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Revisiting amoxicillin prophylaxis for infective endocarditis: a pharmacokinetic and cost-effectiveness analysis

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Abstract

Introduction

The role of antibiotic prophylaxis in preventing infective endocarditis has long been contentious, and recent changes to United Kingdom guidance now recommend prophylaxis for patients at high risk undergoing invasive dental procedures. Comparatively little attention has been directed towards optimisation of the prophylactic amoxicillin regimen itself. This study evaluated the pharmacokinetic and economic rationale underpinning contemporary dental amoxicillin prophylaxis.

Methods

National Health Service dental prescribing data and Drug Tariff pricing information were analysed to characterise amoxicillin prescribing patterns and costs. Published pharmacokinetic studies were reviewed to examine the relationship between amoxicillin dose, bioavailability, and systemic exposure. A model was developed to compare exposure achieved by conventional prophylactic regimens and alternative divided-dose strategies. A previously published cost-effectiveness model was rebuilt as a cost-utility analysis using contemporary amoxicillin pricing, pooled efficacy estimates from a recent meta-analysis, and updated estimates of infective endocarditis incidence following invasive dental procedures. Incremental costs, quality-adjusted life years (QALYs) and threshold acquisition costs were calculated, with deterministic and probabilistic sensitivity analyses.

Results

Amoxicillin remained one of the most prescribed antibiotics in dentistry, accounting for approximately 40% of dental prescribing. Published pharmacokinetic studies demonstrated dose-dependent absorption, with bioavailability declining at higher oral doses. Simulations showed that repeated 500 mg doses administered every 6 hours achieved comparable pharmacodynamic target attainment to conventional 3 g prophylactic regimens despite substantially lower individual doses. The cost of 3 g amoxicillin sachets increased markedly over the study period, producing an approximately 57-fold to 114-fold difference in the cost of a prophylactic course compared with 500 mg capsules, depending on whether a single sachet or a dispensed pack of two was costed. Cost-utility analysis indicated that prophylaxis remained cost-effective in high-risk patients under every costing and formulation examined, with an incremental cost-effectiveness ratio of £140 per QALY for the 3 g sachet and dominance for capsule-based regimens in every group examined.

Conclusions

Current high-dose amoxicillin prophylaxis regimens may be pharmacokinetically inefficient because of dose-dependent absorption. Lower-dose divided regimens achieved comparable simulated pharmacodynamic exposure at substantially lower cost. Formulation choice, rather than dose, determined whether prophylaxis remained cost-saving. Prospective clinical studies are required to

determine whether the pharmacokinetic advantages of lower-dose regimens translate into improved clinical outcomes.

INTRODUCTION

The role of antibiotic prophylaxis (AP) in the prevention of infective endocarditis (IE) has been one of the most contentious issues in contemporary dental practice. Over the last two decades, guideline recommendations diverged internationally, with the American Heart Association and European Society of Cardiology continuing to recommend AP for patients at highest risk of IE undergoing invasive dental procedures, while the United Kingdom adopted a more restrictive approach following publication of National Institute for Health and Care Excellence (NICE) guidance[1]. Recent observational studies and economic analyses renewed this debate, leading some authors to argue for reconsideration of the UK position and reintroduction of AP for selected high-risk patient groups[2]. That position has now changed. Following amendment of NICE Clinical Guideline 64 and publication of the second edition of the Scottish Dental Clinical Effectiveness Programme (SDCEP) implementation advice, dentists throughout the United Kingdom are advised to offer AP to all individuals at high risk of IE before extractions and oral surgery procedures, and to consider AP for high-risk individuals undergoing other procedures involving manipulation of the gingival or periapical region[3,4]. The question has therefore shifted from whether prophylaxis should be given to how it should be given.

Consequently, much of the contemporary literature has focused on identifying which patients should receive prophylaxis, whether prophylaxis is effective, and whether its use is cost-effective. Particular attention has been paid to balancing the level of risk the procedure poses and the susceptibility of the patient. However, comparatively little attention has been paid to the prophylactic regimen itself. Amoxicillin also occupies a unique position within dental prescribing. Despite ongoing efforts to reduce antibiotic consumption, it remains one of the most frequently prescribed antibiotics in dentistry and continues to account for a substantial proportion of dental antibiotic use within the NHS and internationally, as demonstrated by prescribing studies from England[5], the United States[6], Australia[7] and Germany[8].

