PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of community-acquired bacteraemia on return to workforce, risk of sick leave, permanent disability pension and death: A Danish population-based cohort study
AUTHORS	Dalager-Pedersen, Michael; Koch, Kristoffer; Wernich Thomsen, Reimar; Schønheyder, Henrik; Nielsen, Henrik

VERSION 1 - REVIEW

REVIEWER	Alastair Miller Tropical & Infectious Disease Unit Royal Liverpool University Hospital
REVIEW RETURNED	28-Oct-2013

GENERAL COMMENTS	1. The paper gives good data on some sequelae from community acquire bacteraemia. However, the practical benefits of this knowledge are not very clear. It is difficult to see how it will affect patient management either at an individual patient or at a population level. The results are not unexpected and although this is good work then could be a tendency to think "so what?" about the results and conclusions. 2. The advantage of studying this over a long period (15 years) means that there are very many subjects but the disadvantage is that many management issues have changed over the duration and both the epidemiology and management of CAB is probably very different in 2013 from what is ewas in 1996 - therefore it is not clear how up to date any messages are. 3. The study used 7 different population registries. This means that data were more likely to be complete but inevitably there must be some confusion and duplication of data. 4. It is not clear whether all those listed as "controls" were actually free of bacteraemia. Many may have had antibiotics given to them before blood cultures were taken and therefore these were "false negative" blood cultures. This would confound results. This is a well conducted study and I have no quibble with the quality of the methodology or clarity of the paper. I do have concerns about how imprtant these results actually are and I should be grateful if the authors could consider that question before I would recommend publication.

REVIEWER	Eli Perencevich University of Iowa, United States
REVIEW RETURNED	01-Dec-2013

GENERAL COMMENTS	Professor Dalager-Pedersen et al. have completed an outcomes analysis of Community-acquired bacteremia among a cohort of hospitalized patients in Denmark. This is a very difficult topic to study as there are always issues with identifying the proper control group and adjusting for confounders. The authors did an adequate job controlling for confounders using regression modeling but there might be issues with the selected control group (in this case the unexposed patients in the cohort). I have the following comments on the study: 1) The primary aim is to determine the outcomes (sick leave, mortality, disability) associated with community-acquired bacteremia. Community-acquired bacteremia was defined as positive blood culture from a specimen obtained less than 48 hours after hospital admission. The unexposed controls were also hospitalized and had a culture but it was negative. Thus, the outcomes of the study are conditional on hospital admission. They do not tell us the true outcomes of CAB, but rather outcomes of CAB vs outcomes of other various conditions that led to hospitalization. I suspect that this conditional interpretation is not what the authors intended. I suspect that the selecting unexposed controls from the general population would have been more appropriate. This would allow calculation of attributable outcomes associated with CAB alone. Thus, the authors could compare the outcomes in the CAB exposed population (the 450 already included) with age-adjusted outcomes at baseline in the non-hospitalized population. At the very minimum, the authors need to acknowledge the limitation of using the convenient hospital controls, since they don't strictly represent the baseline outcomes in the community population. 2) Another issue is that bacteremia can be primary or secondary to another infection. If possible, the outcomes should be split into those associated with primary CAB and those secondary to another community infection (e.g. pneumonia, UTI). The differences shown in Table 3 for specific organisms suggest that there will be differences in primary vs secondary bacteremia too. This dichotomy is important since CAB secondary to pneumonia would be very different than CAB secondary to a UTI. Thus, it almost doesn't make sense to combine these in an analysis since they are completely different infectious diseases.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Alastair Miller
Institution and Country Tropical & Infectious Disease Unit
Royal Liverpool University Hospital
Liverpool
L7 8XP
Please state any competing interests or state 'None declared': None declared

1. The paper gives good data on some sequelae from community acquire bacteraemia. However, the practical benefits of this knowledge are not very clear. It is difficult to see how it will affect patient

management either at an individual patient or at a population level. The results are not unexpected and although this is good work then could be a tendency to think "so what?" about the results and conclusions.
Author response: We thank Dr. Miller for his excellent review and for his positive view on our data and good work. We also thank him for allowing us to clarify a few issues. Our results and conclusion may not have much impact upon the management of patients with CAB. However, our findings may inform patients who are part of the workforce and who are hospitalised with CAB about their prognosis. Prognosis - foreseeing or foreknowing – have been of interest to humanity for centuries. This year the importance of prognosis studies has been reviewed in the BMJ (Hemingway H, Croft P, Perel P, Hayden JA, Abrams K, Timmis A, Briggs A, Udumyan R, Moons KGM, Steyerberg EW, Roberts I, Schroter S, Altman DG, Riley RD. Prognosis research strategy (PROGRESS) 1: a framework for researching clinical outcomes. BMJ. 2013; 346:e5595).
Patients and next of kin may have an interest in knowing their chance of return to work as well as their risk of long-term sick leave, disability pension, and death. Hitherto, studies on CAB patients of working-age have found 30-day mortality estimates of 11% (see Introduction section) which is quite different from the 4% risk we found in working-age CAB patients who were part of the workforce. If we were to be hospitalised with CAB tomorrow that new information would be of interest to us. Because no studies have examined risk for sick leave and disability pension after CAB, our study may be of special importance. Because some patients may be concerned with these outcomes, some physicians may like to have some knowledge on the subject. Others may not care.
Our study could well be classified as “Fundmamental prognosis research” as reviewed by Hemingway in the reference above. Fundamental prognosis research is not just important for patients and next of kin (see reference) but we believe that our study is of special import for them and for the physicians who care for them.
Our results may be “not unexpected” to some people. However, many of our findings were quite surprising to us, e.g. the high probability of return to work after CAB and the low 30-day mortality of 1.7% in patients with pneumococcal CAB. We acknowledge that whether things are “expected” or “unexpected” is quite subjective.

