Prophylaxis for infective endocarditis: let's end the debate

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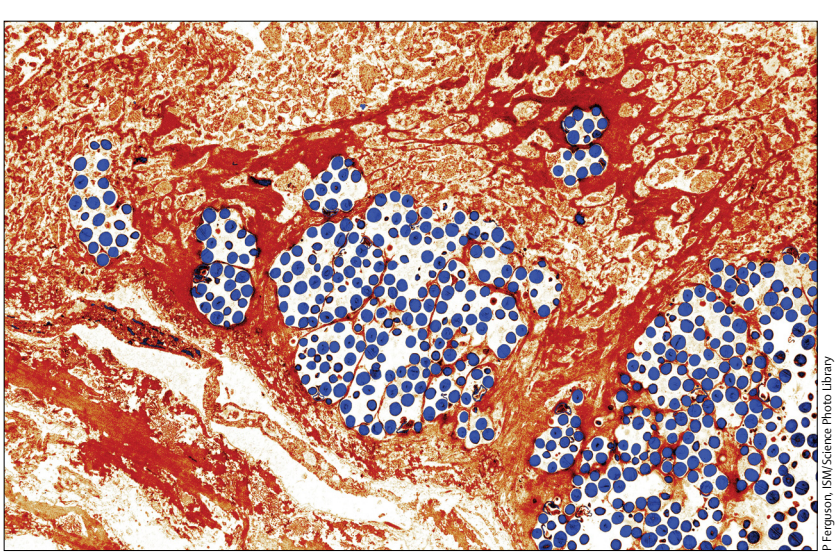
Despite continued progress in the diagnosis and treatment of infective endocarditis, in-hospital mortality associated with this disease remains at about 20%, essentially unchanged for the past two decades.[1] Therefore, increased efforts to reduce the incidence of infective endocarditis are needed. Since 2002, the policy for antibiotic prophylaxis against infective endocarditis has changed substantially in favour of restricted indications, with two different strategies: that in the UK, where the 2008 guidelines[2,3] from the National Institute of Health and Clinical Excellence (NICE) recommended that antibiotic prophylaxis be abandoned in any patient for any procedure; and the strategy adopted elsewhere (and endorsed by guidelines from the American College of Cardiology, American Heart Association [AHA], and European Society of Cardiology [ESC]),[4,5] in which antibiotic prophylaxis is to be reserved for individuals with valve disease at high risk of infective endocarditis (ie, with a prosthetic valve, history of infective endocarditis, or cyanotic congenital heart disease) who undergo an orodental procedure with a high risk of bacteraemia. In both strategies, oral hygiene is strongly promoted. Since 2008, all studies that have analysed the changes in infective endocarditis epidemiology after guidelines partly[6,7] or totally[8] restricted the indications for antibiotic prophylaxis showed no increased incidence of infective endocarditis, including the subgroup caused by oral streptococci. One of these studies[8] was done in the UK and analysed the 3 year period after the NICE guidelines were issued.

In *The Lancet*, Mark Dayer and colleagues[9] report the results of an important study based on an analysis of hospital discharge episode statistics and prescribing patterns in England up to March, 2013. Their findings show a small but significant increase in the incidence of infective endocarditis since 2008, of 0·11 cases per 10 million people per month (95% CI 0·05–0·16) above the projected historical trend, which by March, 2013 would account for an excess of 35 cases per month. This increase was seen both in patients at high risk of infective endocarditis and in those at lower risk (ie, moderate or low risk), as defined in the AHA[5] and ESC[4] guidelines. Concomitantly, the investigators noted a decrease in the use of antibiotic prophylaxis of almost 90%. The temporal link between these two phenomena raises the question of a causal association.

However, we advocate great caution before jumping to any conclusion. Although the cessation of antibiotic prophylaxis was recommended because little evidence existed to support efficacy,[3–5] the present data do not provide very strong evidence either. Among the general limitations of observational, non-randomised studies, several key points should be considered carefully when interpreting the results of Dayer and colleagues' study.

First, in this temporal comparison analysis, various confounders could account for an increased incidence of infective endocarditis irrespective of any change in guidelines for antibiotic prophylaxis. The change could be caused by an increased number of individuals at high risk of infective endocarditis, resulting from several factors: population ageing, increased numbers of patients with implanted intracardiac devices, increased prevalence of diabetes mellitus, or increased chronic dialysis.

Additionally, the diagnoses of infective endocarditis were recorded through UK hospital coding, with no further validation, which could result in biased estimation of incidence. Notably, the UK hospital discharge episode statistics do not include information about the causal organism of infective endocarditis; if the increased incidence were caused by the decreased use of antibiotic prophylaxis for dental procedures, the increased incidence should only be in the subgroup of infective



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Bacterial endocarditis

endocarditis caused by oral streptococcal bacteria, and not in subgroups caused by other microorganisms.

Furthermore, the number of monthly dental procedures done in patients at risk of infective endocarditis that would have been an indication for antibiotic prophylaxis before the introduction of the 2008 NICE guidelines is not known for the time since the cessation of antibiotic prophylaxis prescription. Dayer and colleagues' estimate that 277 prescriptions of antibiotic prophylaxis would be needed to prevent one case of infective endocarditis (which is far greater than previous estimates) is based on the hypothesis that the number of invasive dental procedures done in patients at risk of infective endocarditis has remained stable since 2008.[10]

Finally, the 2008 NICE guidelines[2] strongly promoted oral hygiene for prevention of infective endocarditis, but some of the procedures recommended to ensure oral hygiene might lead to the development of bacteraemia—eg, scaling and toothbrushing.[11,12]

Dayer and colleagues should be commended for their meticulous analysis of epidemiological data, and for their caution in not jumping to conclusions about the causality of the link between cessation of antibiotic prophylaxis and subsequent increased incidence of infective endocarditis. However, their results could introduce confusion in patients' and doctors' minds, both in the UK and elsewhere. In a *Lancet* editorial in 1992,[13] the editors wrote that "the doctrine of faith, hope, and charity may be a philosophy for life: it is no basis for perpetuating costly and possibly ineffective medical practices", and went on to urge the use of prospective randomised controlled studies to assess the efficacy of antibiotic prophylaxis in infective endocarditis. More than 20 years later, no such study has been done. We strongly suggest that experts stop elaborating guidelines for infective endocarditis prophylaxis, and urgently join forces to mount an international collaboration to do the appropriate clinical trials that are needed to answer this important question.

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We declare no competing interests.

