The Cost-Effectiveness of Antibiotic Prophylaxis for Patients at Risk of Infective Endocarditis

BACKGROUND: In March 2008, the National Institute for Health and Care Excellence recommended stopping antibiotic prophylaxis (AP) for those at risk of infective endocarditis (IE) undergoing dental procedures in the United Kingdom, citing a lack of evidence of efficacy and cost-effectiveness. We have performed a new economic evaluation of AP on the basis of contemporary estimates of efficacy, adverse events, and resource implications.

METHODS: A decision analytic cost-effectiveness model was used. Health service costs and benefits (measured as quality-adjusted life-years) were estimated. Rates of IE before and after the National Institute for Health and Care Excellence guidance were available to estimate prophylactic efficacy. AP adverse event rates were derived from recent UK data, and resource implications were based on English Hospital Episode Statistics.

RESULTS: AP was less costly and more effective than no AP for all patients at risk of IE. The results are sensitive to AP efficacy, but efficacy would have to be substantially lower for AP not to be cost-effective. AP was even more cost-effective in patients at high risk of IE. Only a marginal reduction in annual IE rates (1.44 cases in high-risk and 33 cases in all at-risk patients) would be required for AP to be considered cost-effective at £20,000 ($26,600) per quality-adjusted life-year. Annual cost savings of £5.5 to £8.2 million ($7.3–$10.9 million) and health gains >2600 quality-adjusted life-years could be achieved from reinstating AP in England.

CONCLUSIONS: AP is cost-effective for preventing IE, particularly in those at high risk. These findings support the cost-effectiveness of guidelines recommending AP use in high-risk individuals.
Clinical Perspective

What Is New?

- This study uses recent data to evaluate the cost-effectiveness of antibiotic prophylaxis (AP) in preventing infective endocarditis (IE).
- It demonstrates that AP before invasive dental procedures for those at moderate or high risk of IE is very cost-effective, in fact, cost saving.
- Cost-effectiveness is even greater when AP is confined to those at high risk of IE.
- For high-risk individuals, AP is cost-effective even if it only prevents 1.44 cases of IE per year.

What Are the Clinical Implications?

- If AP was reinstated in England for those at moderate or high risk of IE, it could save £5.5 to £8.2 million ($7.3–$10.9 million; €6.6–€9.8 million) and result in health gains >2600 quality-adjusted life-years per year.
- AP is even more cost-effective for those at high risk of IE. Restricting AP to those at high risk would result in cost savings of £4.0 million ($5.32 million; €4.8 million) and health gains of >1070 quality-adjusted life-years per year in England because of the smaller number of individuals at high risk.
- These findings support the cost-effectiveness of guidelines recommending AP use, in particular, in high-risk individuals.

Antibiotic prophylaxis (AP) is a widely used prevention measure for those at risk of developing infective endocarditis (IE). Following the suggestion that bacteremia secondary to invasive dental procedures might cause IE,1 the American Heart Association’s Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis was the first to recommend that individuals at increased risk of IE should be given antibiotic prophylaxis (AP) before invasive dental procedures some 60 years ago.2 Over time, the American Heart Association and other international guideline committees have gradually restricted AP use, moving to single-dose AP strategies and restricting the types of patients for whom AP is recommended.3-4 In 2008, this culminated with the National Institute for Health and Care Excellence (NICE) recommending that the use of AP to prevent IE should cease in the United Kingdom.5 This recommendation was confirmed in a recent review of the NICE guidelines6 but is in contrast with current European,7 North American,4 and other international guidelines that recommend AP for high-risk individuals undergoing invasive dental procedures.

A recent interrupted time series study found that AP prescribing in England fell sharply after the 2008 NICE guidance with a significant increase in the incidence of IE. By March 2013, it was estimated that there were 34.9 (95% confidence interval, 7.9–61.9) more cases of IE per month than would have been expected from the previous trend.8 This increase was statistically significant both for those at high risk (previous history of IE, prosthetic heart valve, valve repaired with prosthetic material, un repaired cyanotic congenital heart disease, or some repaired congenital heart defects) and moderate risk (native valve disease, un repaired congenital heart valve anomalies, or previous rheumatic fever) of IE. This study provides unique evidence for evaluating the cost-effectiveness of AP, because the United Kingdom is the only country to have transitioned from recommending AP for those at high risk or moderate risk of IE to recommending its complete cessation. Another recent UK study demonstrated that the incidence of adverse drug reactions associated with AP was much lower than previously estimated.9

This article estimates the cost-effectiveness of AP (single-dose amoxicillin or clindamycin for those allergic to penicillin) in patients at risk of IE by using (1) recent estimates of the effect of AP on IE in the English population,8 (2) rates of AP adverse drug reactions,9 and (3) estimates for the probability of developing IE after dental procedures derived from French data10 as the foundation for analysis of cost and health benefits.

Methods

Comparators and Patient Population

The cost-effectiveness of the AP regimen that was in use in the United Kingdom before the 2008 NICE guidelines (a single 3-g oral dose of amoxicillin or a single 600-mg oral dose of clindamycin for those allergic to penicillin or who had received amoxicillin in the previous month) for all at risk individuals (ie, those at moderate risk or high risk of IE) was compared with a strategy of no AP (as per the NICE guidelines5,6). We also compared no AP with a strategy restricting AP to just those at high risk of IE (as per the European7 and North American4 guidelines). English National Health Service costs were estimated and health effects measured in quality-adjusted life-years (QALYs).

Model Structure

A decision model, based on the decision model used by NICE for the health-economic analysis performed to inform the 2008 guidelines,5 was constructed to estimate differences in costs and health benefits accruing from the short-term consequences of the decision to administer AP, or not, and the longer-term sequelae of AP and IE (Figure). AP-related adverse events and IE may be fatal or lead to differences in the probability of a patient being otherwise healthy, requiring valve replacement surgery or experiencing congestive heart failure (CHF). These longer-term impacts were captured by using a state transition model, with 1-year cycle periods and a lifetime (50 years) time horizon. We used TreeAge Pro software (https://www.treeage.com) and the Sheffield Accelerated Value of Information Tool (http://savi.shef.ac.uk/SAVI/).
Parameter Values
Data used to calculate the probability of IE after a high-risk (invasive) dental procedure were based on previous definitions and estimates of the risk of adults with predisposing cardiac conditions developing IE.10 The number of IE hospital admissions (International Classification of Diseases, 10th Revision code I33.0) was obtained from Hospital Episode statistics (HES; http://www.hscic.gov.uk/hes)11 and population data from the Office of National Statistics.12 A more detailed explanation of the calculations and values is provided in the online-only Data Supplement Methods and online-only Data Supplement Tables I and II).

Probability of IE Following a High-Risk Dental Procedure
The probability of IE after a high-risk dental procedure was based on analysis of recent English data8 that estimated that reduced use of AP was associated with 34.9 (95% confidence interval, 7.9–61.9) additional IE cases per month.

The incidence of IE with AP use was derived from 2007, the year immediately before the introduction of NICE guidance (1486 cases, 28.91 per million). Table 1 reports parameter estimates required to translate this incidence into an estimate of the probability of IE. All other probabilities are shown in Table 2. Duval et al10 provided data on the proportion of IE cases associated with a predisposing cardiac condition, the proportion associated with a high-risk dental procedure, the mean number of high-risk dental procedures per year in those with a predisposing cardiac condition, and the prevalence of a predisposing cardiac condition, resulting in an estimated probability of IE of 17.98 per million high-risk dental procedures where routine AP would be provided.

The higher estimated annual incidence of IE in the absence of AP leads to an estimated probability of IE of 1785.13 cases per million in the high-risk group and 204.33 cases per million dental procedures in the all-at-risk group.

Mortality From IE
All patients were tracked for mortality within 1 year of IE diagnosis (International Classification of Diseases, 10th Revision code I33.0) using HES.11 Deaths in the community secondary to IE were not included because HES only records in-hospital mortality, resulting in a small underestimate of IE-related mortality, a limitation of this data set.

Fatal and Nonfatal Reactions to AP
NHS Business Service Authority prescribing data were cross-referenced with adverse drug reaction data for prescriptions.
Table 1. Data Used to Estimate the Probability of IE After a High-Risk (Invasive) Dental Procedure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Population (N)</th>
<th>Occurrence (R)</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-at-risk group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Incidence of IE (per million people per annum)</td>
<td>28.9</td>
<td>51.4 m&lt;sup&gt;12&lt;/sup&gt;</td>
<td>1486&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Beta</td>
</tr>
<tr>
<td>b. Incident cases that would have occurred in at-risk patients*</td>
<td>0.521</td>
<td>1370&lt;sup&gt;10&lt;/sup&gt;</td>
<td>714&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Beta</td>
</tr>
<tr>
<td>c. IE cases attributed to dental procedures in at-risk group</td>
<td>0.052</td>
<td>714&lt;sup&gt;10&lt;/sup&gt;</td>
<td>37&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Beta</td>
</tr>
<tr>
<td>d. Number of dental procedures/patient/y for at-risk patients*</td>
<td>1.32</td>
<td>1287296&lt;sup&gt;10&lt;/sup&gt;</td>
<td>1704195&lt;sup&gt;10&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>e. Prevalence of at-risk patients</td>
<td>3.30%</td>
<td>39000000&lt;sup&gt;10&lt;/sup&gt;</td>
<td>1287296&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Beta</td>
</tr>
<tr>
<td>f. Increase in cases of IE per month as a result of AP cessation†</td>
<td>34.9&lt;sup&gt;8&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td>Gamma</td>
</tr>
<tr>
<td>Estimated number of dental procedures per year for at-risk patients‡</td>
<td>2.24 m</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Probability of IE after a dental procedure with AP (per million people)§</td>
<td>17.87</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Probability of IE after a dental procedure without AP (per million people)‖</td>
<td>204.33</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>High-risk group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of IE (per million people per annum)</td>
<td>28.9</td>
<td>51.4 m&lt;sup&gt;12&lt;/sup&gt;</td>
<td>1486&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Beta</td>
</tr>
<tr>
<td>Incident cases that would have occurred in high-risk patients*</td>
<td>0.288</td>
<td>1486&lt;sup&gt;11&lt;/sup&gt;</td>
<td>428&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Beta</td>
</tr>
<tr>
<td>IE cases attributed to dental procedures in high-risk group</td>
<td>0.031</td>
<td>224&lt;sup&gt;10&lt;/sup&gt;</td>
<td>7&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Beta</td>
</tr>
<tr>
<td>Number of dental procedures/patient/y in high-risk patients*</td>
<td>0.33</td>
<td>228570&lt;sup&gt;10&lt;/sup&gt;</td>
<td>75409&lt;sup&gt;10&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Prevalence of high-risk patients</td>
<td>0.59</td>
<td>39000000&lt;sup&gt;10&lt;/sup&gt;</td>
<td>228570&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Beta</td>
</tr>
<tr>
<td>Increase in cases of IE per month as a result of AP cessation#</td>
<td>13.7&lt;sup&gt;7&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td>Gamma</td>
</tr>
<tr>
<td>Estimated number of dental procedures per year for high-risk patients</td>
<td>0.1 m</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Probability of IE after a dental procedure with AP (per million people)</td>
<td>134.58</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Probability of IE after a dental procedure without AP (per million people)‖</td>
<td>1785.13</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

