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## An Alarming Rise in Incidence of Infective Endocarditis in England Since 2009: Why?

**Martin H. Thornhill, MBBS, BDS, PhD<sup>a,b</sup>, Mark J. Dayer, MBBS, PhD<sup>c</sup>, Jon Nicholl, DSc<sup>d</sup>, Bernard D. Prendergast DM, FRCP<sup>e</sup>, Peter B. Lockhart, DDS<sup>b</sup>, Larry M. Baddour, MD<sup>f</sup>.**

<sup>a</sup>Unit of Oral & Maxillofacial Medicine Surgery and Pathology, School of Clinical Dentistry, University of Sheffield, Sheffield, UK; <sup>b</sup>Department of Oral Medicine, Carolinas Medical Center – Atrium Health, Charlotte, NC; <sup>c</sup>Department of Cardiology, Taunton and Somerset NHS Trust, Taunton, Somerset, UK; <sup>d</sup>School of Health and Related Research, University of Sheffield, Sheffield, UK; <sup>e</sup>Department of Cardiology, St Thomas' Hospital, London, UK; <sup>f</sup>Division of Infectious Diseases, Departments of Medicine and Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, MN.

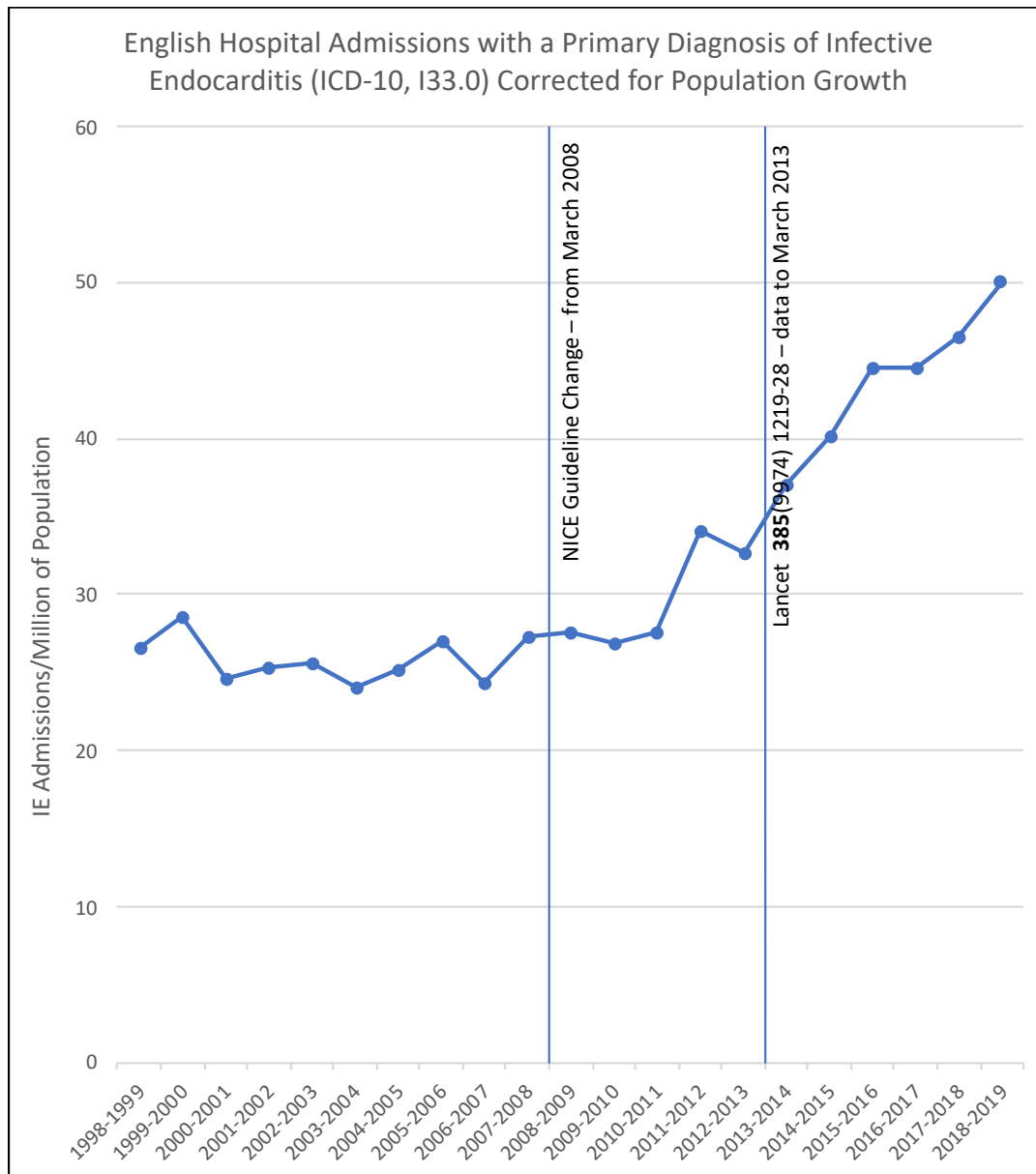
Infective endocarditis (IE) is a life-threatening condition with a 50% requirement for early cardiac surgery and 30% mortality at 1 year.<sup>1</sup> We have recently used publicly available annual admission data for hospitals in England <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity>, to examine the incidence of IE admissions (primary ICD-10 diagnostic code I33) between 1998-2019. These data demonstrate stable incidence between 1998-9 (26.6 cases/million) and 2009-10 (26.9 cases/million) but an 86% increase to 50.0 cases/million in 2018-19 (Figure).