1 Hoen B, Duval X. Infective endocarditis. *N Engl J Med* 2013; **368:** 1425–33.
2 NICE. Prophylaxis against infective endocarditis. National Institute for Health and Clinical Excellence, 2008. http://www.nice.org.uk/CG064 (accessed Nov 12, 2014).
3 Stokes T, Richey R, Wray D. Prophylaxis against infective endocarditis: summary of NICE guidance. *Heart* 2008; **94:** 930–31.
4 Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J* 2009; **30:** 2369–413.
5 Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; **116:** 1736–54.
6 Duval X, Delahaye F, Alla F, et al. Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications: three successive population-based surveys. *J Am Coll Cardiol* 2012; **59:** 1968–76.
7 Pasquali SK, He X, Mohamad Z, et al. Trends in endocarditis hospitalizations at US children's hospitals: impact of the 2007 American Heart Association antibiotic prophylaxis guidelines. *Am Heart J* 2012; **163:** 894–99.
8 Thornhill MH, Dayer MJ, Forde JM, et al. Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. *BMJ* 2011; **342:** d2392.
9 Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH. Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series analysis. *Lancet* 2014; published online Nov 18. http://dx.doi.org/10.1016/S0140-6736(14)62007-9.
10 Duval X, Alla F, Hoen B, et al. Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. *Clin Infect Dis* 2006; **42:** e102–07.
11 Lacassin F, Hoen B, Leport C, et al. Procedures associated with infective endocarditis in adults: a case control study. *Eur Heart J* 1995; **16:** 1968–74.
12 Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. Bacteremia associated with toothbrushing and dental extraction. *Circulation* 2008; **117:** 3118–25.
13 The Lancet. Chemoprophylaxis for infective endocarditis: faith, hope, and charity challenged. *Lancet* 1992; **339:** 525–26.

Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series analysis

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Summary

Background **Antibiotic prophylaxis given before invasive dental procedures in patients at risk of developing infective endocarditis has historically been the focus of infective endocarditis prevention. Recent changes in antibiotic prophylaxis guidelines in the USA and Europe have substantially reduced the number of patients for whom antibiotic prophylaxis is recommended. In the UK, guidelines from the National Institute for Health and Clinical Excellence (NICE) recommended complete cessation of antibiotic prophylaxis for prevention of infective endocarditis in March, 2008. We aimed to investigate changes in the prescribing of antibiotic prophylaxis and the incidence of infective endocarditis since the introduction of these guidelines.**

Methods **We did a retrospective secular trend study, analysed as an interrupted time series, to investigate the effect of antibiotic prophylaxis versus no prophylaxis on the incidence of infective endocarditis in England. We analysed data for the prescription of antibiotic prophylaxis from Jan 1, 2004, to March 31, 2013, and hospital discharge episode statistics for patients with a primary diagnosis of infective endocarditis from Jan 1, 2000, to March 31, 2013. We compared the incidence of infective endocarditis before and after the introduction of the NICE guidelines using segmented regression analysis of the interrupted time series.**

Findings **Prescriptions of antibiotic prophylaxis for the prevention of infective endocarditis fell substantially after introduction of the NICE guidance (mean 10 900 prescriptions per month [Jan 1, 2004, to March 31, 2008] *vs* 2236 prescriptions per month [April 1, 2008, to March 31, 2013], p<0·0001). Starting in March, 2008, the number of cases of infective endocarditis increased significantly above the projected historical trend, by 0·11 cases per 10 million people per month (95% CI 0·05–0·16, p<0·0001). By March, 2013, 35 more cases per month were reported than would have been expected had the previous trend continued. This increase in the incidence of infective endocarditis was significant for both individuals at high risk of infective endocarditis and those at lower risk.**

Interpretation **Although our data do not establish a causal association, prescriptions of antibiotic prophylaxis have fallen substantially and the incidence of infective endocarditis has increased significantly in England since introduction of the 2008 NICE guidelines.**

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Introduction

Infective endocarditis is uncommon, but has high morbidity and mortality.[1] Oral viridans group streptococci are implicated as causal organisms in 35–45% of cases.[2–5] Antibiotic prophylaxis given before invasive dental procedures has been the focus for infective endocarditis prevention for more than 50 years and remains the standard of care for patients at high risk in most parts of the world.[6,7] The aim of antibiotic prophylaxis is to reduce or eliminate bacteraemia[8–11] that can cause infective endocarditis in susceptible individuals. No randomised clinical trials of antibiotic prophylaxis have been done[12] and little evidence exists to support its effectiveness.[2,4,9]

Until recently, standard of care in most parts of the world was to provide antibiotic prophylaxis to patients at high risk of infective endocarditis (ie, those with previous infective endocarditis, prosthetic heart valves or valves repaired with prosthetic material, unrepaired cyanotic congenital heart disease, or some repaired congenital heart defects) and those at moderate risk (ie, with previous rheumatic fever, heart murmur, or evidence of native valve disease). In March, 2008, the UK National Institute for Health and Clinical Excellence (NICE; now the National Institute for Health and Care Excellence) produced new guidance recommending complete cessation of antibiotic prophylaxis.[13–15] By contrast, the American Heart Association (AHA)[7] and the European Society of Cardiology (ESC)[6] produced new guidelines in 2007 and 2009, respectively, recommending cessation of antibiotic prophylaxis for patients at moderate risk only.

The NICE guidance[13] provided an opportunity for a retrospective study to investigate the effect of antibiotic prophylaxis versus no prophylaxis on the incidence of infective endocarditis in England. In a preliminary study,[16] 2 years after the introduction of the NICE guidelines, no significant increase in incidence of infective endocarditis was identified, despite a 78% reduction in the prescription of antibiotic prophylaxis. However, some researchers and clinicians expressed concerns that 2 years was not long enough to detect a clinically significant change.[17] Moreover, 2500 prescriptions for antibiotic prophylaxis per month were still being issued at this point, with

evidence of targeting of individuals at high risk.[18] Therefore, the aim of this study was to investigate changes in the prescribing of antibiotic prophylaxis and the incidence of infective endocarditis over a longer timeframe.

Methods

Study design and data sources

We did a retrospective secular trend study, analysed as an interrupted time series, to investigate the effect of antibiotic prophylaxis versus no prophylaxis on the incidence of infective endocarditis in England, using data for antibiotic prophylaxis prescribing from Jan 1, 2004, to March 31, 2013, and hospital discharge episode statistics for patients with a primary diagnosis of infective endocarditis from Jan 1, 2000, to March 31, 2013.

Before the introduction of the 2008 NICE guidelines,[13] a single 3 g dose of oral amoxicillin (or a 600 mg dose of oral clindamycin for patients allergic to penicillin) was prescribed before invasive dental procedures as antibiotic prophylaxis to patients at moderate or high risk of developing infective endocarditis. These doses and modes of administration of amoxicillin and clindamycin are almost uniquely associated with antibiotic prophylaxis prescribed to cover invasive dental procedures in the UK.[16] Data for the prescription of antibiotic prophylaxis were obtained from the National Health Service (NHS) Business Services Authority.

For the **NHS Business Service Authority** see http://www.nhsbsa.nhs.uk/

Incidence data for infective endocarditis and associated in-hospital mortality were obtained from national hospital episode statistics for inpatient hospital activity, as previously described.[16] All patients admitted to UK hospitals have standard data recorded, including their primary discharge diagnosis (and up to 12 secondary diagnoses) in accordance with the 10th revision of the International Classification of Diseases (ICD-10) coding system). These anonymised data are reported to the warehouse of the Secondary Uses Service.

For the **ICD-10** see http://apps.who.int/classifications/apps/icd/icd10online

For the **Secondary Uses Service** see www.connectingforhealth.nhs.uk/systemsandservices/sus

We identified all patients with a primary discharge diagnosis of "acute or subacute infectious endocarditis" (ICD-10 code I33.0), including those who died in hospital. Such inpatient episodes are referred to as spells. Sometimes patients with disorders such as infective endocarditis are transferred from their local hospital to a regional centre for further treatment; even though this is a single continuous hospital stay for one disorder, it could result in the same case being counted twice. To avoid this issue, we used standard methods[19] to ensure that when such a transfer occurred the case was only counted once. A single continuous stay in hospital (whether or not a transfer took place) is referred to as a superspell and all the data related to infective endocarditis cases used in this study were superspells.

