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## Risk factors for *Staphylococcus aureus* bacteremia in patients with rheumatoid arthritis and incidence compared with the general population. Protocol for a Danish nationwide observational cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030999
Article Type:	Protocol
Date Submitted by the Author:	10-Apr-2019
Complete List of Authors:	Dieperink, Sabine; Rigshospitalet Glostrup, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre of Head and Orthopaedics Glintborg, B.; Rigshospitalet Glostrup, DANBIO and Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre of Head and Orthopaedics; University of Copenhagen Faculty of Health Sciences, Department of Clinical Medicine Oestergaard, Louise ; Herlev and Gentofte University Hospital, Cardiovascular Research Center Nørgaard, Mette; Aarhus Universitetshospital, Department of Clinical Epidemiology Benfield, Thomas; Copenhagen University Hospital, Department of Infectious Diseases; Copenhagen University Hospital, Clinical Research Centre Mehnert, Frank; Aarhus University Hospital, Department of Clinical Epidemiology Petersen, Andreas; Statens Serum Institut, Lund Hetland, Merete; Rigshospitalet Glostrup, DANBIO and Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre of Head and Orthopaedics; University of Copenhagen Faculty of Health Sciences, Department of Clinical Medicine
Keywords:	rheumatoid arthritis, staphylococcus aureus, Staphylococcus aureus bacteremia, Antirheumatic agents, Bacteremia

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# Risk factors for *Staphylococcus aureus* bacteremia in patients with rheumatoid arthritis and incidence compared with the general population. Protocol for a Danish nationwide observational cohort study

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## Abstract

### Introduction

*Staphylococcus aureus* bacteremia (SAB) is an invasive infection with high mortality and morbidity. Rheumatoid arthritis (RA) is associated with increased risk of infections due to the disease per se and the use of immunosuppressing anti-rheumatic treatments. The few minor studies that

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4 previously have investigated risk of SAB in patients with RA have indicated increased risk  
5 compared with the general population.  
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8 This nationwide observational study aims to investigate incidence of and risk factors for SAB in  
9 adult patients with RA compared with the general population. The effect of disease characteristics  
10 (e.g. joint erosions, disease duration and - activity), different anti-rheumatic treatments, and  
11 smoking on SAB risk will be evaluated.  
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### 16 **Methods and analysis**

17 All adults (>18 years of age) alive and living in Denmark in 1996-2017 will be identified in The  
18 Danish Civil Registration System. Incident patients with RA are identified in the Danish National  
19 Patient Registry (DNPR) and the nationwide rheumatology registry, DANBIO, in which information  
20 on e.g. anti-rheumatic treatments, disease characteristics, and smoking is collected prospectively  
21 in routine care. Information on comorbidities, invasive procedures and prescribed drugs are  
22 identified in the DNPR and in The Register of Medicinal Product Statistics. Socioeconomic status is  
23 evaluated in national registers on income and education. Incident cases of first-time SAB are  
24 identified in The Danish National SAB Database. All registers are linked on an individual level by  
25 unique civil registration numbers. Incidence rates (IR) and ratios (IRR) will be analyzed using  
26 Poisson regression models and the impact of possible risk factors will be evaluated.  
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### 37 **Ethics and dissemination**

38 All data will be handled in accordance with the General Data Protection Regulation (EU) 2016/679.  
39 No ethical approval is necessary in Denmark when handling registry data only.  
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42 The results will be presented in accordance with the STROBE initiative in international peer-  
43 reviewed journals and at medical conferences.  
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### 47 **Trial registration**

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## 54 **Article Summary**

### 55 **Strengths and limitations of this study**

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#### Strengths:

- We will identify patients with incident rheumatoid arthritis (RA) (the exposure of interest) and *Staphylococcus aureus* bacteremia (SAB) (the outcome of interest) in a nationwide cohort study including all adult Danes (1996-2017) identified by national registries
- Nationwide medical databases are used to assess SAB incidence rates in the RA cohort and in the general population and to evaluate the impact of RA disease characteristics and treatments on SAB risk
- We will assess the impact of possible confounding factors (e.g. comorbidities, surgeries, prescriptions, and socioeconomic factors) by linkage of national registries

#### Limitations:

- Misclassification of RA and of SAB may occur, resulting in underestimation of the SAB incidence and potentially leading the relative estimates towards the null
- Data on lifestyle factors (alcohol and smoking) are available in the RA cohort but lack in the background population, and other lifestyle factors (as e.g. illicit drug use) are generally unavailable.

## Introduction

*Staphylococcus aureus* bacteremia (SAB) is an invasive infection with an estimated overall annual incidence rate of 36/100,000 person-years.<sup>1</sup> Mortality is high (20-30%) and morbidity significant due to the frequent occurrence of secondary infections e.g. endocarditis, spondylitis, septic arthritis and prosthetic joint infections.<sup>1-3</sup> SAB among adults is more common in males, in the elderly and in patients with comorbidities and low socioeconomic status.<sup>4,5</sup> The risk of SAB is increased in patients treated with immunosuppressive drugs (including glucocorticoids) and inserted devices as prosthetic joints serve as additional risk factors for SAB due to both postoperative infections and hematogenous seeding of *S. aureus*.<sup>6-8</sup> SAB is a leading cause of joint and bone infections due to affinity of *S. aureus* to these sites.<sup>9</sup>

Rheumatoid arthritis (RA) is a chronic autoimmune joint disorder that affects 0,5–1 % of the population.<sup>10</sup> Genetic factors, female sex, smoking and low socioeconomic status are risk factors of RA.<sup>10-12</sup> Joint inflammation can lead to joint destruction, and patients with RA more often have joint replacements than the general population.<sup>13</sup> RA is associated with an increased risk of other chronic diseases such as diabetes mellitus and cardiovascular disease.<sup>14,15</sup>

Patients with RA are at increased risk of infections affecting especially lungs and joints.<sup>16</sup> This has been observed even before the era of widespread use of the immunosuppressing disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids, indicating that the immune defense is compromised in patients with RA irrespective of treatment.<sup>17,18</sup> Furthermore, high RA disease activity has been reported to increase the risk of infections.<sup>19</sup> Antirheumatic treatments such as conventional synthetic DMARDs (csDMARDs, e.g. methotrexate) and biologic DMARDs (bDMARDs, e.g. tumor necrosis factor alpha inhibitors (anti-TNFs)) and the newer targeted synthetic DMARDs (tsDMARDs, e.g. tofacitinib and baricitinib) as well as glucocorticoids are all associated with increased infection risk in patients with RA.<sup>20,21</sup>

Patients with RA are likely at increased risk of SAB due to the RA disease per se (altered immunological response to infections due to systemic inflammation and local inflammation in joints leading to erosions), or due to the antirheumatic treatment, the prevalence of joint prostheses and comorbidity. Furthermore, it can be speculated whether a higher frequency of smoking among patients with RA could influence this risk.