The rationale underpinning current prophylactic regimens deserves closer scrutiny. Amoxicillin is a β-lactam antibiotic whose antibacterial activity is primarily time-dependent, with efficacy determined by the duration for which free drug concentrations remain above the minimum inhibitory concentration (MIC). This pharmacodynamic principle was first described by Eagle *et al*. (1953) and subsequently formalised by Vogelman and Craig (1986), who demonstrated that antimicrobial efficacy is driven by time above MIC rather than peak concentration[9,10]. Consistent with this, contemporary therapeutic drug-monitoring studies in infective endocarditis emphasise maintaining amoxicillin concentrations above target thresholds throughout treatment[11]. For this reason, β-lactam therapy traditionally favours dosing strategies that maximise exposure over time rather than peak plasma concentrations. This principle underpins virtually all therapeutic amoxicillin regimens, which employ repeated dosing at regular

intervals to maintain antimicrobial activity. In contrast, contemporary dental prophylaxis guidelines recommend a single large oral dose of amoxicillin, typically 2 g internationally and, until recently, 3 g in the United Kingdom and Australia[1,12]. Current SDCEP advice lists 2 g given as four 500 mg capsules alongside the 3 g oral sachet, and states that the choice between them should reflect patient and clinician preference, availability and cost-effectiveness[4].

Such regimens implicitly prioritise peak exposure despite the absence of concentration-dependent killing behaviour. Furthermore, pharmacokinetic studies by Sjövall et al. (1985)[13], Paintaud et al. (1992)[14], Chulavatnatol and Charles (1994)[15], and de Velde et al. (2016)[16] demonstrated evidence of dose-dependent absorption and reduced bioavailability at higher oral doses of amoxicillin. These findings suggest that increasing the dose above a certain threshold may produce progressively smaller gains in systemic exposure while increasing treatment cost and potentially contributing to adverse effects.

Against this background, the present study re-examines the pharmacokinetic rationale for dental amoxicillin prophylaxis. We first contextualise amoxicillin use within contemporary dental prescribing and pricing data. We then review the pharmacokinetic behaviour of commonly used prophylactic regimens and develop a pharmacokinetic model to compare drug exposure achieved by current and alternative dosing strategies. Finally, we explore the economic implications of these findings by rebuilding the cost-effectiveness model developed by Franklin et al. (2016)[17] as a cost-utility analysis incorporating contemporary pricing, pooled efficacy estimates and updated incidence data.

Methods

Study design

This study combined analysis of national dental prescribing data, pharmacokinetic modelling, and a cost-effectiveness re-analysis to evaluate the pharmacological and economic rationale underpinning contemporary amoxicillin prophylaxis regimens used for the prevention of infective endocarditis.

Dental prescribing and pricing data

National Health Service (NHS) dental prescribing data were extracted from the English Dental Prescribing Statistics dataset (July 2025 release), covering the period January 2022 to June 2025. Prescribing volumes for total prescriptions, antibiotics, and amoxicillin-containing products were evaluated to contextualise the role of amoxicillin in contemporary dental practice. Historical pricing information for amoxicillin 500 mg capsules and 3 g oral sachets was obtained from Drug Tariff data and used to examine changes in formulation costs over time.

Pharmacokinetic analysis and modelling

A narrative review of published amoxicillin pharmacokinetic studies was undertaken to evaluate the relationship between oral dose, bioavailability, peak concentration (C_{max}), and systemic exposure. Data describing amoxicillin absorption and disposition following oral administration were extracted from studies reporting doses between 250 mg and 3 g. Particular attention was given to evidence of dose-dependent absorption and non-linear pharmacokinetics. Extraction of the literature data was facilitated using WebPlotDigitizer (version 3.4) and compartmental modelling was conducted using MagicPlot software (version 3.0.1, MagicPlot Systems LLC, Saint Petersburg Russia).

Pharmacokinetic data extracted from the literature was used to develop a model in Monolix (Simulations Plus, version 2024R1) to compare exposure following currently recommended prophylactic regimens and alternative dosing schedules. Oral absorption was described using first-order absorption with transit compartments, whilst plasma pharmacokinetics were characterised using a two-compartment model with a linear elimination rate. Previous work suggested this as an appropriate model[18]. Simulated serum concentrations were compared with target concentrations derived from published minimum inhibitory concentration (MIC) values (0.1 mg/L)[19] for oral streptococci and reported amoxicillin protein binding (17%)[20,21]. Pharmacodynamic exposure was assessed using the proportion of time that free-drug concentrations remained above four times the MIC (fT > 4×MIC). This target was selected as a conservative pharmacodynamic surrogate based on established β-lactam pharmacology, whereby antibacterial efficacy is principally determined by the duration that free-drug concentrations exceed the MIC. Although no validated pharmacodynamic target exists for the prevention of procedure-related bacteraemia or infective endocarditis, concentrations several-fold above the MIC are commonly used in pharmacokinetic-pharmacodynamic analyses as indicators of robust antimicrobial exposure. Accordingly, fT > 4×MIC was used as a comparative measure of pharmacodynamic target attainment between regimens rather than as a validated predictor of clinical prophylactic efficacy.

Cost-effectiveness analysis

The cost-effectiveness model developed by Franklin et al.[17] was rebuilt as a cost-utility analysis from the perspective of the National Health Service. The model takes the form of a decision tree applied to a single invasive dental procedure, with lifetime cost and health consequences, comparing amoxicillin prophylaxis against no prophylaxis.