AP indicates antibiotic prophylaxis; and IE, infective endocarditis.

*At risk of IE patients are mainly defined as those patients with a predisposing cardiac condition, although at risk has been defined by Duval et al<sup>10</sup> and Dayer et al<sup>8</sup> from which these data were obtained.

†Mean extra cases per month<sup>8</sup>: 34.9 cases (95% confidence interval<sup>8</sup>, 7.9–61.9; standard errors, 13.78); mean extra cases per year: 418.8 cases.

‡Mean extra cases per month<sup>8</sup>: 13.7 cases (95% confidence interval<sup>8</sup>, –3.29 to 30.64; standard errors: 8.66); mean extra cases per year: 164.0 cases.

§Calculated as (a.b.c)/(d.e).

‖Calculated as ((a+f).b.c)/(d.e).

*Mean extra cases per month<sup>8</sup>: 13.7 cases (95% confidence interval<sup>8</sup>, –3.29 to 30.64; standard errors: 8.66); mean extra cases per year: 164.0 cases.

of standard AP (single oral dose amoxicillin 3 g or clindamycin 600 mg) from the Medicine and Health Products Regulatory Agency Yellow Card reporting scheme.<sup>9</sup> The fatal and nonfatal adverse drug reaction rates per million prescriptions were 0 and 22.6, and 12.6 and 149.1 for amoxicillin and clindamycin, respectively.<sup>9</sup>

**Long-Term Survival and Outcomes**

Age-adjusted, all-cause mortality was estimated by using Office of National Statistics Population Prediction statistics for 2012 to 2013.<sup>23</sup> Mortality risk for patients that survive valve surgery or develop CHF (International Classification of Diseases, 10th Revision code I50) was estimated by using published prosthetic valve endocarditis registry data.<sup>13</sup> One, 5, and 10 year survival in this cohort was 67.1%, 55%, and 37.6%, respectively, and used to estimate a Weibull survival function.<sup>5</sup> Mortality after valve replacement surgery was estimated using HES data for patients admitted for valve replacement surgery (OPCS-4 Classification of Interventions and Procedures version 4 codes: K25.1–K25.4, K26.1–K26.4, K27.1–K27.4, K28.1–K28.4, or K29.1–K29.4) and discharged as dead within the same spell for the year 2012.

The annual probability of IE survivors developing CHF over 5-year follow-up was estimated from HES. Of the 19804 patients with IE and reliable 5-year follow-up data, the numbers diagnosed with CHF were 2152, 387, 292, 170, and 157 in years 1 to 5, respectively. The subsequent probability of developing CHF until the end of the model’s time horizon was assumed to be constant after year 5. Recent studies show that 40% to 50% of patients now undergo valve replacement surgery as part of their initial IE treatment,<sup>14–16</sup> and, for this transition probability, we adopted a conservative 40% estimate. The annual probability of IE survivors needing valve surgery after the initial admission was estimated by using HES. Of the 19804 patients diagnosed with IE and followed for 5 years, 1278 required valve replacement surgery during the first year after their initial IE treatment, and 329, 158, 75, and 74 required valve replacement surgery in years 2 to 5, respectively. The subsequent probability of needing valve surgery is assumed to remain at 74 cases per year through to year 9, before falling to 17 cases per year until the end of the model’s time horizon.
Table 2. Summary of Transitional Probabilities for Adverse Health States, Mortality, and Adverse Side Effects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base Case</th>
<th>R (Occurrences)</th>
<th>N (Population)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse health states</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developing congestive heart failure after IE*</td>
<td>1–5 y prognosis: 0.109; 0.02; 0.015; 0.009; 0.008</td>
<td>1–5 y No. cases: 2,152; 387; 292; 170; 157</td>
<td>19,804†</td>
<td>Probability assumed constant after the fifth year.</td>
</tr>
<tr>
<td>Developing congestive heart failure (non-IE cases) *</td>
<td>0.007</td>
<td>360,471†</td>
<td>53,500,000‡</td>
<td>–</td>
</tr>
<tr>
<td>Valve replacement during or immediately after IE*</td>
<td>0.400</td>
<td>7922</td>
<td>19,804†</td>
<td>Number of occurrences (7922) based on assumed 40% of patients requiring immediate valve replacement surgery in a population of 19,804 people.14–16</td>
</tr>
<tr>
<td>Valve replacement/repair, years 1–10 (IE cases)*</td>
<td>1–5 y prognosis: 0.065; 0.017; 0.008; 0.004; 0.004</td>
<td>1–5 y No. cases: 1278; 329; 158; 75; 74</td>
<td>19,804†</td>
<td>Number of events does not include those patients included in the valve replacement during or immediately after IE arm; probability assumed constant after the fifth year until year 9, before falling to 17 cases/y.</td>
</tr>
<tr>
<td>Valve replacement/repair (non-IE cases)*</td>
<td>&lt;0.001</td>
<td>2340†</td>
<td>53,500,000‡</td>
<td>–</td>
</tr>
<tr>
<td>Valve replacement/repair, after 10 y (IE cases)*</td>
<td>0.001</td>
<td>17†</td>
<td>19,804†</td>
<td>–</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality from IE: general</td>
<td>0.108</td>
<td>232†</td>
<td>2145§</td>
<td>Death from AE within the first year (calculated from Hospital Episode Statistics data for the year 2012).</td>
</tr>
<tr>
<td>Death from valve surgery</td>
<td>0.040</td>
<td>64†</td>
<td>2340‖</td>
<td>Discharged as dead within the same spell as valve surgery (calculated from Hospital Episode Statistics for the year 2012).</td>
</tr>
<tr>
<td>Death for patients with a successful valve replacement</td>
<td>Weibull function (lambda = 0.144; gamma = 0.368)</td>
<td>Weibull function as used in the NICE prophylaxis against infective endocarditis model for the 2008 guidance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death for all patients developing congestive heart failure</td>
<td>Weibull function as per patients with a successful valve replacement/repair</td>
<td>Weibull function as used in the NICE prophylaxis against infective endocarditis model for the 2008 guidance</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse side effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal side effect to amoxicillin</td>
<td>22.62 per million</td>
<td>–</td>
<td>–</td>
<td>No distinction on type of nonfatal side effect.</td>
</tr>
</tbody>
</table>

(Continued)
Health-Related Quality of Life (Utility) Weights

Mean health state utility values, required for estimating QALYs, and associated standard deviations were taken from different sources that are described in this section. UK population age norms were used to adjust and parameterize all utility values for the 5 health states in the model.

Adults in the well state were considered to be equivalent to patients with a New York Heart Association class 1 (ie, people with cardiac disease but no symptoms or limitations in function). Patients in the needing-valve-surgery state were assumed to correspond to New York Heart Association class III/IV. We assumed the utility value of 0.525 would be relevant only for 6 months before the same value as the Successful-valve-surgery state utility value would be relevant. Successful valve surgery was estimated by using data for New York Heart Association class I/II patients after valve replacement, with a utility value of 0.855.

The health state and age utility values used are shown in Table 3.

Costs

National sources for unit costs were used. The cost of amoxicillin (£2.28 [$3.03, €2.74]) and clindamycin (£1.14 [$1.52, €1.37]) were obtained from the British National Formulary (Number 65) for 2013. Secondary care costs were estimated using 2012 to 2013 National Reference costs. General practice consultation costs for AP adverse events were from Curtis. Exchange rates shown between UK£, US$, and the Euro € were calculated on the July 1, 2016 using the midmarket rate (£1=$1.33=€1.20).

Patients with CHF or previous valve surgery were assumed to require 2 cardiology outpatient visits per year. Those with CHF were assumed to require treatment with angiotensin-converting enzyme/angiotensin II inhibitors, β-blockers, digoxin, and high-dose loop diuretics at typical daily doses. A summary of these unit costs is provided in Table 4.

All costs were discounted by 3.5% as suggested by NICE 2013 technology appraisal guidelines. A range of sensitivity analyses was performed, including probabilistic sensitivity analysis, to reflect different aspects of uncertainty in the evidence.

