Author's response to reviews

Title: Clinical features and predictors of mortality in admitted patients with community- and hospital-acquired legionellosis: A Danish historical cohort study.

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Author's response to reviews: see over
Dear Ms Roxane Rajabi,

Thank you very much for the comments from the reviewers and for the opportunity to revise our manuscript. We found that the comments added to the quality of our manuscript. We have done our best to revise the manuscript in accordance with the comments and when we disagreed, we have argued why we did not consider that the suggested changes should be made. All comments have been highlighted and assigned a letter and number (C1-C14) and all answers directly follow each comment (A1-A14). Please find all the comments and answers below. A revised manuscript with “tracked changes” has also been submitted.

Please do not hesitate to contact us if further explanation or clarification is needed.

Best regards,

Sanne Jespersen.
Referee 1: Roberto Esposito

C1: The main criticism concerns the terminological confusion. The term legionellosis encompasses all diseases caused by Legionella species, whereas Legionnaires’ disease is a synonym of Legionella pneumonia, not just of Legionella infection. Consequently, it is not correct to say "wide ranges of disease manifestations have been reported, ranging from a self-limiting flu-like illness." (page 3). If only the cases of pneumonia were considered, it is rather surprising that in 20% of the hospital-acquired cases the initial x-ray was normal (page 7; but in page 10 authors say that "20% of community acquired cases did not have abnormalities on chest x-ray at symptom onset"). In this context it is impossible, in my opinion, to compare the cases studied by the authors with those of Benin et al. (CID 2002; 35:1039-46). The definition of "case patient" by Benin et al., in fact, was "a person with pneumonia that was diagnosed by chest radiography and.". In conclusion, it should be clearly stated whether all the patients had a pneumonic illness or some of them could had only a febrile nonpneumonic disease like Pontiac fever.

A1: We have now clarified how “case patients” in our study were defined. We have added the following paragraph with the definition of definitive and presumptive cases as suggested: “Within the surveillance system cases are classified as either definitive, presumptive or unlikely cases. According to Danish guidelines a definitive case is a patient with at least one of the following: 1) Culture isolation of Legionella species; 2) Detection of Legionella antigen in urine with a level of antigen >10 aU/ml; 3) Fourfold rise or fall of immunofluorescence titers against L. pneumophila serogroup 1, 3 or 6 obtained with paired serum specimen, provided a titer of at least 1:128 was obtained; 4) Detection of L. pneumophila DNA by PCR in a sample from the lower airways or a Legionella antibody titer >1:256 against L. pneumophila serogroup 1, 3 or 6 combined with Legionella urinary antigen test >5aU/ml and <10aU/ml, or 5) Positive Legionella PCR and Legionella antibody titer >1:256 against L. pneumophila serogroup 1, 3 or 6. A presumptive case is
defined as a patient with at least one of the following: 1) Legionella urinary antigen test >5 aU/ml and < 10 aU/ml; 2) Positive Legionella PCR; 3) An antibody titer >1:256 against L. pneumophila serogroup 1, 3 or 6; 4) A fourfold rise or fall of antibody titers with paired sera against L. pneumophila serogroup 2, 4 or 5 or against L. micdadei or L. bozemanii provided that a titer of least 1:128 is reached; 5) A compatible history of LD during an outbreak but without diagnostic tests being obtained, or 6) Any combination of diagnostic results that justifies a classification as a possible case.” (page 5, line 11-23 + page 6, line 1-3)

Since the definition was based on results of microbiological tests rather than on clinical and chest x-ray findings, some of the patients in our study could have had a febrile nonpneumonic disease like Pontiac fever. However, most patients probably had Legionnaires’ disease rather than Pontiac fever since only hospitalized patients were included in our study, indicating a considerable degree of disease severity. We have chosen to change the term “Legionnaires’ Disease” to “legionellosis” throughout the paper to avoid confusion. Furthermore, we have underscored that the “case definition” in the study by Benin et al. was different from ours by adding the following paragraph: “A direct comparison with the studies of Benin et al. and Pedro-Botet et al. is not possible due to differences in case definitions. The studies by Benin et al. and Pedro-Botet et al. only included patients with Legionella pneumonia whereas we included all patients with legionellosis. Since patients with Pontiac fever have a lower risk of dying, mortality in our study would probably have been higher if we had excluded these patients from our analyses.” (page 14, line 25 + page 14, line 1-4)