Amoxicillin acquisition costs were taken from the Drug Tariff and applied to four regimens: a 3 g oral sachet costed as the pack of two in which it is supplied, the same sachet costed as the single dose actually taken, 3 g given as six 500 mg capsules, and 2 g given as four 500 mg capsules. Franklin et al. costed a single 3 g sachet at its pack-unit price, then £2.28, the sachet being supplied at that time in packs of fourteen[17], so the single-sachet costing preserves methodological consistency with the original analysis whilst the pack of two reflects the cost of supplying one prophylactic course under current pack sizes. Incremental costs, incremental QALYs and incremental cost-effectiveness ratios were calculated for each regimen in each risk group. Threshold analysis was used to identify the maximum acquisition

cost per dose at which prophylaxis would remain cost-saving, and at which it would remain cost-effective at £20,000 and £30,000 per QALY.

The two structural payoffs required by the model, namely the net lifetime NHS cost averted and the quality-adjusted life years (QALYs) gained per case of IE prevented, were derived directly from the published analysis. With the assistance of Claude (Opus 5, Anthropic), the incremental cost and incremental QALYs reported by Franklin et al. were divided by the corresponding number of IE cases averted, obtained from the absolute probabilities of IE with and without prophylaxis in their Table 1. This gave £25,479 and 6.44 QALYs per case prevented in the all-at-risk arm and £25,483 and 6.45 in the high-risk arm. The two arms agree to within 0.01% on cost and 0.7% on QALYs, and the derived values reproduce the published annual population savings and QALY gains to within 0.7%. A mean of £25,481 per case (2012/13 prices) and 6.44 QALYs per case was carried forward. All non-drug costs were inflated to 2024/25 prices using the NHS Cost Inflation Index[22]. Efficacy of prophylaxis was taken from the pooled relative risk reported in a recent systematic review and meta-analysis (RR 0.41, 95% CI 0.29 to 0.57)[23]. The incidence of IE in the four months following an invasive dental procedure was taken from a cohort of 9.6 million patients undergoing 53.6 million procedures, which reported 2,195 cases per million procedures in high-risk individuals, rising to 8,680 following extractions and 13,458 following other oral surgical procedures, and falling to 131 per million in moderate-risk and 17 per million in low-risk individuals[24]. Adverse drug reaction rates were taken from a national analysis of approximately three million amoxicillin prophylaxis prescriptions, which reported 22.6 non-fatal reactions per million prescriptions and no fatal reactions[25]. A rule-of-three upper limit of one fatal reaction per million prescriptions was carried into sensitivity analysis. Deterministic sensitivity analysis was performed on all model parameters, and probabilistic sensitivity analysis used 20,000 Monte Carlo iterations with lognormal distributions for the relative risk and incidence, gamma distributions for costs and QALYs, and beta distributions for adverse reaction probabilities.

Results

Dental prescribing patterns

NHS dental prescribing data demonstrated that although overall antibiotic prescribing declined between 2022 and 2025, amoxicillin remained consistently prescribed, accounting for approximately 40% of all dental prescriptions and around two-thirds of prescribed antibiotics throughout the study period (Table 1). Co-amoxiclav prescribing remained uncommon, representing approximately 0.3% of total dental prescriptions.

Table 1
Dental prescriptions extracted from NHS Dental Prescribing Statistics, July 2025 release. For each row, the total count is written in millions (except for co-amoxiclav which is given as an exact count) and the percentage of total prescribing is inset. Data for 2025 cover January to June only and the absolute prescribing numbers are not directly comparable with the full calendar years.

Year	***2022***	***2023***	***2024***	***2025***
Total (million)	4.20	4.05	3.97	2.25
Antibiotics (million)	2.69 (64.0%)	2.51 (62.0%)	2.41 (60.7%)	1.36 (60.4%)
Amoxicillin (million)	1.79 (42.6%)	1.68 (41.5%)	1.62 (40.8%)	0.91 (40.6%)
Co-amoxiclav	11,778 (0.3%)	10,740 (0.3%)	10,095 (0.3%)	5799 (0.3%)

Pharmacokinetics of high-dose amoxicillin

Published pharmacokinetic studies demonstrated that increasing oral amoxicillin doses led to higher peak plasma concentrations and overall exposure, but with progressively diminishing returns. Studies reporting doses between 250 mg and 3 g identified evidence of dose-dependent absorption, with reduced bioavailability observed at higher doses. Bioavailability declined substantially above approximately 1 g and was reported to be less than 50% following administration of a 3 g dose (Fig. 1A-C).

Analysis of published concentration-time profiles demonstrated that absorption following a 3 g dose was prolonged compared with a 500 mg dose, while elimination characteristics remained similar. Although higher doses achieved greater peak concentrations, increases in systemic exposure were proportionally smaller than increases in dose.