Statistical Analysis

An initial decision tree model leading to a state transition model was used to estimate the cost per QALY gained of AP versus no AP over a time horizon of 50 years. One-way and probability sensitivity analysis and expected value of perfect information (EVPI) analysis were also conducted. We used Treeage Pro software (https://www.treeage.com) to construct the decision tree and state transition model and the Sheffield Accelerated Value of Information Tool (http://savi.shef.ac.uk/SAVI/) for the EVPI analysis.

This analysis was performed in compliance with the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) guidelines for the reporting of health economic analyses. Ethics approval was not required for this study because it was confined to analysis of publicly available data containing no identifiable patient information.
In comparison with no AP, both amoxicillin and clindamycin AP were associated with lower costs and better health outcomes (Table 5) for both high-risk and all-at-risk populations. In the all-at-risk group, there were mean cost savings of £2.47 (95% credible interval [Crl], £0.48–£6.96) ($3.29; Crl $0.64–$9.26; €2.96, Crl €0.58–€8.35) per person with amoxicillin AP and £3.65 (95% Crl, £0.69–£8.14) ($4.86; 95% Crl, $0.92–$10.83; €4.38, 95% Crl, €0.83–€9.77) with clindamycin AP, in comparison with no AP (the difference between the drugs being driven by the lower cost of clindamycin: £1.14 versus £2.28 [$1.52 versus $3.03; €1.37 versus €2.74]).

With an estimated 2.24 million dental procedures per year in this population (Table 1), AP would lead to savings of £5.5 million to £8.2 million per annum ($7.3 million to $10.9 million; €6.6 million to €9.8 million). We calculated a mean health improvement of 0.0012 (95% CrI, 0.000–0.003) and 0.0010 (95% Crl, 0.000–0.002) QALYs per person for amoxicillin and clindamycin, respectively (equivalent to 2687 QALYs gained per annum at the population level if amoxicillin AP were used for all-at-risk patients).

These cost savings were substantially greater in the high-risk group at a mean of ≈£40 (€53.2; $48.00) per patient (or £4.0 million ($5.3 million; €4.8 million) per annum in England on the basis of an estimated 100,000 dental procedures in this population). The most effective strategy would be amoxicillin, leading to gains of 0.0107 QALYs per person (or 1071 QALYs for the population) per annum.

### Sensitivity Analysis
A sensitivity analysis on the effectiveness of AP was performed by varying the number of additional IE cases associated with AP withdrawal from 35 per month (base case) to zero (implying AP has no protective effect). For the all-at-risk group, amoxicillin remained cost saving until the rate of IE cases avoided fell below 16.8 per month and cost-effective (at £20,000 ($26,600; €24,000) per

---

**Table 4. Summary of Unit Costs**

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>25%</th>
<th>75%</th>
<th>SD</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP (per course)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral amoxicillin 3 g</td>
<td>2.28</td>
<td></td>
<td></td>
<td></td>
<td>3 g sachet, powdered sugar free (14 sachet pack=£31.94)</td>
</tr>
<tr>
<td>Oral clindamycin 600 mg</td>
<td>1.14</td>
<td></td>
<td></td>
<td></td>
<td>4 capsules × 150 mg dose (24 × 150 mg: £6.85)</td>
</tr>
<tr>
<td>Hospitalization for endocarditis</td>
<td>5136</td>
<td>2604</td>
<td>6943</td>
<td>1220</td>
<td>Weighted average nonelective long stay cost for “Endocarditis with CC scores”; Weighted average length of stay=12.71 days</td>
</tr>
<tr>
<td>Hospitalization for valve surgery</td>
<td>10,204</td>
<td>8082</td>
<td>11,712</td>
<td>1018</td>
<td>Weighted average elective long stay cost for “Single Cardiac Valve Procedure with CC scores”; Weighted average length of stay=6.61 days</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>2647</td>
<td>2040</td>
<td>3116</td>
<td>317</td>
<td>Weighted average nonelective long stay cost for “Heart Failure or Shock with CC scores”; Weighted average length of stay=7.53 days</td>
</tr>
<tr>
<td>Fatal anaphylaxis</td>
<td>375</td>
<td>265</td>
<td>447</td>
<td>49</td>
<td>Weighted average nonelective short stay cost for “Shock and Anaphylaxis, with CC Scores”</td>
</tr>
<tr>
<td>Cardiology OP visit</td>
<td>126</td>
<td>85</td>
<td>147</td>
<td>14</td>
<td>Consultant-led outpatient cost for “Non-Admitted Face to Face Attendance, Follow-up” for service “Cardiology”</td>
</tr>
<tr>
<td>Death</td>
<td>230</td>
<td>207</td>
<td>255</td>
<td>17</td>
<td>Ambulance service cost for “See and treat and convey”</td>
</tr>
<tr>
<td>Annual drug cost for patients with heart failure</td>
<td>76.12</td>
<td>69.33</td>
<td>80.08</td>
<td>5.87</td>
<td>Drug type and dose as described by Fox et al for patients in NYHA class III; prices from BNF 65.</td>
</tr>
<tr>
<td>Nonfatal allergic reaction</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
<td>General practice surgery consultation lasting 11.7 min.</td>
</tr>
</tbody>
</table>

All costs are in £. AP indicates antibiotic prophylaxis; BNF, British National Formulary; DoH, Department of Health; NYHA, New York Health Association; OP, Outpatient; and SD, standard deviation.

---

**RESULTS**

In comparison with no AP, both amoxicillin and clindamycin AP were associated with lower costs and better health outcomes (Table 5) for both high-risk and all-at-risk populations. In the all-at-risk group, there were mean cost savings of £2.47 (95% credible interval [Crl], £0.48–£6.96) ($3.29; Crl $0.64–$9.26; €2.96, Crl €0.58–€8.35) per person with amoxicillin AP and £3.65 (95% Crl, £0.69–£8.14) ($4.86; 95% Crl, $0.92–$10.83; €4.38, 95% Crl, €0.83–€9.77) with clindamycin AP, in comparison with no AP (the difference between the drugs being driven by the lower cost of clindamycin: £1.14 versus £2.28 [$1.52 versus $3.03; €1.37 versus €2.74]).

With an estimated 2.24 million dental procedures per year in this population (Table 1), AP would lead to savings of £5.5 million to £8.2 million per annum ($7.3 million to $10.9 million; €6.6 million to €9.8 million). We calculated a mean health improvement of 0.0012 (95% Crl, 0.000–0.003) and 0.0010 (95% Crl, 0.000–0.002) QALYs per person for amoxicillin and clindamycin, respectively (equivalent to 2687 QALYs gained per annum at the population level if amoxicillin AP were used for all-at-risk patients).

These cost savings were substantially greater in the high-risk group at a mean of ≈£40 (€53.2; $48.00) per patient (or £4.0 million ($5.3 million; €4.8 million) per annum in England on the basis of an estimated 100,000 dental procedures in this population). The most effective strategy would be amoxicillin, leading to gains of 0.0107 QALYs per person (or 1071 QALYs for the population) per annum.
QALY) until the rate fell below 2.76 per month (33.12 cases per year). In the same population, use of clindamycin was cost saving until the rate fell below 8.1 cases per month and cost-effective (at £20,000 per QALY) until the rate fell below 6.2 cases per month.

In the high-risk group, amoxicillin remained cost saving provided the number of IE cases avoided with AP use was >0.74 per month and cost-effective (at £20,000 per QALY) provided the number of IE cases avoided was >0.12 per month (base case estimate 13.67 extra high-risk IE cases per month) or 1.44 cases per year. For clindamycin, the corresponding values were 0.36 and 0.27, respectively.

### Value of Information
Cost-effectiveness estimates are subject to uncertainty relating to values of the input parameters on clinical effectiveness, costs, and health outcomes. This uncertainty is a genuine concern because any decision could be incorrect: health benefits could be lost because of investment in a treatment that is not cost-effective. The value of eliminating all uncertainty, such that there is no risk of an incorrect decision, is called the Expected Value of Perfect Information (EVPI),31 which provides an estimate of the upper bound of the cost of any additional research that would reduce uncertainty. For the all-at-risk population, the EVPI is near zero (£9020 [$11,997; €10,824] for amoxicillin, £11,409 [$15,174; €13,691] for clindamycin over 10 years in England). This is because there is little uncertainty; AP is almost certainly cost-effective, and, therefore, reducing uncertainty in any of the input parameters would be unlikely to lead to a different conclusion. However, the clinical effectiveness of AP is subject to some uncertainty because of reliance on observational data and interrupted time-series analysis.8

Accordingly, we conducted an additional exploratory analysis in which assumptions concerning uncertainty around the efficacy of AP in the all-at-risk population were increased. The base case analysis assumes that withdrawal of AP led to 34.9 additional cases of IE per month. Therefore, a model averaging approach was used such that half the sample maintained this estimate and half used an estimate of zero (ie, AP has no effect). This resulted in AP (amoxicillin) being less cost saving (now £0.15 per person; 95% CrI, −£5.62 to £2.28 [$0.20; 95% CrI, −$7.48 to $2.74; €0.18, 95% CrI, −€6.74 to €2.74]) and more effective, although less so than in the base case (0.00061 QALYs; 95% CrI, 0.000–0.002). The probability of being cost saving is 0.48, and the probability of being cost-effective (at a £20,000 threshold) is 50. In this situation, the EVPI rises to £25.3 million ($33.7 million; €30.4 million), driven almost entirely by the introduced uncertainty concerning AP effectiveness.