C2: Although in Denmark a restrictive antibiotic policy exists, it is singular that in 26.7% of hospital-acquired episodes the initial antibiotic therapy (Table 2) was "penicillin immunotherapy". Probably, not penicillin but another beta-lactam drug was used.
A2: Referee 1 questions that 26.7% of HALD cases received penicillin monotherapy as the initial empirical antibiotic therapy or whether another beta-lactam drug was used. It is correct that benzylpenicillin was used as monotherapy initially in 26.7% of HALD cases.

C3: The classification of cases of Legionella infection as definitive and presumptive should be clearly explained, together with the diagnostic laboratory methods used. Were PCR and Legionella urinary antigen test always evaluated, as it seems suggested in page 10?

A3: Please see A1.

LUT and PCR were not evaluated in all cases. We have described diagnostic testing in details in reference 13: Jespersen S, Sogaard OS, Fine MJ, Ostergaard L. The relationship between diagnostic tests and case characteristics in Legionnaires’ disease. Scand J Infect Dis 2009 May 8:1-8.

Referee 2: Francesco Castelli

The Authors investigate differences in 30 and 90 days case-fatality rates between community acquired and hospital-acquired Legionnaire’s diseases in 4 Danish counties over a 10 years period. The topic is relevant and may well be of interest to the readers of BMC.

The question posed by the Authors is well defined.

However, in my opinion, the following methodological issues are to be addressed by the Authors:

C4: I feel uncomfortable with the case-definition of HALD and CALD. To my knowledge, incubation period of Legionnaires’ Disease ranges between 2-10 days. A 14-day period after
discharge seems to be too long for a pneumonia to be considered as HALD. Please comment.

A4: We agree that the most commonly reported incubation period of Legionnaires' Disease reported in the literature ranges between 2-10 days. The reason why we chose a 14-day period after discharge was that sometimes a longer incubation period has been reported (http://www.cdc.gov/legionella/top10.htm) (http://www.who.int/mediacentre/factsheets/fs285/en/index.html)

After reviewing the data, it turned out that none of our cases of hospital-acquired LD occurred later than 10 days after discharge so we have decided to change the definition of HALD: “We defined legionellosis as hospital-acquired if a patient had been discharged within the preceding 10 days or if symptoms of legionellosis appeared >2 days after hospital admission.” (page 6, line 9-10)

C5: Equally, I feel uncomfortable with the definition of travel-associated LD for those cases whose admission occurred within a month from travelling.

A5: We agree in accordance with guidelines from “The European Working Group for Legionella Infections” that it would be more correct to define travel-associated LD as cases who in the 10 days before onset of illness visited a foreign country. We have redefined cases as travel-associated if they fulfill these criteria: “A case was defined as possibly travel-associated if the patient had been visiting a foreign country within 10 days of onset of symptoms.” (page 6, line 11-12) Thus, three travel-associated cases were re-classified as not travel-associated resulting in minor changes the uni- and multivariate analysis but the conclusions are the same.

C6: Hyponatremia was associated with a lower risk of death in CALD. The Authors suggest that earlier LD suspicion and treatment may be responsible for better outcome in these cases. However, it is not clear if this association with earlier specific anti-LD treatment was in fact observed in the study sample.

A6: We observed that patients with hyponatriemia were diagnosed and treated earlier with anti-legionella treatment than patients without hyponatriemia. We have added this observation in the following paragraphs: “Median duration of time from in-hospital symptoms to diagnosis was shorter among patients with hyponatriemia compared with patients without, 5 days and 10 days, respectively (p<0.001). Furthermore, 18% of patients with hyponatriemia received treatment with an anti-legionella antibiotic within 24 hours of admission compared to 10% of patients without hyponatriemia (p=0.04).” (page 10, line 18-21) and “The association between hyponatriemia and
legionellosis is well documented. Thus, increased awareness of legionellosis in patients with pneumonia and hyponatriemia may have caused physicians to request diagnostic testing for legionellosis and to prescribe anti-legionella antibiotics as observed in our study which could explain the lower mortality in this group.” (page 15, line 8-11)

C7: I believe that the definition of presumptive cases is important and should not be only left to a reference. What do the Author mean by “presumptive”? Which parameters are taken into account?
A7: Please see A3.

