Prophylaxis against infective endocarditis
Consultation on draft guideline - Stakeholder comments table
1 June 2015 – 29 June 2015

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Anticoagulation Europe	Addendum	8	139	You have a significantly higher risk of developing infective endocarditis is you have already had an episode, because of tissue damage caused by the first episode. These patients should be treated as a higher risk group that need prophylaxis. (American Heart Association Guidelines 2007)	Thank you for your comment. People with prior IE have been identified as a high risk group based on the current recommendation 1.1.1. However the committee concluded that antibiotic prophylaxis is not recommended for dental, upper and lower GI tract and respiratory tract, genitourinary procedures because there is very limited evidence from 3 observational studies, all inconclusive as to whether prophylaxis prevents the development of IE.
Anticoagulation Europe	Addendum	8	142	Prevention of infective endocarditis is paramount and also knowing what symptoms to look for and when to seek help. Therefore the recommendation wording should be Healthcare Professionals **MUST** offer people at risk clear and consistent information	Thank you for your comment. Based on NICE The Manual (2014), we only use 'must' if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening. We do not believe either of the above scenarios applies to recommendation 1.1.2.
Anticoagulation Europe	Addendum	9	153	Prosthetic valve patients are at much higher risk than patients with native valve lesions, Prosthetic valve endocarditis (PVE) is the most serious complication of valve replacement, associated with high mortality, greater than 50% in some series. Analysis from the International Collaboration on Endocarditis, based on data from 28 countries (JAMA 2007;297:1354-61), reported an average hospital mortality of 22.8%, although in some subgroups the mortality was higher, notably the elderly (37%) and patients on dialysis (40%). It is therefore of great concern that the NICE is recommending that antibiotic prophylaxis should not be given to prosthetic heart valve patients undergoing dental treatment or other procedures associated with transient bacteraemia, irrespective of their risk profile, contradicting guidelines from the British Cardiac Society (Clin Med 2004;4:545-50), the British Society for Antimicrobial Chemotherapy (J Antimicrob Chemother 2006;57:1035-42), the European Society of Cardiology (EHJ 2004;25:267-76, 2005;26:2463-71, 2007;28:230-68), the American College of Cardiology and the American Heart Association (JACC 2006;48:e1-148, Circulation 2007;116:1736-54). PVE has devastating consequences for the individual patient and, apart from pathologists conducting autopsies, only cardiac surgeons witness the extent of destruction of cardiac tissues it causes, with peri-annular abscesses, intracardiac fistulae, damage to conducting tissue, etc., together with the complicated and prolonged postoperative course that patients often have to endure. If they escape mortality and recover from complications, they remain at risk of recurrent infection. Few regain their previous functional status and quality of life. We have been contacted by patients who have suffered infective endocarditis and by relatives of those who have died as a result. The impact on these patients and relatives cannot be underestimated. All had been ill for some months before diagnosis was made and required further extensive cardiac surgery plus weeks of intravenous antibiotics. If lucky enough to survive they never reach the level of health that they had before and some are severely incapacitated.	Evidence from the NICE review showed that people with prosthetic heart valves do not appear to be at increased risk of developing IE than people without prosthetic heart valves, based on two studies with high risk of bias. This point was discussed by the Committee, as it was acknowledged that the studies found did not reflect what is widely considered in practice to be true – i.e. that people with prosthetic valves are at increased risk of developing IE. The evidence statement and the LETR table have been updated to reflect the Committee's views on this point. The JAMA study (Wang et al 2007) was included in review Q2 - outcomes for people with IE and previous cardiac conditions and it was also included in the original guideline, however it did not meet the criteria for Q1. The study design was such that it included people with IE and reported on the percentage of these who had prosthetic valves. It did not predict risk of IE, since to do that, it would have needed to follow up people with and without prosthetic valves, over time, to see who developed IE and who didn't.
Anticoagulation Europe	Addendum	11	203	You state that there is limited evidence about the effectiveness of antibiotic prophylaxis in reducing the incidence of infective endocarditis. Yet the incidence has increased since NICE guidelines 2008. You recommend further research and trials. Surely absence of definite proof of the effectiveness of antibiotic prophylaxis	Thank you for your comment. We did not find evidence that antibiotic use was effective and there are numerous reasons why incidence may have increased, please refer to section 2.6.5 of the full Addendum to see a summary of the committee discussion of this area. You are right in that the incidence of IE has increased since NICE guidelines 2008 including within the low risk population; however the reasons for such increase are unknown; interestingly, mortality from IE has not increased in parallel with the increase

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				in preventing infective endocarditis does not constitute proof of ineffectiveness. In a situation of inconclusive evidence, patient safety should be given greater priority than economic considerations. Whilst implementation of the NICE guidelines will undoubtedly save money for the NHS, it will almost certainly result in a higher incidence of endocarditis and many more deaths. Even if only a proportion of patients avoid infective endocarditis with antibiotic prophylaxis, it must surely be justified on clinical and ethical grounds.	in incidence. Furthermore, the epidemiology overview illustrated that the incidence of IE continues to increase in the US and European countries, where more conservative antibiotic prophylaxis guidelines are in place compared to the UK. As commented by the critique of the Dayer study, the postulation that the change in slope after the introduction of the NICE guidance was based on the assumption that there were 2 linear trends before and after 2008. There is no rationale provided in the Dayer study to justify such an assumption. Sensitivity analyses using different assumptions were conducted by the critique author and it demonstrated that if different assumptions were used, different results were likely to be produced. Absence of definite proof does not constitute ineffectiveness and therefore prioritising patient safety including the consequences of resistance due to antibiotic overuse for prophylaxis led the committee to keeping the existing recommendations of not offering antibiotics. Economic considerations were taken into account by comparing cost and health consequences. Health benefits are a critical part of economic evaluations considered by NICE. Three studies were considered in this guideline update. The first was a US study comparing 7 prophylactic strategies against no prophylaxis (Agha et al. 2005). The second was the model developed for the 2008 NICE guideline comparing 8 pre-dental antibiotic prophylaxis regimens with no prophylaxis. The third was an unpublished study that incorporated the data on the increased incidence of IE (Franklin et al.). The base case analysis of all 3 studies found that antibiotic prophylaxis was not cost effective. Further details on these studies can be found in the Addendum in section 2.6 and appendices I to P.
British Cardiovascular Society	Addendum	11	General	Endocarditis is a serious condition which is associated with high rates of morbidity and mortality. Certain patient groups can be identified which are at increased risk of infective endocarditis and which might benefit from antibiotic prophylaxis against its occurrence. There are two key questions in formulating guidance for antibiotic prophylaxis against infective endocarditis. Firstly, is this strategy effective? and, secondly, is it safe? In the absence of randomised controlled trial data in this area, observational studies form the evidence base for guideline development and for clinical decision making. Some studies have reported benefit from antibiotic prophylaxis in high risk groups (1,2). These observations are supported by a substantial body of animal work which shows that a single dose of amoxicillin can prevent streptococcal endocarditis (3,4). A study published recently in The Lancet reported that rates of infective endocarditis in England increased significantly after the 2008 NICE guidance which heralded a 90% decrease in prescribing rates for infective endocarditis prophylaxis (5). By March 2013 there were about 35 additional cases of infective endocarditis per month compared with the expected number based upon pre-2008 guideline endocarditis incidence rates. As the authors acknowledged, it was not possible to demonstrate a causal relation between reduced antibiotic prophylaxis and the increased incidence of infective endocarditis In 2008, NICE quoted a risk of fatal anaphylaxis from amoxicillin of approximately 20 per million doses. This estimate was based mainly on data published in the 1960s using parenteral rather than oral penicillin, often for treating syphilis. More recent UK Yellow Card return data suggest that fatal anaphylaxis is exceedingly rare (6). Indeed, there have there been no reports in the world literature of fatal anaphylaxis after oral amoxicillin prophylaxis for infective endocarditis. A new study (7) found that the incidence of adverse drug reactions following amoxicillin prophylaxis was extremely low (no fatal and 22.62 non-fatal reactions per million prescriptions). Reactions to prophylaxis with clindamycin were higher than anticipated, suggesting an alternative prophylaxis regimen is needed for	Thank you for your comment. People with prior IE have been identified as high risk group based on current recommendation 1.1.1. However the committee concluded that antibiotic prophylaxis is not recommended for dental, upper and lower GI tract and respiratory tract, genitourinary procedures because there is very limited evidence that prophylaxis prevents the development of IE (please see section 2.6 of addendum for details of the evidence base). The Lancet study you refer to is addressed specifically by this evidence review and update. Referring to the Ramsey analysis of this study, the postulation that the change in slope after the introduction of the NICE guidance was based on the assumption that there were 2 linear trends before and after 2008. There is no rationale provided in the Dayer study to justify such an assumption. Sensitivity analyses using different assumptions were conducted by the critique author and it demonstrated that if different assumptions were used, different results were likely to be produced. Also, the epidemiology overview illustrated that the incidence of IE continues to increase in the US and European countries, where more conservative antibiotic prophylaxis guidelines are in place compared to the UK. As you say, the uncertainty regarding its effectiveness will not be resolved without a high quality randomised controlled trial hence the committee recommended additional research recommendation in this area highlighting the need for an RCT. Furthermore, this particular guideline only covers dental procedures, upper and lower GI procedure, upper and lower respiratory tract procedures and genitourinary procedures; all other high risk procedures were outside the scope of this guideline.

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				people who are allergic to penicillin. In conclusion, there are observational data which can be used to support the use of antibiotic prophylaxis to prevent endocarditis. The uncertainty regarding its effectiveness will not be resolved without a high quality randomised controlled trial. Contemporary data show that the incidence of serious harm from a single dose of amoxicillin is very low. The British Cardiovascular Society believes that the potential benefits of prevention from antibiotic prophylaxis outweighs the risks in high risk individuals. BCS would like to see a guideline which better reflects the uncertainties in this area and allows clinicians room to use antibiotic prophylaxis in high risk individuals undergoing high risk procedures without them being seen to practice against NICE recommendations. These individuals would include those with previous infective endocarditis, prosthetic heart valves or some forms of congenital heart disease References 1. Horstkotte D, Rosin H, Friedrichs W, Loogen F. Contribution for choosing the optimal prophylaxis of bacterial endocarditis. *Eur Heart J* 1987;8(Suppl J):379-81. 2. 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 Infectious Dis* 2006;42:e102-7. 3. Glauser M, Bernard J, Moreillon P, *et al*. Successful single–dose amoxicillin prophylaxis against experimental streptococcal endocarditis: evidence for two mechanisms of protection. *J Infect Dis* 1983;147:568–75. 4. Berney P, Francioli P. Successful prophylaxis of experimental streptococcal endocarditis with single-dose amoxicillin administered after bacterial challenge. *J Infect Dis* 1990;161:281-5. 5. 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* 2015;385:1219-28. 6. Lee P, Shanson D. Results of a UK survey of fatal anaphylaxis after oral amoxicillin. *J Antimicrob Chemother* 2007;60:1172-3. 7. Thornhill MH, Dayer MJ, Prendergast B, Baddour LM, Jones S, Lockhart PB. Incidence and nature of adverse reactions to antibiotics used as antibiotic prophylaxis. *J Antimicrob Chemo*. 2015 doi:10.1093/jac/dkv115.	Thank you for also providing a list of potential studies. Study reference 1 met the review protocol criteria and was included – please see section 2.6 of the addendum for the committee's interpretation of this evidence. Study references 2, 6 and 7 did not meet the pre-specified criteria of RCTs or comparative observational studies and were therefore not included. Study references 3 and 4 were studies performed in animals – NICE does not consider animal studies to be an appropriate source of evidence due to the lack of applicability to the human population. And finally, study reference 5 was the study that triggered the update of this guideline – please see section 2.1.2 for the critique of this study and also section 2.6.5 for the committee's interpretation of this evidence.
British Dental Association	Addendum	11	1.1.2	Under recommendations, Patient advice: Definition and agreement on what is meant by the 'importance of maintaining good oral health' is important, with appropriate advice available for distribution to patients. The imperative for good oral health is an easy statement to make, but very much more difficult to describe, deliver and achieve. Patients should receive recommended advice & messages regarding oral hygiene, the need for regular recalls to the dentist, diet advice, smoking cessation, and prevention with appropriate use of fluoride. Exemplar information leaflets would be welcomed. Should the British heart Foundation warning card advising patients of the signs of endocarditis and the actions to take, be issued for dentists to use?	Thank you for your comment. The Committee discussed this issue and agreed that it is not possible to have a single definition for good oral health because there is still a clear gap in the knowledge of the variations in individuals' and communities' perceptions of oral health, and that a person's oral health may be subject to their own personal values and attitudes. We will however publish an 'information for patients and the public' version which will contain all the relevant patient support resources suggested by experts in this area to address this issue. Finally, we will also pass on this message to the implementation team so that they can support implementation of the ercommendations.
British Dental Association	Addendum	12	5-8	1.3 Patient-centered care: It is noted that 'treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals'. If a patient elects to	Thank you for your comment. We agree patients should have the opportunity to make informed decisions hence NICE recommends healthcare professionals should offer people at risk clear and consistent information about prevention including why prophylaxis is no longer recommended. (please see recommendation 1.1.3). We would further like to highlight that NICE clinical guidelines are guidance only

