NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Centre for Clinical Practice

Review of Clinical Guideline (CG64) – Prophylaxis against infective endocarditis

Background information

Guideline issue date: 2008

3 year review: 2011

National Collaborating Centre: Short Clinical Guidelines - Centre for Clinical Practice (NICE)

Review recommendation

- The guideline should not be updated at this time.

Factors influencing the decision

Literature search

1. From initial intelligence gathering and a high-level randomised control trial (RCT) search clinical areas were identified to inform the development of clinical questions for focused searches. Through this stage of the process eight studies were identified relevant to the guideline scope. The identified studies were related to the following clinical area within the guideline:
    - Antibiotic prophylaxis to prevent infective endocarditis

2. Two clinical questions were developed based on the clinical area above, qualitative feedback from other NICE departments and the

views expressed by the Guideline Development Group, for more focused literature searches. No conclusive new evidence was identified which would change the direction of current guideline recommendations.

Guideline Development Group and National Collaborating Centre perspective

3. A questionnaire was distributed to GDG members and the National Collaborating Centre (NCC) to consult them on the need for an update of the guideline. Six responses were received with respondents highlighting that since publication of the guideline the European Society of Cardiology and the American Heart Association have published updated guidelines on prophylaxis against infective endocarditis. In addition, GDG members also highlighted that there is concern among cardiologists that not providing prophylaxis against infective endocarditis poses a risk to patients with valvular heart disease or a history of valve replacement. This feedback contributed towards the development of the clinical questions for the focused searches.

4. Ongoing research relevant to the guideline was highlighted by GDG members including:
    - A study suggesting that there has been no increase in infective endocarditis in children and that dental treatment does not appear to be the cause when infective endocarditis does occur
    - Researchers are applying for a grant to conduct a controlled study of prophylaxis in valve patients (RCT of antibiotic prophylaxis versus no prophylaxis for patients with prosthetic heart valves)
    - Potential pilot of a national endocarditis registry in the north of England

5. The majority of questionnaire respondents felt that there is insufficient variation in current practice supported by adequate evidence at this time to warrant an update of the current guideline.

Implementation and post publication feedback

6. In total 204 enquiries were received from post-publication feedback, most of which were routine. The main theme emerging from post-publication feedback was concern about the recommendations relating to antibiotic prophylaxis. This feedback contributed towards the development of the clinical questions described above.

7. An analysis by the NICE implementation team was undertaken as part of the review process. As such, qualitative input from the field team was identified which indicated that implementation of the guideline has been variable.

Relationship to other NICE guidance

8. NICE guidance related to CG64 can be viewed in Appendix 1.

Summary of Stakeholder Feedback

Review proposal put to consultees:
The guideline should not be updated at this time.
The guideline will be reviewed again according to current processes.

9. In total eight stakeholders commented on the review proposal recommendation during the two week consultation period. The table of stakeholder comments can be viewed in Appendix 2.

10. Six stakeholders agreed with the review proposal and one disagreed with the review proposal. One stakeholder did not state a definitive decision.

11. The stakeholder that disagreed with the review proposal commented that:
    - Antibiotic prophylaxis should still be recommended in high-risk cardiac patients (predominantly with prior endocarditis or prosthetic

valves) having high-risk dental procedures. However, following the review of the guideline the conclusion was that no new evidence was identified which would invalidate current guideline recommendations in this area.

Anti-discrimination and equalities considerations

12. No evidence was identified to indicate that the guideline scope does not comply with anti-discrimination and equalities legislation. The original scope contains recommendations for adults and children with known underlying structural cardiac defects, including those who have previously had infective endocarditis and adults and children who have previously had infective endocarditis (irrespective of whether they have a known underlying cardiac defect).

Conclusion

13. Through the process no additional areas were identified which were not covered in the original guideline scope or would indicate a significant change in clinical practice. There are no factors described above which would invalidate or change the direction of current guideline recommendations. However, GDG members highlighted that researchers are applying for a grant to conduct a controlled study of prophylaxis in valve patients (RCT of antibiotic prophylaxis versus no prophylaxis for patients with prosthetic heart valves). The results of this study will be considered in a future review of this guideline. The Prophylaxis against infective endocarditis guideline should not be updated at this time.

