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Meteorological factors are associated with an increased risk of community-acquired Legionnaires' disease in Switzerland: an epidemiological study

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Keywords: *Legionella*, Legionnaires' disease, vapour pressure, temperature, meteorological factors.

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Abstract

Objectives: The aim of this study was to identify meteorological factors that could be associated with an increased risk of community-acquired LD in two Swiss regions.

Design: Retrospective epidemiological study using discriminant analysis and multivariable Poisson regression.

Setting: We analysed legionellosis cases notified between January 2003 and December 2007 and we looked for a possible relationship between incidence rate and meteorological factors.

Participants: Community-acquired LD cases in two Swiss regions, the Canton Ticino and the Basle region, with climatically different conditions were investigated.

Primary outcomes measures: Vapour pressure, temperature, relative humidity, wind, precipitation and radiation recorded in weather stations of the two Swiss regions during the period January 2003 and December 2007.

Results: Discriminant analysis showed that the two regions are characterised by different meteorological conditions. A multiple Poisson regression analysis identified region, temperature and vapour pressure during the month of infection as significant risk factors for legionellosis. The risk of developing LD was 129.5% (or 136.4% when considering vapour pressure instead of temperature in the model) higher in the Canton Ticino as compared to the Basle region. There was an increased relative risk of LD by 11.4% (95% CI=7.70-15.30) for each 1% rise of vapour pressure or by 6.7% (95% CI=4.22-9.22) for 1 °C increase of temperature.

Conclusion: In this study higher water vapour pressure and warm were associated with a higher risk of community-acquired LD in two regions of Switzerland.

Article summary

Article Focus

Identify meteorological factors that could be associated with an increased risk of community-acquired LD in two Swiss regions.

A link between community-acquired Legionnaires' disease (LD) and warm, wet weather is established. However, risk factors and epidemiology of LD are not well understood.

Compare 2 different regions (with different climatic conditions) and including vapour pressure for LD infection risk.

Key Messages

In Switzerland, there was an increased relative risk of LD of 11.4% (95% CI=7.70-15.30) for each 1% rise of vapour pressure or of 6.7% (95% CI=4.22-9.22) for 1 °C increase of temperature.

In the southern Swiss region of Canton Ticino, the incidence during the period 2003-2007 was three-times higher than northern Swiss region. Our model revealed that the region has also an influence on the incidence of LD.

Strenghts and Limitations

The originality of this study is to use vapour pressure as variable instead of relative humidity for multivariable Poisson regression analysis to identify weather main risk factors for LD.

The main limitation of this study is the use of monthly mean of the month during which the LD case occurred because the incubation period of 14 days for every case cannot be determined exactly.

INTRODUCTION

Bacteria of the genus *Legionella* colonise natural and man-made aquatic environments, soils or free-living amoebae.[1] Some species may cause Legionnaires' disease (LD) and Pontiac fever.[2] Transmission occurs by inhalation of contaminated bioaerosols, generated by the evaporation of water droplets from different reservoirs, such as air-conditioning units,[3, 4] cooling towers,[5] whirlpool spas,[6] soils,[7] sinks taps and shower heads.[8]

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 mortality rate 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 mortality rate of about 7.1%.[9] In the southern Swiss region of Canton Ticino, however, the incidence was three-times higher (approx. 6/100,000).[9] In Switzerland, community-acquired LD cases are not randomly distributed. So far, it is not clear why the incidence is so high in southern Switzerland and the sources of *Legionella* infections could rarely be identified.

Switzerland is divided in two parts by the Alps, with the mountains acting as a barrier that create two distinct climatic zones.[10] The northern part is characterised by rigid, rather dry winters and warm summers with frequent precipitations. The climatic conditions in the South are influenced by the geography, with lakes that favour dry and mild winters with a very low relative humidity. The summers are normally hot, with heavy thunderstorms and short, heavy spells of precipitations that rise the vapour pressure in the air.[11]

Previous studies showed that warm, wet weather and rainfalls were associated with an increased risk for legionellosis.[12-14] Therefore, in Switzerland, the climate could play an important role in the transmission of LD from sources located within the community.

The aim of this study was to investigate whether or not the occurrence of community-acquired LD could be associated with specific meteorological factors (such as temperature, relative humidity, vapour pressure, wind, radiation and precipitation) during the month of occurrence of the disease in two different Swiss regions characterised by two distinct climatic conditions.

