## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | 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 |
| **AUTHORS** | Dieperink, Sabine; Glintborg, B.; Oestergaard, Louise; Nørgaard, Mette; Benfield, Thomas; Mehnert, Frank; Petersen, Andreas; Lund Hetland, Merete |

## VERSION 1 – REVIEW

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| **REVIEWER** | Dafna Yahav<br>Rabin medical center, Beilinson hospital |
| **REVIEW RETURNED** | 17-Apr-2019 |

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| **GENERAL COMMENTS** | The protocol is well written and planned and the study's questions are of interest. The expected number of cases will enable practical conclusions.<br>Few comments.<br>Page 5 – Lines 57-59: "Furthermore, it can be speculated whether a higher frequency of smoking among patients with RA could influence this risk." – in the introduction there is an emphasize on smoking as an important risk factor for SAB. Actually, smoking is mainly described as a risk factor for nasal colonization with staph aureus and less direct evidence supports is role as a risk factor for clinical infection.<br>Page 12-13: Statistical analysis plan – in order to make things clearer for the reader I would categorize this part according to the objectives of the study, as described in pages 6-7 - "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."<br>Moreover, perhaps another section called "comparisons" should be added or planned tables/figures in order to clarify the data analysis plan. It is clear that a regression for risk factors for SAB will be conducted among the population of RA patients. It is not clear for the entire population what is the plan (objective 2 is not clear) – to perform a regression for risk factors in the entire population and add RA as a variable? Other? I think this second objective and the analysis plan for achieving it should be better descried.<br>General comments: |

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| | - To my knowledge MRSA in not common in Denmark, however still a plan to separate risk factors for MRSA and MSSA should be described.<br>- It is stated that data on IVDU is missing. Other risk factors for SAB, at least in the general population, should be mentioned – HIV, nasal colonization of SA, implanted foreign body other than orthopedic devices (central lines, prosthetic valves, etc), hospitalizations.<br>- Some patients with RA receive TMP/SMX as prophylaxis for PCP. This may influence the risk for SAB and if available, should be documented. |

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| **REVIEWER** | Insa Joost<br>Institute of Medical Microbiology and Hospital Hygiene Heinrich-Heine-University Düsseldorf<br>Germany |
| **REVIEW RETURNED** | 19-Jun-2019 |

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| **GENERAL COMMENTS** | Thank you for giving me the opportunity to review the manuscript „Risk factors for *Staphylococcus aureus* bacteremia in patients with rheumatoid arthritis and incidence with the general population. “Protocol for a Danish nationwide observational cohort study “.<br><br>The authors propose a study protocol to establish the incidence of *S. aureus* bacteremia (SAB) in patients with rheumatoid arthritis (RA) compared to the general population in Denmark by using registration data from different databases. They aim to identify risk factors for the acquisition of SAB in the RA cohort. Assumed risk factors include age, sex, steroid use and the prevalence of prosthetic joints. Furthermore, they plan to investigate the potential influence of disease activity, duration, anti-rheumatic treatment, and smoking on the incidence of SAB in RA patients.<br><br>The manuscript is well written, logically composed and the aim is set clear.<br><br>General comments:<br><br>1. A number of risk factors for the acquisition of SAB have already been identified previously, e.g. intravenous drug abuse, diabetes mellitus and hemodialysis [Nielsen, 2015; Kaasch, 2014]. These factors should be recorded additionally and considered in the statistical analysis to prevent confounding. Smoking, however, has not yet been identified as a risk factor and it seems unlikely that smoking as a single factor will have a significant contribution to the acquisition SAB (it might, though, have influence on mortality and outcome). Furthermore, the information about smoking status might not be very reliable. Thus, it should be interpreted with caution.<br><br>2. The stratification of SAB into hospital acquired versus non-hospital infections should include healthcare associated infections as a third variable. |

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| | 3. It has been demonstrated that patients with RA and SAB have a higher mortality and suffer significantly more often from (poly)osteoarticular infections than patients with SAB without RA [Joost, 2017]. The influence of immunosuppressive treatment on mortality and outcome remains unclear. It would be very interesting and helpful if the authors could extend their analysis to these variables in their study.<br><br>4. For the same reason, the rate of SAB relapse within 1 year should be recorded. It is very likely that RA patients are more susceptible to relapses due to the more invasive nature of SAB in these group.<br><br>Minor comments:<br><br>Page 5, Line 34: „…affecting especially lungs and joints “. In the paper cited, rate ratios for septic arthritis and osteomyelitis are much higher than for pneumonia (14.89 and 10.63 vs. 1.68). Mentioning pneumonia and osteoarticular infections in one breath gives a false impression and should be avoided.<br><br>Page 5, line 41: The authors claim that all antirheumatic treatments are associated with an increased infection risk for patients with RA. However, the risk of infection associated with antirheumatic drugs, especially with biologicals, is still a matter of debate. Furthermore, Sams et al investigated SAB within a cohort of RA patients and found no increased risk for those with immunosuppressive therapy. Consider rephrasing |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name: Dafna Yahav
Institution and Country: Rabin medical center, Beilinson hospital Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below:
The protocol is well written and planned and the study's questions are of interest. The expected number of cases will enable practical conclusions.
Few comments.
Page 5 – Lines 57-59: "Furthermore, it can be speculated whether a higher frequency of smoking among patients with RA could influence this risk." – in the introduction there is an emphasize on smoking as an important risk factor for SAB. Actually, smoking is mainly described as a risk factor for nasal colonization with staph aureus and less direct evidence supports is role as a risk factor for clinical infection.

