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Summary of Research:

Background:
Infective endocarditis (IE), an infection of the lining of the heart – particularly the heart valves, is a serious disease with high morbidity and mortality.(1) Viridans group streptococci (VGS) from the oral cavity are implicated as the cause in 35-45% of cases.(2-5) It is not clear if, and to what extent, VGS enter the circulation during daily activities such as chewing food and cleaning teeth or as a result of invasive dental procedures such as extractions, endodontic treatment and dental scaling, particularly in those with poor oral hygiene(6). Because of the hypothesised link to invasive dental procedures, antibiotic prophylaxis (AP) prior to invasive dental procedures has been the main focus of IE prevention for over 60 years and remains the standard of care for individuals at high-risk of IE in most of the world.(7, 8) However, there has never been a randomised clinical trial (RCT) of AP. Because of this, NICE produced a guideline recommending cessation of AP in 2008.(9) The UK is now the only country in the world where AP is not recommended for patients at high-risk of IE.(7, 8) Recent research, however, has shown a significant increase in the incidence of IE following introduction of the NICE guidelines in March 2008(10) and this has raised concerns about the advice not to give AP prior to invasive dental procedures in the UK.

Ethical concerns along with the size, cost and complexity of an RCT, explain why no RCT to evaluate AP has taken place to date and why there is unlikely to be an RCT in the near future. Before an RCT would be worthwhile, we need to be certain that there is an association between invasive dental procedures and IE and that is the purpose of the IDEA-study. Indeed, such a study could render an RCT unnecessary.

Methods:
The IDEA-Study will link national data on courses of dental treatment and hospital admissions for IE to investigate if there is a link between invasive dental procedures and the development of IE. Time to diagnosis data for IE indicate that ~90% of cases present within 3 months of a causal bacteraemic event such as an invasive dental procedure.(11) So we will address the following questions:

1. Is the frequency of invasive dental procedures higher in the 3 months immediately preceding an IE diagnosis than in earlier 3 month control periods (a case-crossover design study(12))?
2. Is the incidence of IE higher in the 3 months immediately following a CoT that involves an invasive dental procedure than in the 3 months following a CoT that does NOT involve an invasive dental procedure (a cases-control study)?
3. If there is an association between invasive dental procedures and IE, how soon after the invasive dental procedure is the peak incidence of IE? We will plot Kaplan-Meier survival analysis curves comparing IE free survival following CoT with and without an invasive dental procedure.
4. If there is an association between invasive dental procedures and IE, do some types of invasive dental procedure have a greater likelihood of causing IE than others (comparing tooth extractions with scale and polish and endodontic treatments)?
5. Is the risk of IE following an invasive dental procedure greater in those considered at 'high-risk' of developing IE?

Importance:
This study is important because there are currently ~2,000 cases of IE annually associated with ~600 deaths and the incidence of IE is steadily increasing in England.(1) All require hospitalization and intensive long-term treatment with antibiotics.(1) A high proportion of patients require surgery to replace damaged heart valves and long-term morbidity is high.(1) The resulting cost to individuals, families, society and the NHS is extremely high. In contrast, AP is cheap and comparatively safe.(13) So if there is a link between invasive dental procedures and IE, there may be substantial financial, personal and societal savings in giving AP. Alternatively, if there is no link, then AP use is unnecessary and could be stopped with significant financial savings, a reduction in the risk of individuals developing adverse drug reactions to the antibiotics used for prophylaxis and a reduction in the risk to society as a whole of antibiotic resistant organisms developing from the unnecessary use of antibiotics for prophylaxis. Furthermore, it would suggest that IE prevention should re-focus on improving the oral hygiene of those at high-risk of IE.

This study will also provide important data upon which NICE and other guideline committees around the world can base their guidelines.