See Online for appendix

Hospital admissions are recorded as emergency or elective; elective admissions are subdivided into booked (patient admitted having been given a date at the time the decision to admit was made, determined mainly on the basis of resource availability), planned (patient admitted having been given a date or approximate date at the time the decision to admit was made), or waiting list (patient admitted electively from a waiting list having been given no date of admission at the time the decision to admit was made). Infective endocarditis is a serious acute disorder and a preliminary analysis of admissions confirmed that all such cases were coded as emergency, booked, or planned. A few waiting list cases were recorded but preliminary analysis showed these were infective endocarditis cases being readmitted for follow-up care or surgery and not new acute cases. We therefore excluded waiting list cases.

Statistical analysis

We corrected the incidence of infective endocarditis for changes in the size of the English population and compared data from before and after the introduction of the NICE guideline using segmented regression analysis of the interrupted time series.[20] We used R statistical software[21] for this analysis. Examination of the partial autocorrelation function for the dataset confirmed that no adjustment for seasonality was required. To allow for autocorrelation in the data, we fitted the segmented regression[20] using R's gls function from the nlme package.[22] This package allows for the regression model to be estimated under the condition of autocorrelation. We obtained the order of autocorrelation by examining both the autocorrelation and partial autocorrelation functions. To confirm the robustness of the segmented regression, we used change-point analysis to calculate the optimum positioning and number of data change-points using the R change-point package that implements the Hinkley algorithm.[23]

For each individual with a primary diagnosis of infective endocarditis, we looked at secondary coding information and also looked back in time in the database to identify whether they had previously been diagnosed with infective endocarditis or another cardiac condition that put them at high risk of infective endocarditis or had previously had an operative procedure done that put them at high risk, as defined by AHA[7] and ESC[6] guidelines. We defined such individuals as having been at high risk in our analysis. All other patients were regarded as having been at lower risk (ie, moderate risk or low risk). Additional details are provided in the appendix. We also used secondary and supplemental codes to try to identify the causal organisms for each case of infective endocarditis (appendix).

We used data from hospital episode statistics to identify and quantify other variables that might affect the incidence of infective endocarditis over time. Thus, we collected annual data for the number of individuals undergoing valve replacement, valve repair, or percutaneous valve implantation; new inpatient diagnoses of cyanotic congenital heart disease; surgical or percutaneous procedures in patients with congenital heart disease; and

the number of cardiovascular implantable electronic devices implanted.[24] Finally, we obtained data from the NHS Business Service Authority to identify the number of individuals who accessed primary care dental services between March, 2006, and December, 2013 (expressed as a percentage of the adult and child population of England).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MHT and MJD had full access to the prescribing data. SJ had full and MJD partial access to the hospital episode statistics data. The authors had final responsibility for the decision to submit for publication.

Results

Before 2008, the prescribing of antibiotic prophylaxis for prevention of infective endocarditis had remained fairly constant for many years. After the introduction of NICE guidelines recommending cessation of antibiotic prophylaxis,[13] the mean number of antibiotic prophylaxis prescriptions per month fell significantly (from 10 900 [Jan 1, 2004, to March 31, 2008] to 2236 [April 1, 2008, to March 31, 2013]; p<0·0001). In the last 6 months studied

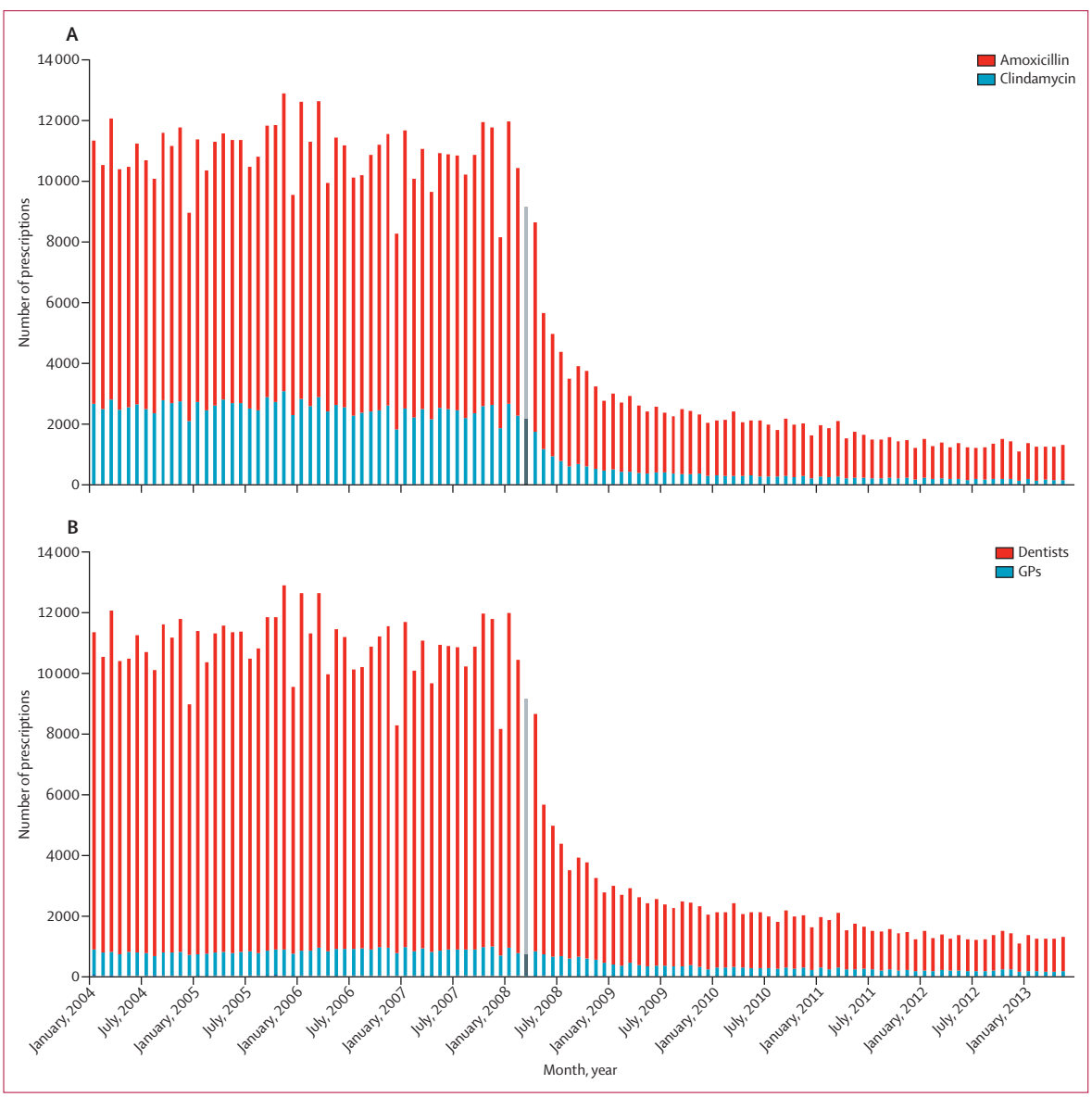

Figure 1: **Prescriptions of antibiotic prophylaxis, by drug type (A) and prescriber (B)**
The figures show the total number of prescriptions for antibiotic prophylaxis (a single dose of 3 g oral amoxicillin or a single dose of 600 mg oral clindamycin) dispensed in England each month from January, 2004, to March, 2013, divided by antibiotic drug type (A) and prescriber (B). The grey bars indicate March, 2008, the month in which cessation of antibiotic prophylaxis for infective endocarditis was recommended by the National Institute for Health and Clinical Excellence.[13] A few prescriptions were issued by hospitals and nurses, but numbers were not high enough to be seen on a graph of this scale.