METHODS

Study area and design

The Canton Ticino ("Ticino") and the region of Basle ["Basle": Cantons Basel-Stadt (BS), Basel-Land (BL), Aargau (AG) and Solothurn (SO)] were chosen to estimate the risk of occurrence of legionellosis. The Canton Ticino is located in southern Switzerland and is a mountainous region with valleys and lakes, as opposed to the region of Basle, located in the north-western part of the country on the Swiss Plateau, which is an almost flat region, covered with rolling hills, lakes and rivers. The climate in Canton Ticino is generally very warm in the summer, with some days of very high humidity.[10] The northern region was chosen to have a higher LD incidence than other Swiss cantons and thus to be comparable to Canton Ticino.

Case identification

We defined a case as a patient with laboratory confirmed pneumonia when, in addition to the clinical diagnosis of pneumonia, at least one of the following criteria were met: a) isolation in culture and identification of *Legionella* in secretions from the respiratory tract, lung tissue or blood; b) at least a four-fold increase in antibody titer against *Legionella pneumophila* serogroup 1 (Lp1); c) detection of specific *L. pneumophila* antigen in urine.[9]

Only autochthonous cases with sporadic community-acquired LD, for which a travel-associated or nosocomial origin could be excluded and for which the date of onset was known and occurred between 1 January 2003 and 31 December 2007, were included in the study.

Data collection

Meteorological data were obtained from three main weather stations in Ticino (covering the most populated areas) and two in Basle. The meteorological data evaluated in this investigation were the monthly means of daily average relative humidity, vapour pressure, mean temperature, global

radiation, daily amount of precipitations, wind speed, and occurrence of strong warm winds in the Alps (Foehn).[10]

Information on sporadically occurring, community-acquired cases (date of onset, age and sex of the patients) of the two regions were provided by the Swiss Federal Office of Public Health (FOPH).

Data analysis

Discriminant analysis

A canonical discriminant analysis was performed to assess differences in meteorological conditions between the two regions. The analysis was carried out using monthly means of daily average data for relative humidity, vapour pressure, mean temperature, global radiation, wind speed and daily amount of precipitations recorded in Ticino and Basle. The analysis was carried out with SPSS version 17.0 (SPSS Inc., Chicago, Illinois, USA).

Multivariable Poisson regression

A multivariable Poisson regression was used to identify the main risk factors for LD. The cases are the prevalence of LD per 100,000 inhabitants grouped by month of onset and for each meteorological variable a monthly average was calculated using data from the closest weather station. For those months with no case reported, the monthly mean of each variable was used in the model.

A preliminary analysis indicated that the model constructed using contemporaneously both temperature and vapour pressure suffered from collinearity problems, because the correlations between vapour pressure and average temperature, and vapour pressure and minimal and maximal temperature were almost 100% ($r > 0.96$). Thus, we first carried out two separate multiple Poisson regression models: the first included average, minimum, and maximum temperatures but no vapour pressure, while the second considered vapour pressure but no temperature data. Both models included additionally relative humidity, vapour pressure, radiation, Foehn, wind speed, precipitation and year as dependent variables.

The final model included only those variables that reached a *P* value of <0.05 in the preliminary model with all the variables. To quantify the effects of meteorological variables, we computed the influences (e^{β}-1), which virtually correspond to the relative risks. These analyses were carried out using SAS (version 8.01, SAS Institute, Cary, NJ, USA). Data are presented as relative risk and corresponding 95% confidence intervals (95% CI). *P* values < 0.05 were considered statistically significant.

RESULTS

Demographics

17.8% of the patients were over 64 years old and 2/3 were male. Between 2003 and 2007, 101 cases of community-acquired LD were reported in Ticino and 154 in Basle. The number of cases fluctuates and follows seasonality: more events are reported in spring and summer (April to September; Figure 1).

Meteorological characterisation of the two regions studied

Canonical discriminant analysis carried out using daily average data for relative humidity, vapour pressure, mean temperature, global radiation, wind speed and daily amount of precipitations revealed that the Basle data can be grouped consistently according to their meteorological characteristics and were well separated from Ticino (Figure 2). The first three canonical discriminant functions explain 95.8% of the variance of the model. When the four cantons grouped in the Basle region were considered separately, the predictive values based on the new canonical variables were only moderately concordant with the original grouping, because only 53.3% of all cases were correctly classified in their original categories (Table 1). The two regions, Ticino and Basle, however, could be clearly separated, with 91% of the cases correctly classified. Thus, discriminant analysis has confirmed that the two regions investigated have clearly distinct climatic situations, with the four northern Cantons being meteorologically quite similar. The most important variable that influenced the first function of the model was the temperature; vapour pressure was determining the second and third functions.

Table 1 **Classification of results.** 53.3% of original grouped cases correctly reclassified.