Background and Rationale:

Infective endocarditis (IE), an infection of the lining of the heart – particularly the heart valves, is a serious disease with high morbidity and mortality.(1) Viridans group streptococci (VGS) from the oral cavity are implicated as the cause in 35-45% of cases.(2-5) It is not clear if VGS enter the circulation as a result of daily activities such as chewing food and cleaning teeth in those with poor oral hygiene(6) or due to invasive dental procedures such as extractions, endodontic treatment and dental scaling. However, because of the hypothesised link to invasive dental procedures, antibiotic prophylaxis (AP) prior to invasive dental procedures has been the main focus of IE

prevention for over 60 years and remains the standard of care for individuals at high-risk of IE in most of the world.(7, 8) None-the-less, there has never been a randomised clinical trial (RCT) of AP(14) and there is little good quality evidence to support its effectiveness.(2, 4, 15)

Because of this lack of evidence, NICE produced a guideline recommending cessation of AP in 2008.(9) Since then, the UK has been the only country in the world where AP is not recommended for patients at high-risk of IE. Guideline committees elsewhere in the world have continued to recommend AP prior to invasive dental procedures for all individuals considered at high-risk of IE, including the European Society for Cardiology (ESC) – who produce AP guidelines for the whole of Europe,(7, 16) and the American Heart Association (AHA) – who produce the guidelines for North America and are also used widely in the Middle East, Asia and South America.(8) Recently, a study published in the Lancet(10) showed a significant increase in the incidence of IE following introduction of the 2008 NICE guideline. This has raised concerns about the advice not to give AP prior to invasive dental procedures in the UK and provided support for the recommendation to give AP that exists everywhere else. As a result, NICE undertook a review of the evidence relating to AP. At the same time the ESC undertook a review of its AP guidelines.

In September 2015, after evaluating exactly the same evidence, NICE and the ESC announced the result of their reviews. The results could not have been more different. NICE announced there was insufficient evidence to warrant a change to their existing guidance and continue to recommend no AP.(17) In contrast, the ESC concluded "the weight of evidence and opinion was in favour of the efficacy and usefulness of antibiotic prophylaxis in preventing IE in those at high-risk".(7) They also concluded that the risk of not giving antibiotic prophylaxis outweighed any risk of giving it and therefore recommended that "antibiotic prophylaxis should be given before invasive dental procedures to all patients at high-risk of IE". The ESC guideline committee(7) also considered but rejected the NICE view for the following reasons: (a) the remaining uncertainties regarding estimations of the risk of IE; (b) the worse prognosis of IE in high-risk patients, in particular those with prosthetic valves; (c) the fact that high-risk patients account for a very small proportion of those previously covered by antibiotic prophylaxis, thereby reducing the number exposed to any possible harmful adverse effects. Currently, the AHA guidelines committee take a very similar view to the ESC.(8) The result of these reviews is even more confusion and uncertainty on the part of dentists, cardiologists and their patients in the UK about how to prevent oral bacteria related IE in those at risk of the disease.(18)

The main reason NICE felt there was insufficient evidence to support AP in 2008 (9) was the lack of RCT data on the efficacy of AP. This was also the reason cited by NICE in 2015 for deciding that there was insufficient evidence to warrant any change in their guidance.(17) In contrast, in the absence of RCT data, the ESC, AHA and most other guideline committees around the world have put more emphasis on the evidence provided by good quality observational and animal studies, and also took into account the potential risks to patients of recommending, or not recommending, AP.

There are several reasons why a RCT of AP has not been performed to date, and is unlikely to be performed in the foreseeable future. AP is not a treatment, it is a prevention strategy and IE is comparatively rare. This means that hundreds of individuals at risk of endocarditis would need to receive AP to prevent one case of IE. The Lancet data suggest the number of individuals that would need to receive AP to prevent one case of IE is 277 (95%CI. 156-1217).(10) The need to randomise patients to placebo or active prophylaxis would further double the size of the study. Furthermore, to be effective AP has to be administered immediately before an invasive dental procedure is performed. This means the decision to give AP has to be made by dentists. However, each dental practice only sees a small number of individuals at risk of IE. So large numbers of dental practices across the country would need to be involved in recruiting and randomising patients to AP or placebo prophylaxis. All this means that the size, cost and complexity of a RCT to evaluate AP would be huge. Several attempts have been made to fund such an RCT – including by NIHR-HTA and NIH (see grant form section on 'Previous Application History'). Ultimately, the high cost has prevented these and other funders from funding an RCT of AP. A further barrier to

an RCT, particularly in countries where AP is the current standard of care, are the ethical and medico-legal concerns about withholding AP from individuals at high-risk of IE who are randomised to placebo prophylaxis. This is because of concern that individuals randomised to placebo prophylaxis could develop IE and die. So far this concern has prevented attempts to perform an RCT of AP in countries outside the UK.(19) Together, these reasons explain why an RCT has not taken place to date and may never do so.