2. The advantage of studying this over a long period (15 years) means that there are very many subjects but the disadvantage is that many management issues have changed over the duration and both the epidemiology and management of CAB is probably very different in 2013 from what is ewas in 1996 - therefore it is not clear how up to date any messages are.
Author response: We agree with the reviewer. We have added supplementary analyses in which we examine the risk of outcomes in the latter half of the study period (2003-2011) to make sure that the messages are up to date). See Methods and Results p.12, l.9:
“During 2003 to 2011, the association between CAB and study outcomes remained essentially unchanged when compared to culture negative controls (4-week sick leave 37.7% vs. 23.6%, adjusted RR, 1.40; 95% CI 1.18-1.66, and, 1-year disability pension 3.4% vs. 2.4%, adjusted RR, 1.58; 95% CI 0.54-4.59, and, 30-day mortality 3.0% vs. 1.1%, adjusted RR, 2.09; 95% CI 0.76-5.70, and, 1-year mortality 7.6% vs. 3.3%, adjusted RR, 2.14; 95% CI 1.29-3.52).”

3. The study used 7 different population registries. This means that data were more likely to be complete but inevitably there must be some confusion and duplication of data.
Author response: The reviewer touches upon a strength of our study. In Denmark, all residents can be identified through unique 10-digit personal identification numbers (the Central Person Registry number). This number is used for all health-care contacts and is recorded in national databases. These databases are complete and contain highly valid data, see for example reference #10, 11, 14, and 15. Still, we did find that <1% of patients had missing data on marital status (see Table 1) and 2% had missing DREAM data (see Flow Chart, subjects with missing DREAM data were excluded). Each registry used in the present study contained different types of data pertaining to unique identification numbers. We did not find duplicate entries in this study which is likely due to continued maintenance

of the databases by implicated authorities.

4. It is not clear whether all those listed as "controls" were actually free of bacteraemia. Many may have had antibiotics given to them before blood cultures were taken and therefore these were "false negative" blood cultures. This would confound results.
Author response: We agree. We have retrieved information on recent out-of-hospital antibiotic use (more common in culture negative controls than in CAB patients) and have conducted supplementary analyses in which we restricted to patients who had no recent out-of-hospital antibiotic use and who had blood culture draw performed on admission. These analyses gave similar results to those found in analyses pertaining to all study subjects.
Results section p. 12, l. 14:
“Analyses restricted to 352 CAB patients and 4078 culture negative controls who had no previous antibiotic therapy (blood culture draw performed on admission and no recent out-of-hospital antibiotic use) did not materially influence the association between CAB and 4-week sick leave (adjusted RR, 1.71; 95% CI 1.48-1.97), 1-year disability pension (adjusted RR, 1.00; 95% CI 0.06-16.82), 30-day mortality (adjusted RR, 1.73; 95% CI 0.68-4.41), or 1-year mortality (adjusted RR, 1.70; 95% CI 1.02-2.84).”

This is a well conducted study and I have no quibble with the quality of the methodology or clarity of the paper. I do have concerns about how imprtant these results actually are and I should be grateful if the authors could consider that question before I would recommend publication.
Author response: Please see above (comment #1). Again, thank you very much for your review.

Reviewer Name Eli Perencevich
Institution and Country University of Iowa, United States
Please state any competing interests or state ‘None declared’: none declared

Professor Dalager-Pedersen et al. have completed an outcomes analysis of Community-acquired bacteremia among a cohort of hospitalized patients in Denmark. This is a very difficult topic to study as there are always issues with identifying the proper control group and adjusting for confounders. The authors did an adequate job controlling for confounders using regression modeling but there might be issues with the selected control group (in this case the unexposed patients in the cohort). I have the following comments on the study:

1) The primary aim is to determine the outcomes (sick leave, mortality, disability) associated with community-acquired bacteremia. Community-acquired bacteremia was defined as positive blood culture from a specimen obtained less than 48 hours after hospital admission. The unexposed controls were also hospitalized and had a culture but it was negative. Thus, the outcomes of the study are conditional on hospital admission. They do not tell us the true outcomes of CAB, but rather outcomes of CAB vs outcomes of other various conditions that led to hospitalization. I suspect that this conditional interpretation is not what the authors intended.