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				have antibiotic prophylaxis, can this be refused? Are there any perceived barriers for staff in this situation with prescribing e.g. for dental procedures for a patient with a previous history of endocarditis?	and that patient choice and clinical judgement will always remain important in every individual's treatment decision.
British Dental Association	Addendum	21	5-23	We note the critique of the Dayer *et al.* paper and agree that the existing NICE guidance should not be changed on the basis of these data. The study did not demonstrate any causal relationship between a lack of antibiotic prophylaxis and increased IE incidence; nor did it examine whether subjects had undergone dental treatment. It also appears that mortality from IE has not increased in parallel with incidence. A range of demographic and other factors could have contributed to the increase in incidence, including migration and the aging population. We would recommend that NICE continue to monitor new evidence on IE and review the guidance as appropriate.	Thank you for your comment.
British Dental Association	General	General	General	The BDA welcomes this thorough review of the evidence since 2008 and supports the recommendations.	Thank you for your comment.
British Dental Association	Short	8	143	We agree that advice from healthcare professionals must be "clear and consistent". However, we are aware that some cardiologists in particular are still informing "at risk" patients that dentists should provide prophylaxis for IE. We would strongly urge NICE to ensure that the guidance is widely disseminated and accepted by the appropriate professional bodies.	Thank you for your comments and concerns being raised. We will inform all stakeholders when this update is due to be published, and also to pass this message on to NICE implementation team to ensure recommendations will be implemented accordingly.
British Dental Association	Short	8	145-152	We would welcome the provision of some standardised information, outlining the key messages in lay terms, which could be distributed to patients.	Thank you for your comment. Yes, there will be an 'information for patients and public' version published along with this guidance.
British Dental Association	Short	8	148	We agree that the importance of maintaining good oral health should be highlighted in particular to those at risk of IE. Again, we would particularly welcome the provision of patient information, based on the Department of Health's *Delivering Better Oral Health* guidance, for distribution by both medical and dental practitioners.	Thank you for your comment. The Committee discussed this issue and agreed that it is not possible to have a single definition for good oral health because there is still a clear gap in the knowledge of the variations in individuals' and communities' perceptions of oral health, and that a person's oral health may be subject to their own personal values and attitudes. We will however publish an 'information for patients and the public' version which will contain all the relevant patient support resources suggested by experts in this area to address this issue. Finally, we will also pass on this message to the implementation team to support implementation of the recommendations.
British Heart Foundation	General	General	General	The British Heart Foundation supports the proposed recommendations, including the research recommendation, in the updated guideline on prophylaxis against infective endocarditis	Thank you for your comment.
British Heart Valve Society	Addendum	11	Section1.2	Implanted electronic devices should be included on the list of high-risk cardiac conditions. A review and guidance on management is imminently being published in the Lancet (Sandoe et al. Guidelines for the diagnosis, prevention and management of Implantable Cardiac Electronic Device Infection.Report of a joint working party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organisation), British Heart Rhythm Association (BHRA), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS) and British Society for Echocardiography (BSE).	Thank you for your comments. We acknowledge your concerns and consider this specific population warrants a separate guideline. This information has been sent to the surveillance team for considerations..
British Heart Valve Society	Addendum	14	general	A recent study showed a statistically significant increase in the incidence of Streptococcal endocarditis following the introduction of the 2007 AHA guidelines. This should be included. The reference is Pant et al. JACC 2015;65:2070-6	Thank you for the information. The newly published Pant el al. (2015) study has now been added to the Overview of epidemiology of the Addendum. This particular study is in line with other US and European studies in the overview section that, despite antibiotic prophylaxis is recommended in these countries, the incidence of IE continue to rise over the years.
British Heart Valve	Addendum	21	6	Why were data abstracted from the graphs rather than the raw data obtained from the authors? The use of the equivocal statement 'multiple change points seem possible' in rejecting the study of Dayer et al implies bias in this critique.	Thank you for your comments. Raw data provided by the online Appendices of the Lancet paper (Dayer et al.) was used to conduct some sensitivity analyses.

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Society					
British Heart Valve Society	Addendum	22 35	General	The discussion of prosthetic valve endocarditis appears insufficiently clinically informed. There is a relatively high incidence in the first year after implantation caused predominantly by Staphylococcus aureus and Coagulase Negative Staphylococci (CNS). Thereafter oral organisms are more likely to occur. It may be possible to sterilise prosthetic valves infected by oral organisms but endocarditis caused by S aureus or CNS almost always needs surgery.	Sorry but we cannot see the discussion you are referring to on p22 or P35. The introductory paragraph and evidence statement on p32 summarises the findings from the evidence review. This point was discussed by the Committee who acknowledged there is an inconsistency between the evidence found and what is widely embedded in practice (i.e. that prosthetic valves increase the risk of IE). There were no other studies found in the review, nor any studies subsequently identified by topic experts or stakeholders which demonstrate this increased risk when compared to the general population. To take account for this, the evidence statement and the LETR table have been amended to reflect the Committee's views on this inconsistency.
British Heart Valve Society	NICE	General	General	We are concerned that important studies have been misquoted or misinterpreted. This has led to serious errors in conclusions drawn by NICE in many areas particularly the safety of oral antibiotic prophylaxis, the relative risk of endocarditis in prosthetic heart valves and the effect of antibiotics on reducing bacteraemia. We suggest that a thorough new review of all the evidence is undertaken by clinical members of the panel who would be able to appreciate the clinical significance of the studies.	Thank you for your comments. The systematic reviews are undertaken by the technical team at NICE along with clinical input from the topic expert members as required. The evidence has been discussed and interpreted in detail by the Committee, made up of clinicians, methodologists and clinical experts, therefore we do not believe the studies have been misquoted or misinterpreted. Please see the Addendum for a full list of the Committee members.
British Heart Valve Society	NICE	General	General	It is likely to be cost-effective to confine antibiotic prophylaxis to people with high-risk cardiac lesions having invasive dental procedures. There is published evidence to support this and a new study in progress also supports this.	We note the stakeholder has not provided the details of any studies or specific details of the scenarios where they believe antibiotic prophylaxis to be cost effective. Three economic studies were considered in this guideline update. The first was a US study comparing 7 prophylactic strategies against no prophylaxis (Agha et al. 2005). The second was the model developed for the 2008 NICE guideline comparing 8 pre-dental antibiotic prophylaxis regimens with no prophylaxis. The third was an unpublished study that incorporated the data on the increased incidence of IE (Franklin et al.). The base case analysis of all 3 studies found that antibiotic prophylaxis was not cost effective. Further details on these studies can be found in the Addendum in section 2.6 and appendices I to P. In regards to the unpublished economic analysis conducted by the University of Sheffield (Franklin et al.), the first draft of a full detailed report was considered by the Committee. The results of the study were highly sensitive to the risk of developing infective endocarditis following a dental procedure, the efficacy of antibiotic prophylaxis to reduce this risk, the cost of amoxicillin and clindamycin and the rate of fatal adverse events. Variation of these key parameters resulted in incremental cost-effectiveness ratios for antibiotic prophylaxis compared with no prophylaxis ranging from highly cost effective to highly cost ineffective and dominated (more costly and a reduction in health benefits). The incremental cost-effectiveness ratio increased to £53,000 per QALY using less optimistic estimates of prophylactic efficacy. Both amoxicillin and clindamycin are more cost effective if the baseline risk is higher. Using a baseline risk for patients with a prosthetic heart valve (based on estimates used in previous economic studies) resulted in incremental cost-effectiveness ratios of £6,487 and £13,182 for amoxicillin and clindamycin respectively. However, the Committee were cautious in their interpretation of the economic evidence because they determined that the clinical evidence reviews had not shown that dental procedures increase the risk of infective endocarditis nor that antibiotic prophylaxis is able to reduce that risk.
British Heart Valve Society	NICE	General	General	All guidelines agree that the maintenance of good oral health is important for the prevention of endocarditis. We suggest that NICE issues comprehensive guidelines on this subject.	Thank you for your comment. The Committee discussed this issue and agreed that it is not possible to have a single definition for good oral health because there is still a clear gap in the knowledge of the variations in individuals' and communities' perceptions of oral health, and that a person's oral health may be subject to their own personal values and attitudes. We will however publish an 'information for patients and public' version which will contain all the relevant patient support resources suggested by experts in this area to address this issue. Finally, we will also pass on this message to the implementation team support implemenatation of the recommendations.
British	NICE	Gen	Gen	The advice about when to suspect endocarditis is likely to alarm many people with simple	Thank you for your comments. All recommendations from the guideline are based on available evidence.

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Heart Valve Society		eral	eral	coryzal illnesses and other causes of fever. We suggest that more detailed advice is given and the British heart Valve Society would be happy to advise on this.	The Committee does not feel that more detailed advice can be given with limited available evidence. We appreciate that your concern that it may raise unnecessary alarm, but equally we believe patients have the right to be informed as soon as possible whenever there is a suspicion.
British Heart Valve Society	NICE	General	General	We suggest that NICE revises its guidelines to allow antibiotic prophylaxis for the small group at high-risk of endocarditis and who have a poor prognosis in the presence of endocarditis and are having high-risk dental procedures. This would be in line with our interpretation of the evidence. It would also bring NICE in line with all other national guidelines and with the practice of cardiologists and cardiac surgeons in the UK. This would eliminate the uncertainty that currently exists where advice from the dental surgeon and cardiologist may differ.	Thank you for your comment. People with prior IE have been identified as high risk group based on current recommendation 1.1.1. However the committee concluded that antibiotic prophylaxis is not recommended for dental, upper and lower GI tract and respiratory tract, genitourinary procedures because there is very limited evidence from 3 observational studies, all inconclusive as to whether prophylaxis prevents the development of IE. Please refer to tables 4 and 5 in the addendum for the full list of procedures reviewed. The incidence of IE continues to increase also in the US and European studies, where more conservative antibiotic prophylaxis guidelines are in place compared to the UK. With such unknown phenomena, the Committee has decided not to change current recommendations.
British Heart Valve Society	NICE	32	33 34	The statement that people with prosthetic valve do not appear to be at higher risk of endocarditis than those without prosthetic valves is incorrect. The incidence of prosthetic valve endocarditis beyond the first year is 0.3-0.4% in most published series which far exceeds the population estimate of up to 10 cases per 100,000 p.a. or 0.01%. NICE considered only two studies. The first (Alagna 2014) investigated the recurrence rate in a total of only 447 prosthetic valves and 1427 native valves with an index episode of endocarditis using an International registry. The second (Ammar 2013) was a small case-controlled study from Egypt which included only 49 patients with prosthetic valves. The aim was to investigate potential culprit procedures causing endocarditis and not the relative risk of endocarditis in prosthetic compared with native valves. Neither of these two studies addresses the primary question of how often endocarditis occurs in patients with prosthetic valves and the second study addresses a completely separate question. NICE did not reference any of the thousands of series investigating complication rates after implantation of prosthetic valves which cumulatively involve population sizes in the many thousands.	The evidence statement (for question 1a) provided reflects the evidence reviewed in this update. Two studies were found which met the protocol criteria based on the search strategy described. This point was discussed by the Committee who acknowledged there is an inconsistency between the evidence found and what is widely embedded in practice (i.e. that prosthetic valves increase the risk of IE). There were no other studies found in the review, nor any studies subsequently identified by topic experts or stakeholders which demonstrate this increased risk when compared to the general population. To take account for this, the evidence statement and the LETR table have been amended to reflect the Committee's views on this inconsistency. Based on NICE's robust methodology, the Committee will base their decision on the highest quality of evidence available to them. To established the associations between pre-existing cardiac conditions and the risk of IE, multivariate regression modelling is the best methodology for quantifying such associations. In the hierarchy of evidence, case series are at higher risk of bias compared to other study designs due the lack of a comparison group and therefore its generalisability. The Topic experts therefore pre-specified that studies of this design would not be included for this review question. Please see the review protocol (Appendix C).
British Heart Valve Society	NICE	33	25 29	The conclusion that mortality from endocarditis is only inconsistently shown to be higher in prosthetic valves appears to be based on erroneous interpretation of some of the studies. For example the Wang (2007) paper in Table 3 is wrongly stated as describing 2670 adults with prosthetic endocarditis. In fact there were 556 with prosthetic endocarditis and 1895 with native valve endocarditis. The mortality was 22.8% with prosthetic endocarditis and 16.4% (P<0.001) with native valve endocarditis. Despite this a relative risk of death of 0.74 (0.49-1.12) is given within the effects column. The implication within the context of the Table is that this describes the effect of prosthetic valves on mortality. However this figure in fact refers to the effect of prior endocarditis within the 556 patients with prosthetic valve endocarditis.	Thank you for your comment. The study by Wang et al (2007) was not actually included in this analysis (table 150 page 404). Thank you for pointing out this error in Table 3. This has been updated. The evidence table and result summary table has also been updated. The OR for mortality between PVE and NVE has been calculated by the reviewer as 1.51 (95%CI: 1.2-1.91). Adding this to the summary results means that there are now 5 studies (low risk of bias) showing an increase in in-hospital death in PVE and 4 studies (3 high risk and 1 low risk of bias) indicating no difference. The evidence statement for risk of mortality in people with prosthetic valves who get IE has been updated to reflect this.