In the absence of a RCT we need to identify other ways of addressing this issue. AP only makes sense if there is a link between invasive dental procedures and IE. Yet there are few studies that have specifically looked at the existence of a temporal link between invasive dental procedures and IE and the results of these are contradictory and questionable. In 1995, Lacassin *et al* performed a small case control study in France in which they compared the occurrence of invasive procedures in the 3 months prior to hospital admission in 171 patients with IE and a control population.(2) They found a significantly elevated risk of IE in those who had undergone an invasive procedure and estimated that AP could reduce the risk of IE by 5-10%. However, they acknowledged that their study was underpowered and the case –control design was criticised with regard to the risk of selection bias and confounding due to potential differences in IE risk factors between cases and controls. In 1998, Strom *et al* performed a case control study in the Philadelphia area.(4) They compared the incidence of invasive dental procedures in the 3 months prior to hospital admission in 273 IE cases and controls and found no evidence for an association between invasive dental procedures and IE. However, again the authors acknowledged the study was underpowered to identify an association and at risk of selection bias and confounding due to differences in the risk of IE in the cases and controls. In an attempt to avoid the issues of selection bias and risk factor confounding, Porat Ben-Amy *et al*, performed a case-crossover design study to address the same problem.(20) They identified 170 Israeli patients with IE and used a patient questionnaire to identify any dental visits over the previous 2 years. The frequency of dental visits in the 3 months immediately before IE diagnosis was compared with the frequency in earlier 3-month periods. Again this study suffered from too small a sample size and from recall bias caused by the difficulty of patients recalling the timing and nature of dental procedures performed over the preceding 2 years. Recently, Pei-Chun Chen *et al* performed a larger case-crossover design study using a Taiwanese Longitudinal Health Insurance Database.(21) They identified 739 patients with IE and compared the incidence of invasive dental procedures in the 3 months immediately prior to IE diagnosis (cases) with earlier 3-month periods (matched control periods). They did not find a significant difference in the incidence of invasive dental procedures between cases and controls. However, they acknowledged the small number of IE cases in their study and the likelihood that they had insufficient statistical power to detect an association between IE and invasive dental procedures.

All of these studies were underpowered but even more importantly they were all performed in populations where the standard of care was to prescribe AP prior to invasive dental procedures. At the time of the Lacassin and Strom studies, patients at moderate- and high-risk of IE would have been given AP and in the case of the Porat Ben-Amy and Pei-Chun Chen studies, those at high-risk would have received AP. Clearly, it would be difficult to identify an association between invasive dental procedures and IE in a situation where patients at risk of IE were being given AP to prevent them developing the disease.

The purpose of the IDEA-study is to perform a much larger case-crossover study in a population where the standard of care is not to give AP. This is why we have chosen a study period from April 2009 – March 2016. Although the NICE guidelines recommending cessation of AP came into effect in March 2008, and AP prescribing fell quickly after their introduction,(10) by waiting an extra year before collecting data we will ensure that any carry-over effect of AP prescribing is minimised. This will optimise the chance of identifying any association between invasive dental procedures and IE that might exist and provide much more reliable data on this important issue. Currently, because the UK is the only country in the world where AP is not recommended, it is the only place where a study to investigate the association between invasive dental procedures and IE can be performed without the confounding effect of AP hiding any association.

The case-crossover design removes problems about selection bias and confounding for risk of IE because each case acts as its own control.(12, 22) Furthermore, by linking national dental and hospital episode statistics we do not have to rely on patient's recall to determine the timing and nature of any dental procedures that were performed. At the same time, we will also be able to perform a more traditional case-control study comparing the incidence of IE in individuals having a course of dental treatment that involves an invasive dental procedure with individuals having a course of dental treatment that does not involve an invasive dental procedure.