Region	Canton	Predicted Group Membership [%]				
		Aargau	Basel-Land	Basel-Stadt	Solothurn	Ticino
Basle	Aargau	12.5	**65.6**	6.3	6.3	9.3
	Basel-Land	4.0	**70.0**	2.0	14.0	10.0
	Basel-Stadt	2.5	**60.0**	5.0	15.0	17.5
	Solothurn	0.0	**65.6**	9.4	9.4	15.6
Ticino	Ticino	1.0	3.0	4.0	1.0	**91**

Influence of meteorological factors on LD

The study of correlations between the independent variables at the regional and global level revealed a nearly perfect correlation ($r > 0.96$) between vapour pressure and average temperature, and vapour pressure and minimal and maximal temperature. Therefore, to avoid collinearity problems, we decided to explore the relationship of temperature and vapour pressure with LD cases by using two different models, including either temperature or vapour pressure together with all other predictors. In the two models, temperature ($P = 0.0002$) and vapour pressure ($P = 0.0014$) were highly significant; year and region were also significant in both models (Table 2).

The final model showed that vapour pressure and temperature, respectively, are highly significant factors that influence the risk of LD (both $P < 0.0001$). Each 1% raise of vapour pressure corresponds to an increase in the number of cases by 11.4% (95% CI=7.70%-15.30%); likewise, a raise of 1 °C corresponds to an increase of 6.7% (95% CI=4.22%-9.22%). The results show that in Ticino the risk of being infected by *Legionella* is much higher than in Basle (129.5% or 136.4%, depending on the variable considered in the model; see Table 2). The variable year is also significant using either vapour pressure ($P = 0.0034$) or temperature ($P = 0.0073$) as dependent variables. During the period 2003-2007, the relative risk of LD has been increasing in both regions

at an annual rate of approximately 16%, after adjusting by region and vapour pressure or temperature effect (Table 2).

Table 2 Poisson regression model of meteorological factor associated with risk of LD. Multiple Poisson regression model for legionellosis without temperature (A) and without vapour pressure (B). Final models without temperature (C) and without vapour pressure (D).

		β	$(e^{\beta}-1)$ = RR	*P* value
A)				
	Intercept	-356.746		0.0027
	relative humidity	0.0051	0.51%	0.8161
	vapour pressure	0.1220	12.98%	0.0014*
	region	0.7665	115.22%	0.0036*
	radiation	-0.0011	-0.11%	0.7130
	boehn	-0.0189	-1.87%	0.4660
	wind	0.0224	2.27%	0.8311
	precipitation	0.0260	2.63%	0.3804
	year	0.1766	19.32%	0.0030*
B)				
	Intercept	-347.822		0.0031
	relative humidity	0.0189	1.91%	0.3207
	temperature	0.1036	10.92%	0.0002*
	region	0.7985	122.22%	0.0021*
	radiation	-0.0030	-0.30%	0.3357
	boehn	-0.0193	-1.91%	0.4608
	wind	0.0361	3.68%	0.7329
	precipitation	0.0272	2.76%	0.3532
	year	0.1717	18.73%	0.0035*
C)				
	Intercept	-321.042		0.0032*
	vapour pressure	0.1083	11.44%	<0.0001**
	region	0.8603	136.39%	<0.0001**
	year	0.1587	15.87%	<0.0034*
D)				
	Intercept	-299.281		0.0069*
	temperature	0.0647	6.68%	<0.0001**
	region	0.8309	129.54%	<0.0001**
	year	0.1481	15.96%	0.0073*

* *P* values < 0.05 were considered statistically significant. ** *P* values < 0.0001 were considered statistically highly significant. RR: relative risk.

DISCUSSION

Our study indicates that temperature and vapour pressure during the month of disease are the meteorological factors that influence most the occurrence of sporadic community-acquired LD.

The two regions studied, Ticino and Basle, can be separated using meteorological parameters. Multiple Poisson regression identified vapour pressure and temperature as important contributing factors influencing the occurrence of legionellosis in both regions.

Association of weather factors with legionellosis has been described in previous studies that identified relative humidity and temperature as the most important risk for infection,[12, 13, 15] but to date the role of vapour pressure has not been investigated.

The relative humidity is the ratio between the partial pressure of water vapor in the air-water mixture to the saturated vapor pressure of water at the same conditions of temperature and pressure. Thus, relative humidity explains how far the air is from a saturated condition. In contrast, the vapour pressure is the measure of the partial pressure of water vapour in air-water mixture saturated with water and decreases non-linearly with temperature.[12] Vapor pressure increases with increasing relative humidity.