Relationship to quality standards

14. This topic is not currently being considered for inclusion in the scope of a quality standard.

15. This topic is not currently being considered as a proposed core library topic.

Fergus Macbeth – Centre Director
Sarah Willett – Associate Director
Emma McFarlane – Technical Analyst

Centre for Clinical Practice
September 2011

Appendix 1

The following NICE guidance is related to CG64:

Guidance	**Review date**
CG74: Prevention and treatment of surgical site infection, 2008.	Currently being considered for an update. Review decision date October 2011.
PA25: Prevention of cardiovascular disease at the population level, 2010.	Review date: TBC.
Related NICE guidance in progress	
Clinical guideline: Infection control, prevention of healthcare-associated infection in primary and community care (update of CG2).	Currently in progress. Expected publication date March 2012.

Appendix 2

National Institute for Health and Clinical Excellence

Prophylaxis against infective endocarditis
Guideline Review Consultation Comments Table
11-25 July 2011

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
Royal College of Nursing	Agree	We agree that the guideline should not be updated at this time but would urge NICE to require formal reporting of endocarditis to ensure accurate data is available for future reviews on this controversial topic.			Thank you for your comment.
Royal College of Nursing		There is no significant increase of infective endocarditis related to the previous guideline			Thank you for your comment.
Royal College of Nursing		There is a need for formal reporting of all endocarditis cases in order to guide any future development of guidelines			Thank you for your comment.
Royal College of Nursing		Oral hygiene is a factor in children and the guideline needs to emphasise this			Thank you for your comment. This will be considered at the next review.
Department of Health		To confirm that the Department of Health has no substantive comments to make regarding this consultation.			Thank you for your comment.
British	Agree	We still await results of RCT's to establish whether			Thank you for your comment.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
Society for Disability and Oral Health		or not the incidence of IE has increased following the cessation of antibiotic prophylaxis. We would suggest the guidelines are reviewed when such evidence is clearly available			
British Society of Gastroenterology	Agree	BSG Endoscopy (formerly BSG Endoscopy Committee) are content with the NICE stance and have no reason to change/add to the guideline as it stands.			Thank you for your comment.
British Cardiovascular Society and British Heart Valve Society	Disagree	The Societies accept almost all the NICE recommendations. The sole exception is our view that antibiotic prophylaxis should still be recommended in high-risk cardiac patients (predominantly with prior endocarditis or prosthetic valves) having high-risk dental procedures (until evidence to the contrary becomes available).			Thank you very much for your comment. Following the review of the guideline the conclusion was that no new evidence was identified since the publication of the original guidance which would invalidate current guideline recommendations. In particular, a recent study was identified through the in-house review process which aimed to quantify the change in prescribing of antibiotic prophylaxis before invasive dental procedures for patients at risk of infective endocarditis following the introduction of the NICE guideline. The results indicated that following introduction of the NICE

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
					guideline there has been a significant reduction in prescribing of antibiotic prophylaxis whilst there has been no significant increase in the number of cases of infective endocarditis, as measured using data from hospital episode statistics. (Thornhill MH, Dayer MJ, Forde JM, Corey GR, Chu VH, Couper DJ, et al. Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. BMJ 2011;342:d2392).
British Cardiovascular Society and British Heart Valve Society	Disagree	The NICE guidelines are out of step with the ESC and AHA and this causes considerable confusion for cardiologists, cardiac surgeons, dentists and patients.			Thank you for your comment. The guideline provides a clear and detailed explanation as to how the recommendations were derived from the available evidence. Following the review of the guideline the conclusion was that no new evidence was identified since the publication of the original guidance which would invalidate current

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
					guideline recommendations.
British Cardiovascular Society and British Heart Valve Society	Disagree	The need for a registry and an appropriately designed RCT in the high-risk group needs to be stressed. The Societies believe that a change from AHA and ESC guidelines to the NICE position should only be made after an RCT in high-risk patients having high-risk dental procedures.			Thank you for your comment. The GDG highlighted that a controlled study of prophylaxis in valve patients (RCT of antibiotic prophylaxis versus no prophylaxis for patients with prosthetic heart valves) may inform future guideline recommendations. In addition, the original guideline states that: It is noted that infective endocarditis (IE) is a rare condition and that research in this area in the UK would be facilitated by the availability of a national register of cases of IE that could offer data into the 'case' arm of proposed case–control studies.
British Cardiovascular Society and British Heart Valve Society	Disagree	The Societies accept the NICE committee statement that, in the absence of a prospective randomised clinical trial, the clinical effectiveness of antibiotic prophylaxis is not proven. However a number of studies suggest a benefit. A Dutch case-controlled study[1] suggested a reduction in risk of only 49%, but excluded high-risk patients with prosthetic valves. In a study specifically of prosthetic valves[2] there were 6 cases of			Thank you very much for your comment. The references supplied are outwith our date period of this review (2007-2011). These studies were identified and considered by the GDG during the development of the guideline. The aim of this review is to