Pharmacokinetic modelling of prophylactic regimens

Pharmacokinetic simulations demonstrated that a conventional 3 g prophylactic dose produced high initial plasma concentrations but progressively approached target antimicrobial thresholds during the dosing interval (Fig. 1D). In comparison, repeated administration of 500 mg every 6 hours produced lower peak concentrations but maintained concentrations above the predefined pharmacodynamic target for a longer duration. Simulated exposure profiles suggested comparable target attainment between the two regimens despite substantially lower total drug exposure in the divided-dose regimen.

Cost analysis

The cost differential between amoxicillin 500 mg capsules and 3 g sachets increased substantially over the study period (Fig. 2). In 2025, a 3 g prophylactic dose supplied as six 500 mg capsules cost approximately £0.40, and a 2 g dose supplied as four capsules approximately £0.30. The 3 g oral sachet

cost £22.86 per sachet. Because the sachet is supplied in packs of two whilst the recommended regimen requires only a single dose, the cost of one prophylactic course dispensed in this form was £45.72. A single sachet therefore cost approximately 57 times the equivalent capsule regimen, and a dispensed pack approximately 114 times.

In high-risk patients undergoing invasive dental procedures, prophylaxis prevented an estimated 1,295 cases of IE per million procedures and gained 0.0083 QALYs per procedure. Prophylaxis using capsules was dominant, saving £44.25 per procedure with the 2 g regimen and £44.15 with the 3 g regimen. Costed on the same basis as the original analysis, as a single sachet, the 3 g sachet was also dominant, saving £21.69 per procedure. Only when the sachet was costed as a dispensed pack of two did prophylaxis cease to be cost-saving in this group, adding £1.17 per procedure; even then it gave an incremental cost-effectiveness ratio of £140 per QALY and remained far below conventional cost-effectiveness thresholds (Table 2).

For the procedures for which prophylaxis is now most strongly recommended, namely extractions and oral surgery, prophylaxis was cost-saving under every costing and formulation examined. In patients at moderate risk the position reversed. Prophylaxis using the 3 g sachet gave an incremental cost-effectiveness ratio of £40,572 per QALY costed as a single sachet and £86,480 costed as a dispensed pack, and would not be considered cost-effective on either basis, whereas prophylaxis using capsules remained cost-saving. Formulation therefore determined whether prophylaxis could be justified in this group. For comparison, at the acquisition cost used by Franklin et al., inflated to current prices, prophylaxis in moderate-risk patients would have cost £844 per QALY.

Threshold analysis indicated that the NHS could justify an acquisition cost of up to £44.55 per dose before prophylaxis in high-risk patients ceased to be cost-saving, and up to £211.45 before it ceased to be cost-effective at £20,000 per QALY (Table 3). The corresponding values were £176.16 and £836.18 for extractions, and £2.66 and £12.62 for patients at moderate risk. A single 3 g sachet at £22.86 fell below the cost-saving threshold for high-risk patients, whereas a dispensed pack at £45.72 exceeded it by £1.17 whilst remaining £166 below the cost-effectiveness threshold. In low-risk patients the margin was narrow enough to separate the two capsule regimens: at £0.40 the 3 g capsule course exceeded the £0.34 cost-saving threshold and gave an incremental cost-effectiveness ratio of £870 per QALY, whilst the 2 g course at £0.30 remained cost-saving.

Probabilistic sensitivity analysis supported these findings. In high-risk patients undergoing any invasive dental procedure, prophylaxis with a single 3 g sachet had a 97.8% probability of being cost-saving, falling to 41.1% when costed as a dispensed pack, but the probability of being cost-effective at £20,000 per QALY was 100% on either basis. The equivalent probabilities for the 2 g capsule regimen were both 100%. In patients at moderate risk, prophylaxis with the 3 g sachet had a zero probability of being cost-saving and no more than a 0.3% probability of being cost-effective at £20,000 per QALY, whereas the capsule regimen was cost-saving in every iteration. Deterministic sensitivity analysis identified the QALY value assigned to a prevented case of IE as the most influential parameter, followed by the proportion of

post-procedural IE attributable to the procedure and the pooled relative risk. Net monetary benefit remained positive across the plausible range of every parameter examined. Adverse drug reaction rates contributed £0.20 of a net monetary benefit of £166 per procedure and had negligible influence on the result.

Table 2

Cost-utility analysis of amoxicillin antimicrobial prophylaxis (AP) against infective endocarditis, by patient risk group, procedure type and formulation. Costs are expressed per invasive dental procedure in 2024/25 prices and reflect Drug Tariff prices at 13/Nov/2025. A regimen described as dominant is both less costly and more effective than no prophylaxis. The 3 g sachet is supplied in packs of two whilst the regimen requires a single dose, so both the dispensed pack (2-pack) and the dose actually taken (1 dose) are costed, the latter matching the costing convention used by Franklin et al.