(Oct 1, 2012, to March 31, 2013), the mean number fell further to 1307 prescriptions per month (figure 1). Most of the prescriptions were for amoxicillin, and roughly 90% were issued by dentists (figure 1).

We identified 19 804 patients with a primary diagnosis of infective endocarditis between Jan 1, 2000, and March 31, 2013. 17 031 (86%) were emergency admissions and 2773 (14%) were booked or planned admissions (usually because of inadequate availability of beds, because the patient needed to make arrangements before admission, or because the general practitioner had discussed the patient directly with a hospital specialist and the patient had been booked for admission without passing through the emergency department).

Before March, 2008, a consistent upward trend was apparent in the population-corrected incidence of infective endocarditis in England (figure 2). However, soon after the implementation of the NICE guidelines, the slope of the trend line increased significantly by 0·11 cases per 10 million people per month (95% CI 0·05–0·16, p<0·0001); this change was also apparent in the uncorrected incidence data (appendix p 7). By March, 2013, we estimate that there were 34·9 (95% CI 7·9–61·9) more cases of infective endocarditis per month than would have been expected if the previous trend had continued. Because antibiotic prophylaxis prescribing had fallen from a mean of 10 900 before the NICE guidelines to 1235 by March, 2013 (a fall of 9665 or 89%), we can estimate that 277 (95% CI 156–1217) prescriptions of antibiotic prophylaxis would be needed to prevent one case of infective endocarditis. Even with the outlier value from March, 2012, removed, the upward change in the slope of the trend line remained significant for the population-corrected (figure 2) and uncorrected data (appendix p 7).

Both high-risk and lower-risk (ie, moderate-risk and low-risk) individuals were affected by this increase (figure 3), with a statistically significant increase noted for both trend lines (p=0·025 for high-risk individuals, p=0·0002 for lower-risk individuals). We also noted a significant change in the uncorrected data for high-risk and lower-risk individuals (appendix p 9). A breakdown of the incidence of infective endocarditis in different high-risk categories is shown in figure 4 (and appendix p 5).

We also noted a non-significant increase in the slope of the trend line for population-corrected infective endocarditis-associated mortality of 0·01 cases per 10 million people per month (95% CI –0·01 to 0·02, p=0·394; figure 2), which was also apparent in the uncorrected data (appendix p 7).

Change-point analysis of the population-corrected (figure 5) and uncorrected (appendix p 8) data for incidence of infective endocarditis shows that the change in incidence occurred in June, 2008, 3 months after the change in guidelines for the use of antibiotic prophylaxis. This 3 month lag between the change in incidence and its putative cause is plausible since the incubation period of

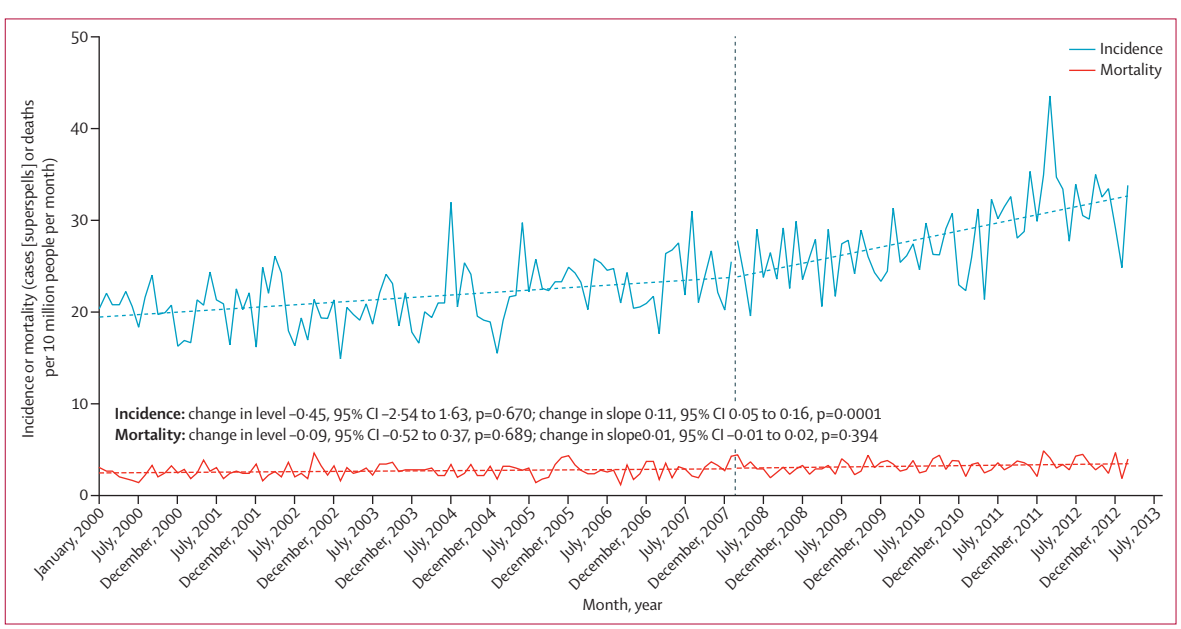

Figure 2: **Incidence of infective endocarditis and infective endocarditis-related mortality**
The figure shows the number of cases of infective endocarditis (superspells) recorded each month (solid blue line) and associated in-patient mortality (solid red line). Data are corrected for change in the size of the English population. The vertical dashed line indicates March, 2008, the month in which cessation of antibiotic prophylaxis for infective endocarditis was recommended by the National Institute for Health and Clinical Excellence (NICE).[13] The trend lines for infective endocarditis incidence (dashed blue line) and associated in-patient mortality (dashed red line) before and after introduction of the NICE guidelines are also shown. With the outlier value for incidence of infective endocarditis in March, 2012, removed, the change in the incidence trend line remains significant (change in level –0·28, 95% CI –2·27 to 1·70, p=0·78; change in slope 0·09, 95% CI 0·04 to 0·14, p=0·0001).

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infective endocarditis is usually less than 6 weeks and hospital episode statistics data capture the discharge diagnosis—in 2008 the median duration of hospital stay for patients in this study was 25 days (IQR 9–42).

Comparing patients diagnosed with infective endocarditis before and after March, 2008, we noted no significant change in the sex distribution (before: male 10 606 [69%], female 4823 [31%]; after: male 2963 [68%], female 1411 [32%]; p=0·394), age (mean 59·0 years [SD 20·3] before; 59·3 years [20·8] after; p=0·139), or median length of stay in hospital (24 days before; 25 days after; p=0·224).