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
		endocarditis (IE) in 304 who were unprotected by antibiotics, but no cases in 229 protected patients. A French study[3] estimated an incidence of IE in patients with valve disease of 1 case per 46,000 unprotected dental procedures compared with 1 case per 149,000 protected procedures. The protective effect of antibiotics has been estimated at 46-91%[3-5]. (Ref 1.Van der Meer JTM et al. Lancet 1992; 339: 135-9. Ref 2. Horstkotte D et al. Europ Heart J 1987; 8 (Suppl J): 379-81. Ref 3. Duval X et al. Clin Infectious Dis 2006; 42: e102-7. Ref 4. Lacassin F et al. Europ Heart J 1995; 16: 1968-74. Ref 5. Imperiale TF et al. Am J Med 1990; 88: 131-6)			consider new evidence published since the publication of the guideline. Following the review of the guideline the conclusion was that no new evidence was identified which would invalidate current guideline recommendations. In particular, a recent study was identified through the in-house review process which aimed to quantify the change in prescribing of antibiotic prophylaxis before invasive dental procedures for patients at risk of infective endocarditis following the introduction of the NICE guideline. The results indicated that following introduction of the NICE guideline there has been a significant reduction in prescribing of antibiotic prophylaxis whilst there has been no significant increase in the number of cases of infective endocarditis, as measured using data from hospital episode statistics. (Thornhill MH, Dayer MJ,

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
					Forde JM, Corey GR, Chu VH, Couper DJ, et al. Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. BMJ 2011;342:d2392).
British Cardiovascular Society and British Heart Valve Society	Disagree	The NICE committee considered, but decided against, defining a high risk group to include patients with prosthetic valves. This was because the committee felt that this would be confusing rather than that it was clinically unjustified. The Societies disagree with this decision. Patients with prosthetic valves have a 5-fold higher risk of developing IE than those with native valve disease[6]. The mortality is substantially higher, about 25% during the acute event[7], and up to 41% at 30 days[8]. Long-term survival rates are only 55% at 5 years and 38% at 10 years[9]. This is largely because 10-35% of survivors need further cardiac surgery which is at markedly increased risk[9,10]. The Societies, International guideline groups, and clinical studies conclude (differently from NICE) that antibiotic prophylaxis, while no longer generally advisable, should be focused on such high-risk groups. (Ref 6. Chambers J et al. J Roy Soc Med 2011; 104: 138-40. Ref 7. Wang A et al. JAMA 2007; 297: 1354-61. Ref 8. Habib G et al. Heart 2005; 91: 954-9. Ref 9. Edwards MB et al. Eur J Cardiothoracic Surg 1998; 14: 156-64. Ref 10.			Thank you for your comment. As detailed in the relevant evidence to recommendations section in the full guideline [2.2], the GDG considered the potential confusion which can arise from a detailed stratification into different risk groups, and given the difficulties in relative risk definition the GDG decided that a simple classification of conditions into either at risk or not at risk groups is both supported by the available evidence and would help clarity. One of the highlighted studies (Chambers J et al., 2011) which falls within our date period for review (2007-2011)

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
		Farina G et al. J Heart Valve Dis 1994; 3: 165-71)			is a Letter which is a study type that we would not include in our process as they typically do not undergo peer review. The second study that you highlighted (Wang A et al., 2007) was identified through our focused search but was excluded as it did not match the inclusion criteria for the clinical questions we were focusing on. The additional references supplied are outwith our date period of this review (2007-2011). These studies were identified and considered by the GDG during the development of the guideline. Following the review of the guideline the conclusion was that no new evidence was identified which would invalidate current guideline recommendations. In particular, a recent study was identified through the in-house review process which aimed to quantify the change in prescribing of antibiotic