Group and procedure	Formulation	Drug cost (£)	Δ cost (£)	Δ QALYs	ICER (£/QALY)
High-risk, all IDPs	3 g sachet (2-pack)	45.72	+ 1.17	0.0083	140
High-risk, all IDPs	3 g sachet (1 dose)	22.86	−21.69	0.0083	Dominant
High-risk, all IDPs	3 g, 6 × 500 mg caps	0.40	−44.15	0.0083	Dominant
High-risk, all IDPs	2 g, 4 × 500 mg caps	0.30	−44.25	0.0083	Dominant
High-risk, extractions	3 g sachet (2-pack)	45.72	−130.44	0.0330	Dominant
High-risk, extractions	3 g sachet (1 dose)	22.86	−153.30	0.0330	Dominant
High-risk, extractions	2 g, 4 × 500 mg caps	0.30	−175.86	0.0330	Dominant
High-risk, oral surgery	3 g sachet (2-pack)	45.72	−227.42	0.0512	Dominant
High-risk, oral surgery	2 g, 4 × 500 mg caps	0.30	−272.84	0.0512	Dominant
Moderate-risk, all IDPs	3 g sachet (2-pack)	45.72	+ 43.06	0.0005	86,480
Moderate-risk, all IDPs	3 g sachet (1 dose)	22.86	+ 20.20	0.0005	40,572
Moderate-risk, all IDPs	2 g, 4 × 500 mg caps	0.30	−2.36	0.0005	Dominant

Table 3
Maximum amoxicillin acquisition cost per prophylactic dose at which prophylaxis remains cost-saving, and at which it remains cost-effective at conventional thresholds, by patient risk group and procedure type. Values are in 2024/25 prices.

Group and procedure	Cost-saving (£)	£20,000 per QALY (£)	£30,000 per QALY (£)
High-risk, all IDPs	44.55	211.45	294.90
High-risk, extractions	176.16	836.18	1,166.19
High-risk, oral surgery	273.14	1,296.47	1,808.14
Moderate-risk, all IDPs	2.66	12.62	17.60
Low-risk, all IDPs	0.34	1.63	2.28

Discussion

Reconsidering the pharmacokinetic rationale for amoxicillin prophylaxis

The principal finding of this study is that contemporary amoxicillin prophylaxis regimens appear inconsistent with the pharmacodynamic principles that underpin the clinical use of β-lactam antibiotics. Current debates surrounding infective endocarditis prophylaxis have largely focused on patient selection, effectiveness, and cost-effectiveness, with recent contributions from Thornhill and colleagues advocating reconsideration of prophylaxis in high-risk patient groups (Thornhill et al. 2024[2]; Thornhill et al. 2026[3]), a position now reflected in revised United Kingdom guidance. Comparatively little attention has been directed towards optimisation of the prophylactic regimen itself.

Amoxicillin exhibits time-dependent antibacterial activity, with efficacy primarily determined by the duration that free-drug concentrations remain above the minimum inhibitory concentration (MIC) rather than peak plasma concentrations. This concept has been recognised since the seminal work of Eagle et al.[9] and was subsequently formalised by Vogelman and Craig[10], who demonstrated the importance of time above MIC for β-lactam efficacy. Likewise, therapeutic drug-monitoring studies in infective endocarditis continue to emphasise maintenance of adequate amoxicillin exposure throughout the treatment period rather than attainment of high peak concentrations alone (Dorel et al. 2023[11]).

In contrast, current dental prophylaxis protocols employ a single large oral dose of amoxicillin, a strategy more consistent with concentration-dependent antibiotics than with the established pharmacology of β-lactams (Habib et al. 2015[12]; SDCEP 2026[4]). Historically, prophylactic regimens were developed to maximise circulating antibiotic concentrations during the anticipated period of procedure-related bacteraemia rather than to optimise conventional β-lactam pharmacodynamic targets. The present modelling suggests that alternative divided-dose regimens may achieve comparable pharmacodynamic

exposure despite substantially lower individual doses, raising questions regarding whether current prophylactic schedules represent the most efficient use of amoxicillin.

Dose-dependent absorption and diminishing pharmacokinetic returns

A second important finding was the consistent evidence for dose-dependent absorption of oral amoxicillin. Multiple pharmacokinetic studies have demonstrated that bioavailability declines as oral doses increase, with doses exceeding approximately 1 g producing progressively smaller gains in systemic exposure. In particular, studies by Sjövall et al.[13], Paintaud et al.[14], Chulavatnatol and Charles[15], and de Velde et al.[16] observed reduced bioavailability following administration of high oral doses, suggesting that the relationship between dose and exposure is not strictly linear.

