Article:
Thornhill, M. orcid.org/0000-0003-0681-4083, Dayer, M., Prendergast, B. et al. (1 more author) (2025) Endocarditis prophylaxis – indications, application and current controversies. Canadian Journal of Cardiology. ISSN: 0828-282X

https://doi.org/10.1016/j.cjca.2025.10.011

Supplementary Appendix S1

Endocarditis prophylaxis – indications, application and current controversies

Short title: Endocarditis prevention

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Research methodologies discussed in this review

A variety of different research methodologies have been employed in this narrative review. These have largely evaluated the association between different interventions, e.g. invasive dental procedures, and the outcome of interest e.g. developing infective endocarditis (IE), or the effectiveness of antibiotic prophylaxis in reducing the likelihood of developing AP. To facilitate understanding of these studies, a brief outline of the different methodologies is provided here.

Studies are descriptive (case reports, case series, descriptive surveys) or analytical. We have only included analytical studies in this review. There are two main types of analytical study: (i) observational or (ii) experimental/interventional studies. At the end, we also discus (iii) Meta-analysis which can bring together data from multiple studies.

(i) OBSERVATIONAL STUDIES

Observational study designs are used to investigate the relationship (or association) between an exposure (like a risk factor e.g. invasive dental procedures, or a treatment/prevention strategy e.g. AP) and a health outcome (like a disease, e.g. IE).

Advantages of Observational Studies

- Ethical and Practical Feasibility: Observational studies are often the only option when an experimental study would be unethical or impractical. For example, you can't ethically randomize people to smoke to study the effects of tobacco.

- Real-World Data: These studies use data from real-world settings, which makes their findings highly generalizable to the broader population. This is known as high external validity.
- Cost and Speed: They are typically faster and less expensive than randomised controlled trials (RCTs) since they can often use pre-existing data (e.g., medical records, health registries) and don't require the creation of a new, complex intervention.
- Investigation of Rare Outcomes: Observational studies, particularly case-control designs, are ideal for investigating rare diseases or health outcomes because they can enrol enough affected individuals to draw meaningful conclusions.
- Hypothesis Generation: The findings from observational studies can lead to new hypotheses that can then be tested more rigorously in experimental designs.

Limitations of Observational Studies

- Lack of Causality: The biggest limitation is that observational studies cannot definitively prove causation. They can only show an association or correlation between an exposure and an outcome. A classic example is the early observational studies suggesting a link between coffee drinking and heart disease; it was later found that many coffee drinkers also smoked, and smoking was the true cause.
- Bias and Confounding: They are highly susceptible to bias, which is a systematic error in the study design or conduct that can lead to a misleading result. Common biases include:
    - Selection Bias: The study groups are not truly comparable from the start. For example, a study on the effects of exercise may compare a group of naturally fit, active people with a group of people who are less healthy to begin with.
    - Recall Bias: Participants may not accurately remember past events or exposures, especially in retrospective studies. For example, people with a disease may be more likely to remember a specific exposure than healthy people.
    - Confounding: An unmeasured variable is associated with both the exposure and the outcome, distorting the true relationship. This is a major challenge and can make it difficult to determine if the exposure or the confounder is responsible for the outcome. Even when studies make concerted efforts to control for potential confounders, unidentified residual confounders may remain, or methods used to control for confounders are inadequate. This makes it extremely difficult to draw definitive conclusions about cause and effect from observational studies.
- Limited Control: Researchers have no control over the exposure or the environment. This makes it impossible to isolate a single variable's effect, unlike in an experimental study.

The five main types of observational study reported in this review are outlined below:

Cohort Study

A cohort study follows a group of people (a "cohort") over time to see who develops a specific outcome. Researchers identify a group of individuals who are initially free of the outcome of interest and then classify them based on their exposure status (e.g., to invasive dental procedures). They then track both groups over a period to compare the incidence of the outcome (e.g. IE) in the different groups.

- Example: A study enrols 1,000 people who do not have lung cancer. Researchers record their smoking habits and follow them for 20 years to see how many people in each group develop lung cancer.
- Key Feature: Researchers start with the exposure and look forward to the outcome. This design is good for rare exposures and can assess multiple outcomes.

Case-Control Study

A case-control study works in reverse. Researchers identify a group of individuals who already have the outcome of interest (the "cases") and a similar group who do not (the "controls"). They then look back in time to compare the exposure history of the two groups.