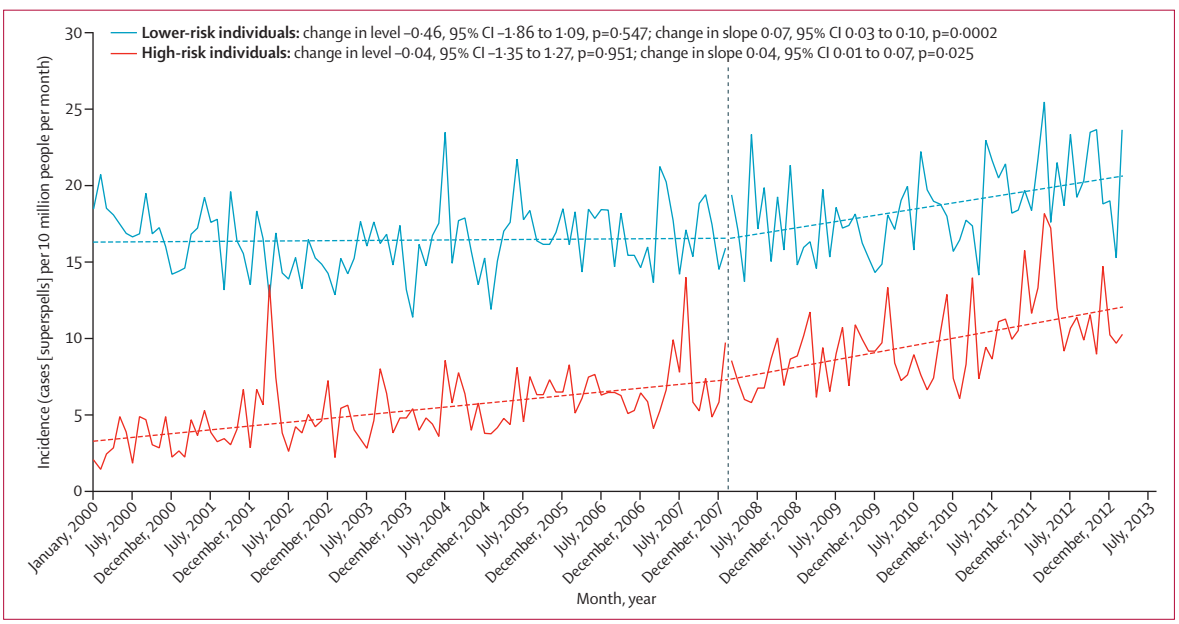

Figure 3: **Incidence of infective endocarditis, by risk group**
The figure shows the number of cases of infective endocarditis (superspells) recorded each month in individuals at high risk of developing infective endocarditis (solid red line) and those at lower risk (solid blue line). Data are corrected for change in the size of the total English population (not for change in the size of the high-risk or lower-risk groups). The vertical dashed line indicates March, 2008, the month in which cessation of antibiotic prophylaxis for infective endocarditis was recommended by the National Institute for Health and Clinical Excellence (NICE).[13] The trend lines for high-risk (dashed red line) and lower-risk (dashed blue line) individuals before and after introduction of the NICE guidelines are also shown.

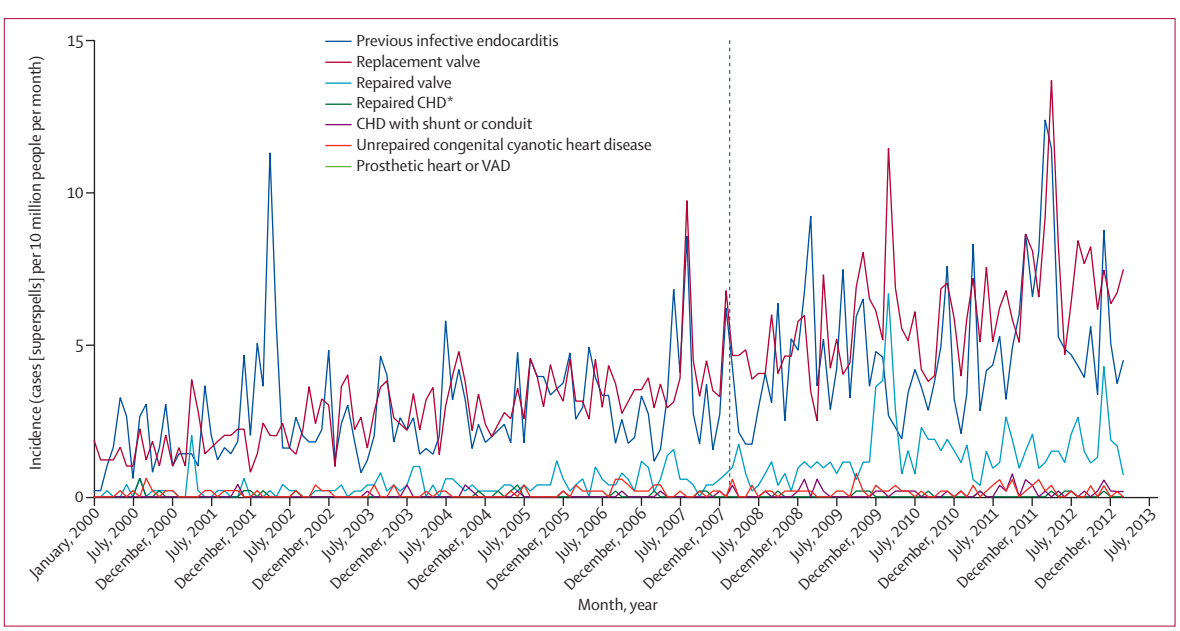

Figure 4: **Incidence of infective endocarditis in high-risk individuals, by reason for classification as high risk**
The vertical dashed line indicates March, 2008, the month in which cessation of antibiotic prophylaxis for infective endocarditis was recommended by the National Institute for Health and Clinical Excellence.[13] CHD=congenital heart disease. VAD=ventricular assist device. *Only within the previous 6 months.