>> Response 1) This sentence has been deleted in the revised version of the article.

Page 12-13: Statistical analysis plan – in order to make things clearer for the reader I would categorize this part according to the objectives of the study, as described in pages 6-7 - "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."
Moreover, perhaps another section called "comparisons" should be added or planned tables/figures in order to clarify the data analysis plan. It is clear that a regression for risk factors for SAB will be conducted among the population of RA patients. It is not clear for the entire population what is the plan (objective 2 is not clear) – to perform a regression for risk factors in the entire population and add RA as a variable? Other? I think this second objective and the analysis plan for achieving it should be better descried.

>>Response 2) Since our ability to stratify will depend on the number of events in the cohorts, we cannot yet decide on the planned figures for the article. The following has been revised and added to the “methods and analysis” section:
“Incidence rates (IR) of SAB in the RA and in the general population cohorts will be calculated and multivariable Poisson regression models will be used to estimate IRRs. IRRs will be presented crude (adjusted for age, sex and calendar year) and further adjusted for potential confounders.
We will use a dynamic statistical method to assess the impact of an RA diagnosis while accounting for other possible and known risk factors (e.g. SES, comorbidities and dialysis procedures). The Lexis macro will be used to split follow-up time according to calendar time, age and exposure status (e.g. comorbidities and SES). Comorbidities will be entered as time-varying variables in the model.
The impact of risk factors for SAB in patients with RA compared with the general population will be analysed as events in the exposed time-period compared to events in the unexposed time-period using the multivariable Poisson regression model. If statistical interaction is observed between RA and any of the potential or known risk-factors, stratified analyses will be performed.”

General comments:
- To my knowledge MRSA in not common in Denmark, however still a plan to separate risk factors for MRSA and MSSA should be described.

>>Response 3) The number of cases of MRSA in Denmark is very low (e.g. 47 in 2017 corresponding 2.2% of all cases) [Petersen, 2017], which does not allow us to perform meaningful statistical analysis of risk factors for MRSA SAB and MSSA SAB separately in patients with RA. Numbers of events attributable to MRSA and MSSA respectively will be described. A comment on this added to the revised manuscript in the “methods and analysis” section.

- It is stated that data on IVDU is missing. Other risk factors for SAB, at least in the general population, should be mentioned – HIV, nasal colonization of SA, implanted foreign body other than orthopedic devices (central lines, prosthetic valves, etc), hospitalizations.

>>Response 4) We have now included the other known risk factors for SAB in the introduction by rephrasing into:
“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.[Petersen, 2017; Laupland, 2008; Smit, 2016; Bassetti, 2004; Jacobsson, 2007] 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. [Bhattacharya, 2015] 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 [Laupland, 2008; Oestergaard, 2017; Wertheim, 2004; Smit,

2016] whereas treatment with statins and trimethoprim-sulfamethoxazole (TMP/SMX) has been associated with a decreased risk. [Smit, 2017; Hughes, 1977; Gurwith, 1979]"

- Some patients with RA receive TMP/SMX as prophylaxis for PCP. This may influence the risk for SAB and if available, should be documented.

>>Response 5) Denmark has no national guidelines for PCP prophylaxis in RA patients, thus, we expect the use of TMP/SMX to be low. We have added information on TMP/SMX in the "introduction" section, as mentioned in response 4 above, and revised the following sentence in the "methods and analysis" section:
"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."

Reviewer: 2
Reviewer Name: Insa Joost
Institution and Country: Institute of Medical Microbiology and Hospital Hygiene Heinrich-Heine-University Düsseldorf Germany Please state any competing interests or state 'None declared': None declared

Thank you for giving me the opportunity to review the manuscript „Risk factors for Staphylococcus aureus bacteremia in patients with rheumatoid arthritis and incidence with the general population. "Protocol for a Danish nationwide observational cohort study ".
The authors propose a study protocol to establish the incidence of S. aureus bacteremia (SAB) in patients with rheumatoid arthritis (RA) compared to the general population in Denmark by using registration data from different databases. They aim to identify risk factors for the acquisition of SAB in the RA cohort. Assumed risk factors include age, sex, steroid use and the prevalence of prosthetic joints. Furthermore, they plan to investigate the potential influence of disease activity, duration, antirheumatic treatment, and smoking on the incidence of SAB in RA patients.
The manuscript is well written, logically composed and the aim is set clear.
General comments:
1. A number of risk factors for the acquisition of SAB have already been identified previously, e.g. intravenous drug abuse, diabetes mellitus and hemodialysis [Nielsen, 2015; Kaasch, 2014]. These factors should be recorded additionally and considered in the statistical analysis to prevent confounding. Smoking, however, has not yet been identified as a risk factor and it seems unlikely that smoking as a single factor will have a significant contribution to the acquisition SAB (it might, though, have influence on mortality and outcome). Furthermore, the information about smoking status might not be very reliable. Thus, it should be interpreted with caution.