Why this research is needed now:

There is a lack of good quality data on this issue. Most of the literature consists of case reports, animal studies and poorly designed or underpowered observational studies. Hence the dilemma facing guideline committees around the world and the difference of opinion on the use of AP that exists between NICE(17) – that recommends no AP - and that of the American Heart Association (AHA),(8) European Cardiac Society (ESC),(7) and most other guideline committees around the world - who continue to recommend AP for those at 'high-risk' of IE. The recent publication of data in the Lancet(10) showing an increase in the incidence of IE in England following introduction of the NICE guidelines along with new data published in the Journal of Antimicrobial Chemotherapy(13) showing that the risk of adverse drug reactions to the antibiotics used for AP is much lower than previously thought have re-ignited the debate about the link between invasive dental procedures and IE and the value of AP. Hence the need for this study.

All of the major guideline committees around the world (including NICE, AHA and ESC) have identified the lack of evidence on the link between invasive dental procedures and IE as a major problem for them in issuing guidance on how to prevent IE and have called for more research on this important topic as being essential in helping them to guide clinicians and protect patients.(7, 8, 17)

Currently, there are over 2,000 cases of IE annually in England and the incidence of IE in England is increasing steadily. These cases are associated with a 15-20% immediate mortality and 30% one-year mortality i.e. ~600 deaths annually.(1, 10) All IE patients require hospitalisation and intensive long-term treatment with antibiotics.(1) A high proportion (~45%) require surgery to replace damaged heart valves and to remove sites of infection.(1) Long-term morbidity is very high with many patients suffering long term ill health including congestive heart failure, the need for continuing medical care and medication. Long term mortality is around 50%.(1) The resulting cost to individuals, families, society and the NHS is extremely high. In contrast, AP is cheap and comparatively safe.(13) So, if there is a link between invasive dental procedures and IE, there may be a substantial financial, personal and societal saving in giving AP prior to invasive dental procedures. Indeed, a recent health economic analysis has shown that each year AP could save the NHS £5.3-7.9 million and achieve health gains of 2,500 QUALYs (in press). Alternatively, if no such link exists, it is unlikely AP will be of any benefit and the cost of AP (and any RCT to prove its benefit) could be saved. And the unnecessary risk to individuals of adverse drug reactions and the risk to society from the unnecessary use of AP potentially furthering the development of antibiotic resistant bacteria, could be avoided. Furthermore, the lack of an association between invasive dental procedures and IE would suggest that the 35-45% of IE cases caused by VGS are more likely to result from daily activities such as chewing and tooth brushing in individuals with poor oral hygiene. In which case, we would have evidence to support a shift in the emphasis of IE prevention away from AP towards improving the oral hygiene of individuals at risk of IE.

Importantly, this study will provide data upon which NICE and other guideline committees around the world can base their recommendations and help dentists, cardiologist and their patients identify the most effective ways of preventing this devastating disease.

Aims and objectives:

The IDEA-Study will link national data on courses of dental treatment and hospital admissions for infective endocarditis (IE) to investigate if there is a temporal link or association between invasive dental procedures and the development of IE.

Hypothesis:
Our Null hypothesis is that: There is no temporal association between invasive dental procedures and the development of IE.

- If the null hypothesis is proven, this would suggest there is no rationale for AP and AP is unlikely to be effective in preventing IE. It would suggest other prevention strategies, such as improving oral hygiene, are likely to be more effective in preventing IE

Our alternative hypothesis is that: There is a temporal association between invasive dental procedures and the development of IE.

- If the alternative hypothesis is proven, whilst not proving the efficacy of AP, it would demonstrate that there is a logical rationale for prescribing AP prior to invasive dental procedures to protect those at risk of developing the disease and would add considerable weight to the recommendation to give AP.

Note:
Previous research has shown that ~90% of IE cases caused by an invasive dental procedure will result in hospital admission and a definitive diagnosis of IE within 3 months of that procedure.(11) This 3 month period is widely accepted within research studies for defining IE cases associated with a causal invasive procedure (see also 'Response to board's feedback' – item 4).

Primary Aim of the Study:
- Our primary aim is to perform a case-crossover design study(12) to quantify the incidence of invasive dental procedures in the 3 months immediately preceding an IE diagnosis (cases) and to compare this with the incidence of invasive dental procedures in earlier three months periods i.e. months 3-6, 6-9, 9-12 before the IE diagnosis (matched control periods) - to see if there is an association between invasive dental procedures and IE.