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British Heart Valve Society	NICE	67	General	The studies suggesting an inconstant link between dental procedures and endocarditis tend not to analyse high-risk procedures like dental extraction separate from all other procedures. In considering all procedures together it is expected that the effect of high-risk procedures will be diluted. Studies showing a link with specific procedures include: Strom BL et al. Ann Intern Med 1998; 12: 761–9; Van der Meer JT et al. Arch Intern Med 1992; 152: 1869–73; Lacassin F et al. Europ Heart J 1995; 16: 1968-74; Horstkotte D et al. Europ Heart J 1987; 8 (Suppl J): 379-81; Van der Meer JTM et al. Lancet 1992; 339: 135-9; Starkbaum M et al. Yale J Biol Med 1977; 50: 49–58.	Thank you for your comments. In the Addendum, section 2.4.3, we have separate statements directed to different dental procedures; we did not group all the procedures together. In section 2.4.4 Evidence to recommendations section of the Addendum, we have documented the Committee's discussion and interpretation of the evidence, on both evidence that suggested a link as well as evidence that suggested no link. Overall, due to the very low quality of the evidence that raised high uncertainty, the Committee felt the inconclusive evidence does not allow them to draw firm conclusion on which procedure has a significant link to bacteraemia. Regarding the studies you have provided, please see below: • Strom BL et al. Ann Intern Med 1998; 12: 761–9 (already included in this update, please see section 2.3.2 of the addendum). • Van der Meer JT et al. Arch Intern Med 1992; 152: 1869–73. (excluded because it is a case series study). • Lacassin F et al. Europ Heart J 1995; 16: 1968-74. (already included in this update, please see section 2.3.2 of the addendum). • Horstkotte D et al. Europ Heart J 1987; 8 (Suppl J): 379-81. (already included in this update, please see section 2.6.2 in the addendum). • Van der Meer JTM et al. Lancet 1992; 339: 135-9. (already included in this update, please see section 2.6.2 in the addendum). • Starkbaum M et al. Yale J Biol Med 1977; 50: 49–58. (excluded because it is a case reports study).
British Heart Valve Society	NICE	81	General	Although there is no randomised trial of antibiotic prophylaxis, a number of observational clinical studies suggest a benefit in high-risk groups, for example: Duval X et al. Clin Infectious Dis 2006; 42: e102-7; Horstkotte D et al. Europ Heart J 1987; 8 (Suppl J): 379-81.	Thank you for your comment. As you say, there were no RCTs and evidence was limited to 3 observational studies, all showing inconclusive findings. Please refer to table 155 and section 2.6.5 of the addendum for the committee's interpretation of this evidence. Thank you for providing us with references of potential studies. The Horskotte 1987 study was included in this update (table 155). The Duval study 2006 did not meet the study design criteria for review question 6 (cross sectional study with no comparison group) and was therefore not included.
British Heart Valve Society	NICE	81	General	In the absence of an RCT in humans it is reasonable scientifically and clinically to consider the animal data. There is a substantial body of work showing that a single dose of amoxicillin can blunt bacteraemia and prevent streptococcal endocarditis. Example studies include : Sakka. J Antimicrob Chemoth 2005; 56:1160-2; Glauser M et al. J Infect Dis 1983;147:568–75; Berney Pet al. J Infect Dis 1990;161:281-5; Dall. J Infect Dis 1990;161:1221-4; James. J Antimicrob Chemoth 1987;20:883-5; Longman. J Antimicrob Chemoth 1987 ;20:557-62; Tsitsaka. Antimicrob Agents Chemoth 2000;44:1754-6; Rouse. Antimicrob Agents Chemoth 1997;41:1673-6; Vermot. Antimicrob Agents Chemoth 1996;40:809-11; Fluckiger. Antimicrob Agents Chemoth 1994;38:2846-9; Pujadon. Antimicrob Agents Chemoth 1986;29:909-12; Malinverni. Circulation 1988;77:182-7.	Thank you for your comment. In the absence of RCT evidence, NICE considers comparative observational studies as the next best available source of evidence. NICE does not consider animal studies to be an appropriate source of evidence due to the lack of applicability to the human population.
British Heart Valve Society	NICE	91	General	This section states that 'the committee noted the lack of data on side-effects including anaphylaxis'. No detailed examination of evidence was offered. In fact estimates of harm used by NICE for the 2008 guidelines were based mainly on data published in the 1960s using parenteral rather than oral penicillin often for treating syphilis. Recent UK Yellow Card return data shows that fatal anaphylaxis is exceedingly rare (Lee P, Shanson D. J Antimicrob Chemother 2007;60:1172-3). There have there been no reports in the world literature of fatal anaphylaxis after oral amoxicillin prophylaxis for IE. A new study (Thornhill MH et al. J Antimicrob Chemo. 2015 doi:10.1093/jac/dkv115) found no fatal and only 22.62 non-fatal reactions per million prescriptions of oral amoxicillin for dental prophylaxis. NICE should correct this error.	Thank you for your comments. Neither of the studies mentioned here were RCTs or comparative observational studies and were therefore outside of our inclusion criteria. Although anaphylaxis may be rare, the committee concluded that in the absence of clear evidence on efficacy, overuse of antibiotics should be avoided to prevent community resistance.
British Heart	NICE	93	General	The lay members raised the issue of conflicting information being given by different healthcare professionals. It would also be worth referring to the confusion engendered by	Thank you for your comment. As noted in the LETR section of this guideline, the incidence of IE continues to increase also in the US and European countries, where unlike the UK, antibiotic prophylaxis is offered

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Valve Society				the NICE guidelines deviating from those from the US, Australia and Europe.	to certain risk groups. . Therefore, further taking into account the following reasons, the committee felt the deviation from other guidelines was acceptable: - very limited evidence from 3 observational studies all inconclusive as to whether prophylaxis prevents the development of IE - evidence did not cover other effects of antibiotic usage including resistance - reasons for the increased incidence of IE (including within the low risk population) indicated by the study (Dayer et al 2014) that triggered this update are still unknown. It also appears that mortality from IE has not increased in parallel with incidence. - the postulation of the change in slope after the introduction of the NICE guidance was based on the assumption that there were 2 linear trends before and after 2008. There is no rationale provided in the Dayer study to justify such an assumption. Sensitivity analyses using different assumptions were conducted by the critique author and it demonstrated that if different assumptions were used, different results were likely to be produced
British Society for Antimicrobial Chemotherapy	General	General	General	Welcome the clarity of the advice and explanation of difficulties with the recent Lancet paper	Thank you for your comment.
British Society for Antimicrobial Chemotherapy	General	General	General	There is a flux of medical and dental professionals in to and out of the UK. For example, some 28% of general practice dentists were trained outside of the UK. So my further thought is that, given the very different position re prophylaxis for cardiac patients in England compared to the rest of the world, NICE needs to regularly promulgate its messages and rationale for their stated position on a regular basis.	Thank you for your comments and concerns being raised. We will inform all stakeholders when this update is due to be published, and also to pass this message on to NICE implementation team to ensure recommendations will be implemented accordingly.
British Society for Antimicrobial Chemotherapy	General	General	General	The potential impact of dental prophyalxis on resistance and CDI- both are significant contributory factors. Due to lack of good surveillance we have not been able to gauge an impact on this of reducing prescribing on this. While this may not represent an immediate threat to the patient, it certainly will in the medium to long term- the resistant pathogens that will cause endocarditis will also probably lead to poorer outcomes. By continuing to prescribe amoxil unnecessarily we may drive resistance, particularly amongst alpha-haemolytic streptococci, Prevotella and perhaps even CNS further.	Thank you for your comment. As noted in the LETR, evidence on antibiotic resistance was lacking but the committee noted the impact of this and that if people at risk of IE developed resistance due to antibiotic prophylaxis overuse, when they do contract IE in the future, antibiotics will become less effective for treating the actual infection and patients will have poorer outcomes.
British Society for Antimicrobial Chemotherapy	Short	General	General	NICE states there is a lack of evidence linking dental procedures and endocarditis as well as no evidence either for or against the efficacy of antibiotic prophylaxis for preventing endocarditis.However , a number of studies suggest a link between invasive dental procedures ,such as extraction , and endocarditis,especially involving high risk cardiac patients (Starkbaum M ,Durack D ,Beeson P The incubation period of subacute bacterial endocarditis .Yale J Biol Med 1977 ,50 ,49-58) –this paper emphasised extractions and the onset of endocarditis within 2 to 4 weeks after the procedure., analysing many case reports. The papers by Horstkotte and also Duval ,included in the NICE discussions ,also suggested an association between prophylaxis and a reduced incidence of endocarditis in higher risk cardiac patients.	Thank you for your comments. Based on NICE's rigorous methodology, the Committee did not just focus on those studies that suggested an association between extraction and bacteraemia, the Committee also considered other studies that suggested there isn't an association (please see Table 6 in the Addendum) and then made a decision based on all the evidence according to the quality assessment as well. Please also see Table 7, 8 and 9 in the Addendum that also included studies reported different results compared to the Horstkotte and the Duval study. Further in section 2.4.4 Evidence to recommendations section of the Addendum, it documented the Committee's discussion and interpretation of the evidence, on both evidence that suggested an association as well as evidence that suggested no association. Overall, due to the very low quality of the evidence that raised high uncertainty, the Committee felt the inconclusive evidence does not allow them to draw firm conclusion on which procedure has significant association to bacteraemia.
British Society for	Short	General	General	A substantial body of stringent animal model work shows that a single large dose of amoxicillin can prevent streptococcal endocarditis (Glauser M ,et al Successful single-dose amoxicillin prophylaxis against experimental streptococcal endocarditis : evidence for	Thank you for your comment. In the absence of RCT evidence, NICE considers comparative observational studies as the next best available source of evidence. NICE does not consider animal studies to be an appropriate source of evidence due to lack of applicability to the human population.

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Antimicrobial Chemotherapy				two mechanisms of protection . J Infect Dis 1983 ,147 ,568-75 ; and Berney P and Francioli P , Successful prophylaxis of experimental streptococcal endocarditis with single-dose amoxicillin administered after bacterial challenge J Infect Dis 1990, 161 , 281-5	
British Society for Antimicrobial Chemotherapy	Short	General	General	While recommending that patients maintain good oral health, no detailed advice has been given on what standards should be maintained and how they should be achieved. Also it would be useful for NICE to recommend free dental care for patients with susceptible cardiac lesions.	Thank you for your comment. The Committee discussed the issue of dental standards and agreed that it is not possible to have a single definition for good oral health because there is still a clear gap in the knowledge of the variations in individuals' and communities' perceptions of oral health, and that a person's oral health may be subject to their own personal values and attitudes It is outside the remit of NICE to make any recommendation regarding free dental care.
British Society for Antimicrobial Chemotherapy	Short	74-79	General	The idea that toothbrushing results in the same level of bacteraemia as extractions was not supported by the studies especially when endocarditis causing bacteria were investigated in patients not receiving amoxicillin. Oral amoxicillin prophylaxis greatly reduced the incidence of streptococcal bacteraemia during the first 5 min after extraction,compared to controls, in virtually all of the studies . The first paper in the literature on high dose oral amoxicillin was not included by NICE(Shanson D C , Cannon P , Wilks M ,Amoxycillin compared with penicillin V fr the prophylaxis of dental bacteraemia Journal of Antimicrob Chemother ,1978 ,4 ,431-436 .)This paper showed post-extraction streptococcal bacteraemic rates for a control group , 35 %,oral penicillin V 12 % , and amoxicillin 5 %and the comparisons were valid , even though blood cultures were not collected before the intervention. This paper was also the subject of an editorial "Preventing endocarditis " Br Med J , 1979 ,1 ,290-291	Thank you for your comment. Yes, the evidence on levels of bacteraemia associated with toothbrushing was inconsistent with some showing similar levels to extraction and others not. The Shanson 1978 study has now been added but does not change the overall conclusion showing inconsistent evidence for the use of antibiotics to reduce levels of bacteraemia post procedure.
British Society for Antimicrobial Chemotherapy	Short	67 - 69	6-13, 30, General.	Statements suggest no consistent association of bacteraemia with extractions but some evidence of this with ultrasonic scaling in adults. In fact the papers reviewed do show consistent substantial bacteraemia rates with extractions in the control/placebo arms of many studies reviewed by NICE. All the studies on repeated blood draws showed the highest bacteraemic rates during the first 5 to 10 min after an invasive dental procedure and some studies did show the duration of bacteraemia was less than 60 min. The conclusion of the section that it is very difficult to establish the association between procedures and bacteraemia is questionable since many studies confirm substantial viridans streptococcal bacteraemia rates during the first few minutes after dental extraction..The finding of positive blood cultures before an intervention, in some studies, should not automatically be interpreted as spontaneous bacteraemia as skin organisma were often isolated and contaminants associated with intravascular lines cannot be excluded ---viridans streptococci were infrequently observed.	Thank you for your comments. Based on NICE's rigorous methodology, the Committee focused on all studies that met the pre-specified inclusion criteria regardless of whether the underlying result of the study suggested an association or not between the extraction and bacteraemia. (please see Table 6 in the Addendum). The committee then made a decision based on all the evidence according to the quality assessment as well. Regarding extraction and scaling (Addendum table 6), 2 studies suggested there was no significant bacteraemia while 1 study suggested there was significant bacteraemia. For scaling, 2 studies suggested significant bacteraemia up to 3 minutes, whilst 2 other studies suggested there was no significant bacteraemia up to 10 minutes. This inconsistency, together with the high risk of bias of all the evidence, informed the Committee's ultimate decision. , The Committee also had concerns regarding the duration of these studies: for adults, most studies only had one repeated blood test less than 20 minutes after the procedures, with mixed results. 2 studies (with more than 1 repeated blood tests, up to 60 minutes after the dental procedure) actually showed bacteraemia tailed off over 60 minutes of timeframe. For children, all studies only had 1 repeated blood test 30 seconds after the dental procedure, and the populations of all these studies were already bacteraemic before the dental procedures. The Committee felt the duration and number of repeated blood tests cannot support the hypothesis that dental procedures caused significant bacteraemia, and that bacteraemia in some of these studies may be spontaneous or transient.
British Society for Antimicrobial Chemot	Short	8	143	As a general practice dentist, it is frustrating that 'Clear and consistent information' is not being provided to all patients – I still have 'at risk' patients expecting prophylactic antibiotics for scaling and polishing having been told by their cardiologist that it is essential. When I called the microbiology department of the hospital to ask why their cardiologist was still giving this advice, they said that it was not for all patients but that in some cases he used his discretion and they had not problems with this. If this is the	Thank you for your comments and concerns being raised. We will inform all stakeholders when this update is due to be published, and also to pass this message on to NICE implementation team to ensure recommendations will be implemented accordingly. There will also be an 'information for patients and the public' version of the guideline, outlining the key messages in lay terms.