Our analysis indicates that vapour pressure is the most important factor that influences the increase in number of cases of legionellosis in both regions. The two regions investigated in this study differ from each other by their geographic and climatic features. Summers in Ticino are characterised by days with very high vapour pressure, for example after thunderstorms,[11] as opposed to the northern Swiss regions.[10] In general, throughout the year, the relative humidity is higher and the temperature is lower in Basle as compared to Ticino. By contrast, the vapour pressure is higher in Ticino than in Basle during summer.[10]

In Ticino the risk of being infected is much higher than in Basle; this is confirmed by the much higher incidence of cases in Ticino than in northern Switzerland. The risk of being infected in Canton Ticino rises by 11.4% for each 1% increase in vapour pressure: this is in accordance with clinical observations that set the highest incidence of LD in the summer months, when in Ticino the

vapour pressure is higher (e.g., the monthly mean of August 2007 for Ticino was 16.9 hPa vs. 15.2 hPa of region Basle).[10]

LD in Switzerland exhibits a strong seasonality, with a summer-early autumn increase of notified LD cases, as noted also in America[13-15] and Europe.[16, 17] The number of LD cases notified in Switzerland is increasing yearly in both regions, as is in whole Europe.[2] This is why we inserted the variable year in the Poisson model to control for additional confounding unknown factors and indeed, in both models, the variable year was highly significant.

Poisson regression models are often not suitable to study infectious disease because of the non-independence of events caused by person-to person transmission: it is, however, appropriate for LD because contagion occurs mainly through aerosol.

Some methodological limitations must be acknowledged for this study: the incubation period of 14 days for every case cannot be determined exactly and this is why we choose to use monthly mean of the month during which the LD case occurred; the use of aggregate or average meteorological data, which are approximations for each daily and monthly value or the aggregation of LD cases for months; the direction of these approximations, however, are likely to be random, suggesting that our risk estimates are reliable. We also used clinical data provided to the Swiss Federal Office of Public Health by several laboratories: we cannot exclude that our dataset can be incomplete because of lack of case notifications or by missing or wrong bacterial identifications: undercounting of legionellosis cases, on the other hand, is a bias that should not influence the outcome of the analysis. Our study was performed only for the period 2003-2007 because more recent, updated data were not easily available. Finally, this investigation being an ecological study, we cannot exclude that we could not identify and consider some potential confounding variables.

In conclusion, high vapour pressure and temperature were associated with a higher risk of community-acquired LD in two regions of Switzerland, characterised by two distinct climatic conditions. These findings strongly support the hypothesis that climatic factors in general and vapour pressure and temperature in particular are risk factors for the transmission of community-acquired LD and should increase awareness of the increased risk of LD after days with humid and warm weather conditions.

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We thank the Federal Office of Meteorology and Climatology (MeteoSwiss) for kindly providing meteorological data. The financial support by Ticino Pulmonary League is gratefully acknowledged. PD Dr. Orlando Petrini (Cantonal Institute of Microbiology, Bellinzona) gave constructive advice, helped with the statistical analysis and read critically the manuscript.

COMPETING INTEREST

None.

CONTRIBUTORSHIP

LC, SC, VG, CL conception and design, or analysis and interpretation of data.

LC drafting the article.

SC, VG, CL revising it critically for important intellectual content.

LC, SC, VG, CL final approval of the version to be published.

DATA SHARING

There is no additional data available.

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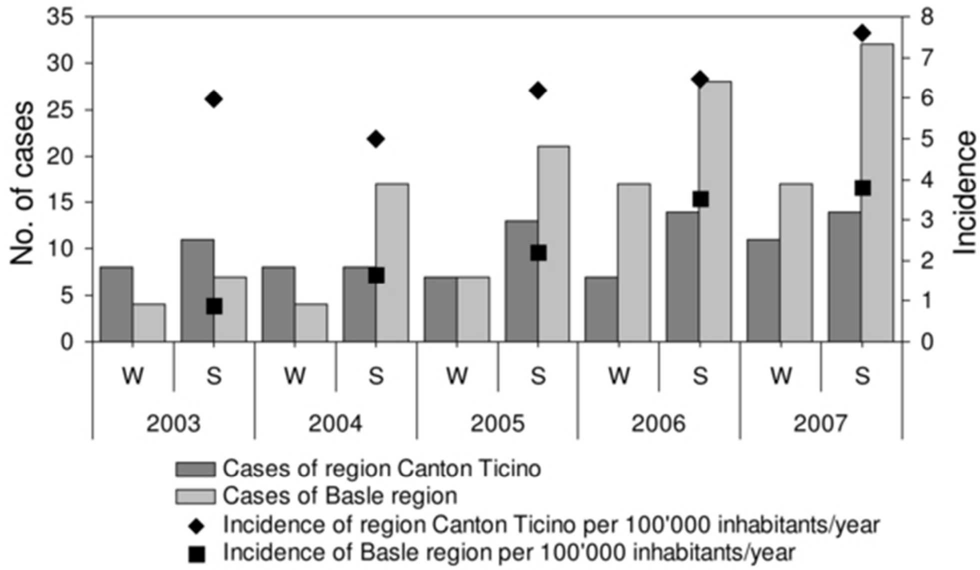
LIST OF FIGURES

Figure 1 Seasonal distribution and incidence of LD cases according to onset date in Ticino and Basle from 2003-2007.[9] W: winter (October-March), S: summer (April-September).