  Possible outcomes:
  - If there is a link between invasive dental procedures and IE, we would expect courses of dental treatment involving an invasive dental procedure to occur with significantly higher frequency in the 3 months immediately preceding the IE diagnosis than in earlier 3 month matched control periods (see the Flow Diagram).
  - Alternatively, if there is no link between invasive dental procedures and IE, we would expect there to be no significant difference in the incidence of invasive dental procedures in the 3 months immediately preceding an IE diagnosis and earlier 3 month periods (see the Flow Diagram).

Secondary Aims:
1. We will also perform a case-crossover design study comparing the incidence of courses of dental treatment that do NOT contain an invasive dental procedure (cases) in the 3 months immediately before an IE diagnosis with the incidence in periods 3-6, 6-9 and 9-12 month before the IE diagnosis (matched control periods).

Possible outcomes:

- Whether there is a link between invasive dental procedures and IE or not, we would not expect a significant difference in the frequency of courses of dental treatment that did NOT contain an invasive dental procedure between any of the 3 month periods. These data however, are important for the case-control analysis below and an important control to show if there is anything about a visit to a dentist (other than an invasive dental procedure) to associate it with the development of IE (see the Flow Diagram).

2. In addition, we will perform a case-control study comparing the frequency of courses of dental treatment that include an invasive dental procedure (cases) with the frequency courses of dental treatment that did NOT include an invasive dental procedure (controls) in the 3-month period preceding an IE diagnosis. This will enable us to further test if there is an association between invasive dental procedures and IE using a different analytical/statistical approach to that used in our primary aim.

   Possible outcomes:

   - If there is a link between invasive dental procedures and IE, we would expect a significantly higher incidence of courses of dental treatment involving an invasive dental procedure than courses of dental treatment NOT involving an invasive dental procedure in the 3 months immediately preceding an IE diagnosis (see the Flow Diagram).
   - Alternatively, if there is no link between invasive dental procedures and IE, we would expect there to be no significant difference in the incidence of cases and controls in the 3 months immediately preceding an IE diagnosis.

3. We will also plot Kaplan-Meier survival analysis curves comparing monthly IE free survival following courses of dental treatment that contain an invasive dental procedure (cases). For comparison we will also plot Kaplan-Meier survival curves comparing monthly IE free survival following courses of dental treatment that do NOT contain an invasive dental procedure (controls). If there is a link between invasive dental procedures and IE, this will give us more precise data about how soon after an invasive dental procedure IE is likely to occur. If a link exists, we can also stratify the data by type of invasive dental procedure to assess the relative risk of IE associated with each type of invasive dental procedure (extractions, scale and polish or endodontic treatment).

   Possible outcomes:

   - If there is a link between invasive dental procedures and IE, we would expect the Kaplan-Meier curve to a show a significant and more rapid fall in IE free survival in the first 3 months following an invasive dental procedure (cases). While in the controls we would expect a very small but continuous fall in IE survival spread evenly over the 12-month study period – reflecting the background incidence of IE.
   - Alternatively, if there is no link between invasive dental procedures and IE, we would expect both the case and control curves to display a similar small but steady fall in IE survival spread evenly over the 12-month study period.

4. Current ESC,(7) AHA(8) and NICE(17) guidelines define certain individuals as being at 'high-risk' for IE. This includes individuals with a previous history of IE, those with prosthetic or repaired heart valves or certain congenital heart conditions. Using methodology we previously developed,(10) it is possible to use the HES database to identify IE cases that occurred in 'high-risk' individuals (HR-IE cases) and we therefore propose to repeat the above analyses to see if invasive dental procedures occur more frequently in the 3 months immediately preceding diagnosis of an HR-IE case than in earlier 3 month periods and if HR-IE occurs more frequently following courses of dental treatment that contain an invasive dental procedure than following courses of dental treatment that do not contain an invasive dental procedure.