One hypothesised cause of IE is oral pathogens entering the bloodstream during invasive dental procedures. Consequently, use of antibiotic prophylaxis (AP) prior to invasive dental procedures in at risk patients is a long-held preventive measure - but its use remains controversial. Since 2007, international guidelines have recommended that AP should be restricted to patients at highest-risk of adverse outcome (those with a previous history of IE, prosthetic or repaired heart valves, or complex congenital heart disease), reflecting a lack of evidence for AP efficacy, concerns for risk of adverse drug reactions, and the possibility that AP contributes to an ever-increasing global burden of antibiotic resistance. In March 2008, however, the National Institute for Health and Care Excellence (NICE) boldly recommended complete cessation of AP to prevent IE in the UK, thereby creating conditions for a natural experiment of its efficacy.

In 2014, our paper in this journal<sup>2</sup> demonstrated a large and significant ( $p < 0.0001$ ) fall in AP prescribing in England following implementation of NICE guidance and a parallel significant increase in IE incidence ( $p < 0.0001$ ) beyond the preceding upward trend; by March 2013, there were 35 extra cases of IE per month (419 per annum).<sup>2</sup> Since then, NICE has acknowledged public and professional concern, and adjusted wording of their guidance to indicate that AP is not 'routinely' recommended (<https://www.nice.org.uk/guidance/cg64>).<sup>3</sup> This subtle change, however, failed to define routine *versus* non-routine and has caused confusion for dentists, cardiologists and their patients. In response, the Scottish Dental Clinical Effectiveness Programme (SDCEP) produced advice for dentists on clinical implementation of the NICE guidelines (<http://www.sdcep.org.uk/published-guidance/antibiotic-prophylaxis/>). Key points include explanation of the risk of developing IE after invasive dental procedures to those at increased-risk, clarification of the risks and

benefits of AP, and empowerment of individual patients to determine whether or not they receive AP. Although endorsed by NICE and the British Cardiovascular Society, this advice has not been widely publicised and is not referred to in the NICE guidelines, hence most dentists remain unaware of it or are confused about its implementation.

In the absence of microbiological data, the rapidly increasing incidence of IE in England cannot be attributed solely to cessation of AP in the wake of NICE recommendations. Indeed, multiple contributory factors may be implicated, including an ageing population with associated comorbidities, increased use of intra-cardiac devices (permanent pacemakers, implantable cardioverter-defibrillators, surgical and transcatheter heart valves) and vascular interventions (including haemodialysis in the growing population with chronic renal failure), epidemic levels of injection drug use and increased diagnostic awareness of IE. The emergence of staphylococci and enterococci (neither of which are targeted by current AP strategies) as common causes of nosocomial infection could also have contributed to this increase. Nevertheless, these findings are disturbing and contrast with reports of falling incidence in the US<sup>4-7</sup> and falling or more modest increases in Europe,<sup>8-10</sup> where contributory factors are likely to be similar to those in England. Greater public health awareness and further investigation of the causes of this alarming increase in IE incidence in England are warranted alongside renewed emphasis on education of patients at risk, maintenance of good oral hygiene, early IE diagnosis, timely referral, and specialist care.



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#### **Author Contributions:**

Martin H. Thornhill - conception, literature search, figures, study design, data collection, data analysis, data interpretation, writing and editing.

Mark J. Dayer - conception, literature search, figures, study design, data collection, data analysis, data interpretation, writing and editing.

Jon Nicholl - study design, data interpretation, writing and editing.

Bernard D. Prendergast - data interpretation, writing and editing.

Peter B. Lockhart - data interpretation, writing and editing.

Larry M. Baddour - data interpretation, writing and editing.

#### **Conflicts of Interest:**

MT, JN, BP, PL and LB report no conflicts of interest. Dr. Dayer reports personal fees from Biotronik, unrelated to the submitted work.

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