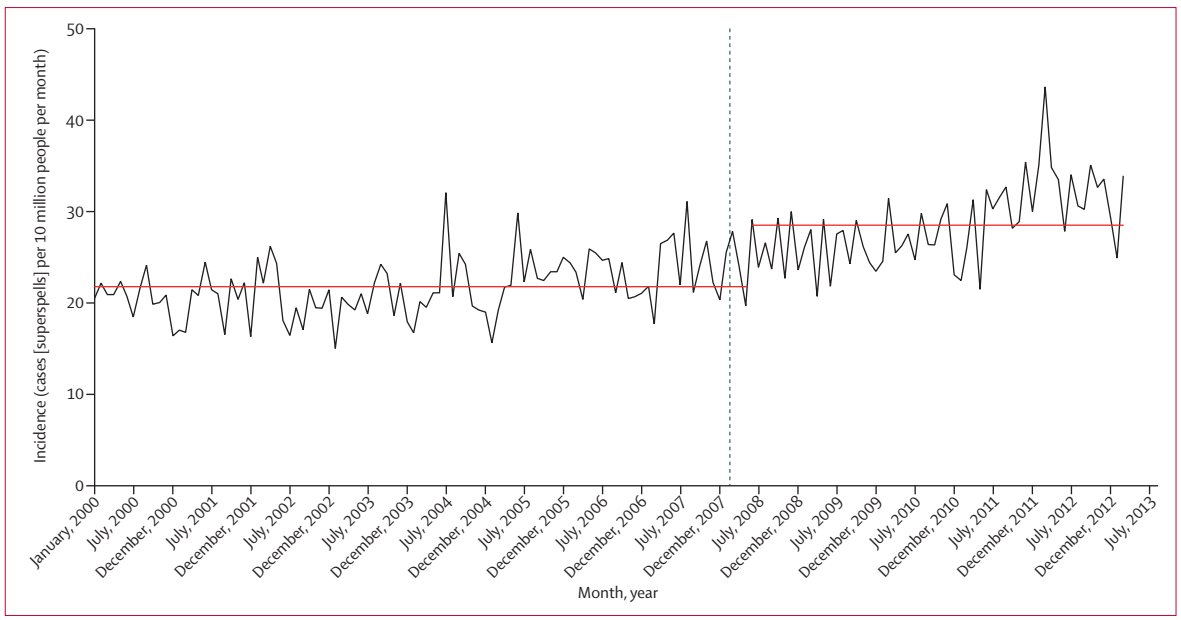

Figure 5: **Change-point analysis for incidence of infective endocarditis**
The solid black line shows the population-corrected number of cases of infective endocarditis. The vertical dashed black line indicates March, 2008, the month in which cessation of antibiotic prophylaxis for infective endocarditis was recommended by the National Institute for Health and Clinical Excellence.[13] The red lines show the result of change-point analysis, indicating that the change occurred in June, 2008.

Pathogen-specific secondary or supplementary coding of causal organism in cases of infective endocarditis was unevenly distributed and increased from 32% to 49% during the study period (data not shown). The rate of increase was also uneven and diminished over the last 4 years of the study (April, 2009 to March, 2013). Furthermore, no specific codes could be used to identify oral viridans group streptococci. As a result, we could not obtain any meaningful information from this data with respect to the effect of the change in prescription of antibiotic prophylaxis on the nature of the organisms that caused the reported cases of infective endocarditis.

We used hospital episode statistics data to quantify several other variables that might affect the incidence of infective endocarditis over time. We were unable to identify a large enough change in any one of these variables to wholly account for the increase in the incidence of infective endocarditis that has occurred since the introduction of the NICE guidelines (appendix pp 10–11). However, we cannot exclude the possibility that changes in other variables or changes in a combination of variables could account for the increase.

Discussion

Since the introduction of the NICE guidelines[13] in March, 2008, which recommended cessation of antibiotic prophylaxis to prevent infective endocarditis, the number of prescriptions for antibiotic prophylaxis has fallen sharply and the incidence of infective endocarditis in England has increased significantly. This increase in incidence has affected both high-risk and lower-risk individuals. Infective endocarditis-associated in-hospital mortality also increased, although this increase was not significant, possibly because of the lower mortality associated with infective endocarditis caused by oral streptococci, the general fall in infective endocarditis mortality, and inadequate statistical power resulting from the small number of deaths compared with the number of cases (panel).

Of paramount importance is whether the fall in prescriptions for antibiotic prophylaxis caused the increase in incidence of infective endocarditis. Although we identified a temporal association, we were not able to prove a causal relation. We previously analysed these data 2 years after the introduction of the NICE guidelines.[16] At that time, a significant increase in the incidence of infective endocarditis incidence was not demonstrable despite a significant 78·6% reduction ($p<0·0001$) in the prescription of antibiotic prophylaxis.

The effect of the 2007 AHA guidelines[7] was examined in four investigations[25–28] and no increase in the incidence of infective endocarditis was seen after their implementation. However, all of these US studies involved a smaller population size than was assessed in our study, a shorter period of follow-up, or both. One of the studies[27] was done only 9 months after the change in guidelines and included only 396 cases of infective endocarditis. Another,[26] done 3 years after the introduction of the guidelines, was restricted to children and included 1157 cases.[26] The third[28] used Medicare records to identify the incidence of infective endocarditis in roughly 75% of Medicare beneficiaries aged 65 years and older for about

2·5 years after the introduction of the AHA guidelines. The fourth[25] contained two different cohorts: first, an in depth study of the incidence of infective endocarditis in Olmsted County, MN, USA (adult population less than 150 000) for 3 years after introduction of the guidelines; second, a much larger study that used ICD-9 coding data from the Nationwide Inpatient Sample database, which contains data for patients from a roughly 20% stratified sample of US community hospitals. This study[25] more closely resembled our own, but only examined the incidence of infective endocarditis for 2 years after the introduction of the AHA guidelines. Although our initial assessment 2 years after the introduction of the NICE guidelines showed no change in the incidence of infective endocarditis incidence,[16] the present, more sophisticated reanalysis after 5 years has detected a significant change.

Similarly, Duval and colleagues[29] reported a follow-up study in three French regions (with a total adult population of about 11 million) where a guideline change in 2002 restricted antibiotic prophylaxis to patients at high risk of infective endocarditis (roughly 10% of the total cases). They identified no significant increase in the incidence of oral streptococcal infective endocarditis in 2008 compared with their findings from 1991 and 1999. Although these data were collected 6 years after the guideline change, the methods were different and the population size studied was smaller than in the present study. Moreover, antibiotic prophylaxis remained the standard of care for high-risk patients in both the US and French studies.

Our estimate of the number of antibiotic prophylaxis prescriptions needed to prevent one case of infective endocarditis is substantially lower than other estimates.[30,31] Our results are based on prescribing data and data for the incidence of infective endocarditis obtained from a large population. Nonetheless, our results had large CIs, and to make the estimates we had to make the assumption that there is a causal link between the prescribing and incidence data that might not be true. Other estimates also make assumptions and are generally derived from complex calculations that involve estimated figures derived from fairly small samples. Such calculations based on several estimates tend to multiply the uncertainty, but are nonetheless valid.

On the positive side, dental management of patients at risk of infective endocarditis has been simplified by the NICE guidelines and the fall in prescriptions of antibiotic prophylaxis will have reduced associated costs and the number of antibiotic prophylaxis-related adverse drug reactions.

Our study has several limitations. The data used rely on UK hospital coding and might not be generalisable to other populations. In the UK, data are collected on every patient admitted to hospital by trained and accredited coders. Although these data are subject to error, they have been shown, for example, to provide more reliable and complete data capture for vascular surgery than did a UK national research database designed specifically for that purpose.[32] Furthermore, because the coding was done independently of our study, it was not subject to study-related bias or affected in any other way by the introduction of the NICE guidelines. Moreover, the size of the dataset and the consistency of the underlying coding process are likely to negate the effect of any systematic error. Although cases of infective endocarditis might present to different hospital specialties and cause difficulties in initial diagnosis, hospital episode statistics data record the final diagnosis for each episode, and should reflect as accurately as possible the number of cases of infective endocarditis identified. Nonetheless, the diagnosis of infective endocarditis is sometimes uncertain and will not always have been based on the Duke criteria.[33] Furthermore, because of the high mortality and morbidity associated

