 allergy-related skin disorder reactions). Over the 4 years 2004-2007, the average number of courses of clindamycin prescribed was 91,950 per annum. This allows a crude estimate that 11·3 fatal and 271·5 non-fatal reactions occurred per

million courses of clindamycin. This may represent an underestimate since the prescribing of clindamycin has gradually increased over the period of adverse drug reaction reporting.

When analysis was limited to reports relating to a single 600mg oral dose of clindamycin during the data-recording period of January 1969 to January 2014, there were 15 fatalities, including 1 gastrointestinal (due to colitis), 13 infections (12 due to C. difficile infection and 1 due to peritonitis) and 1 due to vasculitis. In addition, there were 178 non-fatal reactions reported (including 125 gastrointestinal, 17 infections, 1 immune and 60 allergy related skin disorder reactions). Over the same period, we estimate that 1,193,502 courses of a single 600mg oral dose of clindamycin were prescribed. This figure allows a crude estimate of 12·6 fatal and 149·1 non-fatal reported reactions per million courses of clindamycin AP prescribed. For the period before introduction of the NICE guidelines, this equates to 0·38 fatal and 4·48 non-fatal reports per annum. For the level of AP prescribing during the most recent 6 months of the post-NICE guidelines period, this equates to 0·02 fatal and 0·21 non-fatal reports per annum.

In summary, the data suggest that AP in England led to 0·38 fatal and 6·76 non-fatal reported reactions per annum (the vast majority related to clindamycin) before introduction of the NICE guidelines. We estimate that, as a result of the reduction in AP prescribing, the rates fell to 0·02 fatal and 0·49 non-fatal reported reactions per annum since NICE - a fall of 0·37 fatal and 6·27 non-fatal ADR reports per annum.

Discussion

Adverse reactions to amoxicillin

The risk of fatal anaphylaxis with penicillin has previously been estimated at 1:100,000 and is higher in those receiving parenteral rather than oral penicillin.[22] Clemens and Ransohoff[23] estimated the death rate associated with oral penicillin to be closer to 0·9 deaths per million courses and the severe and mild ADR rates to be 400 and 2,400 per million courses, respectively. However, the risk associated with amoxicillin is less well documented. In a cost-effectiveness analysis of the use of AP to prevent IE, Agha et al. cited a death rate of 20 per million and a non-fatal hypersensitivity rate of 20,000 per million for amoxicillin or ampicillin.[14] However, this was not for the specific dose and route of administration used for AP and did not differentiate between parenteral or oral antibiotic administration. In contrast, Devereux et al. estimated that fatal allergic reactions to oral amoxicillin occurred with a frequency of 0·9 per million patients.[24] However, Devereux et al. derived this figure from the work of Clemens and Ransohoff, which related to penicillin rather than amoxicillin. Again, these figures were for any dose or duration of penicillin and not for the specific dose of amoxicillin and route of administration used for AP.

Our analysis of ADR reports and prescribing data for all doses, duration and routes of administration of amoxicillin produced an estimate of 0·1 fatal and 4·7 non-fatal reactions per million courses of amoxicillin. This is considerably lower than the rate of fatal (0·9/million) or severe (400/million) reactions calculated by Clemens and Ransohoff.[23] Looking specifically at the risk associated with a single 3g oral dose of amoxicillin as used for AP in the UK, no fatal ADR reactions were

reported over a period encompassing nearly 3 million prescriptions. This suggests that the incidence of fatal ADRs associated with a single 3g oral dose of amoxicillin is considerably less than previously estimated for AP related ADR, or that for other doses/routes of amoxicillin administration. However, at 22·62 per million prescriptions, the rate of non-fatal ADR associated with amoxicillin AP in the UK, while considerably less than previous estimates,[23] appears similar to that for all other doses and routes of administration of amoxicillin in the UK.

Adverse reactions to clindamycin

Although the association of clindamycin with C. difficile infection is well established,[25] estimates for its frequency range from 0·01% to 10%.[26-29] In contrast, the occurrence of other ADR to clindamycin, such as anaphylaxis, is thought to be rare.[30, 31] Our data suggest a rate of 11 fatal and 270 non-fatal reactions of all types per million courses of clindamycin. This is lower than previous reports in the literature, although our study examines the community-wide use of clindamycin, whereas previous studies were largely performed in hospital settings and among patients more susceptible to C. difficile infection.