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4 Despite the severity of SAB, the incidence and risk factors for SAB among patients with RA are  
5 poorly investigated. Two previous studies of SAB incidence in adult patients with RA, both  
6 characterized by few events of SAB in patients with RA, reported incidence rate ratios (IRR) of 2.6  
7 (95% CI 1.8-3.7)<sup>5</sup> and 9.2 (95% CI 1-20)<sup>6</sup> compared with the background population.  
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12 One small nested case control study reported indwelling central venous catheters (odds ratio (OR)  
13 15.97, 95% CI 5.09 to 50.10) and congestive heart failure (OR 2.89, 95% CI 1.26 to 6.63) as risk  
14 factors for RA patients being hospitalized with SAB compared with being hospitalized for other  
15 reasons. But the study found no association for DMARD treatment, glucocorticoids and prosthetic  
16 joints.<sup>22</sup>  
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21 Thus, the evidence gap regarding SAB in patients with RA is substantial: the incidence of SAB in the  
22 RA population is unknown and there is insufficient knowledge on risk factors for SAB.  
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26 This protocol presents a nationwide observational cohort study of SAB focusing on incidence rates  
27 and risk factors in adult patients with RA compared with the adult general population. The study is  
28 expected to become the largest and most detailed of its kind due to the availability of unique  
29 national registries of microbiologically verified cases of SAB and of RA patients' demographics,  
30 anti-rheumatic treatment, disease characteristics and disease activity including patient reported  
31 outcomes, combined with the possibility of linking to other national registries with information on  
32 e.g. comorbidities (hospital contacts, prescriptions) and socioeconomic parameters (education and  
33 income). Further, the study is expected to conclude whether different antirheumatic treatments  
34 are associated with different risk of SAB in the RA population.  
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44 We hypothesize that patients with RA are at increased risk of SAB compared with the background  
45 population. We expect that higher age, male sex, glucocorticoid use and joint prosthesis increase  
46 this risk in both patients with RA and the background population, and we hypothesize that  
47 additional RA disease-specific factors (e.g. high disease activity, presence of joint erosions, long  
48 disease duration, DMARD treatment and smoking) might be associated with higher risk in patients  
49 with RA.  
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55 The objectives of the study are to 1) assess the incidence rates and incidence rate ratios of SAB in  
56 patients with RA compared with the general population 2) explore the significance of age, gender,  
57 glucocorticoid use and prosthetic joints on SAB risk in patients with RA compared with the general  
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population and 3) identify RA disease-specific risk factors for SAB within the RA cohort and assess the effect of smoking on SAB risk in the RA cohort.

## Methods and analysis

### Study design

Nationwide observational cohort study of SAB incidence and risk factors in adult patients with RA and in the general adult population.

### Study population

All members of the Danish population aged 18 years or more, alive and living in Denmark in the time period from 1996 until 2017 as identified by the Danish Civil Registration System (CRS) (**Table 1**).

Individuals with one of the following prior to start of follow-up will be excluded: 1) SAB (the outcome of interest) 2) a diagnosis of RA (the main exposure of interest).

The Danish Civil Registration system (CRS)	Established in year 1968. All persons alive and living in Denmark are registered for administrative use. Includes complete information on civil registration number, name, gender, date of birth, and continuously updated information on vital status, marital status and place of residence (including immigration and emigration). <sup>23</sup>
The Danish National Patient Registry (DNPR)	Diagnoses listed according to the International Classification of Diseases (ICD) codes from all hospital admissions (from 1977) and outpatient activities (from 1995) in the form of the 8th revision of the ICD (ICD-8) until 1994 and the 10th revision (ICD-10) thereafter. Contains information on surgeries and other procedures performed at hospitals. The register is practically complete. <sup>24</sup>
The Danish Rheumatology Database, DANBIO	Initiated in year 2000. Danish national clinical quality registry of rheumatologic patients treated with biologics. In 2006 it became mandatory to register all newly diagnosed RA patients regardless of treatment. >30.000 patients with RA have been registered (unpublished data). Contains information on e.g. ICD-10 diagnosis code of inflammatory rheumatic disease, date of diagnosis, symptom duration, auto-antibody status of rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA), current and previous treatment with biologic and synthetic disease-



	modifying antirheumatic drugs (DMARDs), treatment with glucocorticoids (injection, oral), X-ray results (hand and feet), and prospectively collected disease activity measures including C-reactive protein (CRP) and patient reported outcomes. Smoking, alcohol consumption and body mass index (BMI) is also registered. <sup>25</sup>
The Danish National <i>Staphylococcus aureus</i> Bacteremia Database	The nationwide registration of <i>S. aureus</i> bacteremias in Denmark since 1957 carried out by the Staphylococcal Laboratory at the Statens Serum Institut (SSI) for surveillance purposes. Linked to civil registration numbers since 1992. The regional microbiology departments send isolates on a voluntary basis. Has a high degree of completeness and >90% of strains isolated from Danish blood cultures are referred to SSI for typing (detection <i>S. aureus</i> protein A (SPA) type) and antibiotic susceptibility testing. <sup>26</sup>
The Register of Medicinal Product Statistics	Information on all prescriptions dispensed from pharmacies has been recorded from 1995 including the anatomical therapeutic chemical class (ATC class), strength, package size, number and date of dispensed prescription. <sup>27</sup>
The Population's Education Registry (PER)	Information on highest attained education. In 2008 PER included 96.4% of the Danish population between 15 and 69 years of age. <sup>28</sup>
The Income Statistics Register	Initiated in 1970. Contains information on the income and its composition (e.g. salary, taxes and public transfer payments) on an individual level as registered by the Tax Administration's registry. <sup>29</sup>
All national registries can be linked on an individual basis using the civil registration number administered at birth or immigration. <sup>23</sup>	