***Panel:* Research in context**

Systematic review

Updated guidelines concerning the role of antibiotic prophylaxis to prevent infective endocarditis vary in different countries, but all share a common theme—the number of patients for whom antibiotic prophylaxis is recommended has been substantially reduced because of the absence of robust data to support its effectiveness and some concerns regarding safety. Continuing surveillance has been recommended to ensure that reduced use of antibiotic prophylaxis does not result in an increase in the incidence of infective endocarditis, necessitating population-based surveys. We did comprehensive and focused reviews of the scientific literature between 2002 and July, 2014, to determine what studies have been done to address the topic of antibiotic prophylaxis for prevention of infective endocarditis. As part of this process, we searched the PubMed and Medline databases for articles published in English up to July 31, 2014. Our search terms included "endocarditis", "infective endocarditis", "prevention", "diagnosis", "therapy", "antimicrobial", "antibiotic", "epidemiology", "risks", "treatment", "indications", "microbiology", "dental", "bacteremia", "clinical trials (human)", and "prophylaxis". No previous studies have identified a change in the incidence of infective endocarditis since guidelines restricting the use of antibiotic phrophylaxis were introduced.[16,25–29]

Interpretation

Our results from a large dataset in England show that prescriptions of antibiotic prophylaxis have fallen substantially and the incidence of infective endocarditis has increased significantly since the introduction of the 2008 National Institute for Health and Clinical Excellence guidelines recommending the cessation of antibiotic prophylaxis.[13] Although we are unable to prove a causal link between the cessation of antibiotic prophylaxis and the increase in incidence of infective endocarditis, further investigation is now warranted to account for these findings and to determine whether similar trends are apparent in other populations.

with infective endocarditis, clinicians might treat some cases as infective endocarditis even when the diagnosis is uncertain. Undoubtedly, therefore, some cases will have been miscoded.

ICD-10 and OPCS-4 codes (appendix) were used to identify episodes of infective endocarditis that occurred in individuals at high risk of infective endocarditis. This approach required us to look backwards in time from the index case of infective endocarditis to identify previous episodes of infective endocarditis, pre-existent cyanotic congenital heart disease, and previous operative procedures (such as valve surgery) that would have defined the individual as at high risk. However, since some of these searches were limited (the dataset did not extend to before 2000) and reliant on accurate recording of risk factors, we probably underestimated the number of high-risk individuals. We also assumed that infective endocarditis cases that did not arise in a high-risk individual must have occurred in individuals who were at moderate risk or low risk. Since we could not distinguish these groups on the basis of data from hospital episode statistics, we clustered them together as lower-risk cases. A few high-risk individuals might have been erroneously included in this group, resulting in overestimation of the size of the lower-risk group.

The data for pathogen-specific causal organisms had some major limitations. Secondary or supplementary coding was unreliable and relevant codes were recorded in only 30–49% of cases (and we cannot be certain that these represented a random subset of the entire population). Additionally, the rate of improvement in secondary or supplementary coding was uneven and there are no pathogen-specific ICD-10 codes that identify oral viridans group streptococci. Furthermore, we could not always be certain that the organism coded was the organism that caused the infective endocarditis and not an organism that caused some other intercurrent infection—eg, a chest or wound infection. Finally, because of the small amount of data for each type of organism, the study was underpowered to detect a significant change. In view of these limitations, it was impossible to draw any conclusions from the organism-specific data with respect to the change in prescription of antibiotic prophylaxis.

Although our data show a rise in the number of cases of infective endocarditis, factors other than the change in the antibiotic prophylaxis guidelines in March, 2008, could have caused this increase. For example, a sudden large increase in the number of individuals at risk of infective endocarditis might have occurred. However, for many of the factors that put an individual at high risk of infective endocarditis, we have shown that this situation is unlikely to be the case (appendix). Using data from hospital episode statistics, we noted an overall annual increase in the number of prosthetic heart valve and valve repair procedures over the study period, but no sudden change in procedure numbers that could account for the increase in incidence of infective endocarditis. Similarly, the number of surgical procedures for congenital heart disease was almost constant over the period, and although the number of percutaneous procedures for congenital heart disease increased sharply in 2005–06, it fell subsequently from 2009–10 onwards. We noted no sudden change in the annual number of pacemaker or cardioverter-defibrillator insertions.

We were unable to obtain data for other groups of individuals potentially at risk of developing infective endocarditis such as people with diabetes, elderly people, and those living in residential care. Nonetheless, publically available data for the prevalence of diabetes in England shows a steady rise from 2 088 335 in 2007–08 to 2 455 937 in 2010–11, which seems to be part of a long-term trend.[34] Additionally, the number of individuals aged 65 year and older living in residential care in England remained almost static between 2001 (290 000) and 2011 (291 000), but fell as a proportion of the total population aged 65 year and older, from 3·5% in 2001 to 3·2% in 2011.[35]

Alternatively, the incidence of infective endocarditis could have increased because of susceptible individuals being exposed to more risk-prone procedures and bacteraemias. Although we identified no major change in the proportion of the English population receiving dental treatment, we were unable to study more subtle changes in the pattern of dental care, standards of oral hygiene, or patterns of oral disease that might affect the extent and frequency of viridans group streptococci-related bacteraemia. Nonetheless, dental statistics for England show that dental extractions have remained fairly constant, at about 2·2 million per year, for many years, whereas the number of scale and polish treatments per year has increased slowly (from 12·0 million to 12·8 million over the period 2009–14).[36] However, we do not know if these patterns of care in the general population are the same in people at risk of infective endocarditis. We also do not know if the interest caused by the publication of the NICE guidelines,[13] or increasing knowledge about bacteraemia related to daily habits such as tooth brushing will have changed the behaviour of patients at risk of infective endocarditis in favour of seeking or avoiding dental care, or improving or neglecting their oral hygiene.

A change in the frequency of other potentially risk-prone procedures such as colonoscopy, renal dialysis, intravenous drug treatment, and wound management, could also have affected the incidence of infective endocarditis. Data are not available for all of these procedures, but hospital episode statistics data for England[37] show no sudden increase in colonoscopies and data from the UK Renal Registry[38] show only a gradual increase in haemodialysis between 2007 and 2009, followed by a reduction. These data also show a fall in the proportion of all patients undergoing dialysis between 2007 and 2012 who developed a methicillin-resistant *Staphylococcus aureus* bacteraemia. Nonetheless, we cannot exclude the possibility that a combination of factors affecting risk-prone individuals and

the number of episodes of bacteraemia to which they are exposed could have caused the increase in incidence of infective endocarditis had they occurred at the right time.

Although we corrected our data for changes in the size of the English population, changes in the age and sex distribution and more subtle population changes—eg, immigration from parts of the world with high prevalence of rheumatic heart disease or poor oral hygiene—might account for the change in incidence of infective endocarditis if large enough in size and coincident with the change in guidelines for the use of antibiotic prophylaxis. Furthermore, other changes in health policy could be possible confounders—eg, new or amended policies that affected the occurrence of transient bacteraemia resulting from procedures such as colonoscopy, intravenous line placement, or others, could have brought about a systematic change in the incidence of infective endocarditis. Additionally, use of more sophisticated diagnostic technologies, improved diagnostic performance, or changes in diagnostic strategy could have increased the number of diagnoses of infective endocarditis. If such changes occurred in the same timeframe as the cessation of antibiotic prophylaxis, it would be difficult if not impossible to distinguish their effects.

In summary, we have shown both a significant reduction in antibiotic prophylaxis prescriptions and a significant rise in the incidence of infective endocarditis cases in England since introduction of the NICE guidelines recommending cessation of antibiotic prophylaxis in 2008. Although we have identified a temporal relation between these two changes, our data do not establish a causal link.