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herapy				response that I get as a dentist and microbiologist, image how confused the patients must be. N.B. I also still get letters from the local orthopaedic surgeon in relation to total joint replacement patients. A recent one told me in very clear terms to give iv flucloxacillin before any treatment which might cause a bacteraemia. It would be helpful if there were a third party to which patients could turn in order to get advice when trying to get definitive advice about whether or not they should consent to treatment without antibiotic prophylaxis. After all, declining treatment (e.g. to treat bleeding gums) would likely put them at higher risk from daily activities such as eating and tooth brushing than accepting a simple treatment for prevention.	
British Society for Antimicrobial Chemotherapy	Short	8	148	'The importance of maintaining good oral health' is a key message – and one which dentists are clearly able to advised patients on. However, there is still a significant proportion of the population who do not have access to a regular dentist – whether that be due to short fall in local provision of general practice dentistry or lack of available cash/different priorities for the patient. Since the original guidance was published in 2008, the Department of Health has issued 'Delivering Better Oral Health' guidance to dentists about how they should be offering preventative advice and treatment for all dental patients. The issue is that there is no accompanying patient focused literature. It would be really helpful for cardiologist and dentists alike if a 'plain English' leaflet aimed at the general public was produced and provided to all 'at risk' patients. Such a leaflet would actually be useful for all of the population – or it might be decided to produce a specific leaflet aimed at the population at risk of IE to include details of: what good oral health looks/feels like and how to maintain it at home, the importance of regular dental check ups and of seeking dental treatment promptly for dental infection, what to do in the event IE warning signs/symptoms are experienced and the rationale behind prophylaxis no longer being recommended. It would be particularly helpful if these leaflets were branded (maybe jointly branded Department of Health, General Dental Council, British Heart Foundation, British Society for Antimicrobial Chemotherapy etc) to make it clear to patients that this is an agreed position across England which has gravitas and gives patients some confidence in the advice that they are being given.	Thank you for your comment. The Committee discussed this issue and agreed that it is not possible to have a single definition for good oral health because there is still a clear gap in the knowledge of the variations in individuals' and communities' perceptions of oral health, and that a person's oral health may be subject to their own personal values and attitudes. We will also pass this message on to the NICE implementation team to support implementation of the recommendations.
British Society for Antimicrobial Chemotherapy	Short	8	148	It would be useful to know what treatments are particularly helpful (and which ones particularly high risk) for patients at risk of infective endocarditis. Whilst I could hazard a guess that those with advanced periodontal disease are more at risk than those with good periodontal health, I am not aware of any research which has proven this. Similarly do antibiotics before during and/or after treatment help to reduce the risk? It would be useful, therefore, for one of the research recommendations to be about investigating which dental conditions and treatments are particularly associated with cases of infective endocarditis. Thornhill et al characterise this in a recent BDJ opinion piece as 'what are the goals of dental treatment to maintain good oral health? And how should these be achieved?'	Thank you for your comments. Due to insufficient evidence, the Committee felt that it is not possible to further quantify which dental procedures or which dental diseases are associated with the risk of IE. Based on the evidence, it is unclear whether antibiotics before during and/or after treatment would reduce risk of IE, therefore antibiotic prophylaxis was not recommended either before, during or after treatment. As evidence looking at antibiotic prophylaxis was limited, the committee highlighted the need for further research via a long term follow up RCT – please refer to research recommendation 1.3.2 for further details. Regarding good oral health, the Committee discussed this issue and agreed that it is not possible to have a single definition for good oral health because there is still a clear gap in the knowledge of the variations in individuals' and communities' perceptions of oral health, and that a person's oral health may be subject to their own personal values and attitudes. We will also pass this message on to the NICE implementation team to support implementation of the recommendations.
British Society for Antimicrobial Chemotherapy	Short	10	185-6	Completely agree with the value of a national register – which would, among other things, help identify the situations, conditions and treatments in the above point which impact positively and negatively on the incidence of IE. Wording of this point has not changed since 2008, yet we are in a very different position now, as a national IE database (although not a register) has been set up (NEEMO). To reflect this, I suggest changing the wording in line 185 from 'would be facilitated by the availability' to 'should be facilitated by the development' and in line 186 from 'could' to 'should'. This would enable extension of the	Thank you for your comments. This research recommendation has been reworded to reflect the need for an 'anonymised' database following the discussion of the Committee – please refer to section 1.3.1 for further details.

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				scope of NEEMO to become a national register – which in turn would enable collection of data relating to all cases of IE in England (and possibly extended to Wales? Scotland? And NI?) rather than just those who have consented to their information being retained for research purposes. And would get us away from the position that we are currently in where the only data available is from an NHS source relating to proxy data and temporal associations. The UK is in a unique position internationally – and NICE has given us this unique position. By our guidance being no prophylaxis for IE in England (and Wales) – we can gather information and data about what happens with and without prophylaxis in a way that it is not ethically possible in other countries. This is the trial recommended in research recommendation 2.3 and a national register would enable collection of that data, together with much more detail about conditions and treatments which are associated with the incidence and causes of infective endocarditis.	
British Society for Antimicrobial Chemotherapy	Short	87	3-4	A cost effective policy is suggested for those with high risk cardiac lesions in the 2008 guideline. NICE should consider revision of the guideline to offer prophylaxis to those with high risk lesions undergoing invasive dental procedures. NICE sated it would be difficult to have such a policy but most cardiologists disagree –the high risk lesions are easily defined. It seems likely that most of the current amoxicillin prophylaxis is for high risk cardiac patients . Many cardiologists do not follow the NICE 2008 guideline for these patients (Dayer M ,Chambers JB, Prendergast B ,Sandoe J ,Thornhill MH .NICE guidance on antibiotic prophylaxis to prevent infective endocarditis: a survey of clinicians attitudes Q J Med 2013, 106(3) :237-43	Thank you for your comment. However the committee concluded that antibiotic prophylaxis is not recommended for dental, upper and lower GI tract and respiratory tract, genitourinary procedures because there is very limited evidence from 3 observational studies, all inconclusive as to whether prophylaxis prevents the development of IE. The reasons for the increased incidence of IE (including within the low risk population) indicated by the study (Dayer et al 2014) that triggered this update are still unknown. It also appears that mortality from IE has not increased in parallel with incidence. The evidence for the association between dental procedures and the development of IE was inconclusive and furthermore, the incidence of IE continues to increase also in the US and European studies, where more conservative antibiotic prophylaxis guidelines are in place compared to the UK. We are unsure what the stakeholder is referring to in regards to the statement that "a cost effective policy is suggested for those with high risk cardiac lesions in the 2008 guideline"; neither the 2008 guideline nor the update recommended antibiotic prophylaxis in these patients. This decision related to the following cost effectiveness evidence which identified three economic studies.. The first was a US study comparing 7 prophylactic strategies against no prophylaxis (Agha et al. 2005). The second was the model developed for the 2008 NICE guideline comparing 8 pre-dental antibiotic prophylaxis regimens with no prophylaxis. The third was an unpublished study that incorporated the data on the increased incidence of IE (Franklin et al.). The base case analysis of all 3 studies found that antibiotic prophylaxis was not cost effective. Further details on these studies can be found in the Addendum in section 2.6 and appendices I to P. In regards to people that may be considered at a high risk of developing IE, both the 2008 NICE model and the unpublished 2015 update by the University of Sheffield (Franklin et al.) contain a range of scenarios in which prophylaxis is highly cost effective and range of scenarios in which it is highly cost ineffective and dominated (more costly with a reduction in health benefits). Overall, the Committee were cautious in their interpretation of the economic evidence because they determined that the clinical evidence reviews had not shown that dental procedures increase the risk of infective endocarditis nor that antibiotic prophylaxis is able to reduce that risk.
British Society for Antimicrobial Chemotherapy	Short	87	15	Anaphylaxis associated with clindamycin is rare –the main risk is pseudomembranous colitis, as discussed in the above paper by Thornhill under comment 5. Erythromycin may be a suitable alternative	Thank you for your comment. All recommendations from the guideline are based on available evidence. The Committee did not come across data on anaphylaxis or pseudomembraneous colitis based on our inclusion criteria of RCTs or comparative observational studies – the Thornhill study mentioned was not of either of these study designs and therefore outside the inclusion criteria agreed by the committee.

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British Society for Antimicrobial Chemotherapy	Short	91	General	In the discussion of Trade-off between benefits and harms the committee noted the lack of data on anaphylaxis associated with antibiotic prophylaxis .However, recent UK yellow card return data suggest that fatal anaphylaxis is exceedingly rare (Lee P , Shanson D .Results of a UK survey of fatal anaphylaxis after oral amoxicillin .J Antimicrob Chemother 2007, 60 ,1172-3). There have been no reports in the world literature of fatal anaphylaxis after oral amoxicillin prophylaxis for infective endocarditis. A new study found that the incidence of adverse drug reaction following Amoxicillin Prophylaxis was extremely low (0 fatal and only 22.62 non-fatal reactions per million prescriptions) : Thornhill MH ,Dayer MJ ,Prendergast B, Baddour LM ,Jones S , Lockhart PB .Incidence and nature of adverse reactions to antibiotics used as endocarditis prophylaxis . J Antimicrob Chemo.2015 doi:10.1093/jac/dkv115 .Oral amoxicillin is very safe in individuals who do not have a history of penicillin allergy.	Thank you for your comments. Neither of the studies mentioned here were RCTs or comparative observational studies (e.g. the studies mentioned here are non-comparative studies such as surveys) and therefore outside of our inclusion criteria. These studies are more subject to bias given their retrospective and non-comparative nature.
Department of Health	General	General	General	No comments	Thank you.
Guy's and St. Thomas' NHS Foundation Trust	NICE	General	General	We are concerned that important studies have been misquoted or misinterpreted. This has led to serious errors in conclusions drawn by NICE in many areas particularly the safety of oral antibiotic prophylaxis, the relative risk of endocarditis in prosthetic heart valves and the effect of antibiotics on reducing bacteraemia. We suggest that a thorough new review of all the evidence is undertaken by clinical members of the panel who would be able to appreciate the clinical significance of the studies.	Thank you for your comments. The systematic reviews are undertaken by the technical team at NICE along with clinical input from the topic expert members as required. The evidence has been discussed and interpreted in detail by the Committee which is made up of clinicians, methodologists and clinical experts. Please see the Addendum for a full list of the Committee members.
Guy's and St. Thomas' NHS Foundation Trust	NICE	General	General	It is likely to be cost-effective to confine antibiotic prophylaxis to people with high-risk cardiac lesions having invasive dental procedures. There is published evidence to support this and a new study in progress also supports this	We note the stakeholder has not provided the details of any studies or specific details of the scenarios where they believe antibiotic prophylaxis to be cost effective. Three economic studies were considered in this guideline update. The first was a US study comparing 7 prophylactic strategies against no prophylaxis (Agha et al. 2005). The second was the model developed for the 2008 NICE guideline comparing 8 pre-dental antibiotic prophylaxis regimens with no prophylaxis. The third was an unpublished study that incorporated the data on the increased incidence of IE (Franklin et al.). The base case analysis of all 3 studies found that antibiotic prophylaxis was not cost effective. Further details on these studies can be found in the Addendum in section 2.6 and appendices I to P. In regards to the unpublished economic analysis conducted by the University of Sheffield (Franklin et al.), the first draft of a full detailed report was considered by the Committee. The results of the study were highly sensitive to the risk of developing infective endocarditis following a dental procedure, the efficacy of antibiotic prophylaxis to reduce this risk, the cost of amoxicillin and clindamycin and the rate of fatal adverse events. Variation of these key parameters resulted in incremental cost-effectiveness ratios for antibiotic prophylaxis compared with no prophylaxis ranging from highly cost effective to highly cost ineffective and dominated (more costly and a reduction in health benefits). The incremental cost-effectiveness ratio increased to £53,000 per QALY using less optimistic estimates of prophylactic efficacy. Both amoxicillin and clindamycin are more cost effective if the baseline risk is higher. Using a baseline risk for patients with a prosthetic heart valve (based on estimates used in previous economic studies) resulted in incremental cost-effectiveness ratios of £6,487 and £13,182 for amoxicillin and clindamycin respectively. However, the Committee were cautious in their interpretation of the economic evidence because they determined that the clinical evidence reviews had not shown that dental procedures increase the risk of infective endocarditis nor that antibiotic prophylaxis is able to reduce that risk.
Guy's and St. Thomas' NHS Foundation Trust	NICE	General	General	All guidelines agree that the maintenance of good oral health is important for the prevention of endocarditis. We suggest that NICE issues comprehensive guidelines on this subject.	Thank you for your comment. The Committee discussed this issue and agreed that it is not possible to have a single definition for good oral health because there is still a clear gap in the knowledge of the variations in individuals' and communities' perceptions of oral health, and that a person's oral health may be subject to their own personal values and attitudes. We will also pass this message on to the NICE implementation team to support implementation of the recommendations.
Guy's	NICE	Gen	Gen	We suggest that NICE revises its guidelines to allow antibiotic prophylaxis for the small	Thank you for your comment. However the committee concluded that antibiotic prophylaxis is not