Figure 2 Graphical plot of the discriminant model. The centroids of the data of Basle (1-4) are grouped and well separated from Ticino (5). 95.8% of the total variance is explained by the first tree discriminant functions.

There is no additional data available.



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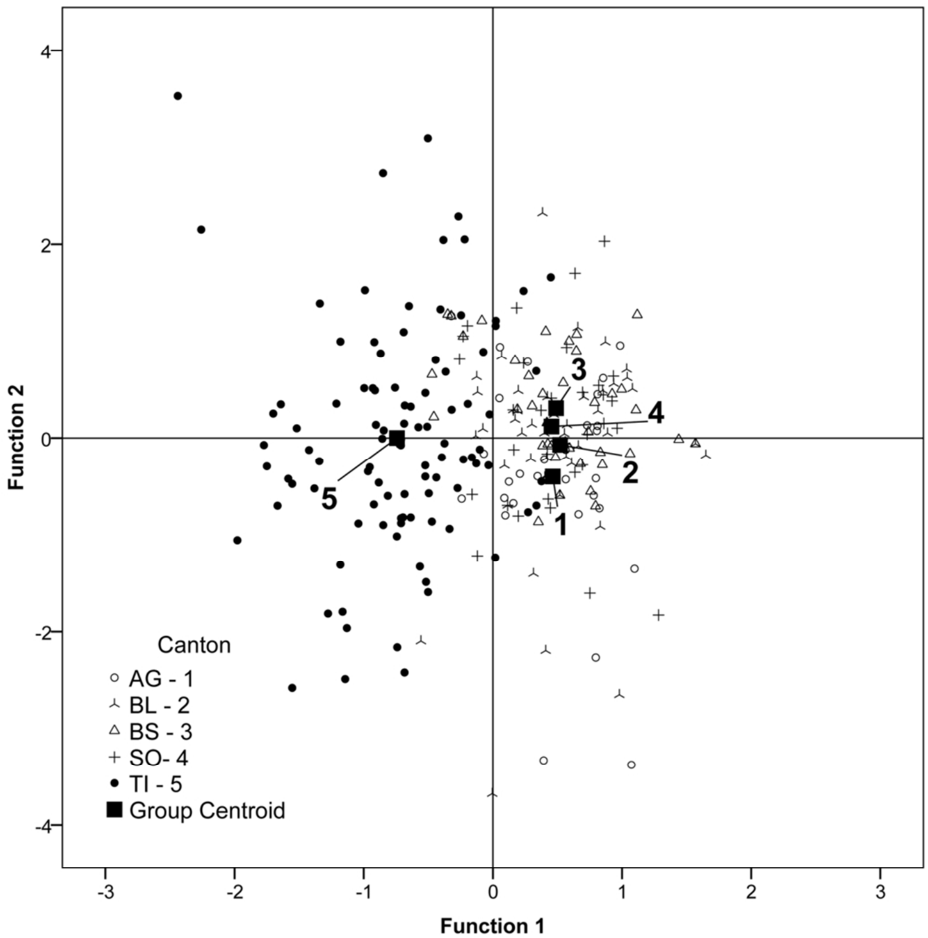
51x29mm (300 x 300 DPI)



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Switzerland is divided in two parts by the Alps, with the mountains acting as a barrier that create two distinct climatic zones.[10] The northern part is characterised by rigid, rather dry winters and warm summers with frequent precipitations. The climatic conditions in the South are influenced by the geography, with lakes that favour dry and mild winters with a very low relative humidity. 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]

Previous studies showed that warm, wet weather and rainfalls were associated with an increased risk for legionellosis.[12-14] Therefore, in Switzerland, the climate could play an important role in the transmission of LD from sources located within the community.