## Exposure

RA is the main exposure of interest. A cohort of incident cases of RA will be identified, based on DANBIO and the Danish National Patient Registry (DNPR). Individuals registered with one of the following International Classification of Diseases codes in its 10<sup>th</sup> revision (ICD-10) in DANBIO are considered patients with RA: M05.9 (RA seropositive), M06.0 (RA seronegative), M06.9 (RA unspecified). Furthermore, in the DNPR individuals with  $\geq 2$  registrations from rheumatology departments with one of the mentioned ICD-10 codes (including also M05.8 (Other types of RA), not used in DANBIO) or the ICD-8 code 712.39 (arthritis rheumatoides alia et non specificata), within a period of 90 days are considered patients with RA. This method has previously been validated with high degree of validity (positive predictive value  $\approx 80\%$ ) and completeness.<sup>30</sup>

## Outcome/event

The outcome of interest is incident first-time SAB as identified in the Danish National *S. aureus* Bacteremia Database. SAB relapses/reinfections will not be included. The SAB cases will be labeled “hospital-acquired” (HA SAB) if the first positive blood culture is obtained 48 hours or more after admission to a hospital and “non-hospital acquired” (non-HA SAB) if it has been obtained less than 48 hours after admission.

## Follow-up

Follow-up starts at December 31, 1996, an individual’s 18<sup>th</sup> birthday, or at the date of immigration, whichever comes last. Individuals are followed up until first-time SAB, emigration, death or December 31, 2017, whichever comes first.

Incident patients with RA contribute with person-years in the RA cohort following diagnosis and until the end of follow-up. The remaining individuals contribute person-years in the general population cohort. RA patients diagnosed after start of follow-up will contribute person-years in the general population cohort until date of RA diagnosis and in the RA cohort thereafter.

## Covariates

Information on other diseases and use of prescription medications will be obtained prior to and during follow-up from the DNPR and the Register of Medicinal Product Statistics. Some conditions (e.g. diabetes mellitus and prosthetic joint insertion) leaves the subject in “forever risk” from the date of diagnosis/operation and until the end of follow-up. Other incidents, as invasive surgical procedures and dialysis procedures are considered temporary risk factors, and subjects are considered “at risk” of one of these in 90 days after the procedure date. Patients with cancer (except non-melanoma skin cancer) are considered “at risk” until five years after the last registration of a cancer diagnosis in the DNPR.

Socioeconomic status will be evaluated by the highest attained educational level identified by the Population’s Education Registry (PER) and by the yearly average personal income level (3 years back) identified by the Income Statistics Register.

To allow for evaluation of RA specific risk factors, information specific to RA-patients will be identified in DANBIO prior to and during follow-up. (**Table 2**).

DANBIO is the main source of information on antirheumatic treatments since in Denmark, some drugs are administered from the hospital departments without prescription (bDMARDs, subcutaneous methotrexate, leflunomide and injections with glucocorticoids) and hence not registered in the Register of Medicinal Products Statistics. A recent audit in DANBIO found a coverage of 98% for bDMARDs.<sup>31</sup>

Information on glucocorticoid use will be identified in both DANBIO and the Register of Medicinal Products Statistics (Table 2).

<b>Table 2</b> Characteristics of patients with RA according to the DANBIO registry		
Variable	Description	Value
CDAI	Composite disease activity score of patient's and doctor's global assessment on a visual analogue scale (VAS)	0.0-76.0
Disease duration	Time passed from RA diagnosis until the first-time SAB	years
Erosive joint disease	X-rays of hands and feet registered before the first-time SAB	erosions/no erosions/unavailable
Auto-antibody status	ACPA and RF registered before SAB	positive/negative/unavailable
Smoking	Smoking status registered as close to SAB as possible	Previous/current/never/occasional/unavailable
<b>csDMARDs</b>		
Methotrexate, sulphasalazine, hydroxychloroquine, leflunomide	Current user: use within 90 days before SAB Previous user: ever used more than 90 days prior to SAB Non-user: Never used	Current/previous/non-user and cumulated exposure (days)

	Cumulated exposure: Days on the drug (for current users)	
<b>bDMARDs</b>		
Anti-TNFs, abatacept, secukinumab, IL6 inhibitors, ustekinumab, apremilast	Current user: use within 90 days before SAB Previous user: ever used more than 90 days prior to SAB Non-user: never used Cumulated exposure: Days on the drug (for current users)	Current/previous/non-user and cumulated exposure (days)
Rituximab	Current user: last dose of rituximab was given within 12 months prior to SAB Previous user: ever used Non-user: never used Cumulated exposure: total dose (both current and previous users)	Current/previous/non-user and cumulated exposure (mg)
<b>tsDMARDs</b>		
JAK inhibitors	Current user: use within 90 days before SAB Previous user: ever used more than 90 days prior to SAB Non-user: never used Cumulated exposure: days on the drug (for current users)	Current/previous/non-user and cumulated exposure (days)
<b>Glucocorticoids (GCs)*</b>		
Oral and injectable (intramuscular and intraarticular) GCs	Current user: use within 90 days before SAB Previous user: ever used more than 90 days prior to SAB	Current/previous/non-user and cumulated exposure (mg)

	Non-user: never used Cumulated exposure: will be calculated as prednisolone-equivalent dose for current users as described elsewhere <sup>7</sup>	
* Use of GCs will be identified in both DANBIO and the Register of Medicinal Products Statistics		
<b>Abbreviations:</b> <b>RA</b> rheumatoid arthritis, <b>SAB</b> staphylococcus aureus bacteremia, <b>CDAI</b> clinical disease activity index, <b>csDMARDs</b> conventional synthetic disease-modifying antirheumatic drugs, <b>bdDMARDs</b> biologic DMARDs, <b>anti-TNF</b> tumor necrosis factor inhibitors (adalimumab, golimumab, etanercept, certolizumab pegol, infliximab), <b>IL6 inhibitors</b> interleukin-6 inhibitors (tocilizumab, sarilumab), <b>tsDMARDs</b> targeted synthetic DMARDs, <b>JAK inhibitors</b> Janus kinase inhibitors (baricitinib, tofacitinib)		

### Expected number of events

When identifying incident RA cases in the DNPR and DANBIO as described above, we expect to identify approximately 500 SAB cases in the RA cohort. This is based on data from the annual report from The Danish National SAB Database.<sup>1</sup> Thus, from year 1996 until 2017 ≈30,000 SAB cases have been reported whereof in the last years approximately 5% (4.7-6.2%) occurred in patients with comorbid “rheumatic diseases”, corresponding ≈1500 cases in total. (5% of 30,000). The expected number of events is based on the conservative assumption that one third of these patients will be incident patients with RA.