I suspect that the selecting unexposed controls from the general population would have been more appropriate. This would allow calculation of attributable outcomes associated with CAB alone. Thus, the authors could compare the outcomes in the CAB exposed population (the 450 already included) with age-adjusted outcomes at baseline in the non-hospitalized population.

At the very minimum, the authors need to acknowledge the limitation of using the convenient hospital controls, since they don’t strictly represent the baseline outcomes in the community population.
Author response: We thank Dr. Perencevich for his excellent review and for his pertinent thoughts concerning the appropriateness of the control group. We did consider the use population controls in our initial manuscript but chose to focus on blood culture negative controls in order to examine the

influence of CAB in itself on the risk of sick leave, disability pension, and death. We believe that the blood culture negative controls allow for some insight into this question (i.e. “Does bacteremia have an effect on the risk of sick leave (etc) in patients that are acutely admitted to hospital from the community”). We agree that population controls also constitute an appropriate control group because bacteremia was community-acquired. However, population controls can be used to investigate a different question: How does CAB and hospitalisation (i.e. CAB disease that is so severe that it warrants hospitalisation) affect the risk of sick leave, disability pension, and death. We have therefore included a second control group of population controls in order to evaluate whether CAB hospitalisation affects the risk of disability pension and death when compared to the source population.

2) Another issue is that bacteremia can be primary or secondary to another infection. If possible, the outcomes should be split into those associated with primary CAB and those secondary to another community infection (e.g. pneumonia, UTI). The differences shown in Table 3 for specific organisms suggest that there will be differences in primary vs secondary bacteremia too. This dichotomy is important since CAB secondary to pneumonia would be very different than CAB secondary to a UTI. Thus, it almost doesn’t make sense to combine these in an analysis since they are completely different infectious diseases.
Author response: We agree with the reviewer that it would be of interest to further examine the risk of outcomes according to type of bacteremia. We have therefore conducted supplementary analyses in which we examine the risk of sick leave, disability pension, and death according to focus of infection (see Supplement, Table 3). Because these patients had CAB, bacteremia secondary to “typical” community-onset infections was most common. Respiratory tract infection was present in 164 patients, UTI in 93, and 144 had “miscellaneous” infection (eg. endocarditis in 27). Still, 49 patients were registered as having an unknown focus of infection or more than one potential focus of infection. We prefer CAB subgroup analysis by etiologic agent and not by type of infection. The reason is that the etiologic agent was present in the bloodstream at time of blood culture draw (and it carries some information on the likely underlying infection, e.g. pneumococcus/pneumonia and coli/UTI). In contrast, whether or not the clinical microbiologists and attending physician jointly were successful in diagnosing the infection which was behind the CAB was highly dependent on how much time they had to make the diagnosis. Patients who were very sick on admission and who died within a few hours were more likely to be categorised as having an unknown focus of infection or more than one possible focus of infection (i.e. initially and maybe very briefly, all patients admitted for CAB or sepsis will have an unknown focus of infection – and only time, interview, clinical examination, and diagnostic tests will move patients from “unknown focus” to “identified focus”). This in part explains why the risk of various outcomes is high in our group of CAB patients with “unknown focus” (e.g. 30-day mortality 14.3%) and why the risk is low for some types of infection (e.g. 30-day mortality of 0 after UTI). Please note this issue is relevant to many studies that examine the risk of outcomes after CAB or sepsis according to underlying infection, not just to our study.
Information and discussion on outcomes by focus of infection can be found in Results (p.11, l.23):
“Irrespective of type of focus, CAB was associated with an increased risk for long-term sick leave when compared to culture negative controls (e.g. 40.2% of CAB patients with respiratory tract infection were on sick leave for at least 4 weeks, adjusted RR, 1.51; 95% CI 1.26-1.83). Mortality was particularly high among patients with an unknown focus or more than one focus of infection (30-day mortality of 14.3%), Table 3 in the supplement.”
And in Discussion (p.15,l.20):
“In analyses of mortality by focus of infection, immortal-time bias may have prompted falsely low risks of death in patients with an identified focus of infection (and a high risk of death in patients with an unknown focus).”

VERSION 2 – REVIEW

REVIEWER	Eli Perencevich University of Iowa Carver College of Medicine; United States
REVIEW RETURNED	07-Jan-2014

GENERAL COMMENTS	The authors have done a commendable job responding to my two queries. The addition of the population controls enhances the utility of the findings and could inform decision makers. For example, comparisons to hospitalized, culture negative patient controls underestimates the burden of disease for CAB. compared to comparisons to population controls. The burden of disease of CAB patients in comparison to population controls could guide future research funding priorities, for example.