### DISCUSSION
We recently estimated the impact of the withdrawal of AP on the incidence of IE in an interrupted time-series analy-
sis of English data.9 This study provided unique evidence for evaluating the cost-effectiveness of AP, because the United Kingdom is the only country to have transitioned from the widespread use of AP to recommending its complete cessation. Using these figures as inputs to a cost-effectiveness analysis indicates that AP is likely to be not just cost-effective, but also cost saving. If AP were used in all those at risk of IE, then amoxicillin and clindamycin AP would result in estimated cost savings of £2.47 ($3.29; €2.96) and £3.65 ($4.86; €4.38) per patient and health gains of 0.0012 and 0.0010 QALYs, respectively. Overall, AP would result in an estimated saving of £5.5 to £8.2 million ($7.3 million to $10.9 million; €6.6 million to €9.8 million) and a health gain of 2687 QALYs in England per year. If AP were restricted to those at high risk of IE, the cost savings and health gain per person would be even greater at £40 ($53.20; €48.00) and 0.0107 QALYs. The overall benefit of using amoxicillin AP in high-risk patients would be a cost savings of £4.0 million ($5.3 million; €4.8 million) and a health gain of 1071 QALYs in England per year.

Because the recent time-series analysis was an observational study,8 we cannot be certain that the number of extra cases of IE identified was caused by the reduction in AP prescribing following the 2008 NICE guidelines.9 It is possible, therefore, that the number of IE cases prevented by AP is less than the identified 34.9 per month. To evaluate the cost-effectiveness of AP across a range of scenarios we performed a sensitivity analysis using a maximum effectiveness of preventing 35 IE cases per month and a minimum of preventing zero cases, ie, where AP is ineffective. Using this approach, we demonstrated that amoxicillin AP has to prevent only 2.76 cases per month in the all-at-risk group to be cost-effective and 16.8 cases per month to be cost saving. Moreover, amoxicillin AP is even more cost-effective in the high-risk group where only 0.12 cases per month need to be prevented for it to be cost-effective and 0.74 cases per month to be cost saving.

These data suggest that a strategy of directing AP at those at high risk of IE is likely to be cost-effective or cost saving, even at very low rates of AP clinical effectiveness. This conflicts with the NICE health economic analysis of AP,5 which used older data on the incidence of adverse drug reactions after the use of parenteral penicillins.5 More recent data suggest that fatal anaphylaxis is exceedingly rare, and there have been no reports of fatal anaphylaxis after oral amoxicillin AP in the world literature.32 The incidence of adverse reactions after amoxicillin AP is extremely low (0 fatal, 22.62 nonfatal reactions per million prescriptions).9,32 Although low, reactions to clindamycin AP were higher than anticipated, suggesting that an alternative AP regimen for those allergic to penicillin would be desirable.9 Our data suggest that AP needs only minimal clinical effectiveness to be cost-effective, because it is so cheap in comparison with the substantial cost and health implications of IE.

International guideline committees have highlighted the lack of evidence for the benefit of AP and called for randomized clinical trials (RCTs) to provide that evidence.4,5,6,7 However, ethical issues and the high cost of performing an RCT have prevented such a study to date. Skepticism concerning noncontrolled data represents a genuine source of uncertainty about the cost and clinical effectiveness of AP that underpin any cost-effectiveness analysis. This uncertainty conveys a risk that the advice given by guideline committees is wrong. However, there is also a cost associated with performing the RCTs needed to eliminate that uncertainty. EVPI analysis provides an estimate of the maximum amount it is worth spending to reduce that uncertainty.31 If there is genuine uncertainty about whether AP is effective or not, then the value of an RCT becomes substantial. Exploratory analysis using the at-risk population of England over a 10-year period estimates the EVPI of amoxicillin at £25.3 million ($33.7 million; €30.4 million). Therefore, although such a study may be costly, its value may well outweigh its cost.

The main limitations of this study are the lack of RCT data and the resulting need to use observational studies to identify the input parameters for health economic analysis. In particular, our data on the effectiveness of AP are based on the increase in IE cases and fall in AP prescribing that occurred after the introduction of the 2008 NICE guideline.9 Although this study demonstrated a temporal association between the fall in AP prescribing and increasing IE incidence, it did not prove a causal link. Hence, we undertook a sensitivity analysis to examine the cost-effectiveness of AP if the level of AP clinical effectiveness was less than anticipated. Furthermore, we used pre- and post-NICE prescribing figures as proxies for the use of AP even though compliance is never 100%. A final limitation is that HES data were used to populate most transitional probability estimates in our model; events occurring outside the hospital setting were not captured. IE is also complicated by a number of high-cost serious outcomes, eg, stroke and renal failure,14,15 that we were unable to take into account. Our analysis is likely, therefore, to have underestimated the impact of IE and cost-effectiveness of AP. Although our analysis is specific to England, its findings are likely to be broadly applicable to other advanced healthcare systems. However, cost-effectiveness may be even greater in nations with higher healthcare costs (eg, United States) but lower in those where healthcare costs are cheaper.

CONCLUSION
Because of the serious consequences and high costs associated with IE and the comparatively low costs as-
associated with AP, this analysis demonstrates that AP is likely to be very cost-effective (and even cost saving) in preventing IE, particularly for those at high risk, even when the number of prevented IE cases is very low. Our data suggest that European and American guidelines recommending AP use in high-risk individuals are likely to be cost-effective.

SOURCES OF FUNDING
This study was supported by the National Institute for Dental and Craniofacial Research (NIDCR) (NIH RO3 grant Ref: 1R03DE023092-01) http://www.nidcr.nih.gov. The views expressed in this publication are those of the authors and not necessarily those of the funders. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

DISCLOSURES
All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare that (1) Dr Thornhill received support from the National Institute for Dental and Craniofacial Research [NIH RO3 grant Ref: 1R03DE023092-01] for the submitted work; (2) none of the authors have a relationship with companies that might have an interest in the submitted work in the previous 3 years; (3) none of the authors spouses, partners or children have a financial relationship that may be relevant to the submitted work; and (4) Drs Franklin, Wailoo, Jones, and Thornhill have no nonfinancial interests that may be relevant to the submitted work. Drs Baddour and Lockhart are members of the American Heart Association’s Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease and were involved in producing the 2007 American Heart Association guideline on prevention of infective endocarditis. Dr Prendergast was a member of the Task Force that produced the 2009 European Society of Cardiology guidelines on the prevention, diagnosis, and treatment of infective endocarditis, and also acted as a consultant to the committee that produced the 2008 NICE clinical guideline 64 on prophylaxis against infective endocarditis, and Dr Dayer was a consultant to the review committee that produced the 2015 update to NICE clinical guideline 64 on prophylaxis against infective endocarditis.

AFFILIATIONS
From School of Health and Related Research, University of Sheffield, UK (M.F., A.W.); Department of Cardiology, Taunton and Somerset NHS Foundation Trust, UK (M.J.D.); Department of Population Health, NYU School of Medicine, (S.J.); Department of Cardiology, Guy’s & St Thomas’ NHS Foundation Trust, London, UK (B.P.); Division of Infectious Diseases, Mayo Clinic College of Medicine, Rochester, MN (L.M.B.); Department of Oral Medicine, Carolinas Medical Center, Charlotte, NC (P.B.L., M.H.T.); and Unit of Oral and Maxillofacial Medicine and Surgery, School of Clinical Dentistry, University of Sheffield, UK (M.H.T.).

REFERENCES


FOOTNOTES
Received February 17, 2016; accepted August 23, 2016. The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.116.022047/-DC1. Circulation is available at http://circ.ahajournals.org.


The Cost-Effectiveness of Antibiotic Prophylaxis for Patients at Risk of Infective Endocarditis
Matthew Franklin, Allan Wailoo, Mark J. Dayer, Simon Jones, Bernard Prendergast, Larry M. Baddour, Peter B. Lockhart and Martin H. Thornhill

Circulation. published online November 13, 2016;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2016/11/08/CIRCULATIONAHA.116.022047
Free via Open Access

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2016/11/08/CIRCULATIONAHA.116.022047.DC1
http://circ.ahajournals.org/content/suppl/2017/07/10/CIRCULATIONAHA.116.022047.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/
Supplemental Material

THE COST-EFFECTIVENESS OF ANTIBIOTIC PROPHYLAXIS FOR PATIENTS AT-RISK OF INFECTIVE ENDOCARDITIS

Matthew Franklin, Allan Wailoo, Mark J Dayer, Simon Jones, Bernard Prendergast, Larry M Baddour, Peter B Lockhart, Martin H Thornhill

Contents

1. Supplementary Methods
   Calculation for risk of IE following an (un)protected high-risk dental procedure 2

2. Supplementary Tables
   Table S1. Logic behind the risk per protected and unprotected dental procedure for all-at-risk patients calculation 4
   Table S2. Logic behind the risk per protected and unprotected dental procedure for high-risk patients calculation 6

3. Supplementary References 8
1. Supplementary Methods

Calculation for risk of IE following an (un)protected high-risk (invasive) dental procedure

A similar method for calculating risk of IE following a dental procedure for patients with a predisposing cardiac condition (PCC) was incorporated in the NICE 2008 model\(^1,2\) and by three other studies.\(^3-5\) This calculation was:

\[
\text{Risk of IE following an unprotected dental procedure =}
\]
\[
(\text{"Incidence of IE" multiplied by "proportion of incident cases that would have occurred with a PCC" multiplied by "proportion of PCC IE cases attributed to dental procedures"}) \div \text{divided by ("number of dental procedures per patient per year" multiplied by "prevalence of PCC")}
\]

Equation 1: Equation to calculate the risk of IE following an unprotected dental procedure

A slightly different and simpler way of presenting Equation 1 is presented as part of Equation 2, where people with a PCC are now defined as people “at-risk” of IE, of which people with PCC are the majority. The steps used to get to the point of estimating Equation 2 are described in this Appendix.

\[
\text{Risk of IE following an (un)protected dental procedure =}
\]
\[
\text{"The risk of IE in an at-risk population per year multiplied by "Number of dental procedures/patient/year for at-risk patients"
\}

Equation 2: Alternative equation to calculate the risk of IE following an unprotected dental procedure

It is information provided by Dayer, et al (2015)\(^6\) and Duval, et al (2006)\(^5\), supplemented with data obtained from HES and ONS\(^7\) which provides the basis for calculating the risk of IE following an unprotected dental procedure for this study. The logic for this calculation using the figures presented in Table 1 are now presented in Table A1 and Table A2 for four hypothetical patient groups:

1) **All-at-risk** patients undergoing a **protected** dental procedure (**AP is used**), Table S1;
2) **All-at-risk** patients undergoing an **unprotected** dental procedure (**AP not used**), Table S1;
3) **High-risk** patients undergoing a **protected** dental procedure (**AP is used**), Table S2;
4) **High-risk** patients undergoing an **unprotected** dental procedure (**AP not used**), Table S2.