Research Plan:

The IDEA-Study will link national data on courses of dental treatment (NHS Business Service Authority Dental Database)(23) and hospital admissions for IE (Hospital Episode Statistics (HES) database)(24) to investigate if there is a link between invasive dental procedures and the development of IE. Time to diagnosis data shows that ~90% of IE cases with a defined cause, such as an invasive dental procedure, result in hospital admission within 3 months.(11) This 3 month figure has been widely used in other studies to define cases.(2, 4, 8, 16, 20, 21) So we will address the following questions:

- Is the incidence of invasive dental procedures higher in the 3 months immediately preceding an IE diagnosis than in earlier 3-month control periods?
- Is the incidence of courses of dental treatment involving an invasive dental procedure greater than courses of dental treatment that do NOT contain an invasive dental procedure in the 3 months preceding an IE diagnosis?
- If there is an association between invasive dental procedures and IE, how soon after the invasive dental procedure does the peak incidence of IE occur?
- If there is an association between invasive dental procedures and IE, what is the relative risk of developing IE with different types of invasive dental procedure (extractions, scale & polish, endodontic treatment)?
- Is the risk of IE following an invasive dental procedure greater in those considered at 'high-risk' of developing IE (i.e. HR-IE cases)?

From March 2008, the use of AP was no longer recommended for 'at risk' patients undergoing invasive dental procedures in the UK.(9) By March 2009, AP prescribing had fallen 76%.(10) So if invasive dental procedures are a risk factor for IE, the risk of developing IE will have been maximised since then. Also from April 2008, dentists working in the English National Health Service (NHS) were required to record if a patient had received a dental extraction, scale and polish or endodontic treatment i.e. an invasive dental procedure, as part of their course of dental treatment using NHS form FP17. Personal identifying data, other types of dental treatment (non invasive) as well as the start and end date of the course of treatment, are also recorded. Dentists must complete an FP17 for each patient they treat and send it to the NHS Business Service Authority (NHSBSA), where the data are recorded, in order to receive payment. Compliance is therefore high. We will, therefore study NHSBSA data from 1st April 2009 until 31st March 2015. By waiting a year after the introduction of the NICE guidelines, and inclusion of dental procedure recording on the FP17 form, before starting to collect data we will minimise any carry-over effect of AP prescribing or changeover effect on dental data recording.

All patients admitted to a hospital for treatment in England have their discharge diagnosis and other details, including patient identifying details, recorded on the Hospital Episode Statistics (HES) database. By searching the HES database using ICD-10 code I33.0 we can identify every patient admitted to hospital in England with a primary discharge diagnosis of IE. Standard protocols will be used to ensure we only record one single continuous hospital stay (superspell) for each patient and transfers between different consultants/hospitals during a single episode of treatment are not counted as multiple episodes of IE. By linking the NHSBSA dental database and the HES database at the individual patient level, we will be able to thoroughly examine the possible link between invasive dental procedures and IE.

The NHS Health & Social Care Information Centre (HSCIC) is the guardian of both datasets. They will link patient data across the 2 databases and anonymise it before making it available to us. The research team will therefore have no identifying information about patients in the study.

First we will identify every patient diagnosed with IE between 1st April 2010 and 31st March 2016. Preliminary data shows there were 10,593 IE diagnoses in England between 1st April 2009 and 31st March 2015 and that the incidence of IE is increasing year on year. Between 1st April 2010 and 31st

March 2016 we therefore expect the incidence of IE to be at least 10,593 and this is the figure we have used in our power calculations (see page 12, "Design and theoretical/conceptual framework" section). In addition, NHS Dental Services data shows that over the period April 2009 – March 2015 56% of the population were regular dental attenders (this does not take account of any of those just attending an NHS dentist in an emergency).(23)

We will also identify every course of dental treatment that occurred between 1st April 2009 – 31st March 2016. We need to use dental data from April 2009 rather than 2010 because we need to be able identify courses of dental treatment occurring in the 12 month observation window before any IE diagnosis. Preliminary analysis shows that between 1st April 2009 and 31st March 2015 there were ~90.6 million (m) courses of dental treatment (13.2m extractions, 78.6m scale and polish and 3.6m endodontic treatments - some courses of treatment contain more than one type of invasive dental procedure). So the actual figures for 1st April 2009 – 31st March 2016 will be larger. We will also identify every course of dental treatment that does NOT include an invasive dental procedure. Preliminary analysis identified ~85.8m of these between 1st April 2009 – 31st March 2015 (176.4m course of dental treatment in all). By linking patient identifying details for every course of dental treatment with the HES database, we will be able to identify all IE patients who had a course of dental treatment (including an invasive dental procedure or not) in the 12 months before their IE diagnosis. We will also be able to tell at what time point in the 12 month observation window before the IE diagnosis that course of dental treatment occurred.