>>Response 1) Please see response 1 to reviewer 1 regarding smoking, and response 2 and 4 to reviewer 1 regarding known risk factors.
The following information has been added to the revised manuscript in the "methods and analysis" section:
"Information on smoking habits is systematically collected annually in DANBIO and has a high degree of completeness. [Glintborg, 2016]"

2. The stratification of SAB into hospital acquired versus non-hospital infections should include healthcare associated infections as a third variable.

>> Response 2) We plan to divide the non-hospital acquired infections into “healthcare-associated” and “community-acquired” infections as suggested. This has been added to the revised section of “methods and analysis”. (See quote below) Unfortunately we do not have access to information on whether patients are nursing home residents.
“The SAB events will be labeled “hospital-acquired” (HA SAB) if the first blood culture with S. aureus is obtained 48 hours or more after admission to a hospital and non-hospital acquired (non-HA SAB) if it is obtained <48 hours after admission. The non-HA SAB may be further subdivided into healthcare-associated SAB (HCA SAB) and community-acquired SAB (CA SAB) based on whether the patient has had recent hospital contact or not”.

3. It has been demonstrated that patients with RA and SAB have a higher mortality and suffer significantly more often from (poly)osteoarticular infections than patients with SAB without RA [Joost, 2017]. The influence of immunosuppressive treatment on mortality and outcome remains unclear. It would be very interesting and helpful if the authors could extend their analysis to these variables in their study.

>>Response 3) We agree to the scientific interest of exploring SAB outcomes in RA. This is, however, beyond the scope of this study, but a logical next step when the magnitude of the problem of SAB among Danish patients with RA is known. Studies of outcome will most likely be made in another study design than the one described in this article, where focus is on the incident RA patients. (A comment regarding these future perspectives has been added to the revised version of the manuscript in the section “ethics and dissemination”).

4. For the same reason, the rate of SAB relapse within 1 year should be recorded. It is very likely that RA patients are more susceptible to relapses due to the more invasive nature of SAB in these group.

>>Response 4) As mentioned above in response 3, this outcome is outside the scope of the current study.

Minor comments:
Page 5, Line 34: „…affecting especially lungs and joints “. In the paper cited, rate ratios for septic arthritis and osteomyelitis are much higher than for pneumonia (14.89 and 10.63 vs. 1.68). Mentioning pneumonia and osteoarticular infections in one breath gives a false impression and should be avoided.

>>Response 5) The cited reference describes relative risks only and the relative risk of joint infection and osteomyelitis are much higher in patients with RA compared with the general population than that of pulmonary infections. Pulmonary infections, though, are the most common infection in patients with RA. The sentence has been rephrased and a reference [Widdifield, 2013] describing the incidence rates and absolute numbers has been added.

Page 5, line 41: The authors claim that all antirheumatic treatments are associated with an increased infection risk for patients with RA. However, the risk of infection associated with antirheumatic drugs, especially with biologicals, is still a matter of debate. Furthermore, Sams et al investigated SAB within a cohort of RA patients and found no increased risk for those with immunosuppressive therapy. Consider rephrasing.

>>Response 6) We agree the current literature does not support that conventional synthetic DMARDS (csDMARDs) are associated with an increased risk of infections. The risk of infections in bDMARD treatment has been elaborated on in the revised manuscript:

“Anti-rheumatic treatments such as biologic DMARDS (bDMARDs, e.g. tumor necrosis factor alpha inhibitors (anti-TNFs)) [Lahiri, 2015; Ramiro, 2017; Ruderman, 2012] and the newer targeted synthetic DMARDs (tsDMARDs, e.g. tofacitinib and baricitinib) [Winthrop, 2016; Cohen, 2017] as well as glucocorticoids [Strangfeldt, 2016; Crowson, 2012; Widdifield, 2013; Dixon, 2012] 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 change in management of patients through screening for infections prior to start of bDMARDs, prophylactic measures as vaccines and treating infections early. [Ramiro, 2017; Aaltonen, 2015]

We agree that Sams et al did not find any association between DMARD treatment and risk of SAB as also mentioned in the original manuscript. We have elaborated on the impact of their choice of control group in the revised manuscript:

“The study found no association between neither conventional synthetic DMARDs (csDMARDs), bDMARDs, glucocorticoids nor prosthetic joints and SAB. [Sams, 2015] However, their comparisons were RA patients hospitalized for other reasons than SAB. These patients were likely at higher risk of SAB than RA patients in general, which may have biased the relative estimates towards no association.”