Since we have more detailed information on RA patients that have been followed in DANBIO (e.g. smoking, disease activity, joint erosions, etc.) compared with RA patients identified in the DNPR, we will consider limiting exposure to only RA according to DANBIO if the number of events is large enough for meaningful statistical analysis. In this case the study period will be limited accordingly to 2006 and onward.

### Data analysis plan

The exact data analysis plan depends on data availability and number of events.

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4 Incidence rates (IR) of SAB in the RA and in the general population cohorts will be described and  
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6 Poisson regression models will be used to estimate IRRs. IR and IRR will be presented crude  
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8 (adjusted for age, sex and calendar year) and further adjusted for potential risk  
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10 factors/confounders.

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12 The impact of possible risk factors (anti-rheumatic treatment, disease duration, disease activity,  
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14 joint erosions, and smoking) for SAB among RA patients will be assessed. The number of covariates  
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16 included in the final model will correspond the number of events in the RA population and will be  
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18 prioritized according to a-priori assumption on clinical relevance.

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20 We plan to study the impact of different DMARD treatments as risk factors for SAB among patients  
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22 with RA separately, alternatively grouped as e.g. bDMARDs, tsDMARDs and csDMARDs.

23  
24 Stratification may be performed when observing interaction in the model.

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26 Sensitivity analyses will include stratified analysis according to outcome defined as HA SAB and  
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28 non-HA SAB.

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30 Further sensitivity analysis will be performed to assess any difference in IR between the RA cohort  
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32 identified in DANBIO and the full RA cohort identified by both DANBIO and the DNPR.

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34 Missing data will be handled by appropriate statistical methods, e.g. multiple imputations.

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36 Data will be hosted and anonymized by Statistics Denmark and data will be processed using the  
37  
38 statistical software SAS.

## 39 40 41 42 43 Ethics and dissemination

44  
45 All data will be handled in accordance with the General Data Protection Regulation (EU) 2016/679.

46  
47 Data processing agreements are set up between all data processors and the data owner (the  
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49 Capital Region of Denmark). Data handling and data processing agreements are approved by the  
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51 Capital Region of Denmark. Access to data from The Register of Medicinal Product Statistics is  
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53 approved by Sundhedsdatastyrelsen, data from DANBIO is approved by The Danish Clinical  
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55 Registries (RKKP) and data from the Danish National SAB Database is approved by Statens Serum  
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57 Institut. Statistics Denmark has authorized the research institution and granted permission to  
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linkage of data based on a written application. No ethical approval is necessary in Denmark when handling registry data only.

The results will be presented in accordance with the STROBE initiative<sup>32</sup> as original articles in international peer-reviewed journals and at medical conferences. Both positive and negative results will be published.

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## 27 Author contributions

28 SD conceptualized the study hypotheses and all authors contributed with the further development  
29 of these and with the study design. SD wrote the first draft of the paper, which was critically  
30 revised by the other authors.  
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## 33 Funding

34 This work was supported by the Danish Rheumatism Association grant number R163-A5715.  
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## 38 Conflicts of interests

39 TB reports grants from Pfizer, grants from Novo Nordisk Foundation, grants from Simonsen  
40 Foundation, grants from GSK, personal fees from Pfizer, and BG reports grants from Pfizer, Biogen  
41 and Abbvie, all outside the submitted work.  
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## 45 Word count

46 2759  
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## 49 Keywords

50 Rheumatoid arthritis

51 Staphylococcus aureus

52 Staphylococcus aureus bacteremia

53 Antirheumatic agents

54 Bacteremia  
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## Acknowledgements

None

## Data statement

Due to local Danish legislation linked data cannot leave the country and the raw data is only available to a selected group of researchers. Additional information on the calculations/codes can be made available on request by contacting the corresponding author.

## Patient and public involvement

The study hypotheses and design have been discussed with a trained patient research partner.

# BMJ Open

## Risk factors for *Staphylococcus aureus* bacteremia in patients with rheumatoid arthritis and incidence compared with the general population. Protocol for a Danish nationwide observational cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030999.R1
Article Type:	Protocol
Date Submitted by the Author:	10-Jul-2019
Complete List of Authors:	Dieperink, Sabine; Rigshospitalet Glostrup, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre of Head and Orthopaedics Glintborg, B.; Rigshospitalet Glostrup, DANBIO and Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre of Head and Orthopaedics; University of Copenhagen Faculty of Health Sciences, Department of Clinical Medicine Oestergaard, Louise ; Herlev and Gentofte University Hospital, Cardiovascular Research Center Nørgaard, Mette; Aarhus Universitetshospital, Department of Clinical Epidemiology Benfield, Thomas; Copenhagen University Hospital, Department of Infectious Diseases; Copenhagen University Hospital, Clinical Research Centre Mehnert, Frank; Aarhus University Hospital, Department of Clinical Epidemiology Petersen, Andreas; Statens Serum Institut, Lund Hetland, Merete; Rigshospitalet Glostrup, DANBIO and Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre of Head and Orthopaedics; University of Copenhagen Faculty of Health Sciences, Department of Clinical Medicine
<b>Primary Subject Heading</b>:	Infectious diseases
Secondary Subject Heading:	Rheumatology
Keywords:	rheumatoid arthritis, staphylococcus aureus, Staphylococcus aureus bacteremia, Antirheumatic agents, Bacteremia

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# Risk factors for *Staphylococcus aureus* bacteremia in patients with rheumatoid arthritis and incidence compared with the general population. Protocol for a Danish nationwide observational cohort study

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## Abstract

### Introduction

*Staphylococcus aureus* bacteremia (SAB) is an invasive infection with high mortality and morbidity. Rheumatoid arthritis (RA) is associated with increased risk of infections due to the disease per se and the use of anti-rheumatic treatments. Few minor studies have previously investigated risk of SAB in patients with RA and indicated increased risk compared with the general population. This nationwide observational study aims to investigate incidence of and risk factors for SAB in adult patients with RA compared with the general population. The effect of disease characteristics (e.g. joint erosions, disease duration and - activity), different anti-rheumatic treatments, and smoking on SAB risk will be evaluated.