Primary Analysis:

We will perform a case-crossover design study(12, 22, 25) comparing the frequency of invasive dental procedures in the 3 months immediately preceding an IE diagnosis (cases) with the frequency of invasive dental procedures in earlier 3-6, 6-9 and 9-12 month periods (matched control periods).

Secondary Analysis:

We will perform a similar case-crossover study comparing the frequency of courses of dental treatment NOT involving an invasive dental procedure (cases) in the first 3 months preceding an IE diagnosis with their frequency in earlier 3-6, 6-9 and 9-12 month periods (matched control periods).

We will also perform a case-control study comparing the frequency of courses of dental treatment involving (cases) and NOT involving (controls) an invasive dental procedure in each 3 month period preceding an IE diagnosis.

We will also plot Kaplan-Meier survival analysis curves comparing monthly IE free survival following a course of dental treatment involving an invasive dental procedure with IE free survival following a course of dental treatment NOT involving an invasive dental procedure. If there is a link, this will give us more precise data about how soon after an invasive dental procedure an IE diagnosis is likely to occur. If a link exists, we will also stratify the data by type of invasive dental procedure to assess the relative risk of IE associated with each type of invasive dental procedure (extractions, scale and polish or endodontic treatment).

We will repeat the above studies restricting our analysis to those IE cases that arose in individuals who would have been considered at 'high-risk' i.e. HR-IE cases.

Design and theoretical/conceptual framework:

The question "Is there a link between invasive dental procedures and IE?" will be addressed using two different study designs:

(i) A case-crossover design study(12) which is a type of self-controlled case-series.(26-28) The Self-Controlled Case Series (SCCS) method was originally developed by Farrington(26) to compare relative incidence of adverse events following vaccination. In brief, the method compares incidence in a 'risk' time period shortly following exposure, to the incidence during the remainder of the observation period, the control periods. In our proposed study we will compare the incidence of IE admission in a risk period which is from 0-3m post-invasive dental procedure (the 'exposure') to the incidence of IE admission in control periods from 3m-12m post exposure. The design resembles a retrospective non-randomised crossover study, but uses control time periods for each patient instead of a control patient group. Thus, each patient acts as their own control and the selection bias of a control population is avoided.(12) This methodology was developed ~25 years ago and is often used to examine the association between transient events and their outcome e.g. to identify events that might trigger a myocardial infarction or stroke, acute alcohol use and injury, cell-phone use and road traffic accidents, air pollution and asthmatic events etc.,(12, 29-32) as well as the link between invasive dental procedures and IE.(20, 21) Sample sizes for self-controlled case series are given by Muscoda(27) and are available from http://powerandsamplesize.com/Calculators/Test-Relative-Incidence-in-Self-Controlled-Case-Series-Studies/SCCS-Alt-2.

The cases in our study will be those IE admissions who had an invasive dental procedure in the 12 months before admission, this is the 'observation period'. The 'risk period' is the last 3 months of the 'observation period' (i.e. the 3 months just before the admission) and the control periods the previous 9 months. Our data will span the period between April 2009 and March 2016. The 6 years from April 2010-March 2016 are expected to identify 10,593 cases of IE admissions in HES data for England whose exposure to invasive dental procedures will be observed in the 7 years of NHS dental service data from April 2009-March 2016. We know that 56% of the population regularly use NHS dentists, and that at least half of all courses of dental treatment include and invasive dental procedure. If we assume that regular NHS dental patients are seen once every 2 years then we would expect that each patient would have an invasive dental procedure at least every 4 years. Bearing in mind that invasive dental procedures include common procedures such as a 'scale & polish' as well as less common procedures such as extractions this estimate is probably conservative.