- Example: Researchers find 100 people with lung cancer (cases) and 100 people without it (controls) and then interview them about their past smoking habits to see if there's a difference in smoking history between the groups.
- Key Feature: Researchers start with the outcome and look back in time for the exposure. This design is efficient for studying rare diseases.

Case-Crossover Study

A case-crossover study is a specialized design used for studying the effects of transient exposures on acute events. It's a "self-controlled" study, meaning each person serves as their own control. Researchers compare a person's exposure during the "case period" (a short time just before the event) to their exposure during one or more "control periods" (other times when the event didn't happen).

- Example: To see if a dental extraction might increase the risk of developing IE, a researcher compares the incidence of dental extractions in the month immediately preceding any hospital admission for IE (case period) with the incidence of invasive dental procedures in a different time window, eg., time periods greater than one month before hospital admission with IE (control period).
- Key Feature: Only individuals who experienced the event (IE) are included. It controls for a person's unchanging characteristics (like genetics, or long-term lifestyle e.g. oral hygiene) because it compares exposure within the same individual.

Nested Case-Control Study

A nested case-control study is a more efficient variation of a large prospective cohort study. Instead of collecting detailed exposure data on every member of the entire cohort, which can be expensive and time-consuming, researchers use the existing cohort to create a

case-control study. When a case of the disease occurs within the cohort, they select one or more controls from the remaining at-risk members of the cohort.

- Example: From a large cohort of 10,000 people with blood samples stored at the start of the study, a researcher wants to study a rare disease. They find 50 people who developed the disease (cases). For each case, they randomly select 5 controls from the cohort who didn't develop the disease. They then analyze the stored blood samples only for these selected cases and controls, which is much cheaper than analysing all 10,000.
- Key Feature: This design combines the benefits of a prospective cohort study (less recall bias) with the efficiency of a case-control study. It's "nested" within the larger cohort.

Interrupted Time Series (ITS)

An ITS study is an observational design used to evaluate interventions that are implemented on a large scale (e.g., a new policy or a public health campaign – such as the change in AP guidelines). It analyses a series of data points collected over a period, with a clear "interruption" where the intervention was introduced. The study seeks to identify a significant change in the trend or level of the outcome of interest (e.g., prescribing of AP or incidence of IE) following the intervention. Because it lacks a concurrent control group, it is more susceptible to confounding by other events that occurred simultaneously.

(ii) EXPERIMENTAL/INTERVENTIONAL STUDIES

Experimental studies are a type of clinical research where some patients receive an intervention (like a new drug, a surgical procedure or a public health programme) and others do not. The effects of the intervention are then outcome of interest e.g. IE, are then observed.

Experimental studies, particularly Randomised Controlled Trials (RCTs), are considered the gold standard in research because they can establish a definitive cause-and-effect relationship between an intervention and an outcome. However, they also have notable drawbacks that limit their use.

Advantages of Experimental/Interventional Studies

- Establish Causality: The primary advantage is their ability to determine causation. By actively manipulating an independent variable and controlling other factors, researchers can be confident that any observed change in the dependent variable is a direct result of the intervention.
- High Internal Validity: Experimental studies have a high degree of internal validity, meaning the study's design effectively isolates the effect of the intervention from other variables. Randomisation is the key to this, as it balances out both known and unknown confounding factors between the groups.
- Control over Variables: Researchers have a high level of control over the study environment and the variables. They can standardize procedures and use techniques

like blinding (where participants and/or researchers don't know who is in which group) to minimize bias.
- Replicability: The highly controlled and structured nature of experimental studies means they can be easily replicated by other researchers. This allows for verification of findings, a cornerstone of the scientific method.

Limitations of Experimental/Interventional Studies

- Ethical Concerns: It is often unethical or impossible to conduct an experimental study. This has been one of the main reasons why no RCT studies have been performed to see if AP is effective in preventing IE. In most countries, the standards of clinical care expect that clinicians will comply with guidelines that recommend that all high-risk individuals receive AP before invasive dental procedures to prevent them developing IE. It is considered unethical, therefore, to randomise high-risk individuals to placebo or no AP, since they could develop IE (with its ~30% first year mortality).
- Limited Generalizability (External Validity): Because they are often conducted in highly controlled or artificial settings (e.g., a lab), the results may not be generalizable to real-world populations or situations. This is known as low external validity. The participants in the study may not be representative of the wider population, and their behaviour in a controlled setting may not reflect their behaviour in their natural environment.
- Cost and Time: Experimental studies, especially large-scale RCTs, are often very expensive and time-consuming to conduct, requiring significant resources and logistical planning. Because of the relative rarity of IE, and because AP is a prevention strategy rather than a treatment, very large numbers of high-risk individuals would need to be randomised to AP or placebo to determine the effectiveness of AP – making this an extremely large and expensive study to perform.
- Prone to Human Error and Bias: Despite being designed to minimise bias, experimental studies are still susceptible to human error. For example, issues with blinding, participant dropout (attrition bias), or flawed data collection can compromise the results. Additionally, a phenomenon known as the Hawthorne effect can occur, where participants alter their behaviour simply because they know they are being studied.

