PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Meteorological factors are associated with an increased risk of community-acquired Legionnaires' disease in Switzerland: an epidemiological study
AUTHORS	Conza, Lisa; Casati, Simona; Limoni, Costanzo; Gaia, Valeria

VERSION 1 - REVIEW

REVIEWER	Dr D. CHE Infectious diseases department National institute for public heatlh surveillance France
REVIEW RETURNED	21-Dec-2012

RESULTS & CONCLUSIONS	The results support the research question but major critical points are not discussed in the paper. For example, the differences observed between the two regions in terms of LD incidence could be related to the characteristics of the populations. It is important to have a brief description of the two populations in terms of age, sexe, and (if available) underlying conditions. These factors can influence the magnitude of the incidence and authors should consider to include demographic variables into their models (proportion of persons aged 60 and over, sex ratio...).
GENERAL COMMENTS	I was very pleased to review this interesting work aiming at identifying environmental factors that could be related to an increased risk of Legionnaires disease. This issue is of major importance to better understand the epidemiology of LD. Many countries have documented variations of the incidence across regions and environmental conditions are important to consider in such perspective. One of the main remark concerns the methodology and the inclusion of demographic variables into the models to take into account the differences between populations in terms of age and sex, two characteristics that are strongly associated with the occurence of LD. The discussion should include words about the ecology of Legionella: do you have any data about the exposures (density of cooling towers for example, and results of sampling). In a previous work, we have demonstrated that the incidence of LD in France at a small geographical scale was associated with the presence of cooling towers in the vicinity of cases. This point must be acknowledged to your results. Year was introduced into the model as dependant variable. As seasonnal variations are described for LD, could you better explain this choice and why you do not consider the months as dependant variables ? Could you please provide data on the number of months with no cases reported, and describe the method used for testing the

	goodness of fit for the final model. Introduction; 3rd sentence : the term "evaporation" is not appropriate for LD.

REVIEWER	Dr. Ioannis Karagiannis, EPIET Coordinator, Robert Koch Institute, Germany. I declare no competing interests.
REVIEW RETURNED	21-Dec-2012

THE STUDY	Article focus: "...and warm, wet weather...". The authors here speak of wet weather, while their findings are actually applicable for "humid" conditions. In the introduction, the authors talk about "mortality rates", while what they mean clearly should read "case fatality". Introduction: "...with heavy thunderstorms and short, heavy spells of precipitations that rise the vapour pressure in the air". Vapour pressure can be high even in warm, drier (less wet) climates. Methods: "The northern region was chosen to have a higher LD incidence than other Swiss cantons and thus to be comparable to Canton Ticino". It is unclear why the authors chose this. Methods: "laboratory-confirmed pneumonia". There is no definition for this. Methods: The authors did not consider a model because of collinearity, but in the immediately next sentence claim to have considered a model with three very similar variables, namely average, minimun and maximum temperatures. Monthly data are used. This does not allow for the exploration of any short-term effect of the weather on legionnaire's disease. There is no definition of "Foehn" days. Southerly winds may cause katabatic Foehn winds in the north of Switzerland (Basle region). Notherly winds, on the other hand, would be considered as katabatic in the Ticino region. It is unclear how authors differentiate between these two conditions -if at all.
RESULTS & CONCLUSIONS	Results are presented (also in the abstract) "for each 1% rise of vapour pressure". Usually, results should be presented by 1 mm Hg changes in vapour pressure. In the abstract's conclusion, it says "...water vapour pressure and warm were associated...". "Warm" should be "heat", but is in any case not defined. IRRs (or RRs) are presented as (exp(beta)-1). This is an unorthodox way, as one would simply report exp(beta), i.e. the RR (or IRR) itself.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Dr D. CHE, Infectious diseases department, National institute for public health surveillance France

1) The results support the research question but major critical points are not discussed in the paper. For example, the differences observed between the two regions in terms of LD incidence could be related to the characteristics of the populations. It is important to have a brief description of the two populations in terms of age, sexe, and (if available) underlying conditions. These factors can influence the magnitude of the incidence and authors should consider to include demographic variables into their models (proportion of persons aged 60 and over, sex ratio...).