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METHODS

Study area and design

The Canton Ticino ("Ticino") and the region of Basle ["Basle": Cantons Basel-Stadt (BS), Basel-Land (BL), Aargau (AG) and Solothurn (SO)] were chosen to estimate the risk of occurrence of legionellosis. The Canton Ticino is located in southern Switzerland and is a mountainous region with valleys and lakes, as opposed to the region of Basle, located in the north-western part of the country on the Swiss Plateau, which is an almost flat region, covered with rolling hills, lakes and rivers. The climate in Canton Ticino is generally very warm in the summer, with some days of very high humidity.[10] The northern region was chosen to have a higher LD incidence than other Swiss cantons and thus to be comparable to Canton Ticino. Moreover, this group of Cantons was chosen due to their similar geography, population characteristics and proportion of urban/rural territory.

Case identification

We defined a case as a patient with laboratory confirmed case of LD when, in addition to the clinical diagnosis of pneumonia, at least one of the following criteria were met: a) isolation in culture and identification of *Legionella* in secretions from the respiratory tract, lung tissue or blood; b) at least a four-fold increase in antibody titer against *Legionella pneumophila* serogroup 1 (Lp1); c) detection of specific *L. pneumophila* antigen in urine.[9]

Only autochthonous cases with sporadic community-acquired LD, for which a travel-associated or nosocomial origin could be excluded and for which the date of onset was known and occurred between 1 January 2003 and 31 December 2007, were included in the study.

Data collection

Meteorological data were obtained from three main weather stations in Ticino (covering the most populated areas) and two in Basle. The meteorological data evaluated in this investigation were the monthly means of daily average relative humidity, vapour pressure, mean temperature, global

radiation, daily amount of precipitations, wind speed, and occurrence of strong warm winds in the Alps (Foehn).[10] We defined Foehn as a dry relatively warm down-slope wind that occurs either in the north or south lee of the Alps.

Information on sporadically occurring, community-acquired cases (date of onset, age and sex of the patients) of the two regions were provided by the Swiss Federal Office of Public Health (FOPH).

Data analysis

Discriminant analysis

A canonical discriminant analysis was performed to assess differences in meteorological conditions between the two regions. The analysis was carried out using monthly means of daily average data for relative humidity, vapour pressure, mean temperature, global radiation, wind speed and daily amount of precipitations recorded in Ticino and Basle. The analysis was carried out with SPSS version 17.0 (SPSS Inc., Chicago, Illinois, USA).

Multivariable Poisson regression

A multivariable Poisson regression was used to identify the main risk factors for LD. The cases are the prevalence of LD per 100,000 inhabitants grouped by month of onset and for each meteorological variable a monthly average was calculated using data from the closest weather station. For those months with no case reported, the monthly mean of each variable was used in the model.

A preliminary analysis indicated that the model constructed using contemporaneously both temperature and vapour pressure suffered from collinearity problems, because the correlations between vapour pressure and average temperature, and vapour pressure and minimal and maximal temperature were almost 100% ($r > 0.96$). Thus, we first carried out two separate multiple Poisson regression models: the first included average temperatures but no vapour pressure, while the second considered vapour pressure but no temperature data. Both models included additionally relative humidity, vapour pressure, radiation, Foehn, wind speed, precipitation and year as independent variables.

The final model included only those variables that reached a *P* value of <0.05 in the preliminary model with all the variables. To quantify the effects of meteorological variables, we computed the influences (e^{β}-1), which virtually correspond to the relative risks. These analyses were carried out using SAS (version 8.01, SAS Institute, Cary, NJ, USA). Data are presented as relative risk and corresponding 95% confidence intervals (95% CI). *P* values < 0.05 were considered statistically significant. Goodness of fit of the final model was tested using the GOF Chi square test applied to the deviance values shown in the SAS output.

RESULTS

Demographics

17.8% of the patients were over 64 years old and 2/3 were male. Between 2003 and 2007, 101 cases of community-acquired LD were reported in Ticino and 154 in Basle. The number of cases fluctuates and follows seasonality: more events are reported in spring and summer (April to September; Figure 1). 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.

Meteorological characterisation of the two regions studied

Canonical discriminant analysis carried out using daily average data for relative humidity, vapour pressure, mean temperature, global radiation, wind speed and daily amount of precipitations revealed that the Basle data can be grouped consistently according to their meteorological characteristics and were well separated from Ticino (Figure 2). The first three canonical discriminant functions explain 95.8% of the variance of the model. When the four cantons grouped in the Basle region were considered separately, the predictive values based on the new canonical variables were only moderately concordant with the original grouping, because only 53.3% of all cases were correctly classified in their original categories (Table 1). The two regions, Ticino and Basle, however, could be clearly separated, with 91% of the cases correctly classified. Thus, discriminant analysis has confirmed that the two regions investigated have clearly distinct climatic situations, with the four northern Cantons being meteorologically quite similar. The most important variable that influenced the first function of the model was the temperature; vapour pressure was determining the second and third functions.