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
					prophylaxis before invasive dental procedures for patients at risk of infective endocarditis following the introduction of the NICE guideline. The results indicated that following introduction of the NICE guideline there has been a significant reduction in prescribing of antibiotic prophylaxis whilst there has been no significant increase in the number of cases of infective endocarditis, as measured using data from hospital episode statistics. (Thornhill MH, Dayer MJ, Forde JM, Corey GR, Chu VH, Couper DJ, et al. Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. BMJ 2011;342:d2392).
British Cardiovascular Society and British Heart Valve Society	Disagree	The NICE committee quoted a risk of fatal anaphylaxis of approximately 20 per million administrations of penicillin. This figure is based mainly on data published in the 1960s when most of the subjects dying received parenteral penicillin[11], often to treat syphilis. There is little			Thank you for your comment. However, no literature relating to anaphylaxis following antibiotic administration was identified through the in-house review of this guideline.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
		published information on the risks of oral amoxicillin, but yellow card returns in the UK suggest that fatal anaphylaxis is extremely rare and the figures quoted by NICE may be an over estimate[12]. In the world literature there have been no reports of fatal anaphylaxis after oral amoxicillin prophylaxis for endocarditis. Patients with prosthetic valves who have received amoxicillin prophylaxis in the past without any problems are unlikely to develop anaphylaxis. Testing for hypersensitivity is now available. (Ref 11. Idsoe O et al. Bull World Health Organ 1968; 38: 159–88. Ref 12. Lee P and Shanson D. J Antimicrob Chemother 2007; 60: 1172–3)			One of the studies (Lee P et al., 2007) that you highlighted which falls within our date period for review (2007-2011) is a Letter which is a study type that we would not include in our process as they typically do not undergo peer review. The additional references supplied are outwith our date period of this review (2007-2011). These studies were identified and considered by the GDG during the development of the guideline.
British Cardiovascular Society and British Heart Valve Society	Disagree	Reference 10 in the new review consultation document is cited as providing evidence that the guidelines do not require to be changed. However, the number of high-risk patients having high-risk procedures was not known and likely to be very small. The incidence of endocarditis even in high-risk patients is low so the study was not powered to detect an effect of with-holding antibiotics in this group.			Thank you very much for your comment. In the process of preparing the consultation document, we do not conduct a full systematic review of the literature and as such we are unable to confirm full details of the identified studies. The purpose of the review is to attempt to identify where there is a significant amount of new evidence that might warrant an update of the guideline

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
					recommendations. However, the study you are referring to concluded that following introduction of the NICE guideline there has been a significant reduction in prescribing of antibiotic prophylaxis whilst there has been no significant increase in the number of cases of infective endocarditis, as measured using data from hospital episode statistics.
British Cardiovascular Society and British Heart Valve Society	Disagree	A substantial proportion of high-risk patients continue to take antibiotics. In an audit, currently in press, of patients with prosthetic heart valves implanted at Guy's and St Thomas and followed up in South East England, only 126 (67%) had regular dental surveillance, but of these 86 (68% of 126) took prophylactic antibiotics. It is likely, but not known, that the patients still taking antibiotics in ref 10 were predominantly high-risk cardiac patients. This further undermines the validity of the comparison before and after the publication of the NICE guidelines.			Thank you very much for your comment. In the process of preparing the consultation document, we do not conduct a full systematic review of the literature and as such have not carried out a full critical assessment of the studies cited in the stakeholder consultation document. The purpose of the review is to attempt to identify where there is a significant amount of new evidence that might warrant more detailed consideration during an update. Therefore, we have reported the