These observations provide a plausible mechanistic explanation for our simulation results, in which repeated 500 mg dosing achieved comparable pharmacodynamic target attainment to substantially larger prophylactic doses. Although higher doses generated greater peak concentrations, much of the additional administered drug appeared to translate into relatively modest increases in systemic exposure. This phenomenon may represent an inherent inefficiency within current prophylactic regimens.

Clinical and economic implications

Amoxicillin remains one of the most frequently prescribed antibiotics in dentistry, accounting for approximately 40% of all dental prescribing in England and demonstrating similar prescribing patterns internationally (Thornhill et al. 2019[5]; Durkin et al. 2017[6]; Walsh et al. 2021[7]; Halling et al. 2017[8]). Consequently, even relatively small improvements in dosing efficiency could have substantial healthcare and economic implications.

Franklin et al.[17] previously demonstrated that prophylaxis was both cost-effective and cost-saving for patients at risk of IE. Incorporating current pricing, pooled efficacy estimates and updated incidence data does not overturn that conclusion for high-risk patients, in whom prophylaxis remained cost-effective under every costing and formulation examined, and cost-saving under all but one. What has changed is that the 3 g sachet, when dispensed as the pack of two in which it is supplied, has ceased to be cost-saving across the whole range of invasive dental procedures. This should be distinguished carefully from a loss of cost-effectiveness, which the present analysis does not support. At £140 per QALY the sachet remains far below any threshold applied by the NHS, and the probabilistic analysis found no plausible parameter set in which it was not cost-effective for high-risk patients.

It is worth emphasising how conservative this conclusion is. The original analysis attributed the entire post-2008 rise in IE incidence to the withdrawal of prophylaxis, which implies a relative risk of approximately 0.08 and a reduction in IE of more than 90%. The pooled estimate used here, 0.41, corresponds to a reduction of 59%, and yields 1,295 IE cases averted per million high-risk procedures against the 1,651 implied by the original model. Prophylaxis in high-risk patients therefore remains cost-

effective under an efficacy assumption considerably less favourable than the one on which the original conclusion rested.

The more consequential finding concerns patients at moderate risk. Recent epidemiological data suggest that some conditions currently classified as moderate risk carry an IE risk approaching that of classical high-risk conditions, and the 2023 European Society of Cardiology guidelines state that prophylaxis may be considered in such patients on an individual basis[26]. In this group the choice of formulation determined whether prophylaxis could be justified at all. Prophylaxis using the 3 g sachet gave an incremental cost-effectiveness ratio of £40,572 per QALY costed as a single dose and £86,480 costed as a dispensed pack, whereas the same dose given as capsules was cost-saving. Any future extension of prophylaxis to moderate-risk patients would therefore depend upon formulation in a way that has not previously been recognised.

Two features of these findings deserve emphasis. First, the economic argument for capsules is independent of the pharmacokinetic argument advanced earlier in this paper. A 3 g dose delivered as six 500 mg capsules is the same dose, and its advantage lies in acquisition cost rather than exposure. This change requires no new clinical evidence and could be implemented immediately. Second, adverse drug reactions made a negligible contribution to the economic result, accounting for £0.20 of a net monetary benefit of £166 per procedure in high-risk patients. The concern that adverse reactions to prophylaxis might outweigh its benefit, which formed part of the original rationale for withdrawing prophylaxis in the United Kingdom, was not supported at any plausible parameter value.

Although economics alone should not dictate clinical decision-making, prescribing regimens that simultaneously improve pharmacokinetic efficiency and reduce healthcare expenditure represent an attractive objective.

Limitations

Several limitations should be acknowledged. First, this study relied upon published pharmacokinetic data drawn from studies performed over several decades, many of which involved relatively small participant numbers. Secondly, the pharmacokinetic model evaluated surrogate markers of antimicrobial exposure rather than direct clinical outcomes. Whilst time above MIC is an accepted predictor of β-lactam activity, it cannot fully account for the complex biological processes involved in prevention of infective endocarditis.

A further limitation is that fT > 4×MIC was used as a surrogate pharmacodynamic endpoint. Although supported by established β-lactam pharmacology, no validated pharmacodynamic threshold currently exists for the prevention of procedure-related bacteraemia or infective endocarditis.

Finally, it is acknowledged that infective endocarditis prophylaxis is intended to prevent bacteraemia occurring during a brief procedural window, whereas the alternative regimen modelled involved repeated 500 mg doses administered over time. Consequently, the aim of this analysis was not to propose a replacement for current prophylactic schedules, but to explore whether the pharmacokinetic rationale

underpinning high-dose amoxicillin prophylaxis is optimal. The findings suggest that comparable pharmacodynamic target attainment may be achievable with lower-dose strategies despite substantially lower individual doses. Although such regimens may not be practical for routine prophylaxis, they highlight the need to re-evaluate whether current schedules represent the most efficient use of amoxicillin. Future studies should compare prophylactic dosing strategies using clinically relevant endpoints, including post-procedural bacteraemia, infective endocarditis incidence, adverse events, patient acceptability, and cost-effectiveness, before any changes to clinical practice can be considered.

