

<p>Institution: The University of Manchester</p>
<p>Unit of Assessment: 3</p>
<p>Title of case study: Cochrane Oral Health Group leads the international evidence base for oral health: Antibiotics for the prevention of bacterial endocarditis. (ICS-07)</p>
<p>1. Summary of the impact Life-threatening bacterial endocarditis occurs on previously damaged cardiac valves. Established dental practice has been to administer antibiotics to patients who are at risk. This practice has been linked with increased antibiotic resistance, which represents one of the greatest threats to public health.</p> <p>Researchers at the University of Manchester (UoM) evaluated the evidence for this practice by undertaking a high quality systematic review (initially published 2004). The review has informed multiple international guidelines. Publication of the NICE guideline led to a fall in the unnecessary prescription of antibiotics from 10,727 to 2,292 per month, an approximate annual saving of £174,580.</p>
<p>2. Underpinning research <i>See section 3 for references [1-2]; see section 5 for corroborating sources (S1-S10); UoM researchers are given in bold. In REF3a and REF5 this case study is referred to as ICS-07.</i></p> <p>The impact here flows from a Cochrane review, and its subsequent update, conducted and coordinated at the editorial base of the Cochrane Oral Health Review Group, UoM. The Cochrane Oral Health Group has been based in Manchester since 1997 and has received consistent funding of over £3m from the Department of Health and currently has funding until 2015. The review was used to inform the NICE guidance issued in 2008 and received specific funds from the Cochrane Incentive Scheme.</p> <p>Key researchers were:</p> <ul style="list-style-type: none"> • Lee Hooper (Lecturer, 2000-2004) • Richard Oliver (Lecturer, 1998-2005; Senior Lecturer, 2005-2006; Honorary Consultant, 2006-2010) • Helen Worthington (Reader, 1998-2003; Professor of Evidence Based Care, 2003-date) <p>The underpinning research was undertaken by a team of UoM content experts and methodologists who ensured that this review was of high quality. Randomised controlled trials are difficult in this area due to the low incidence of bacterial endocarditis; therefore other study designs were also considered, requiring new methodological approaches and specific expertise. The review was also supported by a team of international clinical experts.</p> <ul style="list-style-type: none"> • We undertook a systematic review which initially investigated penicillin for the prevention of bacterial endocarditis in patients having dental treatment [1]. • Authors' conclusions from 2004 review: there is no evidence about whether penicillin prophylaxis is effective or ineffective against bacterial endocarditis in people at risk who are about to undergo an invasive dental procedure [1]. • We undertook an update of the review, extending it to all antibiotics; the conclusions remained the same [2]. <p>Based on the reviews conducted it was concluded that there is a lack of evidence to support published guidelines which underpin the prescribing of antibiotics prophylaxis for dental procedures</p>

Impact case study (REF3b)

to prevent bacterial endocarditis. There are potential harms and costs of antibiotic administration that outweigh any beneficial effect. There is also an ethical need for practitioners to discuss the potential benefits and harms of antibiotic prophylaxis with their patients before a decision is made. This review continues to be one of the COHG's priority reviews which is closely monitored with regard to the need for updating.

3. References to the research

The review was published in The Cochrane Library.

1. **Oliver R**, Roberts GJ, **Hooper L**. Penicillins for the prophylaxis of bacterial endocarditis in dentistry. Cochrane Database of Systematic Reviews 2004, Issue 2. Art. No.: CD003813. DOI: 10.1002/14651858.CD003813.pub2.
2. **Oliver R**, Roberts GJ, **Hooper L**, **Worthington HV**. Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD003813. DOI: 10.1002/14651858.CD003813.pub3.

4. Details of the impact

See section 5 for numbered corroborating sources (S1-S10).