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and St. Thomas' NHS Foundation Trust		eral	eral	group at high-risk of endocarditis and who have a poor prognosis in the presence of endocarditis and are having high-risk dental procedures. This would be in line with our interpretation of the evidence. It would also bring NICE in line with all other national guidelines and with the practice of most cardiologists and cardiac surgeons in the UK. This would eliminate the uncertainty that currently exists where advice from the dental surgeon and cardiologist may differ.	recommended for dental, upper and lower GI tract and respiratory tract, genitourinary procedures because there is very limited evidence from 3 observational studies, all inconclusive as to whether prophylaxis prevents the development of IE. Apart from clinical evidence, health economic evidence was also considered in this update. Three economic studies were considered in this guideline update. The first was a US study comparing 7 prophylactic strategies against no prophylaxis (Agha et al. 2005). The second was the model developed for the 2008 NICE guideline comparing 8 pre-dental antibiotic prophylaxis regimens with no prophylaxis. The third was an unpublished study that incorporated the data on the increased incidence of IE (Franklin et al.). The base case analysis of all 3 studies found that antibiotic prophylaxis was not cost effective. Further details on these studies can be found in the Addendum in section 2.6 and appendices I to P. In regards to people that may be considered at a high risk of developing IE, both the 2008 NICE model and the unpublished 2015 update by the University of Sheffield (Franklin et al.) contain a range of scenarios in which prophylaxis is highly cost effective and range of scenarios in which it is highly cost ineffective and dominated (more costly with a reduction in health benefits). Overall, the Committee were cautious in their interpretation of the economic evidence because they determined that the clinical evidence reviews had not shown that dental procedures increase the risk of infective endocarditis nor that antibiotic prophylaxis is able to reduce that risk.
Guy's and St. Thomas' NHS Foundation Trust	NICE	Gen eral	Gen eral	The advice about when to suspect endocarditis is likely to alarm many people with simple coryzal illnesses and other causes of fever. We suggest that more detailed advice is given.	Thank you for your comments. All recommendations from the guideline are based on available evidence. The Committee does not feel that more detailed advice can be given with limited available evidence. We appreciate that your concern that it may raise unnecessary alarm, but equally we believe patients have the right to be informed as soon as possible whenever there is a suspicion.
Guy's and St. Thomas' NHS Foundation Trust	NICE	Gen eral	Gen eral	NICE should also consider the wider list of dental procedures that are known to be high-risk in terms of producing operative bacteraemias. This is well-documented. Dental extractions are one of the procedure types implicated here but there are a number of significant and known others that should be considered by NICE and included.	Thank you for your comment. The dental procedures searched for were defined by the original guideline and agreed by the topic experts. Please see Appendix D (page 145 onwards) of the full Addendum for the search strategies and search terms used. However, only those studies looking at dental procedures in relation to bacteraemia/IE met the inclusion criteria for this guideline.
Guy's and St. Thomas' NHS Foundation Trust	NICE	22-35	Gen eral	The discussion of prosthetic valve endocarditis appears insufficiently clinically informed. There is a relatively high incidence in the first year after implantation caused predominantly by Staphylococcus aureus and Coagulase Negative Staphylococci (CNS). Thereafter oral organisms are more likely to occur. It may be possible to sterilise prosthetic valves infected by oral organisms but endocarditis caused by S aureus or CNS almost always needs surgery.	Sorry but we cannot see such a discussion on p22 or P35. The introductory paragraph and evidence statement on p32 summarises the findings from the evidence review. The evidence cited for prosthetic valves as a risk factor for IE was discussed by the Committee who acknowledged there is an inconsistency between the evidence found and what is widely embedded in practice (i.e. that prosthetic valves increase the risk of IE). There were no other studies found in the review, nor any studies subsequently identified by topic experts or stakeholders which demonstrate this increased risk when compared to the general population. To take account for this, the evidence statement and the LETR table have been amended to reflect the Committee's views on this inconsistency. In addition, there has been an amendment to one effect estimate for the risk of mortality in people with prosthetic valves who get IE. This has led to a rewording of the overall evidence statement.
Guy's and St. Thomas' NHS Foundation Trust	NICE	11	1.2	Implanted electronic devices should be included on the list of high-risk cardiac conditions. A review and guidance on management is imminently being published in the Lancet (Sandoe et al. Guidelines for the diagnosis, prevention and management of Implantable Cardiac Electronic Device Infection.Report of a joint working party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organisation), British Heart Rhythm Association (BHRA), British Cardiovascular Society (BCS), British Heart Valve	Thank you for your comments. People with implanted electronic devices are outside the scope of this guideline. We acknowledge your concerns and consider this specific population warrants a separate guideline. We recommend you to propose a new guideline for this population through the Department of Health so that a new guideline could be developed by NICE.

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				Society (BHVS) and British Society for Echocardiography (BSE).	
Guy's and St. Thomas' NHS Foundation Trust	NICE	14	general	A recent study showed a statistically significant increase in the incidence of Streptococcal endocarditis following the introduction of the 2007 AHA guidelines. This should be included. The reference is Pant et al. JACC 2015;65:2070-6	Thank you for alerting us with this newly published study (Pant 2015). This has now been included in the Overview of epidemiology section of the Addendum.
Guy's and St. Thomas' NHS Foundation Trust	NICE	21	6	Why were data abstracted from the graphs rather than the raw data obtained from the authors? The use of the equivocal statement 'multiple change points seem possible' in rejecting the study of Dayer et al implies bias in this critique.	Thank you for your comments. Raw data provided by the online Appendices of the Dayer paper was used to conduct sensitivity analyses in critique.
Guy's and St. Thomas' NHS Foundation Trust	NICE	32	33 34	The statement that people with prosthetic valve do not appear to be at higher risk of endocarditis than those without prosthetic valves is incorrect. The incidence of prosthetic valve endocarditis beyond the first year is 0.3-0.4% in most published series which far exceeds the population estimate of up to 10 cases per 100,000 p.a. or 0.01%. NICE considered only two studies. The first (Alagna 2014) investigated the recurrence rate in a total of only 447 prosthetic valves and 1427 native valves with an index episode of endocarditis using an International registry. The second (Ammar 2013) was a small case-controlled study from Egypt which included only 49 patients with prosthetic valves. The aim was to investigate potential culprit procedures causing endocarditis and not the relative risk of endocarditis in prosthetic compared with native valves. Neither of these two studies addresses the primary question of how often endocarditis occurs in patients with prosthetic valves and the second study addresses a completely separate question. NICE did not reference any of the thousands of series investigating complication rates after implantation of prosthetic valves which cumulatively involve population sizes in the many thousands.	The evidence statement provided reflects the evidence reviewed in this update. Two studies were found which met the protocol criteria based on the search strategy described. This point was discussed by the Committee who acknowledged there is an inconsistency between the evidence found and what is widely embedded in practice (i.e. that prosthetic valves increase the risk of IE). There were no other studies found in the review, nor any studies subsequently identified by topic experts or stakeholders which demonstrate this increased risk when compared to the general population. To take account for this, the evidence statement and the LETR table have been amended to reflect the Committee's views on this inconsistency. In the hierarchy of evidence, case series are more at risk of bias compared to other study designs due the lack of a comparison group and therefore generalisability. The Topic experts therefore pre-specified that studies of this design would not be included for this review question.
Guy's and St. Thomas' NHS Foundation Trust	NICE	33	25 29	The conclusion that mortality from endocarditis is only inconsistently shown to be higher in prosthetic valves appears to be based on erroneous interpretation of some of the studies. For example the Wang (2007) paper in Table 3 is wrongly stated as describing 2670 adults with prosthetic endocarditis. In fact there were 556 with prosthetic endocarditis and 1895 with native valve endocarditis. The mortality was 22.8% with prosthetic endocarditis and 16.4% (P<0.001) with native valve endocarditis. Despite this a relative risk of death of 0.74 (0.49-1.12) is given within the effects column. The implication within the context of the Table is that this describes the effect of prosthetic valves on mortality. However this figure in fact refers to the effect of prior endocarditis within the 556 patients with prosthetic valve endocarditis.	Thank you for your comment. The study by Wang et al (2007) was not actually included in this analysis (table 150 page 404). Thank you for pointing out this error in Table 3. This has been updated. The evidence table and result summary table has also been updated. The OR for mortality between PVE and NVE has been calculated by the reviewer as 1.51 (1.2-1.91). Adding this to the summary results means that there are now 5 studies (low risk of bias) suggesting an increase in in-hospital death in PVE and 4 studies (3 high risk and 1 low risk of bias) indicating no difference. The evidence statements have been updated to reflect this amendment. Meta-analysis of these studies is inappropriate due to substantial heterogeneity in population baseline characteristics, variables being investigated in the studies and variables being adjusted in the studies.
Guy's and St. Thomas' NHS Foundation Trust	NICE	67	General	The studies suggesting an inconstant link between dental procedures and endocarditis tend not to analyse high-risk procedures like dental extraction separate from all other procedures. In considering all procedures together it is expected that the effect of high-risk procedures will be diluted. Studies showing a link with specific procedures include: Strom BL et al. Ann Intern Med 1998; 12: 761–9; Van der Meer JT et al. Arch Intern Med 1992; 152: 1869–73; Lacassin F et al. Europ Heart J 1995; 16: 1968-74; Horstkotte D et al. Europ Heart J 1987; 8 (Suppl J): 379-81; Van der Meer JTM et al. Lancet 1992; 339: 135-9; Starkbaum M et al. Yale J Biol Med 1977; 50: 49–58.	Thank you for your comments. In the Addendum, section 2.4.3, we have separate statements directed to different dental procedures, we did not group all procedure together. Further in section 2.4.4 Evidence to recommendations section of the Addendum, it documented the Committee's discussion and interpretation of the evidence, on both evidence that suggested a link as well as evidence that suggested no link. Overall, due to the very low quality of the evidence that raised high uncertainty, the Committee felt the inconclusive evidence does not allow them to draw firm conclusion on which procedure has significant link to bacteraemia.
Guy's and St.	NICE	81	General	Although there is no randomised trial of antibiotic prophylaxis, a number of observational clinical studies suggest a benefit in high-risk groups, for example: Duval X et al. Clin	Thank you for your comment. As you say, there were no RCTs and evidence was limited to 3 observational studies, all of which found inconclusive findings. Please refer to table 155 and section 2.6.5