The main types of interventional study are outlined below:

Randomised Controlled Trial (RCT)

A randomised controlled trial (RCT) is considered the "gold standard" for determining the effectiveness of an intervention. Participants are randomly assigned to one of two or more groups: an experimental group that receives the intervention (e.g., a new drug) and a control group that receives a placebo or an existing treatment. This random assignment ensures that, on average, the groups are similar in all characteristics, both known and unknown, before the intervention begins. Any differences in outcomes between the groups can then be confidently attributed to the intervention.

- Example: A study to test a new blood pressure medication would randomly assign participants to either receive the new drug or a placebo. Researchers would follow both groups over a period and compare their average blood pressure readings.

Key Feature: Randomisation is the defining characteristic that minimizes selection bias and confounding, allowing for strong conclusions about cause and effect.

Pragmatic Randomised Controlled Trial (PRCT)

A pragmatic randomised controlled trial (PRCT) is a type of RCT designed to evaluate the effectiveness of an intervention in real-world clinical practice. Unlike traditional RCTs, which are often "explanatory" and focus on whether an intervention works under ideal, highly controlled conditions (with strict inclusion criteria and intensive monitoring), a pragmatic trial is designed to answer a question that is directly relevant to clinicians, patients, and policymakers.

- Example: A pragmatic trial of a new drug would compare it to the standard of care already used in hospitals and would enrol a diverse patient population in multiple clinical settings. The goal is to see if the new drug is effective in a typical, "messy" healthcare environment.

Key Feature: The primary focus is on external validity (generalizability), making the results more applicable to the broader patient population. It balances the rigor of an RCT with the practicality of a real-world setting.

Non-Randomised Controlled Trial (Non-RCT)

A Non-RCT is a study where participants are assigned to intervention groups using a non-random method. This might be based on factors like a patient's choice, a doctor's decision, or the date they were admitted to a hospital. While these trials can still include a control group for comparison, the lack of randomisation makes them more susceptible to selection bias and confounding, as the groups may not be comparable at the start.

(iii) META-ANALYSIS

A meta-analysis is a statistical technique that systematically combines and analyses the results of multiple independent studies on the same topic. Instead of simply summarizing the findings, it uses statistical methods to pool data and arrive at a single, more precise estimate of the overall effect or relationship. This process is often part of a systematic review, which is a comprehensive and structured approach to identifying, appraising, and synthesizing all relevant research on a particular question.

Advantages of Meta-Analysis

- Increased Statistical Power: By combining the sample sizes of many individual studies, a meta-analysis increases the statistical power to detect small but significant effects that might have been missed in any single study.

- Greater Precision: The pooled data leads to a more precise estimate of the effect size, narrowing the confidence interval and providing a more reliable and accurate conclusion.
- Resolution of Conflict: It can help resolve conflicting or contradictory results from different studies, providing a clearer overall picture of the evidence.
- Efficiency: A meta-analysis offers an efficient way to synthesize a large body of research, saving time and resources compared to conducting a new, large-scale study.
- Generalizability: Combining findings from various studies with different populations and settings can increase the generalizability of the results to a broader population.

Limitations of Meta-Analysis

- "Garbage In, Garbage Out": The quality of a meta-analysis is highly dependent on the quality of the individual studies included. If the included studies are methodologically flawed, the meta-analysis will produce unreliable results.
- Heterogeneity: One of the biggest challenges is heterogeneity, which refers to the differences between studies in terms of design, populations, interventions, or outcome measures. Combining studies that are too different ("mixing apples and oranges") can lead to meaningless results.
- Publication Bias: This occurs when studies with statistically significant or "positive" results are more likely to be published than those with null or negative findings. A meta-analysis that only includes published studies may overestimate the true effect.
- Data Availability: Meta-analyses rely on the data that is publicly available, and sometimes important data from individual studies is not reported or is difficult to obtain.
- Complexity: Conducting a meta-analysis requires advanced statistical skills and a thorough understanding of the methodology, which can be challenging for researchers without specialized statistical training.