Table 1 **Classification of results.** 53.3% of original grouped cases correctly reclassified.

Region	Canton	Predicted Group Membership [%]				
		Aargau	Basel-Land	Basel-Stadt	Solothurn	Ticino
Basle	Aargau	12.5	**65.6**	6.3	6.3	9.3
	Basel-Land	4.0	**70.0**	2.0	14.0	10.0
	Basel-Stadt	2.5	**60.0**	5.0	15.0	17.5
	Solothurn	0.0	**65.6**	9.4	9.4	15.6
Ticino	Ticino	1.0	3.0	4.0	1.0	**91**

Influence of meteorological factors on LD

The study of correlations between the independent variables at the regional and global level revealed a nearly perfect correlation ($r > 0.96$) between vapour pressure and average temperature, and vapour pressure and minimal and maximal temperature. Therefore, to avoid collinearity problems, we decided to explore the relationship of temperature and vapour pressure with LD cases by using two different models, including either temperature or vapour pressure together with all other predictors. In the two models, temperature ($P = 0.0002$) and vapour pressure ($P = 0.0014$) were highly significant; year and region were also significant in both models (Table 2).

The final model showed that vapour pressure and temperature, respectively, are highly significant factors that influence the risk of LD (both $P < 0.0001$). Each 1 hPa raise of vapour pressure corresponds to an increase in the number of cases by 11.4% (95% CI=7.70%-15.30%); likewise, a raise of 1 °C corresponds to an increase of 6.7% (95% CI=4.22%-9.22%). The results show that in Ticino the risk of being infected by *Legionella* is much higher than in Basle (129.5% or 136.4%, depending on the variable considered in the model; see Table 2). The variable year is also significant using either vapour pressure ($P = 0.0034$) or temperature ($P = 0.0073$) as independent variables. During the period 2003-2007, the relative risk of LD has been increasing in both regions

at an annual rate of approximately 16%, after adjusting by region and vapour pressure or temperature effect (Table 2).

Table 2 Poisson regression model of meteorological factor associated with risk of LD. Multiple Poisson regression model for legionellosis without temperature (A) and without vapour pressure (B). Final models without temperature (C) and without vapour pressure (D).

		β	$(e^{\beta}-1)$ = RR	*P* value
A)				
	Intercept	-356.746		0.0027
	relative humidity	0.0051	0.51%	0.8161
	vapour pressure	0.1220	12.98%	0.0014*
	region	0.7665	115.22%	0.0036*
	radiation	-0.0011	-0.11%	0.7130
	Foehn	-0.0189	-1.87%	0.4660
	wind	0.0224	2.27%	0.8311
	precipitation	0.0260	2.63%	0.3804
	year	0.1766	19.32%	0.0030*
B)				
	Intercept	-347.822		0.0031
	relative humidity	0.0189	1.91%	0.3207
	temperature	0.1036	10.92%	0.0002*
	region	0.7985	122.22%	0.0021*
	radiation	-0.0030	-0.30%	0.3357
	Foehn	-0.0193	-1.91%	0.4608
	wind	0.0361	3.68%	0.7329
	precipitation	0.0272	2.76%	0.3532
	year	0.1717	18.73%	0.0035*
C)				
	Intercept	-321.042		0.0032*
	vapour pressure	0.1083	11.44%	<0.0001**
	region	0.8603	136.39%	<0.0001**
	year	0.1587	15.87%	<0.0034*
D)				
	Intercept	-299.281		0.0069*
	temperature	0.0647	6.68%	<0.0001**
	region	0.8309	129.54%	<0.0001**
	year	0.1481	15.96%	0.0073*

* *P* values < 0.05 were considered statistically significant. ** *P* values < 0.0001 were considered statistically highly significant. RR: relative risk.

DISCUSSION

Our study indicates that temperature and vapour pressure during the month of disease are the meteorological factors that influence most the occurrence of sporadic community-acquired LD.

The two regions studied, Ticino and Basle, can be separated using meteorological parameters. Multiple Poisson regression identified vapour pressure and temperature as important contributing factors influencing the occurrence of legionellosis in both regions.

Association of weather factors with legionellosis has been described in previous studies that identified relative humidity and temperature as the most important risk for infection,[12, 13, 15] but to date the role of vapour pressure has not been investigated.

The relative humidity is the ratio between the partial pressure of water vapour in the air-water mixture to the saturated vapour pressure of water at the same conditions of temperature and pressure. Thus, relative humidity explains how far the air is from a saturated condition. In contrast, the vapour pressure is the measure of the partial pressure of water vapour in air-water mixture saturated with water and decreases non-linearly with temperature.[12] Vapour pressure increases with increasing relative humidity.