With regard to the use of a single 600mg oral dose of clindamycin for AP, there are no reliable data that address the incidence of ADR. It had been thought that use of a single dose of clindamycin for AP purposes would not predispose to C. difficile infection.[32] However, there have been 5 case reports following dental use of clindamycin,[33] including one specifically related to the use of clindamycin for AP.[34] For an assessment of the cost-effectiveness of AP in preventing IE, Agha estimated a fatal ADR rate of 0 and a non-fatal ADR rate of 0·004 for clindamycin.[14] In our study, we estimated a rate of 13 fatal and 149 non-fatal reported ADR per million courses of clindamycin AP, the majority related to C.

difficile infection. Clearly, this is a much higher fatal ADR rate than previously estimated and similar to our rates for all other uses of clindamycin (11/million). While the non-fatal ADR rate was considerably less than previously estimated (4000/million),[14] it was again similar to our rates for all other uses of clindamycin (270/million). These data suggest that use of clindamycin for AP carries a significant risk of ADR that is very similar to the risk associated with the use of clindamycin for treating infections. In the literature, risk factors for developing clostridium difficile infections, aside from antibiotic use, include age and the use of proton pump inhibitors.[35, 36] Increasing age, malignancy, chronic renal failure and increased co-morbidity are thought to be risk factors for a poor outcome.[37] Our study also provides human confirmatory data to support a recent mouse study that identified profound changes in intestinal microbiota leading to C. difficile infection following a single dose of clindamycin.[38]

Assuming that the change in AP prescribing that occurred following introduction of the NICE guidelines did not alter the rate at which ADR occurred, it is possible to calculate the likely impact of the NICE guidelines on the number of ADR occurring each year as a result of AP prescribing. With a mean of 8,395 prescriptions for amoxicillin AP per month before NICE and 1,026 after, the mean annual reported ADR rate would have been 0 fatal and 0·19 non-fatal reactions before NICE and 0 fatal and 0·02 non-fatal reactions after - in both cases very low. For clindamycin AP, with 2,504 prescriptions per month before NICE and 120 after, the mean annual reported ADR rate would have been 0·03 fatal and 0·37 non-fatal reactions before NICE and <0·002 fatal and 0·02 non-fatal reactions after.

This raises a question over the suitability of clindamycin as an alternative for AP in those who report allergy to penicillins, particularly in those countries where AP is still the recommended standard of care. Recent studies have suggest that rates of cross-reaction between penicillins and first- and second-generation cephalosporins are much lower than previously thought and that cephalosporins are associated with low rates of serious ADR compared to clindamycin.[39-42] Perhaps it is time to re-evaluate if cephalosporins, or other antibiotics, would be a safer alternative to clindamycin for AP purposes in those with a history of allergy to penicillins.

Antibiotic prophylaxis prescribing

Before introduction of the NICE guidelines in March 2008, there were an average of 8395 prescriptions per month for a single 3g oral dose of amoxicillin and 2504 per month for a single 600mg oral dose of clindamycin. The vast majority were issued by dentists, a small proportion by general practitioners and a tiny fraction by hospitals and nurses. Approximately 23% of patients requiring AP therefore had clindamycin. The reasons for this are likely a combination of self-reported allergy, and because the older guidelines in place in the UK, prior to the NICE guidelines, suggested that if a patient had had amoxicillin in the previous month then they should receive clindamycin as AP. Although we are not aware of any other studies of self-reported penicillin/amoxicillin hypersensitivity rates in the primary care dental setting, the rate reported in the primary care medical setting is approximately half this figure.[43-45] The true rate of penicillin allergy is likely to be much lower however. Around 2-5% of patients reporting a penicillin “allergy” are found to be allergic when formally tested, and the remainder will tolerate penicillin use.[46-48] This has raised concerns that many patients labelled penicillin allergic, but who are in fact not allergic, are denied penicillins in favour of

antibiotics with potentially worse side effects such as clindamycin, vancomycin, or quinolones.[41] Better screening of patients with self-reported penicillin allergy, through better questioning and/or formal allergy testing, could significantly reduce the number of individuals denied penicillins.[39, 41, 43, 46-48]

Following introduction of the NICE guidelines, there was a highly significant fall in the prescribing of both AP preparations (87·8% for amoxicillin, 95·2% for clindamycin). This fall affected prescribing by dentists and general practitioners but was proportionately higher amongst dentists. With the fall in AP prescribing the proportion of patients receiving clindamycin also fell from a fairly steady ~23% before the NICE guidelines to just 10% in the last six months studied. This fall may reflect the fact that after the NICE guidelines, for patients with a self-reported penicillin allergy, the practitioner was more likely to elect to give no AP than to give clindamycin as an alternative to amoxicillin.