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Thomas' NHS Foundation Trust				Infectious Dis 2006; 42: e102-7; Horstkotte D et al. Europ Heart J 1987; 8 (Suppl J): 379-81.	of the addendum for the committee's interpretation of this evidence. Thank you for providing us with references of potential studies. The Horskotte 1987 study was included in this update (table 155). The Duval study 2006 did not meet the study design criteria for review question 6 and was therefore not included.
Guy's and St. Thomas' NHS Foundation Trust	NICE	81	General	In the absence of an RCT in humans it is reasonable scientifically and clinically to consider the animal data. There is a substantial body of work showing that a single dose of amoxicillin can blunt bascteraemia and prevent streptococcal endocarditis. Example studies include : Glauser M et al. J Infect Dis 1983; 147: 568–75; Berney Pet al. J Infect Dis 1990; 161: 281-5.	Thank you for your comment. In the absence of RCT evidence, NICE considers comparative observational studies as the next best available source of evidence. NICE does not consider animal studies to be an appropriate source of evidence due to the lack of applicability to the human population.
Guy's and St. Thomas' NHS Foundation Trust	NICE	91	General	This section states that 'the committee noted the lack of data on side-effects including anaphylaxis'. No detailed examination of evidence was offered. In fact estimates of harm used by NICE for the 2008 guidelines were based mainly on data published in the 1960s using parenteral rather than oral penicillin often for treating syphilis. Recent UK Yellow Card return data shows that fatal anaphylaxis is exceedingly rare (Lee P, Shanson D. J Antimicrob Chemother 2007;60:1172-3). There have there been no reports in the world literature of fatal anaphylaxis after oral amoxicillin prophylaxis for IE. A new study (Thornhill MH et al. J Antimicrob Chemo. 2015 doi:10.1093/jac/dkv115) found no fatal and only 22.62 non-fatal reactions per million prescriptions of oral amoxicillin for dental prophylaxis. NICE should correct this error.	Thank you for your comments. Neither of the studies mentioned here were RCTs or comparative observational studies and were therefore outside of our inclusion criteria. Although anaphylaxis may be rare, the committee concluded that in the absence of clear evidence on efficacy, overuse of antibiotics should be avoided to prevent community resistance.
Guy's and St. Thomas' NHS Foundation Trust	NICE	93	General	The lay members raised the issue of conflicting information being given by different healthcare professionals. It would also be worth referring to the confusion engendered by the NICE guidelines deviating from those from the US, Australia and Europe.	Thank you for your comment. As noted in the LETR section of this guideline, the incidence of IE continues to increase also in the US and European countries, where more conservative antibiotic prophylaxis guidelines are in place compared to the UK. Therefore, further taking into account the following reasons, the committee felt the deviation from other guidelines was acceptable: - very limited evidence from 3 observational studies all inconclusive as to whether prophylaxis prevents the development of IE - evidence did not cover other effects of antibiotic usage including resistance - reasons for the increased incidence of IE (including within the low risk population) indicated by the study (Dayer et al 2014) that triggered this update are still unknown. It also appears that mortality from IE has not increased in parallel with incidence. - the postulation of the change in slope after the introduction of the NICE guidance was based on the assumption that there were 2 linear trends before and after 2008. There is no rationale provided in the Dayer study to justify such an assumption. Sensitivity analyses using different assumptions were conducted by the critique author and it demonstrated that if different assumptions were used, different results were likely to be produced.
Healthcare Infection Society	Whole	general	general	NICE should review its guidelines to recommend antibiotic prophylaxis for patients with high risk cardiac lesions, such as those with prosthetic valves, and for those who have had previous endocarditis, especially when invasive dental procedures, such as extractions, are carried out.	Thank you for your comment. People with prior IE have been identified as high risk group based on current recommendation 1.1.1. However the committee concluded that antibiotic prophylaxis is not recommended for dental, upper and lower GI tract and respiratory tract, genitourinary procedures because there is very limited evidence from 3 observational studies, all inconclusive as to whether prophylaxis prevents the development of IE. The evidence for the association between dental procedures and the development of IE was inconclusive and furthermore, the incidence of IE continues to increase also in the US and European countries, where more conservative antibiotic prophylaxis guidelines are in place compared to the UK.
Healthcare Infection Society	Whole	general	general	The studies demonstrating increasing incidence of endocarditis have been examined and the impact of the NICE prophylaxis guidelines found to be insignificant in terms of increasing incidence. Data collected elsewhere have shown a welcome reduction in antibiotic usage. I agree that there is no need to alter the guidelines on the basis of the evidence presented.	Thank you for your comments.

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Healthcare Infection Society	Whole	67	general	There is suggestive evidence of a link between certain high risk dental procedures (such as extractions) and endocarditis in susceptible cardiac patients (Starkbaum M et al Yale J Biol Med, 1977, 50. 49-58; Duval X et al. Clin Infect Dis, 2006, 42: e102-7). This link is less apparent if all minor dental procedures, such as routine dental fillings, are examined rather than invasive dental procedures such as dental extractions and scaling.	Thank you for your comments. For evidence on dental extraction and scaling, please see Table 6 and 7 in the full Addendum. There is approximately equal number of studies on dental procedures (extraction or scaling) that suggested there was significant bacteraemia, as well as no significant bacteraemia. Therefore the Committee's conclusion is that there is inconsistent evidence to draw a firm conclusion. The Starkbaum (1977) study is a case reports study that does not meet the review protocol inclusion criteria. The Duval (2006) study is included in this update, please see Table 4 of the full Addendum, and also section 2.3.4 Evidence to recommendations section for Committee's discussion and interpretation of the evidence.
Healthcare Infection Society	Whole	81	general	Although there are no RCT data, because of the rarity of IE, there is suggestive clinical evidence that high dose amoxicillin prophylaxis is effective for preventing endocarditis in patients with higher risk cardiac lesions (Duval X et al. Clin Infect Dis 2006, 42: e102-7; Horskotte D et al. Eur Heart J, 1987, 8, (Suppl J), 379-81 It could be argued that NICE should not have produced endocarditis prophylaxis guidelines when there is a lack of RCT human data either to support or reject the idea that prophylaxis may occasionally prevent endocarditis. There is a lot of indirect evidence which suggests that antibiotic prophylaxis may reduce dental streptococcal bacteraemis and endocarditis. Stringent animal model data clearly show that single dose amoxicillin prophylaxis is effective in preventing streptococcal endocarditis. Glauser M etal. , J Infect Dis, 1983, 147, 568-750)	Thank you for your comments. Although RCT evidence is preferred, in cases of a lack of RCT evidence, NICE considers comparative observational studies. The evidence for antibiotic prophylaxis was limited to 3 observational studies all inconclusive as to whether prophylaxis prevents the development of IE. NICE does not consider animal studies to be an appropriate source of evidence due to the lack of applicability to the human population.
Healthcare Infection Society	Whole	91	general	Recent yellow card data shows that fatal anaphylaxis after oral amoxicillin is exceedingly rare (Lee P, Shanson D. J Antimicrob Chemother 2007, 60,1172-3). There have been no reports of fatal anaphylaxis after oral amoxicillin prophylaxis in the word literature. A new study found no fatal and only 22.62 non-fatal reactions per million prescriptions of oral amoxicillin for dental prophylaxis (Thornhill M et al; J Antimicrob Chemother 2015 doi:10.1093/ jac/dkv115). NICE should amend their statements about the risk of dying from oral amoxicillin anaphylaxis. This risk is far too low to be a factor which influences the decision about whether or not to give antibiotic prophylaxis. Oral amoxicillin is a safe prophylactic agent provided a patient is not known to be allergic to penicillin.	Thank you for your comments. Although anaphylaxis is rare, the committee concluded that in the absence of clear evidence on efficacy, overuse of antibiotics should be avoided to prevent community resistance. Please refer to section 2.6.5 on page 94 of the addendum (trade off between benefits and harms section) to see full discussion of the committee. Thank you for the references provided. These were however non-comparative studies (such as surveys for example) and therefore do not meet the inclusion criteria. These studies are more subject to bias given the retrospective and non-comparative nature.
Heart Research UK	General	General	General	We are concerned about the conclusions of a recent review of clinical guideline 64, "Prophylaxis against infective endocarditis". A recent study (1) suggests that the NICE guideline may not be safe. It analysed the incidence of infective endocarditis (IE) and antibiotic prophylaxis (AP) prescriptions for the 5 years following the introduction of the NICE guideline in March 2008. There was a highly significant fall in antibiotic prophylaxis to about 10% of pre-NICE levels and a statistically significant increase in the incidence of IE. By March 2013 there were about 35 extra cases of IE per month in England above the number expected from pre-NICE incidence rates. Change point analysis confirmed a very close time relationship between the fall in AP prescribing and the increase in IE incidence. A careful search found no other possible causes of the increase. NICE based its 2008 guidance partly on the lack of evidence for a link between dental procedures and IE. However a number of studies suggest such a link particularly in high-risk patients having high-risk procedures (2-7). In 2008 NICE considered that there was no evidence for antibiotic prophylaxis being effective. Although there is no randomised trial of antibiotic prophylaxis, a number of	Thank you for your comment. Although RCT evidence was lacking, the committee considered the next best available source of evidence from observational studies. The committee decided not to offer prophylaxis to this group for the following reasons: - reasons for the increased incidence of IE (including within the low risk population) indicated by the study (Dayer et al 2014) that triggered this update are still unknown. It also appears that mortality from IE has not increased in parallel with incidence. - the postulation of the change in slope after the introduction of the NICE guidance was based on the assumption that there were 2 linear trends before and after 2008. There are no rationales provided in the Dayer study to justify such assumption. Sensitivity analyses using different assumptions were conducted by the critique author and it demonstrated that if different assumptions were used, different results were likely to be produced. - very limited evidence from 3 observational studies all inconclusive as to whether prophylaxis prevents the development of IE - evidence did not cover other effects of antibiotic usage including resistance Furthermore the incidence of IE continues to increase also in the US and European countries, where more conservative antibiotic prophylaxis guidelines are in place compared to the UK. Thank you for providing us with a list of potential studies. Reference 1 was the study that triggered the

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				observational clinical studies suggest a benefit in high-risk groups (5,8). A substantial body of animal work shows that a single dose of amoxicillin can prevent streptococcal endocarditis (9,10). A further reason NICE decided not to recommend AP was that it was potentially dangerous based on a quoted risk of fatal anaphylaxis of approximately 20 per million doses. However this estimate was based mainly on data published in the 1960s using parenteral rather than oral penicillin often for treating syphilis. More recent UK Yellow Card return data suggest that fatal anaphylaxis is exceedingly rare (11). There have there been no reports in the world literature of fatal anaphylaxis after oral amoxicillin prophylaxis for IE. A new study (12) found that the incidence of adverse drug reaction following amoxicillin AP was extremely low (0 fatal and only 22.62 non-fatal reactions per million prescriptions). However reactions to clindamycin AP were higher than anticipated, suggesting an alternative AP regimen is need for those who are hypersensitive to penicillin. Other guideline committees around the world recommend the continued use of antibiotic prophylaxis in highest risk patients given that the risks of endocarditis in this group far outweighed the risk of an adverse drug reaction. NICE did not consider the option of restricted AP to those at high-risk as recommended by all other guideline committees. The recent studies included the entire population of England and, short of a randomised controlled trial, are the best evidence we are likely to get on the effects of antibiotic prophylaxis for endocarditis. Although desperately needed, funding for a randomised controlled trial in this area seems unlikely. The NICE requirement for randomised controlled trial evidence to revoke previous guidance will put thousands of people at risk of developing endocarditis and cause hundreds of unnecessary deaths. Moreover, this decision is already causing huge concern to patients, dentists, cardiologists and GPs and will likely result in many practitioners ignoring NICE guidance and following European or US guidelines instead. (1) 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 2015; 385(9974): 1219-28 (2) 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; 12: 761–9. (3) Van der Meer JT, Thompson J, Valkenburg HA et al. Epidemiology of bacterial endocarditis in the Netherlands II. Antecedent procedures and use of prophylaxis. Arch Intern Med 1992; 152: 1869–73. (4) Lacassin F, Hoen B, Leport C et al. Procedures associated with infective endocarditis in adults. A case control study. Europ Heart J 1995; 16: 1968-74. (5) Horstkotte D, Rosin H, Friedrichs W, Loogen F. Contribution for choosing the optimal prophylaxis of bacterial endocarditis. Europ Heart J 1987; 8 (Suppl J): 379-81. (6) Van der Meer JTM, van Wijk W, Thompson J et al. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. Lancet 1992; 339: 135-9.	update of this guideline. Please see section 2.1.2 for the critique of this study and also section 2.6.5 for the committee's interpretation of this evidence. Study reference 2, 3 and 8 did not meet the pre-specified criteria of question 6 for various reasons– please refer to appendix F.5 for details. References 4, 5 and 6 were included in this update – please see table 155 and section 2.6 of the addendum for the committee's interpretation of this evidence. Studies in references 9 and 10 were performed in animals – NICE does not consider animal studies to be an appropriate source of evidence due to the lack of applicability to the human population. And finally, the studies mentioned in references 7,11,12 were not of appropriate study designs meeting the committee's pre-specified criteria of RCTs or comparative observational studies.

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				(7) Starkbaum M, Durack D, Beeson P. The incubation period of subacute bacterial endocarditis. Yale J Biol Med 1977; 50: 49–58. (8) 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 Infectious Dis 2006; 42: e102-7. (9) Glauser M, Bernard J, Moreillon P et al. Successful single–dose amoxycillin prophylaxis against experimental streptococcal endocarditis: evidence for two mechanisms of protection. J Infect Dis 1983; 147: 568–75. (10) Berney P, Francioli P. Successful prophylaxis of experimental streptococcal endocarditis with single-dose amoxicillin administered after bacterial challenge. J Infect Dis 1990; 161: 281-5. (11) Lee P, Shanson D. Results of a UK survey of fatal anaphylaxis after oral amoxicillin. J Antimicrob Chemother 2007;60:1172-3. (12) Thornhill MH, Dayer MJ, Prendergast B, Baddour LM, Jones S, Lockhart PB. Incidence and nature of adverse reactions to antibiotics used as antibiotic prophylaxis. J Antimicrob Chemo. 2015 doi:10.1093/jac/dkv115	
NHS England	General	General	General	No comments	Thank you.
Royal College of Paediatrics and Child Health	Short guideline	General	Page 6 Line 96	We feel that it should be impact rather than values and preferences.	Thank you for your comment. This is standard terminology used by NICE.
Royal College of Paediatrics and Child Health	Short guideline	General	Page 8 line 132	Congenital heart disease should come before acquired valvular heart disease with stenosis or regurgitation and valve replacement which are rare in children.	Thank you for your suggestion. However, based on NICE style, the order of the bullet points does not indicate importance.
Royal College of Surgeons	General	General	General	No comments	Thank you.
Scottish Antimicrobial Prescribing Group	General	General	General	Comments from one of our SAPG Public Partners is that guidance is not user-friendly for patients and the public. Although this is not the key audience it would be helpful to have a public version/summary. He has also suggested that it may be helpful to promote a patient held card similar to this one from USA http://www.heart.org/idc/groups/heart-public/@wcm/@hcm/documents/downloadable/ucm_307684.pdf	Thank you for your comment. Yes, there will be an 'information for patients and public' version published along with this guidance. We will also pass on this message to the implementation team to ensure recommendations are implemented accordingly.