Contributors

All authors contributed to the study design, writing of the report, and the decision to submit for publication. MHT gathered, analysed, and vouched for the prescribing data, with contributions for MJD. SJ gathered, analysed, and vouched for the incidence data, with contributions for MJD. SJ did the statistical analyses. MJD and MHT created the figures.

Declaration of interests

LMB and PBL are members of the American Heart Association's committee on rheumatic fever, endocarditis, and Kawasaki disease and were involved in the production of the 2007 American Heart Association guideline on the prevention of infective endocarditis. BP was a member of the task force on the prevention, diagnosis, and treatment of infective endocarditis of the European Society of Cardiology that produced the organisation's 2009 guidelines on the prevention, diagnosis, and treatment of infective endocarditis. BP was also a consultant to the committee that produced the 2008 UK National Institute for Health and Clinical Excellence clinical guideline on prophylaxis against infective endocarditis. All other authors declare no competing interests.

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References

1 Prendergast BD. The changing face of infective endocarditis. *Heart* 2006; **92:** 879–85.

2 Lacassin F, Hoen B, Leport C, et al. Procedures associated with infective endocarditis in adults: a case control study. *Eur Heart J* 1995; **16:** 1968–74.

3 Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N Engl J Med* 2001; **345:** 1318–30.

4 Strom BL, Abrutyn E, Berlin JA, et al. Dental and cardiac risk factors for infective endocarditis: a population-based, case-control study. *Ann Intern Med* 1998; **129:** 761–69.

5 Tleyjeh IM, Steckelberg JM, Murad HS, et al. Temporal trends in infective endocarditis: a population-based study in Olmsted County, Minnesota. *JAMA* 2005; **293:** 3022–28.

6 Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J* 2009; **30:** 2369–413.

7 Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; **116:** 1736–54.

8 Lockhart PB, Brennan MT, Kent ML, Norton HJ, Weinrib DA. Impact of amoxicillin prophylaxis on the incidence, nature, and duration of bacteremia in children after intubation and dental procedures. *Circulation* 2004; **109:** 2878–84.

9 Lockhart PB, Loven B, Brennan MT, Fox PC. The evidence base for the efficacy of antibiotic prophylaxis in dental practice. *J Am Dent Assoc* 2007; **138:** 458–74.

10 Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. Bacteremia associated with toothbrushing and dental extraction. *Circulation* 2008; **117:** 3118–25.

11 Lockhart PB, Brennan MT, Thornhill M, et al. Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia. *J Am Dent Assoc* 2009; **140:** 1238–44.

12 Durack DT. Prevention of infective endocarditis. *N Engl J Med* 1995; **332:** 38–44.

13 NICE. Prophylaxis against infective endocarditis. National Institute for Health and Clinical Excellence, 2008. http://www.nice.org.uk/CG064 (accessed Oct 31, 2013).

14 Connaughton M. Commentary: controversies in NICE guidance on infective endocarditis. *BMJ* 2008; **336:** 771.

15 Richey R, Wray D, Stokes T. Prophylaxis against infective endocarditis: summary of NICE guidance. *BMJ* 2008; **336:** 770–71.

16 Thornhill MH, Dayer MJ, Forde JM, et al. Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. *BMJ* 2011; **342:** d2392.

17 Chambers JB, Shanson D, Venn G, Pepper J. NICE *v* world on endocarditis prophylaxis. *BMJ* 2011; **342:** d3531.

18 Dayer MJ, Chambers JB, Prendergast B, Sandoe JA, Thornhill MH. NICE guidance on antibiotic prophylaxis to prevent infective endocarditis: a survey of clinicians' attitudes. *QJM* 2013; **106:** 237–43.

19 HSCIC. Methodology to create provider and CIP spells from HES APC data. Leeds: Health & Social Care Information Centre, 2014. http://www.hscic.gov.uk/media/14627/Provider-Spells-Methodology/zip/Provider_Spells_Methodology.zip (accessed June 9, 2014).

20 Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002; **27:** 299–309.

21 R Core Development Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2008.

22 Fox J. Time-series regression and generalized least squares. Appendix to: an R and S-PLUS companion to applied regression, 2002. http://cran.r-project.org/doc/contrib/Fox-Companion/appendix-timeseries-regression.pdf (accessed June 9, 2014).

23 Hinkley DV. Inference about the change-point in a sequence of random variables. *Biometrika* 1970; **57:** 1–17.

24 Baddour LM, Epstein AE, Erickson CC, et al. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. *Circulation* 2010; **121:** 458–77.

25 Desimone DC, Tleyjeh IM, Correa de Sa DD, et al. Incidence of infective endocarditis caused by viridans group streptococci before and after publication of the 2007 American Heart Association's endocarditis prevention guidelines. *Circulation* 2012; **126:** 60–64.

26 Pasquali SK, He X, Mohamad Z, et al. Trends in endocarditis hospitalizations at US children's hospitals: impact of the 2007 American Heart Association Antibiotic Prophylaxis Guidelines. *Am Heart J* 2012; **163:** 894–99.

27 Rogers AM, Schiller NB. Impact of the first nine months of revised infective endocarditis prophylaxis guidelines at a university hospital: so far so good. *J Am Soc Echocardiogr* 2008; **21:** 775.

28 Bikdeli B, Wang Y, Kim N, Desai MM, Quagliarello V, Krumholz HM. Trends in hospitalization rates and outcomes of endocarditis among Medicare beneficiaries. *J Am Coll Cardiol* 2013; **62:** 2217–26.

29 Duval X, Delahaye F, Alla F, et al. Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications: three successive population-based surveys. *J Am Coll Cardiol* 2012; **59:** 1968–76.

30 Duval X, Alla F, Hoen B, et al. Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. *Clin Infect Dis* 2006; **42:** e102–07.

31 Pallasch TJ. Antibiotic prophylaxis: problems in paradise. *Dent Clin North Am* 2003; **47:** 665–79.

32 Aylin P, Lees T, Baker S, Prytherch D, Ashley S. Descriptive study comparing routine hospital administrative data with the Vascular Society of Great Britain and Ireland's National Vascular Database. *Eur J Vasc Endovasc Surg* 2007; **33:** 461–65.

33 Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000; **30:** 633–38.

34 Health & Social Care Information Centre. Diabetes prevalence. Leeds: Association of Public Health Observatories. http://data.gov.uk/dataset/diabetes_prevalence (accessed Oct 27, 2014).

35 Office of National Statistics. Changes in the older resident care home population between 2001 and 2011. Newport: Office of National Statistics, 2014. http://www.ons.gov.uk/ons/dcp171776_373040.pdf (accessed Oct 27, 2014).

36 HSCIC. NHS dental statistics for England. Leeds: Health & Social Care Information Center. http://data.gov.uk/dataset/nhs_dental_statistics_for_england (accessed Oct 27, 2014).

37 HSCIC. Hospital episode statistics. Leeds: Health & Social Care Information Centre. http://www.hscic.gov.uk/hes (accessed Oct 27, 2014).

38 Gilg J, Rao A, Fogarty D. UK Renal Registry 16th annual report: chapter 1 UK renal replacement therapy incidence in 2012: national and centre-specific analyses. *Nephron Clin Pract* 2013; **125:** 1–27.