Assuming there is no association between invasive dental procedures and IE, we can now estimate that our sample size will consist of 10,593 x 0.56 x 0.25 = 1,483 admissions for IE who had an invasive dental procedure in the previous 12 months. This will give 80% power to detect a relative incidence of 1.18, i.e. +18%, in the 3 month 'risk period' compared to control periods. If regular NHS dental patients have an invasive dental procedure once every 2 years then we will have 2,966 cases and 80% power to detect a relative incidence of 1.12, i.e. of +12%. This will give us the statistical power to detect any association between invasive dental procedures and IE that is likely to be of clinical significance and will greatly exceed the power of any previous study of this association.(2, 4, 20, 21)

(ii) A case-control study, where the frequency of courses of dental treatment involving an invasive dental procedure (cases) before an IE diagnosis is compared with the frequency of course of dental treatment that did NOT involve an invasive dental procedure (controls).

Target population:

The target population will include all IE diagnoses in England between 1st April 2010 and 31st March 2016 and all individuals within England who attended an NHS dentist for a check up or treatment between 1st April 2009 and 31st March 2016. All such courses of dental treatment will be divided into those that involved an invasive dental procedure (recorded on the FP17 data collection form that is returned to the NHS Business Services Authority Dental Data management centre in

Eastbourne as having had a dental extraction [single or multiple], endodontic treatment [root canal treatment] or a scale and polish), and those courses of dental treatment that did not involve an invasive dental procedure.

Inclusion/Exclusion Criteria:

Individuals falling into the target population will only be excluded if their NHS number is missing or cannot be derived using established algorithms from their other personally identifying data (name, date of birth, gender, address etc.). Any missing or corrupt records will also be excluded.

Setting/context:

The study will utilise Hospital Episode Statistics and NHS Business Services Authority Dental Data for the whole of England.

Sampling:

In this study, rather than sampling, we will be taking all individuals in England who were admitted to hospital with a final diagnosis of IE between 1st April 2010 and 31st March 2016 and were entered on the Hospital Episode Statistics database. In addition, we will be obtaining data from the NHS Business Services Authority Dental Database on all courses of dental treatment in England and Wales between 1st April 2009 and 31st March 2016. We will link these two data sets to identify any patients who developed IE and had a course of dental treatment in the preceding 12 months.

Data collection:

From the HES database we will collect data on all individuals who were admitted to hospital between 1st April 2010 and 31st March 2016 with a primary diagnosis of IE – identified by ICD-10 code I33.0. The data will include the hospital admission date and NHS number.

From the NHS Business Services Authority (NHSBSA) Dental Database we will collect data on all courses of dental treatment between 1st April 2009 and 31st March 2016. Included in this will be the date of any course of treatment and whether the treatment included any extraction, endodontic treatment or a scale and polish. In addition, the individual's NHS number will be collected or generated from personally identifying details by the NHSBSA.

Data analysis:

The Health & Social Care Information Centre (HSCIC) will use the NHS number to link the dental and hospital admissions data for each individual and then allocate a study number to replace the NHS number. In this way, the linked data supplied to us will be completely anonymous. We will then generate computer codes to interrogate the database and identify individuals who had a course of dental treatment at any time in the 12 months preceding an IE diagnosis hospital admission. Further analysis will determine exactly how many months before the IE diagnosis the course of dental treatment occurred and if the course of dental treatment involved an invasive dental procedure or not. Conditional logistic regression will be used to compare the likelihood of an invasive dental procedure occurring in the 3 months immediately before an IE diagnosis versus earlier matched control periods. Standard statistical methods will also be used in the case control study to compare the likelihood of an invasive dental procedure occurring in the 3 months preceding an IE diagnosis versus a course of dental treatment that did not involve an invasive dental procedure.

Additionally, we will plot Kaplan-Meier survival analysis curves comparing monthly IE free survival following an invasive dental procedure and a course of dental treatment that did NOT involve an invasive dental procedure.

By going back in time in the HES database (as far back as 2000) we can use previously published methodology(10) to identify those IE patients who were at high-risk of developing IE (HR-IE cases). This will enable us to repeat the analyses already described to determine of there is an increased risk of IE following invasive dental procedures in individuals at high-risk of IE. Our previous studies show that ~55% of IE cases fall into the HR-IE category.(10)

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