> Correction in Manuscript “Discussion”: The population of the two regions is very similar in their characteristics and underlying conditions were not included in the models; e.g. in 2007, 52% was the proportion of woman in Ticino and 50.8% in Basle region; persons aged over 64 were 19.7% in Ticino and 16.8% in Basle region, respectively. Legionellosis in Switzerland is more common in the group of ages between 70 to 79 years (23.4% of reports), but the incidence is highest (8.2/100,000) in the age group over 80 years. 40% of case patients are smokers and 15% of them showed advanced age (over 80 years) and diabetes.

[] FOPH. Legionellose in der Schweiz: Meldejahre 2004 bis 2008. Federal Office of Public Health FOPH. Bern, Switzerland 2008.

Dear Authors,

I was very pleased to review this interesting work aiming at identifying environmental factors that could be related to an increased risk of Legionnaires disease.

This issue is of major importance to better understand the epidemiology of LD. Many countries have documented variations of the incidence across regions and environmental conditions are important to consider in such perspective.

2) One of the main remark concerns the methodology and the inclusion of demographic variables into the models to take into account the differences between populations in terms of age and sex, two characteristics that are strongly associated with the occurence of LD.

> Correction in Manuscript “Discussion”: The population of the two regions is very similar in their characteristics and underlying conditions were not included in the models; e.g. in 2007, 52% was the proportion of woman in Ticino and 50.8% in Basle region; persons aged over 64 were 19.7% in Ticino and 16.8% in Basle region, respectively. Legionellosis in Switzerland is more common in the group of ages between 70 to 79 years (23.4% of reports), but the incidence is highest (8.2/100,000) in the age group over 80 years. 40% of case patients are smokers and 15% of them showed advanced age (over 80 years) and diabetes.

3) The discussion should include words about the ecology of Legionella: do you have any data about the exposures (density of cooling towers for example, and results of sampling). In a previous work, we have demonstrated that the incidence of LD in France at a small geographical scale was associated with the presence of cooling towers in the vicinity of cases. This point must be acknowledged to your results.

> Correction in Manuscript “Discussion”: Che et al. reported that the incidence of LD in France at a small geographical scale was associated with the presence of cooling towers in the vicinity of cases.[18] Swiss cases are usually associated with urban centres but the infection sources remain largely unknown. In 2003, Hohl and Steffen reported in Basle region that Legionella isolates from cooling towers are very similar to three clinical isolates.[19] A survey performed in 2005 in Ticino identified 49 cooling towers but only 29 could be sampled, 69% of them resulted heavily contaminated by Legionella, but any correlation between vicinity of cases and cooling towers could be established.[20] Cooling towers could be the source exposures for LD in both regions.

18. Che D, Decludt B, Campese C, et al. Sporadic cases of community acquired legionnaires’ disease: an ecological study to identify new sources of contamination. J Epidemiol Community Health 2003;57:466-69.

19 Hohl P, Steffen I. Des tours aéroréfrigérantes sont-elles à l'origine de cas de légionellose? Observations faites à Bâle-Ville. Bulletin FOPH 2003;29:504.
20. Gaia V. 2005. Master thesis. Prévention de la légionellose: étude écologique de cas de légionellose diagnostiqués au Tessin pendant l'été 2005, cartographie et contrôle microbiologique des tours de refroidissement. Université Genève, Switzerland.

4) Year was introduced into the model as dependant variable. As seasonnal variations are described for LD, could you better explain this choice and why you do not consider the months as dependant variables ?
> This choice was made because we wanted to test the increase of LD incidence from 2003 to 2007, seen with descriptive statistics (not shown in the manuscript).

5) Could you please provide data on the number of months with no cases reported, and describe the method used for testing the goodness of fit for the final model.
> Correction in Manuscript "Discussion": No cases were reported for 17 and 12 months in Ticino and Basle region, respectively.
> Correction in Manuscript "Methods": Goodness of fit was tested using the GOF Chi square test applied to the deviance values shown in the SAS output.

6) Introduction; 3rd sentence : the term "evaporation" is not appropriate for LD.
> Correction in Manuscript "Introduction": "...generated by the aerosolization of water droplets..."
Reviewer: Dr. Ioannis Karagiannis, EPIET Coordinator, Robert Koch Institute, Germany. I declare no competing interests.