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Society for cardiothoracic surgery of Great Britain and Ireland	NICE	11	General	In the Recommendation page (section 1.2, sub section 1.1.1,) valve repair should be added to valve replacement	Thank you for your comment. As all the included studies for this review question that have been assessed by the Committee use the term 'valve replacement', the Committee felt that it is not appropriate to add another alternative term to the recommendation that is not support by any evidence.
Society for cardiothoracic surgery of Great Britain and Ireland	NICE	11	General	in the recommendation page, the sentence in section 1.1.3, should commence ' In patients at risk of endocarditis....'	Thank you for your suggestion. After the discussion with the medical editor and the Committee, they agreed that current wording is clear and consistent with NICE style.
Society for cardiothoracic surgery of Great Britain and Ireland	NICE	14	33	Studies required to see whether the number of operations for endocarditis have increased in UK and elsewhere since NICE guideline introduced.	Thank you for your comment. This was not prioritised by the group as a recommendation for research as in order to conduct studies on number of operations and IE, a national database would first need to be set up to allow such studies to be conducted. Hence the committee chose to prioritise the national register research recommendation and long term RCT on antibiotic prophylaxis instead. Please refer to this **link http://www.nice.org.uk/Media/Default/About/what-we-do/Research-and-development/Research-recommendations-process-and-methods-guide.pdf** for further details on how the committee prioritises recommendations for research.
Society for cardiothoracic surgery of Great Britain and Ireland	NICE	35	34-37	evidence (as confirmed by yourself because of biased studies) that patients with prosthetic heart valves are not at increased risk of endocarditis is poor and therefore such a statement is misleading and potentially dangerous.	Thank you for the comment. We are saying that based on the evidence reviewed in this update, prosthetic valves did not appear to increase the risk of IE. This point was discussed by the Committee who acknowledged there is an inconsistency between the evidence found and what is widely embedded in practice (i.e. that prosthetic valves increase the risk of IE). There were no other studies found in the review, nor any studies subsequently identified by topic experts or stakeholders which demonstrate this increased risk when compared to the general population. To take account for this, the evidence statement and the LETR table have been amended to reflect the Committee's views on this inconsistency.
Society for cardiothoracic surgery of Great Britain and Ireland	NICE	32	33-34	as above	Thank you.
Society for cardiothoracic	NICE	33	1-2	This alone I.e. Poorer outcomes if patients develop IE together with the vanishingly low risk of oral antibiotic prophylaxis suggests that pending the findings of a RCT in these patients, the guideline for these patients should be reversed.	Thank you for your comments. The Committee considered all of the included clinical evidence as well as cost-effectiveness evidence, and came to the conclusion that pending the findings of more good quality evidence that could establish the efficacy of antibiotics for preventing the incidence of IE, routine antibiotic prophylaxis is not recommended for dental procedures, upper and lower GI, upper and lower respiratory

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surgery of Great Britain and Ireland					tract, and genitourinary procedures.
Society for cardiothoracic surgery of Great Britain and Ireland	NICE	33	28-29	All deaths associated with Prosthetic valve endocarditis occur during the index hospital admission and reflect the seriousness and poor prognosis of the condition.	Thank you for your comment. We appreciate that it may be of limited clinical value to include longer term mortality data but this was included to reflect the way it was reported in the evidence. There seems little value in deleting this finding at this stage.
Society for cardiothoracic surgery of Great Britain and Ireland	NICE	67	5-8	Sufficient evidence to suggest that in some if not all patients, many dental interventions are associated with a bacteraemia and if it is accepted that this is the primary event in many cases of endocarditis, the evidence whether prophylactic antibiotics modified this bacteraemia is of crucial relevance.	Thank you for your comments. Please see Table 6 and 7 in the full Addendum. There are approximately equal number of studies on dental procedures that suggested there was significant bacteraemia (11 studies), as well as no significant bacteraemia (12 studies). Therefore the Committee's conclusion is that there is inconsistency evidence to draw a firm conclusion.
British Society for Oral Medicine	Short	General	General	The British Society for Oral Medicine (BSOM) is pleased to be able to submit a response to NICE in regard to the consultation on prophylaxis against infective endocarditis. Practitioners in oral medicine typically manage a select group of patients. These patients are often more medically-compromised than the general population and have a long list of prescribed medications allied to their sometimes complex medical morbidities. These medical morbidities will include cardiovascular diseases, including valvular disease. Additionally, most consultants in BSOM are based in university dental schools and many also hold dual qualifications in medicine and dentistry, and thus many are involved in the organisation and delivery of teaching in human disease/clinical medical sciences in dentistry (HD/CMSD) and/or Special Care Dentistry. It follows therefore that the teaching delivered to dental undergraduate students, amongst others, needs to be of high quality and appropriately evidence-based. This teaching will include the recommendations for managing patients with cardiac valvular disease. When NICE introduced guidance for the management of patients with cardiac disease who are at risk of infective endocarditis in 2008 the large number of patients receiving antibiotic prophylaxis against infective endocarditis before dental interventions was significantly reduced. This change in policy was not based on randomised-controlled trials (RCTs), and was also not adopted by other recognised groups – for example the American Heart Association – who, like all other guideline committees worldwide, continue to recommend antibiotic prophylaxis for those at high risk. A recent study published in the Lancet (Dayer MJ, *et al.* Incidence of infective endocarditis in England, 2000-13: a secular trend, interrupted time-series analysis. Lancet. 2015 Mar 28;385(9974):1219-28.) noted that prescriptions of antibiotic prophylaxis have fallen	Thank you for your comment. For intervention questions in general, RCTs are usually the preferred source of evidence given the randomised nature of these studies and therefore less liability to inherent bias. However, as stated in the review protocols for this guideline, where RCTs are likely to be rare (eg: when the outcome of interest, in this case IE is rare), NICE's methodology would be to use the best quality evidence available – currently this seems to be from a limited source of comparative observational studies. Given the small number of observational studies available, the committee ultimately decided to make a research recommendation promoting the need for a trial. Further evidence may be available in the future and as standard process, the committee would always consider the highest quality evidence first (for the reasons above) before considering poorer quality evidence. . With regards to the Lancet study, as commented by the critique of this study, the speculation that the change in slope after the introduction of the NICE guidance was based on the assumption that there were 2 linear trends before and after 2008. There is no rationale provided in the Dayer study to justify such an assumption. Sensitivity analyses using different assumptions were conducted by the critique author and it demonstrated that if different assumptions were used, different results were likely to be produced.

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				substantially but that the incidence of infective endocarditis has increased significantly in England since introduction of the 2008 NICE guidelines. This study is not a RCT and therefore unlikely to be considered by NICE as part of evidence when reconsidering the 2008 antibiotic prophylaxis against infective endocarditis guidelines. Below are extracts (2.1 and 2.3) from the current consultation by NICE in relation to prophylaxis against infective endocarditis. Paragraph 2.1 describes research into the risks of developing infective endocarditis associated with acquired valvular disease, and recommends and population-cohort study design. Paragraph 2.3 considers antibiotic prophylaxis against infective endocarditis and insists that studies should be RCTs with long follow up. ***2.1 Cardiac conditions and infective endocarditis*** *What is the risk of developing infective endocarditis in people with acquired valvular disease and structural congenital heart disease?* *Such research should use a population-based cohort study design to allow direct comparison between groups and allow estimation of both relative and absolute risk.* ***2.3 Antibiotic prophylaxis against infective endocarditis*** *Does antibiotic prophylaxis in those at risk of developing infective endocarditis reduce the incidence of infective endocarditis when given before a defined interventional procedure?* ***Why this is important*** *There is limited evidence about the effectiveness of antibiotic prophylaxis in reducing the incidence of infective endocarditis in people at risk of developing infective endocarditis. The current evidence includes very limited data from observational studies with inconclusive findings. The study should be a randomised controlled trial with long-term follow-up comparing antibiotic prophylaxis with no antibiotic prophylaxis in adults and children with underlying structural cardiac defects undergoing interventional procedures. Outcomes should include the incidence infective endocarditis in those receiving prophylaxis compared to those not, and the incidence of adverse effects including anaphylaxis.* The BSOM notes that the introduction of a change of antimicrobial prophylaxis guidance in 2008 by NICE was undertaken without a RCT to inform it, but that to reverse the decision NICE currently insists on a RCT. However, elsewhere in the latest consultation NICE describes non-RCT evidence to be used to change policy. The BSOM is concerned that NICE may therefore exclude useful and important non-RCT evidence when reviewing and possibly reformulating its guidance on the use of antimicrobial agents in the prophylaxis against infective endocarditis, to the detriment of any revised guidance. In view of the importance of this health care concern both for patients and clinicians we would urge NICE to give consideration either for promoting/funding a relevant trial and/or altering the criteria by which it considers evidence to be of suitable quality to lead to changes in clinical guidelines.	

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School of Clinical Dentistry, University of Sheffield	Full	General		Our concerns fall into 4 major categories: 1.The critical analysis of the Lancet paper and the way it is portrayed in the report 2.The validity of the NICE approach for a topic where there is no RCT data and it is unlikely such data will be available in the foreseeable future 3.The way the guideline review process has been conducted 4.The failure of the review to risk assess the consequences of its decisions, putting process and methodology ahead of patient safety. *1.The critical analysis of the Lancet paper and the way it is portrayed in the report* •The authors of the Lancet paper1 that prompted the review, forewarned NICE of its publication, offered full access to the data and full cooperation during the review process. •Nice commissioned Prof Ramsey to produce "a critical appraisal on the methods used in the Lancet paper" •This assessment concluded that the Lancet study was at 'high risk of bias'. This led the Committee to conclude that there was no new evidence to warrant considering a change to the existing guidance. •The whole outcome of the review therefore rested on the opinion of the Lancet paper's methodology by one statistician commissioned specifically by NICE to critically appraise it. •It ignores the fact that this paper was subject to independent review by nine experts in the subject, including 3 independent statisticians, during the publication process, none of which drew Prof Ramsey's conclusion. •At no time were we (the authors) asked to provide the data or respond to the many queries that Prof Ramsey had about the methodology and interpretation of the data (he made his own assumptions about the answers to these questions). Most critically, we were never given the opportunity to respond to the criticism of our paper, explain our choice of methodology or put the study into context. This was like a court with a prosecution but no defense. •Furthermore, whilst the term 'high-risk of bias' has a specific statistical/methodological meaning within the context of EPOC studies, the use of this pejorative term to describe the study in section 2.1.2 of the review and the Appendix 'O' summary implies, to those reading the report, but who are not experts in this specialised area of methodological analysis, that both the study and its authors were highly biased. Casting such doubt on the study has clearly biased the view of the members of Standing Committee A and will also bias the views of those responding to the consultation and thus the consultation itself. •The EPOC/Cochrane tool used to reach this judgment has been inappropriately applied and used. The tool was only made available in February 2015 and has yet to be validated. Indeed, the Cochrane handbook cautions about using such tools to make summary judgments on observational studies such as this and recommends that a minimum of two people are involved in any analyses. According to the EPOC/Cochrane web site referenced by Prof Ramsey, each question in the instrument should be scored – 'low risk', 'unclear risk' or 'high risk', not 'Yes' or 'No' as was done by Prof Ramsey. Furthermore, Prof. Ramsey, has not followed the detailed instructions under each question for determining his response – particularly with regard to the two questions he scored 'No'.	Thank you for raising a number of issues related to the update of our guideline on prophylaxis against infective endocarditis (CG64). First, you say that you are not able to submit comments as a stakeholder. You are able to submit comments in our consultations as a member of the faculty at the University of Sheffield, which would qualify in the category 'organisations that fund or carry out research' as listed on the NICE website. Incidentally, I understand that one of your co-authors on the Lancet paper, Mark Dayer, is a topic expert member of the advisory committee. It is our normal practice to ask topic experts, who will be in attendance at the advisory committee meetings when comments are discussed, not to submit consultation responses, as they would otherwise be in an invidious position when the committee considers stakeholder comments. In the same way that topic experts are used to inform the views of the committee, it is not unusual to invite a view from an expert in a particular methodological field. In this case, we have invited Professor Ramsay. The views from Professor Ramsay are carefully considered by the committee and the interpretation is subject to public consultation. Prof.. Ramsay had conducted an explicit, neutral and transparent assessment of the study using the EPOC tool, an internally well accepted tool used for quality assessment. Both NICE technical team and the Committee agreed with the quality assessment made by Prof. Ramsay. The key uncertainty, as pointed out by the critique, is the assumption that there are 2 linear trends (2 straight lines) before and after the 2008 NICE guidance, but no rationale was provided to justify such linear assumption in the study (e.g. why it's not U-shaped, ∩-shaped or bimodal, etc.) As the raw data points are not on a straight line, we are uncertain what rationales were used to plot such 2 straight lines. You also maintained that "pre-specified analysis" is scientifically more robust. This is only true if rationales for the pre-specified straight lines were provided, and that how sensitivity analysis was going to be conducted to test the model, and how the results from the sensitivity analysis was going to be dealt with. None of these were provided in the study. The critique of the Lancet paper did not propose that the analysis in the study was incorrect. The critique paper did some sensitivity analyses to test the assumption of the 2 linear lines used in the study, and demonstrated that if different assumptions were used the results are likely to be different. The critique paper therefore raised the question of whether the committee really thinks that the assumptions used in the Lancet study are plausible (given that no rationale was provided for the assumptions). Your second point refers to a failure by the committee to consider study designs other than RCTs, but as you point out the committee did consider your Lancet study, which was not an RCT. This update has included more than 100 observational studies as its evidence base. The committee has to take many factors into account in deciding how robust the evidence is for a causal relationship, as outlined in our Guidelines Manual. As you know, bias is a term commonly used in assessing methodological rigour and it is perfectly reasonable for the committee to use this term in its consideration of the evidence. As you state, the health economic model undertaken by your colleagues was presented to the committee