### Methods and analysis

All adults (>18 years of age) alive and living in Denmark in 1996-2017 will be identified in The Danish Civil Registration System. Incident patients with RA are identified in the Danish National Patient Registry (DNPR) and the nationwide rheumatology registry, DANBIO, in which information on e.g. anti-rheumatic treatments, disease characteristics, and smoking is collected prospectively in routine care. Information on comorbidities, invasive procedures and prescribed drugs are identified in the DNPR and in The Register of Medicinal Product Statistics. Socioeconomic status is evaluated in national registers on income and education. Incident cases of first-time SAB are identified in The Danish National SAB Database. All registers are linked on an individual level by unique civil registration numbers. Incidence rates (IR) and ratios (IRR) will be analyzed using Poisson regression models and the impact of possible risk factors will be evaluated.

### Ethics and dissemination

All data will be handled in accordance with the General Data Protection Regulation (EU) 2016/679. No ethical approval is necessary in Denmark when handling registry data only. The results will be presented in accordance with the STROBE initiative in international peer-reviewed journals and at medical conferences.

### Trial registration

NCT03908086

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## Article Summary

### Strengths and limitations of this study

#### Strengths:

- We will identify patients with incident rheumatoid arthritis (RA) (the exposure of interest) and *Staphylococcus aureus* bacteremia (SAB) (the outcome of interest) in a nationwide cohort study including all adult Danes (1996-2017) identified by national registries
- Nationwide medical databases are used to assess SAB incidence rates in the RA cohort and in the general population and to evaluate the impact of RA disease characteristics and treatments on SAB risk
- We will assess the impact of possible confounding factors (e.g. comorbidities, surgeries, prescriptions, and socioeconomic factors) by linkage of national registries

#### Limitations:

- Misclassification of RA and of SAB may occur, resulting in underestimation of the SAB incidence and potentially leading the relative estimates towards the null
- Data on lifestyle factors (alcohol and smoking) are available in the RA cohort but lack in the background population. Other factors as illicit drug use, *S. aureus* nasal carriage and presence of central or peripheral vascular catheters are generally unavailable.

## Introduction

*Staphylococcus aureus* bacteremia (SAB) is an invasive infection with an estimated overall annual incidence rate of 36/100,000 person-years.<sup>1</sup> Mortality is high (20-30%) and morbidity significant due to the frequent occurrence of secondary infections e.g. endocarditis, spondylitis, septic arthritis and prosthetic joint infections.<sup>1-3</sup> SAB among adults is more common in men, in the elderly and in patients with comorbidities such as diabetes mellitus, cancer, hemodialysis, human immunodeficiency virus (HIV) infection, heart failure, liver disease, alcohol abuse, and intravenous drug abuse.<sup>1,4-7</sup> Biofilm of *S. aureus* can form on implanted foreign bodies as prosthetic joints, prosthetic heart valves and intravascular devices serving as an infective focus of SAB.<sup>8</sup> Furthermore *S. aureus* nasal carriage, surgical procedures, treatment with immunosuppressive drugs (including glucocorticoids) and low socioeconomic status has been associated with increased risk of SAB<sup>4,9-11</sup> whereas treatment with statins and trimethoprim-sulfamethoxazole (TMP/SMX) has been associated with a decreased risk.<sup>12-14</sup>

Rheumatoid arthritis (RA) is a chronic autoimmune joint disorder that affects 0,5–1 % of the population.<sup>15</sup> Genetic factors, female sex, smoking and low socioeconomic status increases the risk of RA.<sup>15-17</sup> Joint inflammation can lead to joint destruction, and patients with RA more often have joint replacements than the general population.<sup>18</sup> RA is associated with an increased risk of other chronic diseases such as diabetes mellitus and cardiovascular disease.<sup>19,20</sup>

Patients with RA are at increased risk of infections affecting e.g. lungs, joints and bones.<sup>21,22</sup> This has been observed even before the era of widespread use of the immunosuppressing disease-modifying anti-rheumatic drugs (DMARDs) and glucocorticoids, indicating that the immune defense is compromised in patients with RA irrespective of treatment.<sup>23,24</sup> Furthermore, high RA disease activity has been reported to increase the risk of infections.<sup>25</sup> Anti-rheumatic treatments such as biologic DMARDs (bDMARDs, e.g. tumor necrosis factor alpha inhibitors (anti-TNFs))<sup>26-28</sup> and the newer targeted synthetic DMARDs (tsDMARDs, e.g. tofacitinib and baricitinib)<sup>29,30</sup> as well as glucocorticoids<sup>22,31-33</sup> have been found to be associated with increased risk of infections in patients with RA. Recent studies have, however, reported that the risk of serious infections using bDMARDs is minimal/insignificant suggesting a successful