In order to describe the calculation used to estimate the risk of IE following a protected dental procedure, consider the calculation for the first hypothetical patient group (All-at-risk patients undergoing a protected dental procedure (**AP is used**))
using the figures presented in Table 1 (presented here in *Italic* font) and calculations presented in Table S1 (presented here in **Bold** font).

Step 1 – estimate “Number of IE cases in all-at-risk group”: The “Number of IE cases per year” (1486) is multiplied by the “Incident cases that would have occurred for at-risk-patients” (0.0521) which estimates the “Number of IE cases in all-at-risk group” (1486*0.0521 = **774.46**).

Step 2 – estimate “Number of IE cases due to dental work for all-at-risk”: The “Number of IE cases in all-at-risk group” (**774.46**) is multiplied by “IE cases attributed to dental procedures in at-risk group” (0.052) which estimates the “Number of IE cases due to dental work for all-at-risk” (**774.46***0.052 = **40.13**).

Step 3 – estimate “Size of the population of all-at-risk patients”: The size of the population of interest (for the purpose of this analysis, “Population of England (year 2012)”: 51.4 *million people*) multiplied by the “Prevalence of all-at-risk group” (0.033) estimates the “Size of the population of all-at-risk patients” (51.4 mil * 0.033 = **1,696,590**).

Step 4 – estimate “Risk of IE in this all-at-risk population per year”: The “Number of IE cases due to dental work for all-at-risk” (**40.13**) multiplied by “Size of the population of all-at-risk patients” (**1,696,590**) estimates the “The risk of IE in this all-at-risk population per year” (**40.13** * **1,696,590** = **0.000024**).

Step 5 – estimate “Risk per protected dental procedure for all-at-risk” (Equation 2): “Risk of IE in this all-at-risk population per year” (**0.000024**) multiplied by “Number of dental procedures/patient/year for at-risk patients” (1.32) estimates “Risk per protected dental procedure for all-at-risk” (**0.000024** * 1.32 = **0.000018**).

Step 6 – estimate “Risk per million per protected dental procedure for all-at-risk”: “Risk per protected dental procedure for all-at-risk” (**0.000018**) multiplied by one million people estimates “Risk per million per protected dental procedure for high-risk” (**0.000018** * 1 million people = **17.87**).

When accounting for the increase in cases of IE due to the cessation of AP (unprotected dental procedures), these same steps are taken; however, steps 1 and 2 are replaced by one step which involves adding the “Yearly increase in IE due to no AP for all-at-risk” (**418.8**) to the “Number of IE cases due to dental work for all-at-risk” before the cessation of AP (**40.13**), which now estimates the “Number of IE cases due to dental work for all-at-risk” without the use of AP (**418.8 + 40.13 = 458.93**). These estimated figures are all presented in Table S1 for all-at-risk patients (as described in this example) and Table S2 for high-risk patients.
2. Supplementary Tables

Table S1. Logic behind the risk per protected and unprotected dental procedure for all-at-risk patients calculation

<table>
<thead>
<tr>
<th>Description of estimate</th>
<th>Estimate</th>
<th>Calculation</th>
<th>Description of calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protected dental procedure (AP is used) – all figures for this calculation are presented in Table 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of IE cases per year</td>
<td>1486</td>
<td>-</td>
<td>Number of IE cases per year *</td>
</tr>
<tr>
<td>Number of IE cases in all-at-risk group</td>
<td>774.46</td>
<td>1486 * 0.0521</td>
<td>Incident cases that would have occurred for all-at-risk patients</td>
</tr>
<tr>
<td>Number of IE cases due to dental work for all-at-risk</td>
<td>40.13</td>
<td>774.46 * 0.052</td>
<td>Number of IE cases in all-at-risk group *</td>
</tr>
<tr>
<td>Number of IE cases due to dental work for all-risk group</td>
<td>40.13</td>
<td>774.46 * 0.052</td>
<td>IE cases attributed to dental procedures in all-at-risk group</td>
</tr>
<tr>
<td>Size of the population of all-at-risk patients</td>
<td>1,696,590</td>
<td>51.4mil * 0.033</td>
<td>Population of England (year 2012) *</td>
</tr>
<tr>
<td>Risk of IE in this all-at-risk population per year</td>
<td>0.000024</td>
<td>40.13 / 1,696,590</td>
<td>Prevalence of all-at-risk group</td>
</tr>
<tr>
<td><strong>Risk per protected dental procedure for all-at-risk</strong></td>
<td>0.000018</td>
<td>0.000024 * 1.32</td>
<td>Risk of IE in this all-at-risk population per year *</td>
</tr>
<tr>
<td>Risk per million per protected dental procedure for high-risk</td>
<td>17.87</td>
<td>0.000018 * 1mil</td>
<td>Number of dental procedures/patient/year for all-at-risk patients</td>
</tr>
</tbody>
</table>

**Unprotected dental procedure (AP not used) – all figures for this calculation are presented in Table 1**

<table>
<thead>
<tr>
<th>Description of estimate</th>
<th>Estimate</th>
<th>Calculation</th>
<th>Description of calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly increase in IE due to no AP for all-at-risk</td>
<td>34.9</td>
<td>-</td>
<td>Monthly increase in IE due to no AP for all-at-risk *</td>
</tr>
<tr>
<td>Yearly increase in IE due to no AP for all-at-risk</td>
<td>418.8</td>
<td>34.9 * 12</td>
<td>12 months in a year</td>
</tr>
<tr>
<td>Number of cases due to dental work for all-at-risk</td>
<td>458.93</td>
<td>40.13 + 418.8</td>
<td>Number of IE cases due to dental work +</td>
</tr>
<tr>
<td>Yearly increase in IE due to no AP for all-at-risk</td>
<td>458.93</td>
<td>40.13 + 418.8</td>
<td>Yearly increase in IE due to no AP for all-at-risk</td>
</tr>
<tr>
<td>Calculation</td>
<td>Value</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>---------</td>
<td>----------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Size of the population of all-at-risk patients</td>
<td>1,696,590</td>
<td>Population of England (year 2012) * Prevalence of all-at-risk group</td>
<td></td>
</tr>
<tr>
<td>The risk of IE in this population per year</td>
<td>0.000271</td>
<td>Number of cases due to dental work for all-at-risk * Size of the population of all-at-risk patients</td>
<td></td>
</tr>
<tr>
<td><strong>Risk per unprotected dental procedure for all-at-risk</strong></td>
<td><strong>0.000204</strong></td>
<td>The risk of IE in this all-at-risk population per year * Number of dental procedures/patient/year for all-at-risk patients</td>
<td></td>
</tr>
<tr>
<td>Risk per million per unprotected dental procedure for all-at-risk</td>
<td><strong>204.33</strong></td>
<td>Risk per unprotected dental procedure for all-at-risk * One million people</td>
<td></td>
</tr>
</tbody>
</table>

AP: Antibiotic Prophylaxis; IE: Infective Endocarditis.
Table S2. Logic behind the risk per protected and unprotected dental procedure for high-risk patients calculation

<table>
<thead>
<tr>
<th>Description of estimate</th>
<th>Estimate</th>
<th>Calculation</th>
<th>Description of calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protected dental procedure (AP is used) – all figures for this calculation are presented in Table 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of IE cases per year</td>
<td>1486</td>
<td>-</td>
<td>Number of IE cases per year *</td>
</tr>
<tr>
<td>Number of IE cases in high-risk group</td>
<td>428</td>
<td>1486 * 0.288</td>
<td>Incident cases that would have occurred for high-risk patients</td>
</tr>
<tr>
<td>Number of IE cases due to dental work for high-risk</td>
<td>13.38</td>
<td>428 * 0.031</td>
<td>Number of IE cases in high-risk group *</td>
</tr>
<tr>
<td>Size of the population of high-risk patients</td>
<td>301,244</td>
<td>51.4mil * 0.0059</td>
<td>Population of England (year 2012) *</td>
</tr>
<tr>
<td>The risk of IE in this population per year</td>
<td>0.000044</td>
<td>13.38 / 301,244</td>
<td>Number of IE cases due to dental work *</td>
</tr>
<tr>
<td><strong>Risk per protected dental procedure for high-risk</strong></td>
<td>0.000135</td>
<td>0.000044 * 0.33</td>
<td>The risk of IE in this high-risk population per year *</td>
</tr>
<tr>
<td><strong>Risk per million per protected dental procedure for high-risk</strong></td>
<td>134.58</td>
<td>0.000135 * 1mil</td>
<td>Number of dental procedures/patient/year for high-risk patients</td>
</tr>
<tr>
<td><strong>Unprotected dental procedure (AP not used) – all figures for this calculation are presented in Table 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly increase in IE due to no AP for high-risk</td>
<td>13.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yearly increase in IE due to no AP for high-risk</td>
<td>164.0</td>
<td>13.67 * 12</td>
<td>Monthly increase in IE due to no AP for high-risk *</td>
</tr>
<tr>
<td>Number of cases due to dental work for high-risk</td>
<td>177.42</td>
<td>13.38 + 164.04</td>
<td>12 months in a year</td>
</tr>
<tr>
<td>Size of the population of high-risk patients</td>
<td>301,244</td>
<td>51.4mil * 0.0059</td>
<td>Population of England (year 2012) *</td>
</tr>
<tr>
<td>Description</td>
<td>Value 1</td>
<td>Value 2</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>---------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>The risk of IE in this population per year</td>
<td>0.000271</td>
<td>177.42 / 301.244</td>
<td></td>
</tr>
<tr>
<td>Number of cases due to dental work for high-risk * Size of the population of high-risk patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk per unprotected dental procedure for high-risk</td>
<td>0.001785</td>
<td>0.000271 * 0.33</td>
<td></td>
</tr>
<tr>
<td>The risk of IE in this high-risk population per year * Number of dental procedures/patient/year for high-risk patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk per million per unprotected dental procedure for high-risk</td>
<td>1785.13</td>
<td>0.001785 * 1mil</td>
<td></td>
</tr>
<tr>
<td>Risk per unprotected dental procedure for high-risk * One million people</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AP: Antibiotic Prophylaxis; IE: Infective Endocarditis.
3. Supplementary References:

감염성 심내막염 위험인자가 있는 환자에서 예방적 항생제치료는 비용효율적이다

초록

2008년 3월, 영국의 NICE(National Institute for Health and Care Excellence)는 치료비용의 비용-효과성(cost-effectiveness)에 대해 규격과 가격 비율을 고려하여 감염성 심내막염(infective endocarditis)의 위험인정이 있는 환자 치료시전에 예방적 항생제 치료(antibiotic prophylaxis)를 권장하고 있다. 연구결과 감염성 심내막염의 예방적 항생제 치료에 대한 효과, 비용, 비용-효과비를 통해 신체적, 경제적 비용을 평가하였다.

방법

비용-효과 분석을 통해 결정시 방법을 이용하였으며, 의료비용 및 효과는 영국 주정부 regulbet-adjusted life-year, QALY)으로 평가하였다. 예방적 항생제 치료의 비용은 NICE 가이드라인에 따르는 항생제의 처방, 전문의 감염성 심내막염의 표준 치료에 따른 비용을 산정하였다. 예방적 항생제 치료의 비용은 NICE 가이드라인에 따르는 항생제의 처방, 전문의 감염성 심내막염의 표준 치료에 따른 비용을 산정하였다.

결과

항생제 치료에서는 감염성 심내막염의 위험인자가 있는 모든 환자에게 비용-효과는 10년간 6,600만 유로 살아남은 경우로 로실한 6,600만 유로의 비용을 절약할 수 있다. 2,600만 유로의 QALY를 보존할 수 있다.
The Cost-Effectiveness of Antibiotic Prophylaxis for Patients at Risk of Infective Endocarditis

Matthew Franklin, PhD
Allan Waillo, PhD
Mark J. Dayer, MBBS, PhD
Simon Jones, PhD
Bernard Prendergast, DM
Larry M. Baddour, MD
Peter B. Lockhart, DDS
Martin H. Thornhill, MBBS, BDS, PhD

CONCLUSIONS: AP is cost-effective for preventing IE, particularly in those at high risk of IE. The results are sensitive to AP efficacy, but efficacy would have to be substantially lower for AP not to be cost-effective. AP was even more cost-effective in patients at high risk of IE. Only a marginal reduction in annual IE rates (1.44 cases in high-risk and 33 cases in all-at-risk patients) would be required for AP to be considered cost-effective at £20 000 ($26 600) per quality-adjusted life-year. Annual cost savings of £5.5 to £32.2 million ($7.3–$10.9 million) and health gains >2600 quality-adjusted life-years per year were achieved from reinstating AP in England.

METHODS: A decision analytic cost-effectiveness model was used. Health service costs and benefits (measured as quality-adjusted life-years) were estimated. Rates of IE before and after the National Institute for Health and Care Excellence guidance were available to estimate prophylactic efficacy. AP adverse event rates were derived from recent UK data, and resource implications were based on English Hospital Episode Statistics.

RESULTS: AP was less costly and more effective than no AP for all patients at risk of IE. The results are sensitive to AP efficacy, but efficacy would have to be substantially lower for AP not to be cost-effective. AP was even more cost-effective in patients at high risk of IE. Only a marginal reduction in annual IE rates (1.44 cases in high-risk and 33 cases in all-at-risk patients) would be required for AP to be considered cost-effective at £20 000 ($26 600) per quality-adjusted life-year. Annual cost savings of £5.5 to £32.2 million ($7.3–$10.9 million) and health gains >2600 quality-adjusted life-years per year were achieved from reinstating AP in England.

CONCLUSIONS: AP is cost-effective for preventing IE, particularly in those at high risk. These findings support the cost-effectiveness of guidelines recommending AP use in high-risk individuals.
Supplement Methods and online-only Data Supplement Tables

http://www.hscic.gov.uk/hes)11 and population data from the
International Classification of Diseases, 10th Revision code (1570
based on analysis of recent English data 8 that estimated that
tions developing IE.10 The number of IE hospital admissions
estimates of the risk of adults with predisposing cardiac condi-
sive) dental procedure were based on previous definitions and
Data used to calculate the probability of IE after a high-risk (inva-
sion model used for the analysis.

Key: Blue represents initial decision tree. Red represents subsequent
health state transitions. Solid arrows are feasible pathways. Dashed arrows
represent patient pathways from the decision tree to Markov models (ie, all
living patients begin in either the well or valve surgery states).

Figure. Illustration of the deci-
sion model used for the analysis.

Parameter Values

Data used to calculate the probability of IE after a high-risk (inva-
sive) dental procedure were based on previous definitions and estimates of the risk of adults with predisposing cardiac condi-
tions developing IE.21 The number of IE hospital admissions (International Classification of Diseases, 10th Revision code
133.0) was obtained from Hospital Episode statistics (HES; http://www.hscic.gov.uk/hes)11 and population data from the
Office of National Statistics.12 A more detailed explanation of the
calculations and values is provided in the online-only Data Supplement Methods and online-only Data Supplement Tables I and II.

Probability of IE Following a High-Risk Dental Procedure

The probability of IE after a high-risk dental procedure was
based on analysis of recent English data11 that estimated that
reduced use of AP was associated with 34.9 (95% confidence
interval, 7.9–61.9) additional IE cases per month.

Table 1. Data Used to Estimate the Probability of IE After a High-Risk (Invasive) Dental Procedure

<table>
<thead>
<tr>
<th>Variable</th>
<th>All-at-risk group</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Inocence of IE (per million people per annum)</td>
<td>28.9</td>
<td>51.4 m⁻¹</td>
<td>1486</td>
<td>Beta</td>
</tr>
<tr>
<td>b. Incident cases that would have occurred in at-risk patients*</td>
<td>0.521</td>
<td>1320</td>
<td>714</td>
<td>Beta</td>
</tr>
<tr>
<td>c. IE cases attributed to dental procedures in at-risk group</td>
<td>0.052</td>
<td>714</td>
<td>27</td>
<td>Beta</td>
</tr>
<tr>
<td>d. Number of dental procedures/patient in at-risk patients*</td>
<td>1.32</td>
<td>1 287 2015</td>
<td>1 704 1954</td>
<td>–</td>
</tr>
<tr>
<td>e. Prevalence of at-risk patients</td>
<td>3.30%</td>
<td>38 000 000</td>
<td>1 287 2015</td>
<td>Beta</td>
</tr>
<tr>
<td>f. Increase in cases of IE per month as a result of AP cessation</td>
<td>34.9</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Estimated number of dental procedures per year for at-risk patients</td>
<td>2.24 m</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Probability of IE after a dental procedure with AP (per million people)</td>
<td>17.67</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Probability of IE after a dental procedure without AP (per million people)</td>
<td>204.33</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

AP indicates antibiotic prophylaxis; and IE, infective endocarditis.

*All risk of IE patients are mainly defined as those patients with a predisposing cardiac condition, although at risk has been defined by Dux et al10 and
Dayer et al11 from which these data were obtained.

†Mean extra cases per month: 34.9 cases (95% confidence interval, 7.9–61.9; standard errors, 13.78); mean extra cases per year: 418.8 cases.

‡Calculated as (g.d.e) where (g) is the population of England for the year 2007: 51.4 million.12

b. Incident cases that would have occurred in high-risk patients* | 0.288 | 1486 | 428 | Beta |
| IE cases attributed to dental procedures in high-risk patients | 0.031 | 224 | 7 | Beta |
| e. Prevalence of high-risk patients | 0.33 | 228 570 | 75 408 | – |
| f. Increase in cases of IE per month as a result of AP cessation | 13.7 | – | – | – |
| Estimated number of dental procedures per year for high-risk patients | 0.1 m | – | – | – |
| Probability of IE after a dental procedure with AP (per million people) | 134.58 | – | – | – |
| Probability of IE after a dental procedure without AP (per million people) | 1185.13 | – | – | – |

AP indicates antibiotic prophylaxis; and IE, infective endocarditis.

The annual probability of IE survivors developing CHF over 5 year follow-up was estimated from HES. Of the 19804
patients with IE and reliable 5-year follow-up data, the numbers
diagnosed with CHF were 2152, 387, 292, 170, and 157 in
years 1 to 5, respectively. The subsequent probability of developing
CHF until the end of the model’s time horizon was
assumed to be constant after year 5. Recent studies show that
40% to 50% of patients now undergo valve replacement sur-
ery as part of their initial IE treatment,14–16 and, for this transi-
tion probability, we adopted a conservative 40% estimate. The
annual probability of IE survivors needing valve surgery after
the initial admission was estimated by using HES. Of the 19804
patients diagnosed with IE and followed for 5 years, 1278
required valve replacement surgery during the first year after
their initial IE treatment, and 329, 158, 75, and 74 required
valve replacement surgery in years 2 to 5, respectively. The
subsequent probability of needing valve surgery is assumed to
remain at 74 cases per year through to year 9, before falling
to 17 cases per year until the end of the model’s time horizon.