Context

Many authorities have questioned the routine use of antibiotics for endocarditis prophylaxis, arguing that the adverse effects of antibiotics may outweigh the potential benefits [2] (S3). The over prescription of antibiotics by the whole medical and veterinary professions has resulted in the emergence of resistance of many organisms to the traditional therapeutic antibiotics available. Such antibiotic-resistant bacteria pose a real threat to global health, and England's Chief Medical Officer has called for urgent action to address the overuse of antibiotics. The Department of Health launched a five-year action plan in 2013 to try to address the issue of antibiotic resistance and ensure that they are only prescribed where truly needed. This builds on their original 2000 strategy.

Pathway to impact

The Cochrane review sparked much international debate (S2-4) around the prescribing of antibiotic prophylaxis for the prevention of bacterial endocarditis, with some dentists unwilling to change practice, concerned about the possibility of putting their patients at risk. Following the publication of the NICE guidance (2008) (S1), in which the initial review [1] was used as the highest level of evidence (S3), the findings of the review were able to have a significant impact which resulted in a dramatic reduction of antibiotic prophylaxis for bacterial endocarditis. Two authors on the review (**Oliver** and Roberts) were members of the guidance development group in the development of the NICE guidelines. The 2008 review update [2] was produced alongside the NICE guidance (S3) and the Cochrane Oral Health Group were stakeholders in the development of this guidance.

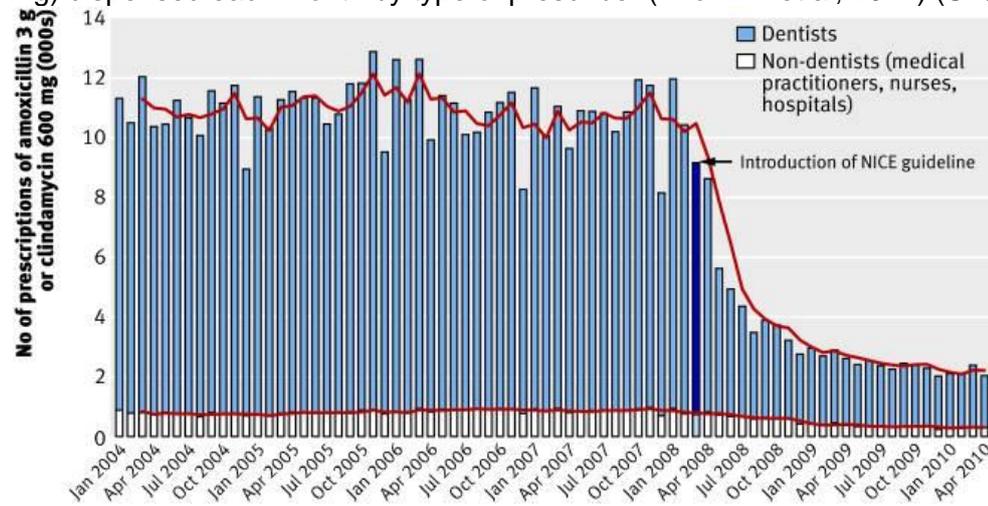
Additionally, the review was used to inform other international guidelines, including the American Heart Association (2007) and the British Society for Antimicrobial Chemotherapy 2006) (S5-9).

Within the UK, NICE recommendations were to stop routinely prescribing antibiotic prophylaxis for patients at risk of bacterial endocarditis undergoing dental and a wide range of other invasive procedures. An update review was undertaken to reflect emerging evidence; no amendments to the initial conclusions were made.