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4 change in management of patients through screening for infections prior to start of bDMARDs,  
5 prophylactic measures as vaccines and treating infections early.<sup>27,34</sup>  
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9 Patients with RA are likely at increased risk of SAB due to the RA disease per se  
10 (altered immunological response to infections due to systemic inflammation and local  
11 inflammation in joints leading to erosions), or due to the anti-rheumatic treatment and the  
12 prevalence of joint prostheses and comorbidities. Despite the severity of SAB, the incidence and  
13 risk factors for SAB among patients with RA are poorly investigated. Two previous studies of SAB  
14 incidence in adult patients with RA, both characterized by few events of SAB in patients with RA,  
15 reported incidence rate ratios (IRR) of 2.6 (95% CI 1.8-3.7)<sup>4</sup> and 9.2 (95% CI 1-20)<sup>7</sup> compared with  
16 the background population. One small nested case control study reported indwelling central  
17 venous catheters (odds ratio (OR) 15.97, 95% CI 5.09 to 50.10) and congestive heart failure (OR  
18 2.89, 95% CI 1.26 to 6.63) as risk factors for RA patients being hospitalized with SAB. The study  
19 found no association between neither conventional synthetic DMARDs (csDMARDs), bDMARDs,  
20 glucocorticoids nor prosthetic joints and SAB.<sup>35</sup> However, their comparisons were RA patients  
21 hospitalized for other reasons than SAB. These patients were likely at higher risk of SAB than RA  
22 patients in general, which may have biased the relative estimates towards no association. Thus,  
23 the evidence gap regarding SAB in patients with RA is substantial: the incidence of SAB in the RA  
24 population is unknown and there is insufficient knowledge on risk factors for SAB.  
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39 This protocol presents a nationwide observational cohort study of SAB focusing on  
40 incidence rates and risk factors in adult patients with RA compared with the adult general  
41 population. The study is expected to become the largest and most detailed of its kind due to the  
42 availability of unique national registries of microbiologically verified cases of SAB and of RA  
43 patients' demographics, anti-rheumatic treatment, disease characteristics and disease activity  
44 including patient reported outcomes, combined with the possibility of linking to other national  
45 registries with information on e.g. comorbidities (hospital contacts, prescriptions) and  
46 socioeconomic parameters (education and income). Further, the study is expected to conclude  
47 whether different anti-rheumatic treatments are associated with different risk of SAB in the RA  
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We hypothesize that patients with RA are at increased risk of SAB compared with the background population. We expect that higher age, male sex, glucocorticoid use and joint prosthesis increase this risk in both patients with RA and the background population, and we hypothesize that additional RA disease-specific factors (e.g. high disease activity, presence of joint erosions, long disease duration, DMARD treatment and smoking) might be associated with higher risk in patients with RA. The objectives of the study are to 1) assess the incidence rates and incidence rate ratios of SAB in patients with RA compared with the general population 2) explore the significance of age, gender, glucocorticoid use and prosthetic joints on SAB risk in patients with RA compared with the general population and 3) identify RA disease-specific risk factors for SAB within the RA cohort and assess the effect of smoking on SAB risk in the RA cohort.

## Methods and analysis

### Study design and population

Nationwide observational cohort study of SAB incidence and risk factors in adult patients with RA and in the general adult population. The population consists of all Danish inhabitants aged 18 years or more, alive and living in Denmark in the period from 1996 until 2017 as identified by the Danish Civil Registration System (CRS) (**Table 1**). Individuals with one of the following prior to start of follow-up will be excluded: 1) SAB (the outcome of interest) 2) a diagnosis of RA (the main exposure of interest).

**Table 1, Data sources, Danish national registries**

The Danish Civil Registration system (CRS)	Established in year 1968. All persons alive and living in Denmark are registered for administrative use. Includes complete information on civil registration number, name, gender, date of birth, and continuously updated information on vital status, marital status and place of residence (including immigration and emigration). <sup>36</sup>
The Danish National Patient Registry (DNPR)	Diagnoses listed according to the International Classification of Diseases (ICD) codes from all hospital admissions (from 1977) and outpatient activities (from 1995) in the form of the 8th revision of the ICD (ICD-8) until 1994 and the 10th revision (ICD-10) thereafter. Contains information on surgeries and other procedures performed at hospitals. The register is practically complete. <sup>37</sup>

<p>The Danish Rheumatology Database, DANBIO</p>	<p>Initiated in year 2000. Danish national clinical quality registry of rheumatologic patients treated with biologics. In 2006 it became mandatory to register all newly diagnosed RA patients regardless of treatment. &gt;30.000 patients with RA have been registered (unpublished data).</p> <p>Contains information on e.g. ICD-10 diagnosis code of inflammatory rheumatic disease, date of diagnosis, symptom duration, auto-antibody status of rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA), current and previous treatment with biologic and synthetic disease-modifying antirheumatic drugs (DMARDs), treatment with glucocorticoids (injection, oral), X-ray results (hand and feet), and prospectively collected disease activity measures including C-reactive protein (CRP) and patient reported outcomes. Smoking, alcohol consumption and body mass index (BMI) is also registered.<sup>38</sup></p>
<p>The Danish National <i>Staphylococcus aureus</i> Bacteremia Database</p>	<p>The nationwide registration of <i>S. aureus</i> bacteremias in Denmark since 1957 carried out by the Staphylococcal Laboratory at the Statens Serum Institut (SSI) for surveillance purposes. Linked to civil registration numbers since 1992. The regional microbiology departments send isolates on a voluntary basis. Has a high degree of completeness and &gt;90% of strains isolated from Danish blood cultures are referred to SSI for typing (detection <i>S. aureus</i> protein A (SPA) type) and antibiotic susceptibility testing.<sup>39</sup></p>
<p>The Register of Medicinal Product Statistics</p>	<p>Information on all prescriptions dispensed from pharmacies has been recorded from 1995 including the anatomical therapeutic chemical class (ATC class), strength, package size, number and date of dispensed prescription.<sup>40</sup></p>
<p>The Population's Education Registry (PER)</p>	<p>Information on highest attained education. In 2008 PER included 96.4% of the Danish population between 15 and 69 years of age.<sup>41</sup></p>
<p>The Income Statistics Register</p>	<p>Initiated in 1970. Contains information on the income and its composition (e.g. salary, taxes and public transfer payments) on an individual level as registered by the Tax Administration's registry.<sup>42</sup></p>
<p>All national registries can be linked on an individual basis using the civil registration number administered at birth or immigration.<sup>36</sup></p>	

## Exposure

RA is the main exposure of interest. A cohort of incident cases of RA will be identified, based on DANBIO and the Danish National Patient Registry (DNPR). Individuals registered with one of the

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4 following International Classification of Diseases codes in its 10<sup>th</sup> revision (ICD-10) in DANBIO are  
5 considered patients with RA: M05.9 (RA seropositive), M06.0 (RA seronegative), M06.9 (RA  
6 unspecified). Furthermore, in the DNPR individuals with  $\geq 2$  registrations from rheumatology  
7 departments with one of the mentioned ICD-10 codes (including also M05.8 (Other types of RA),  
8 not used in DANBIO) or the ICD-8 code 712.39 (arthritis rheumatoides alia et non specificata),  
9 within a period of 90 days are considered patients with RA. This method has previously been  
10 validated with high degree of validity (positive predictive value  $\approx 80\%$ ) and completeness.<sup>43</sup>  
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## 20 Outcome/event