Long-Term Survival and Outcomes

Age-adjusted, all-cause mortality was estimated by using Office of
to 2013.3 Mortality risk for patients that survive valve surgery
was estimated using HES data for patients admitted for valve replacement surgery (OPCS-4 Classification of Interventions and Procedures version 4 codes: K25.1–K25.4, K26.1–K26.4, K27.1–K27.4, K28.1–K28.4, or
K29.1–K29.4) and discharged as dead within the same spell
for the year 2012.

The annual probability of IE survivors developing CHF over
5 year follow-up was estimated from HES. Of the 19804
patients with IE and reliable 5-year follow-up data, the numbers
diagnosed with CHF were 2152, 387, 292, 170, and 157 in
years 1 to 5, respectively. The subsequent probability of developing
CHF until the end of the model’s time horizon was
assumed to be constant after year 5. Recent studies show that
40% to 50% of patients now undergo valve replacement sur-
ery as part of their initial IE treatment,14–16 and, for this transi-
tion probability, we adopted a conservative 40% estimate. The
annual probability of IE survivors needing valve surgery after
the initial admission was estimated by using HES. Of the 19804
patients diagnosed with IE and followed for 5 years, 1278
required valve replacement surgery during the first year after
their initial IE treatment, and 329, 158, 75, and 74 required
valve replacement surgery in years 2 to 5, respectively. The
subsequent probability of needing valve surgery is assumed to
remain at 74 cases per year through to year 9, before falling
to 17 cases per year until the end of the model’s time horizon.

The annual probability of IE survivors developing CHF over
5 year follow-up was estimated from HES. Of the 19804
patients with IE and reliable 5-year follow-up data, the numbers
diagnosed with CHF were 2152, 387, 292, 170, and 157 in
years 1 to 5, respectively. The subsequent probability of developing
CHF until the end of the model’s time horizon was
assumed to be constant after year 5. Recent studies show that
40% to 50% of patients now undergo valve replacement sur-
ery as part of their initial IE treatment,14–16 and, for this transi-
tion probability, we adopted a conservative 40% estimate. The
annual probability of IE survivors needing valve surgery after
the initial admission was estimated by using HES. Of the 19804
patients diagnosed with IE and followed for 5 years, 1278
required valve replacement surgery during the first year after
their initial IE treatment, and 329, 158, 75, and 74 required
valve replacement surgery in years 2 to 5, respectively. The
subsequent probability of needing valve surgery is assumed to
remain at 74 cases per year through to year 9, before falling
to 17 cases per year until the end of the model’s time horizon.
Franklin et al

Death from valve surgery

Developing congestive heart failure

Nonfatal side effect to amoxicillin 22.62 per million – – No distinction on type of nonfatal side effect.

Adverse side effects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base Case</th>
<th>R (Occurrences)</th>
<th>n (Population)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from valve surgery</td>
<td>0.01</td>
<td>0.040</td>
<td>64 – – Beta</td>
<td>Discharged as dead within the same spell as valve surgery (calculated from Hospital Episode Statistics data for the year 2012).</td>
</tr>
<tr>
<td>Number of valve replacements/replacement: years 1–10 (IE cases)*</td>
<td>1–5 y-prognosis: 0.004; 0.005; 0.006; 0.007; 0.008</td>
<td>0.404</td>
<td>7922</td>
<td>19,804</td>
</tr>
<tr>
<td>Number of valve replacements/replacement: years 1–10 (non-IE cases)*</td>
<td>1–5 y-prognosis: 0.004; 0.005; 0.006; 0.007; 0.008</td>
<td>0.404</td>
<td>7922</td>
<td>19,804</td>
</tr>
<tr>
<td>Number of valve replacements/replacement: after 10 y (IE cases)*</td>
<td>1–5 y-prognosis: 0.004; 0.005; 0.006; 0.007; 0.008</td>
<td>0.404</td>
<td>7922</td>
<td>19,804</td>
</tr>
<tr>
<td>Number of valve replacements/replacement: after 10 y (non-IE cases)*</td>
<td>1–5 y-prognosis: 0.004; 0.005; 0.006; 0.007; 0.008</td>
<td>0.404</td>
<td>7922</td>
<td>19,804</td>
</tr>
<tr>
<td>Number of valve replacements/replacement: (non-IE cases)*</td>
<td>1–5 y-prognosis: 0.004; 0.005; 0.006; 0.007; 0.008</td>
<td>0.404</td>
<td>7922</td>
<td>19,804</td>
</tr>
</tbody>
</table>

Costs

National sources for unit costs were used. The cost of amoxicillin (£2.29; €3.03, $4.74) and clindamycin (£1.14; €1.52, $2.37) were obtained from the British National Formulary (Number 60) for 2013. Secondary care costs were estimated using 2012 to 2013 National Reference Costs. General practice consultation costs for AP adverse events were from Curtis. Exchange rates shown between UK, USS, and the Euro € were calculated on the July 1, 2016 using the midmarket rate (£1=$1.33; €1.20).

Patients with CHF or previous valve surgery were assumed to require 2 cardiology outpatient visits per year. Those with CHF were assumed to require treatment with angiotensin-converting enzyme/angiotensin II inhibitors, β-blockers, digoxin, and high-dose loop diuretics at typical daily doses. A summary of these unit costs is provided in Table 4. All costs were discounted by 3.5% as suggested by NICE's technology appraisal guidelines. A range of sensitivity analyses was performed, including probabilistic sensitivity analysis, to reflect different aspects of uncertainty in the evidence.

Statistical Analysis

An initial decision tree model leading to a state transition model was used to estimate the cost per QALY gained of AP versus no AP over a time horizon of 50 years. One-way and probability sensitivity analyses and expected value of perfect information (EVPI) analysis were also conducted. We used TreeAge Pro software (https://www.treeage.com) to construct the decision tree and state transition model and the Sheffield Accelerated Value of Information Tool (http://savy.sfh.ac.uk/) for the EVPI analysis.

This analysis was performed in compliance with the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) guidelines for the reporting of health economic analyses. Ethics approval was not required for this study because it was confined to analysis of publicly available data containing no identifiable patient information.

Table 2. Summary of Transitional Probabilities for Adverse Health States, Mortality, and Adverse Side Effects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base Case</th>
<th>R (Occurrences)</th>
<th>n (Population)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing congestive heart failure after IE*</td>
<td>0.109; 0.02; 0.015; 0.009; 0.008</td>
<td>21.52; 387; 292; 170; 157</td>
<td>19,804</td>
<td>Probability assumed constant after the fifth year.</td>
</tr>
<tr>
<td>Developing congestive heart failure (non-IE cases)*</td>
<td>0.004; 0.005; 0.006; 0.007; 0.008</td>
<td>0.404</td>
<td>7922</td>
<td>19,804</td>
</tr>
<tr>
<td>Value replacement during or immediately after IE*</td>
<td>0.085; 0.017; 0.004</td>
<td>1278; 329; 158; 75; 74</td>
<td>19,804</td>
<td>Number of events does not include those patients included in the valve replacement during or immediately after E; probability assumed constant after the fifth year if unit year 10 before failing in 17 cases.</td>
</tr>
</tbody>
</table>

Table 3. Utility Values, by Health State and Age Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK population norms by age,‡</td>
<td>0.85</td>
<td>0.25</td>
<td>Beta</td>
</tr>
<tr>
<td>50–54</td>
<td>0.85</td>
<td>0.25</td>
<td>Beta</td>
</tr>
<tr>
<td>55–64</td>
<td>0.80</td>
<td>0.26</td>
<td>Beta</td>
</tr>
<tr>
<td>65–74</td>
<td>0.78</td>
<td>0.26</td>
<td>Beta</td>
</tr>
<tr>
<td>75+</td>
<td>0.73</td>
<td>0.27</td>
<td>Beta</td>
</tr>
</tbody>
</table>

Health states

Well‡ | 0.930 | – | – |

Valve replacement/repair needed‡ | 0.525 | – | – |

Successful valve replacement‡ | 0.855 | – | – |

Congestive heart failure‡ | 0.610 | – | – |

Hospitalization with heart failure‡ | 0.570 | – | – |
RESULTS

In comparison with no AP, both amoxicillin and clindamycin AP were associated with lower costs and better health outcomes (Table 5) for both high-risk and all-at-risk populations. In the all-at-risk group, there were mean cost savings of £2.28 million (95% credible interval, £0.20; £7.48 million to £10.9 million; £6.6 million to £9.8 million). We calculated a health improvement of 0.0012 (95% CI, 0.0000–0.003) and 0.0010 (95% CI, 0.0000–0.002) QALYs per person for amoxicillin and clindamycin, respectively equivalent to 2687 QALYs gained per annum at the population level if amoxicillin AP were used for all-at-risk patients.

Some of these savings were substantially greater in the high-risk group at a mean of £40 (55.3–£68.00) per person per year in England (Table 1). AP would lead to savings of £5.5 million to £8.2 million per annum (7.3 million to £10.9 million; £6.6 million to £9.8 million). We calculated a health improvement of 0.0012 (95% CI, 0.0000–0.003) and 0.0010 (95% CI, 0.0000–0.002) QALYs per person for amoxicillin and clindamycin, respectively (Table 5).