7) Article focus: "...and warm, wet weather...". The authors here speak of wet weather, while their findings are actually applicable for "humid" conditions.
> Correction in Manuscript "Article Focus": "A link between community-acquired Legionnaires' disease (LD) and warm, humid weather is established."

8) In the introduction, the authors talk about "mortality rates", while what they mean clearly should read "case fatality".
> Correction in Manuscript "Introduction": The incidence of LD in Europe during the period 2003-2007 amounted to 1-1.3 cases per 100,000 inhabitants per year with a case fatality of 6.6%.[2] In Switzerland, in the same period, the incidence was about 2-2.5 cases per 100,000 inhabitants per year, with a case fatality of about 7.1%.

9) Introduction: "...with heavy thunderstorms and short, heavy spells of precipitations that rise the vapour pressure in the air". Vapour pressure can be high even in warm, drier (less wet) climates.
> Correction in Manuscript "Introduction": The summers are normally hot, with heavy thunderstorms and short, heavy spells of precipitations that with lake water evaporation (likely influenced by local geography) contribute to rise the vapour pressure in the air.[11]

10) Methods: "The northern region was chosen to have a higher LD incidence than other Swiss cantons and thus to be comparable to Canton Ticino". It is unclear why the authors chose this.
> Correction in Manuscript "Methods": Moreover, this group of Cantons was chosen due to their similar geography, population characteristics and proportion of urban/rural territory.

11) Methods: "laboratory-confirmed pneumonia". There is no definition for this.
> Correction in Manuscript "Introduction": "We defined a case as a patient with laboratory confirmed case of LD... ".

12) Methods: The authors did not consider a model because of collinearity, but in the immediately

next sentence claim to have considered a model with three very similar variables, namely average, minimun and maximum temperatures.
> Correction in Manuscript “Method”: “ Thus, we first carried out two separate multiple Poisson regression models: the first included average temperatures but no vapour pressure,”

13) Monthly data are used. This does not allow for the exploration of any short-term effect of the weather on legionnaire's disease.
> We used monthly data because we don’t know the exact data of onset of the disease and we are aware that we cannot evaluate short-term effect of the weather on LD. LD in Switzerland is a mandatory notified disease, however precise information about cases were not easily to recover, in particular we cannot retrieve precise information on data of onset of the symptoms and patients were often not aware of any exposure to traditional sources of infection.
> Correction in Manuscript “Discussion”: “and we are aware that we cannot evaluate short-term effect of the weather on LD”

14) There is no definition of "Foehn" days. Southerly winds may cause katabatic Foehn winds in the north of Switzerland (Basle region). Notherly winds, on the other hand, would be considered as katabatic in the Ticino region. It is unclear how authors differentiate between these two conditions -if at all.
> Correction in Manuscript “Methods”: We defined Foehn as a dry relatively warm down-slope wind that occurs either in the north or south lee of the Alps.

15) Results are presented (also in the abstract) "for each 1% rise of vapour pressure". Usually, results should be presented by 1 mm Hg changes in vapour pressure.
> There was a mistake in the abstract and in the results: the change is in units of vapour pressure, i.e. 1 hPa.

16) In the abstract's conclusion, it says "...water vapour pressure and warm were associated...". "Warm" should be "heat", but is in any case not defined.
> Correction in Manuscript “Abstract”: “Conclusion: In this study higher water vapour pressure and heat were associated with a higher risk of community-acquired LD in two regions of Switzerland.”

17) IRRs (or RRs) are presented as (exp(beta)-1). This is an unorthodox way, as one would simply report exp(beta), i.e. the RR (or IRR) itself.
> We presented RR this way, because (exp(beta)-1) shows the percent change in the LD incidence per unit increase of the independent variable. This seems to us much clearer than the "orthodox way" of reporting (not shown in the manuscript).

VERSION 2 – REVIEW

REVIEWER	Didier CHE, Pharm D, MPH Infectious Diseases Department National Institute for Public Health Surveillance Saint Maurice France I have no competing interests
REVIEW RETURNED	30-Jan-2013

GENERAL COMMENTS	The authors have addressed my comments, making appropriate revisions to the manuscript. This is an interesting research study which makes a great contribution to the knowledge on Legionnaires disease. The comprehension of the geographical disparities is of interest, aiming

	at better controlling the bacteria in the environment. I recommend to accept this paper.