21 The outcome of interest is incident first-time SAB as identified in the Danish National *S. aureus*  
22 Bacteremia Database. SAB relapses/reinfections will not be included. SAB events will be labeled  
23 “hospital-acquired” (HA SAB) if the first blood culture with *S. aureus* is obtained 48 hours or more  
24 after admission to a hospital and non-hospital acquired (non-HA SAB) if it is obtained <48 hours  
25 after admission. The non-HA SAB may be further subdivided into healthcare-associated SAB (HCA  
26 SAB) and community-acquired SAB (CA SAB) based on whether the patient has had recent hospital  
27 contact or not. Cases of SAB will further be classified with regards to the causative microorganism  
28 as cases of Methicillin-resistant *S. aureus* (MRSA) SAB or Methicillin-sensitive *S. aureus* (MSSA)  
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## 42 Follow-up

43 Follow-up starts at December 31, 1996, an individual’s 18<sup>th</sup> birthday, or at the date of immigration,  
44 whichever comes last. Individuals are followed up until first-time SAB, emigration, death or  
45 December 31, 2017, whichever comes first. Incident patients with RA contribute with person-years  
46 in the RA cohort following diagnosis and until the end of follow-up. The remaining individuals  
47 contribute person-years in the general population cohort. RA patients diagnosed after start of  
48 follow-up will contribute person-years in the general population cohort until date of RA diagnosis  
49 and in the RA cohort thereafter.  
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## Covariates

Information on diseases known to affect SAB risk (e.g. diabetes mellitus and hemodialysis) and use of prescription medications (e.g. glucose-lowering medication and TMP/SMX) will be obtained prior to baseline and during follow-up from the DNPR and the Register of Medicinal Product Statistics. Some conditions (e.g. diabetes mellitus and prosthetic joint insertion) leaves the subject in “forever risk” from the date of diagnosis/operation and until the end of follow-up. Other incidents, as invasive surgical procedures and dialysis procedures are considered temporary risk factors, and subjects are considered “at risk” of one of these in 90 days after the procedure date. Patients with cancer (except non-melanoma skin cancer) are considered “at risk” until five years after the last registration of a cancer diagnosis in the DNPR. Socioeconomic status will be evaluated by the highest attained educational level identified by the Population’s Education Registry (PER) and by the yearly average personal income level (3 years back) identified by the Income Statistics Register.

To allow for evaluation of RA specific risk factors, information specific to RA-patients will be identified in DANBIO prior to and during follow-up. (**Table 2**). Information on smoking habits is systematically collected annually in DANBIO and has a high degree of completeness.<sup>44</sup> DANBIO is the main source of information on antirheumatic treatments since in Denmark, some drugs are administered from the hospital departments without prescription (bDMARDs, subcutaneous methotrexate, leflunomide and injections with glucocorticoids) and hence not registered in the Register of Medicinal Products Statistics. A recent audit in DANBIO found a coverage of 98% for bDMARDs.<sup>45</sup> Information on glucocorticoid use will be identified in both DANBIO and the Register of Medicinal Products Statistics (**Table 2**).

<b>Table 2</b> Characteristics of patients with RA according to the DANBIO registry		
Variable	Description	Value
CDAI	Composite disease activity score of patient’s and doctor’s global assessment on a visual analogue scale (VAS)	0.0-76.0

Disease duration	Time passed from RA diagnosis until the first-time SAB	years
Erosive joint disease	X-rays of hands and feet registered before the first-time SAB	erosions/no erosions/unavailable
Auto-antibody status	ACPA and RF registered before SAB	positive/negative/unavailable
Smoking	Smoking status registered as close to SAB as possible	Previous/current/never/occasional/unavailable
<b>csDMARDs</b>		
Methotrexate, sulphasalazine, hydroxychloroquine, leflunomide	Current user: use within 90 days before SAB Previous user: ever used more than 90 days prior to SAB Non-user: Never used Cumulated exposure: Days on the drug (for current users)	Current/previous/non-user and cumulated exposure (days)
<b>bDMARDs</b>		
Anti-TNFs, abatacept, secukinumab, IL6 inhibitors, ustekinumab, apremilast	Current user: use within 90 days before SAB Previous user: ever used more than 90 days prior to SAB Non-user: never used Cumulated exposure: Days on the drug (for current users)	Current/previous/non-user and cumulated exposure (days)
Rituximab	Current user: last dose of rituximab was given within 12 months prior to SAB Previous user: ever used Non-user: never used Cumulated exposure: total dose (both current and previous users)	Current/previous/non-user and cumulated exposure (mg)

<b>tsDMARDs</b>		
JAK inhibitors	<p>Current user: use within 90 days before SAB</p> <p>Previous user: ever used more than 90 days prior to SAB</p> <p>Non-user: never used</p> <p>Cumulated exposure: days on the drug (for current users)</p>	Current/previous/non-user and cumulated exposure (days)
<b>Glucocorticoids (GCs)*</b>		
Oral and injectable (intramuscular and intraarticular) GCs	<p>Current user: use within 90 days before SAB</p> <p>Previous user: ever used more than 90 days prior to SAB</p> <p>Non-user: never used</p> <p>Cumulated exposure: will be calculated as prednisolone-equivalent dose for current users as described elsewhere <sup>10</sup></p>	Current/previous/non-user and cumulated exposure (mg)
* Use of GCs will be identified in both DANBIO and the Register of Medicinal Products Statistics		
<p><b>Abbreviations:</b> <b>RA</b> rheumatoid arthritis, <b>SAB</b> staphylococcus aureus bacteremia, <b>CDAI</b> clinical disease activity index, <b>csDMARDs</b> conventional synthetic disease-modifying antirheumatic drugs, <b>bdDMARDs</b> biologic DMARDs, <b>anti-TNF</b> tumor necrosis factor inhibitors (adalimumab, golimumab, etanercept, certolizumab pegol, infliximab), <b>IL6 inhibitors</b> interleukin-6 inhibitors (tocilizumab, sarilumab), <b>tsDMARDs</b> targeted synthetic DMARDs, <b>JAK inhibitors</b> Janus kinase inhibitors (baricitinib, tofacitinib)</p>		

### Expected number of events

When identifying incident RA cases in the DNPR and DANBIO as described above, we expect to identify approximately 500 SAB cases in the RA cohort. This is based on data from the annual