Several limitations apply specifically to the economic analysis. Costs were inflated from 2012/13 to 2024/25 prices using a single index factor, to which the results were insensitive. The incidence estimates were derived from United States administrative data and applied to a United Kingdom cost model, an approach shared with the original analysis but one which assumes comparability of case mix. The base case assumed that all IE occurring in the four months following a procedure was procedure-related and therefore preventable by prophylaxis. This is internally consistent with the way the pooled relative risk was estimated, but is likely to be generous, and it was the second most influential parameter in sensitivity analysis. The structural payoffs were derived from the published incremental results of the original model rather than by rebuilding its Markov structure, so the long-term transition probabilities and utility weights are inherited rather than re-estimated. Procedure volumes were taken from the original analysis and predate the recent change in guidance, so population-level estimates should be treated as indicative. Finally, the 2 g regimen was costed but was not evaluated pharmacokinetically in this study, and any difference in target attainment between 2 g and 3 g would need to be reflected in the effectiveness parameter rather than in cost.

Conclusion

The current debate surrounding infective endocarditis prophylaxis has largely concentrated on whether prophylaxis should be prescribed. Now that United Kingdom guidance recommends prophylaxis for patients at high risk, equal consideration should be given to how prophylaxis is prescribed. Existing high-dose regimens warrant pharmacokinetic re-evaluation owing to dose-dependent absorption, while divided lower-dose regimens appear capable of achieving comparable pharmacodynamic exposure at substantially lower cost. Prophylaxis remains cost-effective for high-risk patients under every formulation examined, but the choice of formulation determines whether it is also cost-saving, and determines whether prophylaxis could be justified in patients at moderate risk. Substituting 500 mg capsules for the 3 g oral sachet requires no new clinical evidence and would release resources immediately. Further clinical investigation is warranted to determine whether the pharmacokinetic advantages of lower-dose regimens translate into improved patient outcomes.

Declarations

Conflict of interest

The authors declare no conflict of interest.