C8: No reference about the different distribution of “presumptive” cases among HALD and CALD is made in the article. Any difference in case-fatality rates?
A8: Information about the distribution of definitive and presumptive cases has been added: “More cases of CAL (87.5%) were classified as definitive compared to HAL (16.8%) (p=0.05).” (page 9, line 5-6). No statistically significant difference in case-fatality rate among definitive and presumptive cases was observed.

C9: HALD was associated with higher mortality, which is not an unexpected result. How many HALD deaths were likely linked to LD? Which were the causes of the other deaths? Which co-morbidities?
A9: All HALD deaths were likely linked to LD (legionellosis) but due to the considerable number of comorbidities among HALD patients (mentioned in Table 1) competing causes of deaths were present in many patients. Unfortunately we do not have enough information in our dataset to analyze this in details.

C10: Pag. 7: please clarify if the p-value < 0.001 refers to the difference in C-reactive protein, sodium level, potassium level or hemoglobin.
A10: We have clarified that the p-value <0.001 refers to the difference in C-reactive protein, sodium level, potassium level as well as hemoglobin by making the following changes: “CAL had higher median C-reactive protein level (285 mg/L), lower plasma sodium level (132 mmol/L), lower plasma potassium level (3.8 mmol/L) and higher hemoglobin (8.2 mmol/L) compared to HAL (161 mg/L (p<0.001); 136 mmol/L (p<0.001); 4.1 mmol/L (p<0.001) and 7.3 mmol/L(p<0.001). (page 9, line 11-14)

C11: Non-Danish patients were excluded?

A11: Non-Danish patients were not excluded from the study. We included all hospitalized patients fulfilling the criteria for definitive or presumptive cases of legionellosis. Only 4 of the patients in the study were of non-Danish origin.

C12: Data provided are fairly sound and English writing if correct. Statistical analysis is sound. However, no information is given about the distribution of cases among different counties and among different hospitals. Were cluster observed?

A12: It is an interesting question whether clusters were observed in certain hospitals. We do have data about the distribution of cases among different counties and among different hospitals but no obvious clusters and outbreaks were observed by us or noticed by the national surveillance system during that time period. Further, it is difficult to compare the different hospitals since some hospitals were university hospitals with departments specialized in infectious diseases which would be more likely to take care of severe cases compared to the smaller regional hospital.

Referee 3: Pierluigi Viale

The Paper entitled Clinical features and predictors of mortality in community- and hospital acquired Legionnaires’ Disease: A Danish historical cohort study, submitted by Sanne Jespersen and coll offers very intriguing elements which encourage the publication on BMC. Nevertheless few modifications are suggested.

C13: (pag 4 - row 16) Authors state that Only hospitalized cases were included since we did not have access to information from general practitioners for patients with LD managed in
the community setting. To avoid confusing evaluations and other statements in the Discussion, we strongly recommend to insert in the title of the paper the following modification Clinical features and predictors of mortality in hospitalised community- and hospital acquired Legionnaires' Disease: A Danish historical cohort study. With this underlined remark in the title, there are not confounding elements, causes are well exposed in page 4, and more clear is the limit of a retrospective cohort study.

A13: To make the title clear and understandable we have changed it to: “Clinical features and predictors of mortality in admitted patients with community- and hospital-acquired legionellosis: A Danish historical cohort study.” (page 1, line 2-5).

C14: (page 13 - Conclusions) It is recommended an adjunctive statement about the need of National Guideline for diagnosis and therapy.

A14: We agree that this is important and have added the following statement: "National guidelines for diagnosis and treatment of legionellosis could raise awareness of the disease and may improve quality of care." (page 16, line 6-7)