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4 report from The Danish National SAB Database.<sup>1</sup> Thus, from year 1996 until 2017 ≈30,000 SAB  
5 cases have been reported whereof in the last years approximately 5% (4.7-6.2%) occurred in  
6 patients with comorbid “rheumatic diseases”, corresponding ≈1500 cases in total. (5% of 30,000).  
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8 The expected number of events is based on the conservative assumption that one third of these  
9 patients will be incident patients with RA.  
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14 Since we have more detailed information on RA patients that have been followed in  
15 DANBIO (e.g. smoking, disease activity, joint erosions, etc.) compared with RA patients identified  
16 in the DNPR, we will consider limiting exposure to only RA according to DANBIO if the number of  
17 events is large enough for meaningful statistical analysis. In this case the study period will be  
18 limited accordingly to 2006 and onward.  
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## 24 Data analysis plan

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26 The exact data analysis plan depends on data availability and number of events. Incidence rates  
27 (IR) of SAB in the RA and in the general population cohorts will be calculated and multivariable  
28 Poisson regression models will be used to estimate IRRs. IRRs will be presented crude (adjusted for  
29 age, sex and calendar year) and further adjusted for potential confounders. We will use a dynamic  
30 statistical method to assess the impact of an RA diagnosis while accounting for other possible and  
31 known risk factors (e.g. SES, comorbidities and dialysis procedures). The Lexis macro will be used  
32 to split follow-up time according to calendar time, age and exposure status (e.g. comorbidities and  
33 SES). Comorbidities will be entered as time-varying variables in the model.  
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42 The impact of risk factors for SAB in patients with RA compared with the general  
43 population will be analysed as events in the exposed time-period compared to events in the  
44 unexposed time-period using the multivariable Poisson regression model. If statistical interaction  
45 is observed between RA and any of the potential or known risk-factors, stratified analyses will be  
46 performed.  
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52 The impact of possible risk factors (anti-rheumatic treatment, disease duration,  
53 disease activity, joint erosions, and smoking) for SAB among RA patients will be assessed. The  
54 number of covariates included in the final model will correspond the number of events in the RA  
55 population and will be prioritized according to a-priori assumption on clinical relevance. We plan  
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to study the impact of different DMARD treatments as risk factors for SAB among patients with RA separately, alternatively grouped as e.g. bDMARDs, tsDMARDs and csDMARDs.

Sensitivity analyses will include stratified analysis according to outcome defined as HA SAB, and non-HA SAB which can further be distinguished as HCA and CA SAB. The number of MRSA and MSSA SAB events in the RA and general population cohort will be presented. We do not expect the statistical power to allow us to perform separate analysis on risk factors of MRSA SAB due to an expected low number of cases.<sup>1</sup> Further sensitivity analysis will be performed to assess any difference in IR between the RA cohort identified in DANBIO and the full RA cohort identified by both DANBIO and the DNPR. Missing data will be handled by appropriate statistical methods, e.g. multiple imputations.

Data will be hosted and anonymized by Statistics Denmark and data will be processed using the statistical software SAS. Data access is expected in June 2019. Data analysis will start when access is obtained and is expected to end in January 2020.

## Patient and public involvement

The study hypotheses and design were discussed with a trained patient research partner both in the very beginning of the brainstorming phase of the study and later when the study hypotheses were formed. The purpose was to secure that possible risk factors evaluated were also important from a patient perspective, e.g. we agreed on risk associated with different treatments, disease duration and disease activity.

## Ethics and dissemination

All data will be handled in accordance with the General Data Protection Regulation (EU) 2016/679. Data processing agreements are set up between all data processors and the data owner (the Capital Region of Denmark). Data handling and data processing agreements are approved by the Capital Region of Denmark. Access to data from The Register of Medicinal Product Statistics is approved by Sundhedsdatastyrelsen, data from DANBIO is approved by The Danish Clinical Registries (RKKP) and data from the Danish National SAB Database is approved by Statens Serum Institut. Statistics Denmark has authorized the research institution and granted permission to

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4 linkage of data based on a written application. No ethical approval is necessary in Denmark when  
5 handling registry data only. The results will be presented in accordance with the STROBE  
6 initiative<sup>46</sup> as original articles in international peer-reviewed journals and at medical conferences.  
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8 Both positive and negative results will be published.  
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## 11 12 13 Future perspectives

14 The outcome of SAB in patients with RA remains to be investigated in further detail. One study on  
15 the subject suggested that patients with RA are at increased risk of a fatal outcome after SAB and  
16 that multiple metastatic infections in joints and bones are common.<sup>47</sup> When the disease burden of  
17 SAB in Danish patients with RA has been established in the current study, we plan to perform  
18 further studies on outcome after SAB including all-cause mortality, incidence of secondary  
19 infections and frequency of recurrent SAB in patients with RA compared with non-RA patients. We  
20 plan to identify risk factors for poor outcome that can guide physicians in the evaluation of a SAB  
21 patient with comorbid RA.  
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## Author contributions

Sabine Sparre Dieperink conceptualized the study hypotheses and Merete Lund Hetland, Bente Glintborg, Mette Nørgaard, Louise Bruun Oestergaard, Frank Mehnert, Thomas Benfield and Andreas Petersen contributed with the further development of these and with the study design. Sabine Sparre Dieperink wrote the first draft of the paper, which was critically revised by the other authors.

## Funding

This work was supported by the Danish Rheumatism Association grant number R163-A5715.

## Conflicts of interests

TB reports grants from Pfizer, grants from Novo Nordisk Foundation, grants from Simonsen Foundation, grants from GSK, personal fees from Pfizer, and BG reports grants from Pfizer, Biogen and Abbvie, all outside the submitted work.

## Word count

2779

## Keywords

Rheumatoid arthritis

Staphylococcus aureus

Staphylococcus aureus bacteremia

Antirheumatic agents

Bacteremia

## Acknowledgements

We wish to thank patient research partner Pia Lüchau Pedersen for her valuable comments when brainstorming ideas for the study design and hypotheses.

## Data statement

Due to local Danish legislation linked data cannot leave the country and the raw data is only available to a selected group of researchers. Additional information on the calculations/codes can be made available on request by contacting the corresponding author.

For peer review only