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
					conclusion of the Thornhill (2011) study as it is relevant to the guideline recommendations relating to antibiotic prophylaxis. As the conclusion of this study indicated that there has been no significant increase in the number of cases of infective endocarditis following introduction of CG64 we felt that this study supports the current guideline recommendations. As such, we have concluded that the guideline does not warrant an update at this time.
British Cardiovascular Society and British Heart Valve Society	Disagree	Further problems with reference10: (i)Hospital activity data in the UK are notoriously inaccurate and incomplete. IE is not a notifiable disease and there is no national registry to ensure complete capture of all cases. Mortality data may also be inaccurate - IE is often difficult to diagnose and not all patients undergo post mortem. Furthermore, accurate data relating to cardiac surgery will not be available for some years yet. (ii) Trends in the natural history of IE may take longer to emerge than the 18 months of the study. Moreover, the statistical design does not exclude a 10% increase in the incidence or mortality of IE. (iii) The study had very low power to detect a small rise in dental-associated IE, which would have been			Thank you very much for your comment. In the process of preparing the consultation document, we do not conduct a full systematic review of the literature and as such we have not carried out a full critical assessment of the studies cited in the stakeholder consultation document. We therefore cannot comment on the statistical methods used in the study and why no data was presented on viridians group streptococci. However, the

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
		a small proportion (perhaps 20-30%) of the total number of cases. (iv)There were no data on viridans streptococci which are by far the most relevant for a possible dental cause of IE.			abstract conclusion states that although the data presented in the study lends support to the guideline, ongoing data monitoring is needed to confirm this. Any follow-up data will be factored into future reviews of the guideline. The purpose of the review is to attempt to identify where there is a significant amount of new evidence that might warrant an update of the guideline recommendations. Therefore, we have reported the conclusion of the Thornhill (2011) study as it is relevant to the guideline recommendations relating to antibiotic prophylaxis. As the conclusion of this study indicated that there has been no significant increase in the number of cases of infective endocarditis following introduction of CG64 we felt that this study supports the current guideline recommendations. As such, we have concluded that the guideline does not warrant an update at this time.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
British Cardiovascular Society and British Heart Valve Society	Disagree	Reference 9 in the new review consultation document is cited as providing evidence that the guidelines do not require to be changed. However this was a literature review. The description of high-risk cardiac patients was superficial and incomplete describing variation in guidelines and textbooks rather than analysing primary references.			Thank you very much for your comment. Systematic reviews were one of the study types within our inclusion criteria for the in-house review of CG64. In the process of preparing the consultation document, we do not conduct a full systematic review of the literature we have not carried out a full critical assessment of the studies cited in the stakeholder consultation document.. The purpose of the review is to attempt to identify where there is a significant amount of new evidence that might warrant more detailed consideration during an update. The Lockhart (2007) study assessed the evidence relating to the use of prophylactic antibiotics before dental procedures in people with specific medical conditions. The review concluded that there is little or no evidence to support the use of antibiotic prophylaxis in people with the medical conditions (including

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
					people with cardiac-native heart valve disease and prosthetic heart valves) that were the focus of the review. As such, we felt that this study supports the current guideline recommendations and contributed towards our conclusion that the guideline does not warrant an update at this time.
British Cardiovascular Society and British Heart Valve Society	Disagree	Reference 5 in the new review consultation document is cited as providing evidence that the guidelines do not require to be changed. In fact the use of amoxicillin reduced the incidence of endocarditis-related bacteria after dental extraction from 60% to 33%, similar to that after tooth-brushing. The review concludes that toothbrushing may be a greater threat than dental extraction for individuals at risk of endocarditis. However, the Societies suggest that a more plausible conclusion is that amoxicillin is effective in reducing the bacteraemia after dental extraction. This was also included within the conclusions of the reference but not in the NICE review.			Thank you very much for your comment. In the process of preparing the consultation document, we do not conduct a full systematic review of the literature and as such we have not carried out a full critical assessment of the studies cited in the stakeholder consultation document. We therefore were unable to report all the data presented in the study conducted by Lockhart et al (2008). In addition, incidence of infective endocarditis was not reported as a measured outcome in the abstract and, as such, we were limited in the amount of information we were

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
					able to report from this study. You are correct in stating that the full conclusion reported in the abstract was: Although amoxicillin has a significant impact on bacteremia resulting from a single-tooth extraction, given the greater frequency for oral hygiene, toothbrushing may be a greater threat for individuals at risk for infective endocarditis. In particular, we felt that the statement relating to toothbrushing was relevant as this was something that the GDG discussed and concluded in the original guideline.
British Cardiovascular Society and British Heart Valve Society	Disagree	In reference 5 in the new review consultation, the beneficial effect of antibiotic prophylaxis is greater than suggested by the conclusions. Results are given as cumulative for all the draws, but the greatest differences between patient groups occurred early. At 1.5 min, the incidence of Streptococcal bacteraemia was 8%, 14% and 44% for the toothbrushing, extraction-amoxicillin, and extraction-placebo groups respectively. At 5 min, the incidence of streptococcal bacteraemia was 4%,10% and 56%.			Thank you very much for your comment. In the process of preparing the consultation document, we do not conduct a full systematic review of the literature and as such we have not carried out a full critical assessment of the studies cited in the stakeholder consultation document. We therefore were unable to report all the data presented in the study conducted by Lockhart et al (2008). In addition, incidence of