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				The first should arguably be scored 'low risk' (the shape of the intervention effect was pre-specified –the rationale was that it was the date at which the guidelines changed) and the second 'low-risk' or 'unclear risk'. Indeed, in a blind (to Prof Ramsey's review or the view of the Lancet authors) independent review of the Lancet paper three expert Cochrane reviewers, familiar with the EPOC assessment instrument, graded the two parameters scored 'No' by Prof Ramsey as 'low-risk'. Finally, he has summated the results of the 7 questions, using a matrix designed for summating the RCT risk of bias assessment tool to reach the overall 'high-risk of bias' conclusion. Currently, the Cochrane handbook does not advise summation of the question responses in the interrupted time series tool and provides no matrix for doing so. The 'high-risk of bias' conclusion is therefore inappropriately deduced and in itself – biased. •Using the same EPOC/Cochrane tool, an assessment of Prof Ramsey's analysis of our data would result in his analysis receiving more 'high-risk of bias' outcomes than ours did, due largely to selective outcome reporting and failure to pre-specify methodology. •There are multiple ways the data in our study could have been analysed and each would produce a slightly different outcome. However, our analysis was pre-specified and Prof Ramsey has agreed that our methodology was correctly and accurately performed. In contrast, Prof Ramsey did not pre-specify his analysis but tested several different analyses and picked those that demonstrated a smaller, or no, increase in the incidence of infective endocarditis (IE) to compare with ours. Methodological selection bias was therefore used to conclude that the change in slope that we published in the Lancet paper was both biased and too high. •Prof Ramsey, criticizes our method of fitting two straight lines to the data before and after March 2008. But given that March 2008 was the date the AP guidelines changed it was a reasonable choice to pre-specify. In contrast, Prof Ramsey has post-specified 3 change points. He does not propose a reason for choosing the extra two points other than to minimize the significance of any change associated with the guidelines – choosing the methodology to produce the result you want. Inevitably, adding change points reduces the magnitude of the change between each point and will at some stage make the change non significant. There is no obvious explanation for the 1st of his proposed change points. But this one alone has minimal effect on the significance and size of the increase in incidence of IE occurring around March 2008. There is however, a very obvious explanation for his change point 3. Prof Ramsey has made the assumption that the change in guidance caused the increase in incidence of IE. That is not the case. The change in guidance caused the fall in AP prescribing (Prof Ramsey has completely ignored the prescribing data). The important question is whether the fall in AP prescribing resulted in an increase in IE incidence? Prof Ramsey, has assumed that any increase in IE caused by the change in guidelines would have happened in March 2008 with any later change, including his June 2011 change point 3, being caused by something else. But AP prescribing did not stop in March 2008 it fell over time, was still falling in June 2011 and still has not reached zero. Indeed, there is evidence that the fall between March 2008 and early 2011 was largely due to clinicians stopping AP for those at moderate risk of IE.2 By June 2011, this effect had probably become saturated and any further fall in AP prescribing was likely to have involved those at high-risk of IE. It is likely therefore that the June 2011 change point identified by Prof Ramsey was also caused by the fall in AP prescribing, and therefore by the change in guidelines. It is likely, therefore, that Prof Ramsey's conclusion "If an additional interruption is incorporated at June 2011, the change in slope at guideline introduction reduced to zero, suggesting no effect of guidance on trends" – is wrong. •Prof. Ramsey points out in his 'critique' that an autoregressive integrated moving average (ARIMA) model could provide a better test of the intervention effect, particularly for longer time series such as ours, than a simple time series regression. As well as the pre-specified	and considered, as documented in the addendum that has been out for consultation. At the time Professor Wailloo presented the work to the committee, no decision on recommendations had been taken, but there had been some preliminary discussion on the clinical evidence that he might have misinterpreted as a decision. The recommendations were debated later on the agenda. I am sorry that you disagree with the Committee's decisions. They have, carefully, considered the responses made to consultation, including the points made in your comments.

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				analysis that we published, we have since tried other methodologies, including a SARIMA analysis of the type he suggested, all of which have shown a significant increase in the incidence of IE in association with the fall in AP. The SARIMA analysis showed that each prescription of AP is associated with a mean change in IE admissions of -0.0010 (95% CI -0.0018 to -0.0002; p=0.0096) i.e. 1000 (95%CI 556 to 5,000) AP prescriptions are associated with a fall of one case of IE (the exact SARIMA model is Estimate X2.5.. X97.5.. pAprox ar1 0.2027 0.0244 0.3811 0.0259; ar2 0.1338 -0.0443 0.3120 0.1410; sma1 0.1330 -0.0471 0.3132 0.1479; intercept 19.0761 17.9931 20.1591 0.0000). However, using the post specified analysis suggested by Prof. Ramsey still results in a significant association between any change in AP prescribing and the number of cases of IE. *2.The validity of the NICE approach for a topic where there is no RCT data and it is unlikely such data will be available in the foreseeable future.* •In assessing if AP was of value in preventing IE (Review question 6a), 1341 articles were identified but none met the criteria for the review (none were RCTs) and all were excluded. 3 studies were reviewed in more detail – all observational (and from before 2000), but "the committee concluded that there is insufficient evidence to recommend prophylactic use of antibiotics". i.e. to change the guidance. •The GRADE criteria used by NICE to determine what studies should be considered in determining guidance effectively exclude observational studies "as only observational studies were identified for this review, the quality rating began at 'low' and was further downgraded for potential bias" [page 82, lines 13 & 14]. When combined with Prof Ramsey's methodology of assessing bias in observational studies, that inevitably results in observational studies being graded as having "a high likelihood of bias", it is clear that NICE will only accept RCTs as providing a sufficient evidence to be taken into consideration in determining guidance. •The Lancet data does not appear to have been considered under question 6a. Indeed, it is not clear how it was assessed in the review. But it appears to have been damned like all observational studies, particularly following the critical appraisal by Prof Ramsey, as providing "insufficient evidence to recommend a change of guidance". •If there is insufficient evidence to change guidance now, why did NICE change the guidance in 2008, when less evidence was available? Prior to 2008, AP was recommended for all patients at moderate or high risk of developing IE in the UK but this was changed by NICE in 2008 to a recommendation that all AP should cease – despite no evidence to support this change including no RCT data. •NICE appears to have set RCTs as the level of evidence required to change it's guidance – even though that criteria was not met in 2008 when NICE recommended a huge change in guidance. •However, by its own admission no RCT has been performed to date. This is because there are major size (to achieve statistical power), cost, complexity and ethical barriers that prevented an RCT from being funded in the past and will continue to do so into the foreseeable future. In a politically aware and financially constrained funding environment, funders cannot justify the enormous financial commitment necessary for an RCT to evaluate AP in such a rare condition as IE, when RCTs for more common and serious diseases such as cancer, diabetes, hypertension etc cost far less and have wider impact. •By setting RCTs as the level of evidence required to change guidance, NICE has permanently locked in a decision that AP is of no value in preventing IE – even though there was no evidence to support the change to that position in the first place. •In the absence of any RCT data, is it appropriate to exclude all other evidence that could	

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				inform decisions about guidance, including informative observational and animal study data? Surely it is important to consider the evidence provided by the best observational studies. To do this, criteria need to be adopted that allow good quality observational data to be considered in situations like this, where RCT data are not available. Cochrane reviews now include a full assessment of better quality observational studies such as case –control studies, cohort studies and interrupted time series studies, particularly in situations, such as this, where no RCT data are available. Indeed, the Cochrane review of "Antibiotics for the prophylaxis of endocarditis in dentistry", published in July 2008, included both cohort and case control studies because of the absence of RCT data.3 Why doesn't NICE? •Whilst RCT data would be needed to prove that the NICE guidelines caused the increase in IE, the excluded Lancet data shows a close association between the fall in AP prescribing and the rise in IE. A change point analysis shows that the rise in incidence of IE closely followed the change in guidance. And an exploration of other possible reasons for the rise in IE failed to identify another plausible explanation. According to Prof Ramsey the methodology used was "relatively robust" and "There was no factual error with modelling approach undertaken in paper". Furthermore, the study was large, incorporating data for the entire population of England. Short of an RCT, the Lancet data is probably the best evidence we are likely to get on the benefits, or not, of AP. •Clearly, human RCT data on the value of AP in preventing IE would be preferable, but in the absence of this is it right for NICE to exclude the evidence of animal RCT data that could help inform their decision-making about the value of AP? *3.The way the guideline review process has been conducted.* •The review has fixated on demonstrating that there is insufficient evidence to change guidance - to the exclusion of everything else. •We provided the committee with important new data on the risk of adverse reactions to the antibiotics used for AP.4 But having made the dogmatic decision not to change guidance i.e. not to recommend AP, the committee decided it didn't need to consider this evidence – even though it is critical in determining the risks associated with that decision. •Again having decided not to change guidance, the committee decided there was no reason to consider a health economic analysis we had informed them we were carrying out. Having been invited to provide an early appraisal of our health economic analysis to the review committee on the 13th March, Prof. Alan Wailoo was informed before starting his presentation that a decision had already been made not to change the guidance and so his presentation was unnecessary. •We have gone on to complete our health economic analysis, and contrary to what is reported in the review documentation, even our base case analysis shows AP to be very cost effective but if restricted to high-risk individuals it is extremely cost effective. •Both in 2008 and again in 2015, NICE has only looked at AP v no AP. It has failed to consider the option recommended by every other guideline committee in the world of restricting AP to those at highest risk. It is surely hubris for NICE not to consider the views of other guideline committees, or the evidence of the Lancet paper, that its position might be wrong. *4.The failure of the review to risk assess the consequences of its decisions, putting process and methodology ahead of patient safety.* •In it's draft guidance, NICE says "The Guideline Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention" – Yet the	

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				potential benefits and harms of it's decision do not appear to have been given any consideration in this review. •In 2008 NICE concluded there was no evidence that AP was of benefit and they felt that the risks of AP were likely to outweigh the risks of IE. So despite no evidence to justify a change, NICE changed the guidance to recommend no AP. The AHA and ESC independently reviewed the same data but reached a different conclusion (along with every other guideline committee). They felt that the risks of IE were likely to outweigh the risks of AP, particularly for those at high-risk, and, in the absence of evidence that AP was not of benefit, made the pragmatic decision to recommend AP for those at high-risk. •While not providing the proof of an RCT, the Lancet data does suggest that the recommendation to stop AP could have led to an increase in the incidence of IE – and provides figures for the potential risk. Likewise the adverse reaction data published in the Journal of Antimicrobial Chemotherapy4 provides data on the risk of an individual developing an adverse drug reaction (ADR) to the antibiotic prophylaxis. So it is possible to assess the risk trade-off associated with the guideline committee's decisions while we wait for RCT level data to become available. •If NICE continues to recommend no AP and an RCT ultimately corroborates the Lancet data, then in the interim our data shows that there will be an extra 419 cases of IE per year (95%CI: 95-743). And, with our data showing that on average 15.7% of IE patients die during their initial hospital admission, this would include 66 extra deaths (95%CI: 15-117) per year. •Alternatively, if NICE recommended AP and an RCT ultimately showed the Lancet data to be wrong, our ADR data shows that in the interim there would be only 6 non-fatal but reportable ADR per year and one fatal ADR every 3 years. •If an alternative to clindamycin AP was recommended or AP was restricted to those not penicillin sensitive, this would reduce to zero ADR deaths and only 2 non-fatal but reportable ADR per year. •If AP were restricted to those at high-risk of IE the trade-off between benefits and harms would even more strongly favour AP. And our health economic analysis suggests that it would also be extremely cost-effective. •By sticking dogmatically to the requirement for 'better evidence' before considering a change in guidance, NICE could be putting hundreds of patients at unnecessary risk every year. We also have a number of other concerns relating to the review (itemised in the Appendix). However, our main concern is that by sticking to methodological protocols designed for RCT's and failing to consider more fully the available data as well as the potential impact of its decision on patient's lives, NICE could sleep walk into a potentially disastrous final decision.	