Reach and significance of impact

- The NICE guidelines which utilised the Cochrane review have dramatically changed practice as can be seen in the 78.6% drop in prescribing rates for antibiotic prophylaxis in England (Figure 1) (S 7). There has been no evidence of a large increase in the incidence of cases of, nor deaths from, infective endocarditis in the two years after the guideline.
- Patients in the UK no longer routinely receive antibiotic prophylaxis for endocarditis. Resistance to antibiotics is one of the greatest threats to public health. The unnecessary prescribing of antibiotics can lead to increased resistance, which is of concern to the general population as a whole, not just those at risk of bacterial endocarditis.
- Since 2008 there has been a reduction, on average, of 8,000 prescriptions of antibiotic prophylaxis per month in England alone, resulting in a significant cost saving of up to £219,000 per year (S10).
- The range of potential side effects from the administration of antibiotics is vast, largely with a hypersensitive aetiology but some direct toxic effects may also occur. All four types of hypersensitivity reaction have been reported with the use of penicillins including the most severe reaction, anaphylactic shock, and other type I reactions including allergic bronchial obstruction, allergic rhinitis and angio-oedema; haemolytic anaemia, type II, has been recorded; drug fever, a type III reaction and the delayed type hypersensitivity (type IV) of allergic dermatitis. Reduction in use of antibiotics *per se* reduces the risk of such adverse reactions amongst patients.
- The review has additionally been used to inform international guidance in the U.S.A., Europe and Asia Pacific (S7-9).

Figure 1. Total number of prescriptions for antibiotic prophylaxis (amoxicillin 3 g or clindamycin 600 mg) dispensed each month by type of prescriber (Thornhill et al, 2011) (S10).



5. Sources to corroborate the impact

- S1 **National Institute for Health and Clinical Excellence** (Wray D, Keenan D, Franklin D, Gibbs J, Sandoe J, Orr K, et al.) NICE clinical guideline 64: Antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures (March 2008) <http://www.nice.org.uk/nicemedia/pdf/CG64NICEguidance.pdf>
- S2 **Friedlander AH.** Antibiotic Prophylaxis. *Journal of the American Dental Association* 2009;140;11;1347-8

- S3 **Gopalakrishnan PP, Shukla SK, Tak T.** Infective Endocarditis: Rationale for Revised Guidelines for Antibiotic Prophylaxis *Clinical Medicine and Research* 2009;7;3;63-8
- S4 **Duval X, Leport, C.** Prophylaxis of infective endocarditis: current tendencies, continuing controversies *Lancet Infectious Diseases* 2008;8;225-32
- S5 **The Royal College of Surgeons of England and British Society for Antimicrobial Chemotherapy** (Gould FK, Elliott TSJ, Foweraker J, Fulford M, Perry JD, Roberts GJ, et al.) British Society for Antimicrobial Chemotherapy Guidelines for the Prevention of Endocarditis (*February 2006*)
<http://www.rcseng.ac.uk/fds/Documents/Patient%20Information%20Sheet.doc>
- S6 **British Society for Antimicrobial Chemotherapy** (Gould FK, Elliott TSJ, Foweraker J, Fulford M, Perry JD, Roberts GJ, et al.) Guidelines for the prevention of endocarditis: report of the Working Party of the British Society for Antimicrobial Chemotherapy. *Journal of Antimicrobial Chemotherapy*. 2006, 57(6): 1035–42
<http://jac.oxfordjournals.org/content/57/6/1035.full.pdf>
- S7 **American Heart Association** (Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al.) Prevention of infective endocarditis: guidelines from the American Heart Association *Journal of the American Dental Association*. June 2007, 138(6): 739-60
<http://jada.ada.org/content/138/6/739.full.pdf>, and *Journal of the American Dental Association*. January 2008, 139(Suppl 1): 3S-24S http://www.jada-plus.com/content/139/suppl_1/3S.full.pdf
- S8 **National Heart Foundation of New Zealand** (Ellis-Pegler R, Sharpe N, Everts R, Chambers S, Hornung T, Hay KD et al.) Guideline for Prevention of Infective Endocarditis Associated with Dental and Other Medical Interventions (*December 2008*)
<http://www.ttophs.govt.nz/vdb/document/312>
- S9 **European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and by the International Society of Chemotherapy (ISC) for Infection and Cancer** (Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, et al.) Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009). *European Heart Journal*. 2009, 30(19): 2369–413 <http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-IE-FT.pdf>
- S10 **Thornhill MH, Dayer MJ, Forde JM, Corey GR, Chu VH, Couper DJ, Lockhart PB.** Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. *BMJ* 2011;342:d2392
<http://www.bmj.com/content/342/bmj.d2392>