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
					infective endocarditis was not reported as a measured outcome in the abstract and, as such, we were limited in the amount of information we were able to report from this study. However, the authors concluded in the abstract that given the greater frequency for oral hygiene, toothbrushing may be a greater threat for individuals at risk for infective endocarditis which we felt was relevant as this was something that the GDG discussed and concluded in the original guideline.
British Cardiovascular Society and British Heart Valve Society	Disagree	In reference 5 in the new review consultation, the results given for endocarditis-related bacteraemia include unusual organisms such as acinetobacter and stenotrophomonas and the incidence of bacteraemia due to streptococci is much less. The magnitude of streptococcal bacteraemia could have been higher with extractions than with toothbrushing but would not have been detected by this study (less than 10,000 orgs/ml).			Thank you very much for your comment. In the process of preparing the consultation document, we do not conduct a full systematic review of the literature and as such we have not carried out a full critical assessment of the studies cited in the stakeholder consultation document. We therefore cannot comment on the limitations of the study conducted by Lockhart et al (2008) particularly as the full

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
					methodology of the study is not clear from the abstract. However, the authors concluded in the abstract that given the greater frequency for oral hygiene, toothbrushing may be a greater threat for individuals at risk for infective endocarditis which we felt was relevant as this was something that the GDG discussed and concluded in the original guideline.
British Cardiovascular Society and British Heart Valve Society	Disagree	In reference 6 in the new review consultation, the limitations of the Netherlands case-control retrospective study are not discussed including: (i)the lack of known high risk cardiac cases (ii)the comparison of cases up to 180 days after a procedure (when a period up to 14 days would have been more appropriate).			Thank you very much for your comment. In the process of preparing the consultation document, we do not conduct a full systematic review of the literature and as such we have not carried out a full critical assessment of the studies cited in the stakeholder consultation document. We therefore cannot comment on the limitations of the systematic review conducted by Oliver et al (2008). However, the systematic review included no additional studies since the 2004 version which was included in the original

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
					guideline. As such, we concluded that no new evidence was identified which would change the direction of current guideline recommendations and contributed towards our conclusion that the guideline does not warrant an update at this time.
British Cardiovascular Society and British Heart Valve Society	Disagree	Reference 4 in the new review consultation document is cited as providing evidence that the guidelines do not require to be changed. However, this study sought to determine risk factors for in-hospital mortality from IE in children with congenital heart disease. The study is not relevant to the validity of antibiotic prophylaxis.			Thank you very much for your comment. This study was included in the section relating to adults and children with structural cardiac defects at risk of developing infective endocarditis as the aim of the study was to report risk factors for in-hospital mortality during infective endocarditis in patients with congenital heart disease. The study was not discussed under the section relating to antibiotic prophylaxis to prevent infective endocarditis.
RCPCH	Yes	Through the process no additional areas were identified which were not covered in the original guideline scope or would indicate a significant change in clinical practice. There are no factors described in the proposal which would invalidate or	No	No	Thank you for your comment.

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
		change the direction of current guideline recommendations.			
RCPCH		The College thinks it would be helpful if the summary of papers gives an age range to indicate if children are included in the study.			Thank you for your comment. In the process of preparing the consultation document, we have not carried out a full assessment of the studies cited in the stakeholder consultation document and as such we are unable to confirm full details (including the age range of study participants) of the identified studies.
BMFMS	Agree	No new evidence which would warrant updating current guidance			Thank you for your comment.
FGDP(UK)	Agree with the proposal not to update	Recent evidence that NICE guidance on antibiotic prophylaxis has not caused an increase in infective endocarditis confirms the validity of the guidance, the key reference being Thornhill et al *BMJ* (ref 10) in the review document).	None	None	Thank you for your comment.