Although AP is no longer recommended before invasive dental procedures for any patients in the UK, it is still the standard of care for patients at high-risk of IE in most parts of the world.[18, 19] In the USA, and some other parts of the world, AP using oral amoxicillin or clindamycin is often also prescribed before invasive dental procedures for patients with prosthetic joints and a range of other conditions.[16] Indeed, Lockhart et al. have calculated that between 4.9 and 35.6 million courses of AP may be prescribed before invasive dental procedures annually in the USA at a cost of between $19.9 and $143.7 million.[16]

Limitations

In the UK, the Yellow Card reporting scheme is used by clinicians, including dentists, to report adverse drug reactions to the Medicines and Healthcare Products

Regulatory Agency (MHRA). Reporting by healthcare professionals is voluntary and not all adverse reactions are reported. Reported reactions may omit important data or be confounded by other factors. It is also not always certain that the drug identified caused the reported reaction - instead this could relate to the disease being treated, other drugs or completely unrelated factors. Moreover, it is known that healthcare workers are more likely to report serious or fatal ADRs than non-serious reactions. Furthermore, reporting is more common for newer drugs or those with a high public profile than older established drugs such as amoxicillin and clindamycin. It is also likely that there are minor adverse events that patients fail to report. It is likely, therefore, that these data underestimate the incidence of adverse reactions. These limitations, however, are shared by most other voluntary ADR reporting schemes that have been used to estimate ADR rates.

A further limitation is that we did not have access to the indication for the antibiotic being prescribed. However, there are few, if any indications for a single 3g oral dose of amoxicillin or a single 600mg dose of clindamycin other than to prevent infective endocarditis. The dramatic fall after the change in NICE guidance suggests that this was the principal indication. Furthermore, approximately 92% of prescriptions were issued by dentists. We cannot exclude the possibility that some were prescribed for other reasons, however. Anecdotally, in recent years, some dentists have started to use this dose prior to dental implants or to treat a dental infection. This may account for some of the residual prescribing.

Conclusions

AP ADR rates in England are low, and lower than previous estimates, with no fatal ADR recorded for nearly 3 million prescriptions of amoxicillin 3g as a single oral dose and 22·62 non-fatal ADR reported per million prescriptions. Use of amoxicillin AP for patients without a previous history of amoxicillin allergy appears safe. In contrast, the use of clindamycin AP was associated with a sizable ADR rate, including 13 fatal and 149 non-fatal ADR reports per million prescriptions, the majority relating to C. difficile infection. These findings should be incorporated into future discussions concerning the role of AP in the prevention of IE and calculations concerning its clinical and cost effectiveness.

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Transparency declarations:

LB and PL are members of the American Heart Association's Committee on Rheumatic Fever, Endocarditis, Kawasaki Disease and were involved in producing the 2007 American Heart Association guideline on Prevention of Infective Endocarditis. BP was a member of the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC) that produced the 2009 ESC guidelines on the prevention, diagnosis and treatment of infective endocarditis. BP also acted as a consultant to the committee that produced the NICE clinical guideline 64 on Prophylaxis Against Infective Endocarditis. We declare no other competing interests. MD is a topic expert (non-voting) for the current NICE review of clinical guideline 64.