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Figures

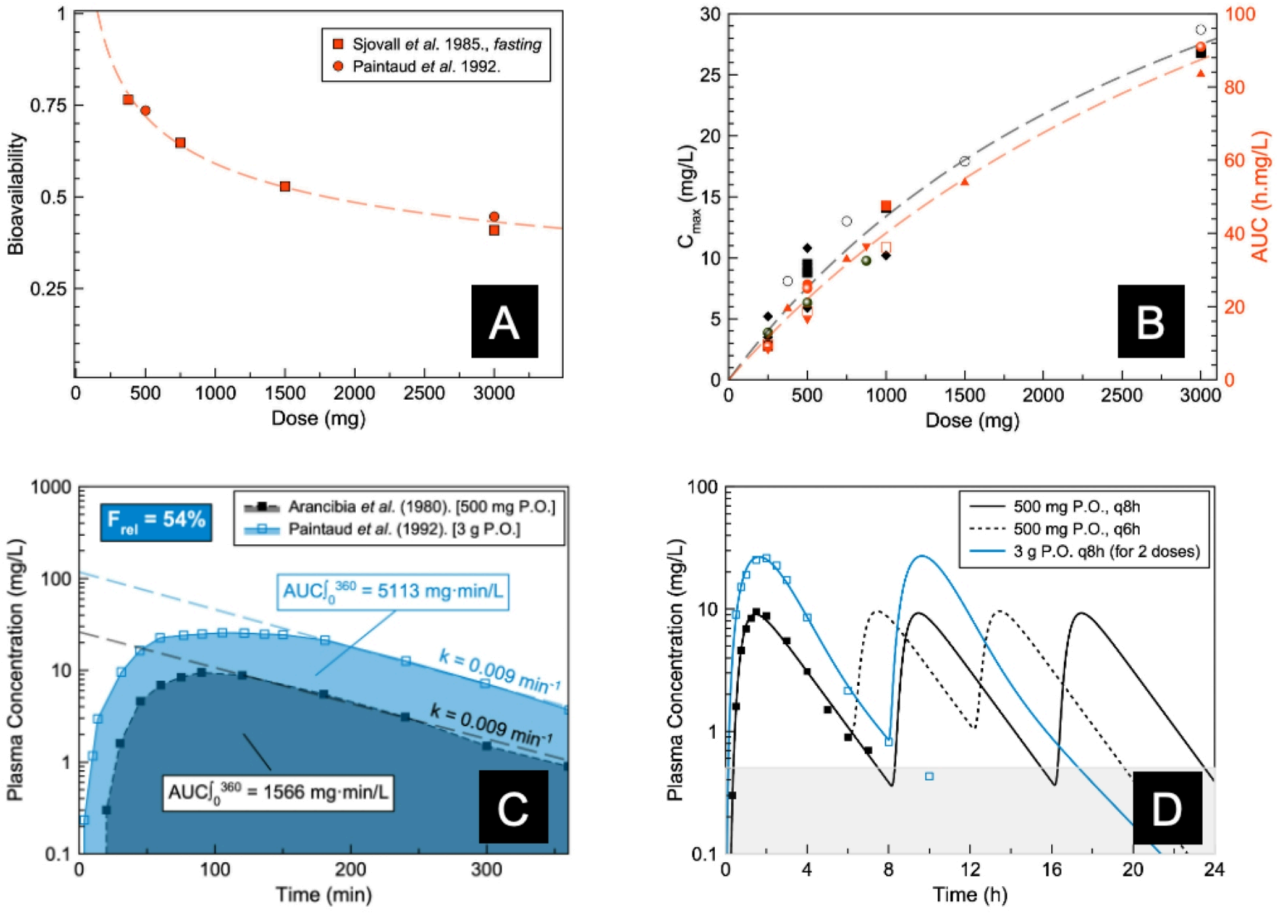


Figure 1

The relationship between dose and (A) bioavailability along with (B) Cmax and drug exposure for amoxicillin. Logistic functions have been fitted to the experimental data to enable interpolation. (C) The pharmacokinetic profile of a single 500 mg and 3 g dose of amoxicillin with AUC inset. A one compartment function has been fitted to the elimination phase to determine the elimination rate constant. (D) Simulated pharmacokinetics of 3 g and two 500 mg dosing regimens, the 0.5 mg/L threshold for antimicrobial activity has been highlighted in grey.

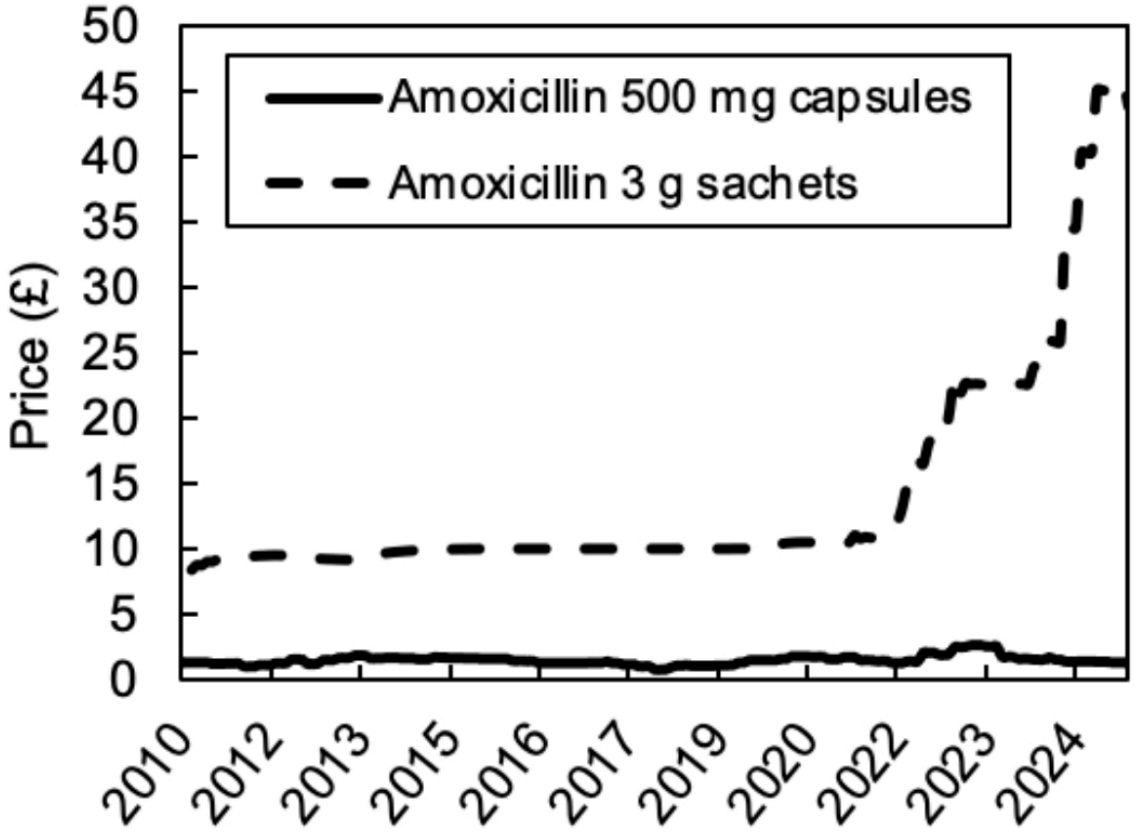


Figure 2

Annual moving average of the Drug Tariff price for amoxicillin 500 mg and 3 g between 01/June/2010 - 01/June/2025.