COPENHAGEN RESPIRATORY RESEARCH

Protocol

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Short-Term risk of major cardiovascular events following common respiratory bacterial infections
A nationwide self-controlled case series study

Thomas Takahashi Bentzon[1], Anna Kubel Vognsen[1], Nicoline Meyer Riisberg[1], Daniel Modin MD[3,4], Barbara Bonnesen Bertelsen MD PhD[1], Josefin Eklöf MD PhD[1], Mats C. H. Lassen[3,4], Jonas Bredtoft Boel[5], Helle Brander Eriksen[5], Ram Benny Dessau[6], Christian Østergaard[7], Mette Pinholt[8], Niklas Dyrby Johansen[3,4], Tor Biering-Sørensen MD PhD[3,4,9], Jens-Ulrik Stæhr Jensen MD PhD[1,2] , Pradeesh Sivapalan[1,2]

[1] Section of Respiratory Medicine, Department of Medicine, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

[2] Department of clinical Medicine, Faculty of Health Sciences, University of Copenhagen.

[3]CTCPR, Copenhagen University Hospital – Herlev and Gentofte, Copenhagen, Denmark.

[4]Department of Cardiology, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark

[5]Department of Clinical Microbiology, Copenhagen University Hospital-Herlev, Herlev, Denmark.

[6]Department of Clinical Microbiology, Zealand University Hospital, Slagelse, Denmark.

[7]Diagnostic Infectious Disease Preparedness, Statens Serum Institut, Copenhagen, Denmark

[8]Department of Clinical Microbiology, Copenhagen University Hospital-Amager and Hvidovre, Denmark

[9] Steno Diabetes Center Copenhagen, Copenhagen, Denmark

Background

Acute respiratory infections are well-documented triggers of cardiovascular complications(1,2). Specifically, infections such as influenza and SARS-CoV-2 have been shown to significantly increase the short-term risk of major adverse cardiovascular events (MACE), including myocardial infarction, stroke, and cardiovascular procedures(3–7). These events are believed to be driven by systemic inflammation, pro-thrombotic responses, endothelial activation, and cytokine release, particularly IL-6, IL-1β, and IL-8(8–11).

Common respiratory bacterial infections (streptococcus, Hemophilus influenzae and Moraxella catarrhalis, Staphylococcus aureus and Klebsiella pneumoniae) are a leading cause of community-acquired pneumonia globally and remains a common pathogen identified in respiratory and blood cultures(12). While pneumococcal infection has been associated with increased morbidity and mortality, the short-term cardiovascular risks following confirmed common bacterial infection in the general population have not been thoroughly quantified using high-quality longitudinal data. This study aims to determine whether a temporal association exists between confirmed common respiratory bacterial infections and the occurrence of MACE in the general Danish population using national registry data.

Objective

The aim of this study is to evaluate whether individuals in the general population who experience a confirmed infection with common respiratory bacterial infections have an increased short-term risk of MACE. Additionally, the study will assess the timing of the peak risk period to identify potential windows for preventive intervention.

Methods

Study Design

This is a retrospective, nationwide self-controlled case series (SCCS) study utilizing individual-level registry data from the entire Danish population.

Data Sources

The study will use the following Danish national health and administrative registers:

The Danish Civil Registration System – Provides demographics, residency, and vital status for all Danish residents.

The Danish National Patient Registry (DNPR) – Contains information on all hospital contacts (inpatient and outpatient) and diagnoses coded in ICD-10.

The Danish Microbiology Database (MiBa) – A complete national database containing all microbiological test results, including respiratory and blood cultures.

The Danish National Prescription Registry – Includes all pharmacy-dispensed prescription medications in Denmark, coded using the ATC system.

The Danish Register of Causes of Death – Provides cause-of-death information for all registered deaths.

Study Population

Inclusion criteria:

All individuals in Denmark with a positive culture for Streptococcus pneumoniae (from lower respiratory tract or blood) between January 1, 1994, and December 31, 2023. A minimum of 180 days of observation before and after the infection date.

Exclusion criteria:

Patients with active cancer (ICD-8: 140-172, 174-239 and ICD-9: 140-172, 174-239 and ICD-10: DC00–C43, DC45–C99) within 5 years prior to the index infection.

Individuals not resident in Denmark at the time of exposure or lacking complete registry linkage.

Exposure and observation periods

Exposure date: Defined as the sampling date of the first positive culture for S. pneumoniae.

Risk period: Day −5 to +14 from the date of the positive sample to account for pre-diagnostic infectious period.

Control period: 180 days prior to and 180 days following the risk period (days −185 to −6 and days +15 to +194).

Only the first pneumococcal infection per person during the study period will be considered to avoid repeated measures bias.

Likewise, only the first occurrence of MACE will be recorded, to avoid dependent events. This introduces negligible bias since MACE is a rare event.

Outcomes

Primary outcome:

A composite of major adverse cardiovascular events (MACE), including:

Acute myocardial infarction (ICD-8: 410.x, 411, 412.x, 414 and ICD-9: 410.x, 412, 413, 414 and ICD-10: DI21, DI23, DI24)

Stroke or transient ischemic attack (ICD-8: 432, 433.x, 434.x, 435.x, 436, 437 and ICD-9: 433.x, 434.x, 435, 436, 438 and ICD-10: DG45, DI63–I66)

Unstable angina pectoris (ICD-8 413 and ICD-9: 413 and ICD-10: DI200)

Death from cardiovascular disease

Secondary outcomes:

Individual components: Separate analysis of AMI or transient ischemic attack, stroke, Unstable angina pectoris, Death from cardiovascular disease and heart failure hospitalization

Only the first event of each type will be included per person.

Statistical Analysis

The primary analysis will use the self-controlled case series (SCCS) design, which compares the incidence of events during risk and control periods within the same individuals, thus inherently controlling for time-invariant confounders such as sex and comorbidities.

Adjustment variables: calendar time will be adjusted for in 3-month intervals in the primary analysis to account for seasonal variation in both infections and cardiovascular events.

In secondary analyses, 1-year intervals will be used due to limited statistical power.

Sensitivity analyses:

Restricting to individuals with no prior MACE.

Restricting analysis to post-infection observation period only.

Applying event dependent observation periods to assess whether the short-term mortality of occurrence of a cardiovascular event affects the results.

Applying an event-dependent exposure model to assess whether the occurrence of a cardiovascular event affects the likelihood of microbiological testing (e.g., hospital-admitted patients being more likely to be tested for infection).

Additional sensitivity analyses will vary the length of the predefined risk period (e.g., restricting it to 7 days or extending it to 30 days after the positive test date) to evaluate the robustness of the temporal risk window definition.

Finally, a negative control outcome analysis will be conducted to assess potential temporal bias inherent to SCCS designs, particularly related to increased healthcare surveillance and physician contact around the time of infection.

Results will be presented as Incidence Rate Ratios (IRRs) with 95% confidence intervals and p-values.

All analyses will be conducted in R (version 4.4.3) using the SCCS package.

Ethical Considerations

The study will be approved by the appropriate regional data protection authority (e.g., Knowledge Centre for Data Reviews). According to Danish law, informed consent is not required for registry-based studies using anonymized data. All data will be handled securely and in compliance with the General Data Protection Regulation (GDPR) and national ethical standards. The study will be conducted in accordance with the Declaration of Helsinki.

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