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Figure legends:

Figure 1. Amoxicillin and clindamycin antibiotic prophylaxis prescribing data

This figure appears in colour in the online version of JAC and in black and white in the printed version of JAC

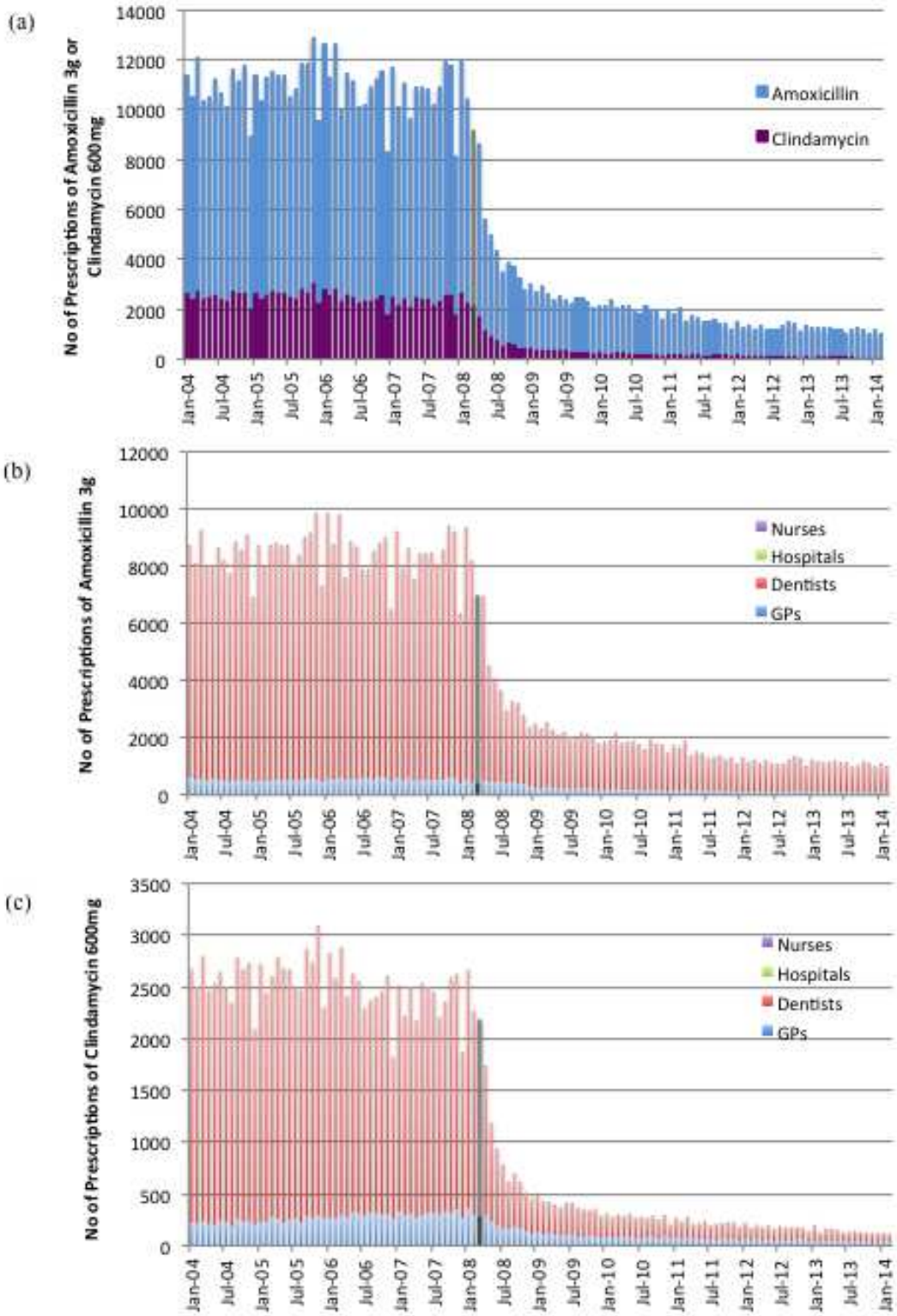
(a) Number of AP prescriptions dispensed each month (single 3g oral dose of amoxicillin [blue bars]; single 600mg oral dose of clindamycin [purple bars]). Note: Figure 1a is similar to a figure we recently had published in the Lancet, but shows a further 10 months of data.[21]

(b) Number of amoxicillin AP prescriptions dispensed each month, by prescriber (dentists – red; general practitioners – blue; hospitals – green; nurses – purple). Note: number of hospital and nurse prescriptions too small to see easily.

(c) Number of clindamycin AP prescriptions dispensed each month, by prescriber (dentists – red; general practitioners – blue; hospitals – green; nurses – purple). Note: number of hospital and nurse prescriptions too small to see easily.

In each case, the grey bars indicate March 2008, when NICE recommended the cessation of AP for IE.

526 **Figure 1**



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