The clinical effectiveness of AP is subject to some uncertainty because of reliance on observational studies. However, the clinical effectiveness of AP is subject to some uncertainty because of reliance on observational data and interrupted time-series analysis. Accordingly, we conducted an additional exploratory analysis in which assumptions concerning uncertainty around the efficacy of AP in the all-at-risk population were decreased. The base case analysis assumes that AP use resulted in a 0.5% increase in the rate of IE cases avoided with AP (amoxicillin) being less cost saving (now £–3.65 million) than the base case (0.00061 QALYs; 95% CI, 0.000–0.002). The probability of being cost saving is 0.48, and the probability of being cost-effective (at a £20 000 threshold) is 0.50. In this situation, the EVPI rises to £25.3 million (95% CI, 0.000–0.002), driven almost entirely by the introduced uncertainty concerning AP effectiveness.

Sensitivity Analysis

A sensitivity analysis on the effectiveness of AP was performed by varying the number of additional IE cases associated with AP withdrawal from 35 per month (base case) to zero (implying AP has no protective effect). For the all-at-risk group, amoxicillin remained cost saving until the rate of IE cases avoided fell below 16.8 per month and cost-effective (£20 000; £26 600; £24 000) per QALY until the rate fell below 2.76 per month (33.12 cases per year). In the same population, use of clindamycin was cost saving until the rate fell below 8.1 cases per month and cost-effective (£20 000 per QALY) until the rate fell below 6.2 cases per month.

In the high-risk group, amoxicillin remained cost saving provided the number of IE cases avoided with AP use was >0.74 per month and cost-effective (£20 000 per QALY) until the rate fell below 4.53 cases per month. In the all-at-risk population, amoxicillin AP was cost saving until the rate fell below 16.8 cases per month and cost-effective (£20 000 per QALY) until the rate fell below 2.76 cases per month. In both populations, AMV were associated with better health outcomes and lower costs than no AP, with the corresponding values being 0.36 and 0.27, respectively.

Value of Information

Cost-effectiveness estimates are subject to uncertainty relating to values of the input parameters on clinical effectiveness, costs, and health outcomes. This uncertainty is a genuine concern because any decision could be incorrect: health benefits could be lost because of investment in a treatment that is not cost-effective. The value of eliminating all uncertainty, such that there is no risk of an incorrect decision, is called the Expected Value of Perfect Information (EVPI), which provides an estimate of the upper bound of the cost of any additional research that would reduce uncertainty. For the all-at-risk population, the EVPI is near zero (£920; £1 957; £10 000) for amoxicillin, £1 409 (£15 174; £13 691) for clindamycin over 10 years in England. This is because there is little uncertainty; AP is almost certainly cost-effective, and, therefore, reducing uncertainty in any of the input parameters would be unlikely to lead to a different conclusion. However, the clinical effectiveness of AP is subject to some uncertainty because of reliance on observational data and interrupted time-series analysis.
sis of English data. This study provided unique evidence for evaluating the cost-effectiveness of AP, because the United Kingdom is the only country to have transitioned from the widespread use of AP to recommending its complete cessation. Using the figures given, our analysis indicates that AP is not likely to be not just cost-effective, but also cost saving. If AP were used in all those at risk of IE, then amoxicillin and clindamycin as prophylaxis were estimated cost savings of £2.47 ($3.29; €2.96) and £3.65 ($4.86; €4.38) per patient and health gains of 0.0012 and 0.0010 QALYs, respectively. Over all, AP would result in an estimated saving of £5.5 to £8.2 million ($7.3 million to $10.9 million per year; £6.6 million to €9.8 million) and a health gain of 2687 QALYs in England per year. If AP were restricted to those at high risk of IE, the cost savings and health gain per patient would be £4.40 ($5.53; €4.80) and 0.0017 QALYs. The overall benefit of using amoxicillin AP in high-risk patients would be a cost saving of £4.0 million ($5.3 million; €4.8 million) and a health gain of 1071 QALYs in England per year. Because the recent time-series analysis was an observational study, we cannot be certain that the number of extra cases of IE identified was caused by the reduction in AP prescribing following the 2008 NICE guidelines. It is possible, therefore, that the number of IE cases prevented by AP is less than the identified 34.9 per 100,000. The underreporting of AP across a range of scenarios we performed a sensitivity analysis using a maximum effectiveness of preventing 35 IE cases per month and a minimum of preventing zero cases, ie, where AP is ineffective. Using this approach, we demonstrated that amoxicillin AP has to prevent only 2.76 cases per month in the all-risk group to be cost-effective and 1.7 cases per month to be cost saving. Moreover, amoxicillin AP is even more cost-effective in the high-risk group where only 0.12 cases per month need to be prevented for it to be cost-effective and 0.74 cases per month to be cost saving.

These data suggest that a strategy of directing AP at those at high risk of IE is likely to be cost-effective or cost saving, even at very low rates of AP and clinical effectiveness. This conflicts with the NICE health economic analysis of AP, which used older data on the incidence of adverse drug reactions after the use of penicillin prophylaxis. The incidence of fatal anaphylaxis is exceedingly rare, and there have been no reports of fatal anaphylaxis after oral amoxicillin AP in the world literature. The incidence of adverse reactions after amoxicillin AP is extremely low (f0.22, 22.62 nonfatal reactions per million prescriptions). However, low, reactions to clindamycin AP were higher than anticipated, suggesting that clindamycin AP might be more effective than these a priori to penicillin would be desirable. Our data suggest that AP needs only minimal clinical effectiveness to be cost-effective, because it is so cheap in comparison with the substantial cost and health implications of IE. International guideline committees have highlighted the lack of evidence for the benefit of AP and called for randomized clinical trials (RCTs) to provide that evidence. However, ethical issues and the high cost of performing an RCT have prevented such a study to date. Skepticism concerning noncontrolled data represents a genuine source of uncertainty about the cost and clinical effectiveness of AP that underpin any cost-effectiveness analysis. This uncertainty conveys a risk that the advice given by guideline committees is wrong. However, there is also an associated cost with performing the RCTs needed to eliminate that uncertainty. EVPI analysis provides an estimate of the maximum amount it is worth spending to reduce that uncertainty. There is genuine uncertainty about whether AP is effective or not, then the value of an RCT becomes substantial. Exploratory analysis using the atrisk population of England over a 10-year period estimates the EVPI of amoxicillin at £25.3 million ($33.7 million; €20.4 million). Therefore, although such a study may be costly, its value may well outweigh its cost.

The main limitations of the study are the lack of RCT data and the resulting need to use observational studies to identify the input parameters for health economic analysis. In particular, our data on the effectiveness of AP are based on the increase and are not the results of AP prescribing that occurred after the introduction of the 2008 NICE guideline. Although this study demonstrated a temporal association between the fall in AP prescribing and increasing IE incidence, it did not prove a causal link. Hence, we undertook a sensitivity analysis to examine the cost-effectiveness of AP if the level of AP clinical effectiveness was less than anticipated. Furthermore, we used prescribing figures as proxies for the use of AP even though compliance is never 100%. A final limitation is that HES data were used to populate most transitional probability estimates in our model; events occurring outside the hospital setting were not captured. IE is also complicated by a number of high-cost serious outcomes, eg, stroke and renal failure, that are not accounted for in our analysis. Our analysis is likely, therefore, to have underestimated the impact of IE and cost-effectiveness of AP. Although our analysis is specific to England, its findings are likely to be broadly applicable to other major healthcare systems. However, cost-effectiveness may be even greater in nations with higher healthcare costs (eg, United States) but lower in those where healthcare costs are cheaper.

CONCLUSION

Because of the serious consequences and high costs associated with IE and the comparatively low costs associated with AP, this analysis demonstrates that AP is likely to be very cost-effective (and even cost saving) in preventing IE, particularly for those at high risk, even when the number of prevented IE cases is very low. Our data suggest that European and American guidelines recommending AP use in high-risk individuals are likely to be cost-effective.

REFERENCES


DISCLOSURES

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare that (1) Dr Thrombino received support from the National Institute for Dental and Craniofacial Research [NIH R03 grant Ref: 1R03DE023092-01] for the submitted work; (2) none of the authors have a relationship with companies that might have an interest in the submitted work in the previous 3 years; (3) none of the authors' spouses, partners or children have a relationship with companies that might have an interest in the submitted work; and (4) Drs Franklin, Wallow, Jones, and Thornhill have no financial interests that may be relevant to the submitted work. Drs Baddour and Lockhart are members of the American Heart Association’s Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease and were involved in producing the 2007 American Heart Association guideline on prevention of infective endocarditis. Dr Prendergast was a member of the Task Force that produced the 2009 European Society of Cardiology guidelines on the prevention, diagnosis, and treatment of infective endocarditis, and also acted as a consultant to the committee that produced the 2008 NICE guideline on prophylaxis against infectious endocarditis, and Dr Dayer was a consultant to the review committee that produced the updated 2011 NICE clinical guideline 64 on prophylaxis against infective endocarditis.

AFFILIATIONS

From School of Health and Related Research, University of Sheffield, UK (M.T., A.W.); Department of Cardiology, Taunton and Somerset NHS Foundation Trust, UK (M.J.D.); Department of Cardiology, Guy’s & St Thomas’ NHS Foundation Trust, London, UK (C.J.S.); Division of Infectious Diseases, Mayo Clinic, Rochester, MN (S.L.M.B.S.); Department of Oral Medicine, Carolinas Medical Center, Charlotte, NC (J.D.B., M.H.T.); and Unit of Oral and Maxillofacial Surgery, Royal Hallamshire Hospital, Sheffield, UK (M.H.T.).

FOOTNOTES

Received February 17, 2016; accepted August 23, 2016. The online-only Data Supplement is available at http://circ.ahajournals.org/Downloaded from