Our analysis indicates that vapour pressure is the most important factor that influences the increase in number of cases of legionellosis in both regions. The two regions investigated in this study differ from each other by their geographic and climatic features. Summers in Ticino are characterised by days with very high vapour pressure, for example after thunderstorms,[11] as opposed to the northern Swiss regions.[10] In general, throughout the year, the relative humidity is higher and the temperature is lower in Basle as compared to Ticino. By contrast, the vapour pressure is higher in Ticino than in Basle during summer.[10]

In Ticino the risk of being infected is much higher than in Basle; this is confirmed by the much higher incidence of cases in Ticino than in northern Switzerland. The risk of being infected in Canton Ticino rises by 11.4% for each 1 hPa increase in vapour pressure: this is in accordance with clinical observations that set the highest incidence of LD in the summer months, when in Ticino the

vapour pressure is higher (e.g., the monthly mean of August 2007 for Ticino was 16.9 hPa vs. 15.2 hPa of region Basle).[10]

LD in Switzerland exhibits a strong seasonality, with a summer-early autumn increase of notified LD cases, as noted also in America[13-15] and Europe.[16, 17] No cases were reported for 17 months in Ticino and for 12 months in Basle region.

The number of LD cases notified in Switzerland is increasing yearly in both regions, as is in whole Europe.[2] This is why we inserted the variable year in the Poisson model to control for additional confounding unknown factors and indeed, in both models, the variable year was highly significant.

Poisson regression models are often not suitable to study infectious disease because of the non-independence of events caused by person-to person transmission: it is, however, appropriate for LD because contagion occurs mainly through aerosol.

Some methodological limitations must be acknowledged for this study: the incubation period of 14 days for every case cannot be determined exactly and this is why we choose to use monthly mean of the month during which the LD case occurred; the use of aggregate or average meteorological data, which are approximations for each daily and monthly value or the aggregation of LD cases for months; the direction of these approximations, however, are likely to be random, suggesting that our risk estimates are reliable. Moreover, with this set up we cannot evaluate short-term effect of the weather on LD. We also used clinical data provided to the Swiss Federal Office of Public Health by several laboratories: we cannot exclude that our dataset can be incomplete because of lack of case notifications or by missing or wrong bacterial identifications: undercounting of legionellosis cases, on the other hand, is a bias that should not influence the outcome of the analysis. Our study was performed only for the period 2003-2007 because more recent, updated data were not easily available. Finally, this investigation being an ecological study, we cannot exclude that we could not identify and consider some potential confounding variables.

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.[9]

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.

In conclusion, high vapour pressure and temperature were associated with a higher risk of community-acquired LD in two regions of Switzerland, characterised by two distinct climatic conditions. These findings strongly support the hypothesis that climatic factors in general and vapour pressure and temperature in particular are risk factors for the transmission of community-acquired LD and should increase awareness of the increased risk of LD after days with humid and warm weather conditions.

ACKNOWLEDGEMENTS AND FUNDING

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COMPETING INTEREST

None.

CONTRIBUTORSHIP

LC, SC, VG, CL conception and design, or analysis and interpretation of data.

LC drafting the article.

SC, VG, CL revising it critically for important intellectual content.

LC, SC, VG, CL final approval of the version to be published.

DATA SHARING

There is no additional data available.

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LIST OF FIGURES

Figure 1 Seasonal distribution and incidence of LD cases according to onset date in Ticino and Basle from 2003-2007.[9] W: winter (October-March), S: summer (April-September).

Figure 2 Graphical plot of the discriminant model. The centroids of the data of Basle (1-4) are grouped and well separated from Ticino (5). 95.8% of the total variance is explained by the first tree discriminant functions.

There is no additional data available.

Meteorological factors are associated with an increased risk of community-acquired Legionnaires' disease in Switzerland: an epidemiological study

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Word count: 2853

Abstract

Objectives: The aim of this study was to identify meteorological factors that could be associated with an increased risk of community-acquired LD in two Swiss regions.

Design: Retrospective epidemiological study using discriminant analysis and multivariable Poisson regression.

Setting: We analysed legionellosis cases notified between January 2003 and December 2007 and we looked for a possible relationship between incidence rate and meteorological factors.

Participants: Community-acquired LD cases in two Swiss regions, the Canton Ticino and the Basle region, with climatically different conditions were investigated.

Primary outcomes measures: Vapour pressure, temperature, relative humidity, wind, precipitation and radiation recorded in weather stations of the two Swiss regions during the period January 2003 and December 2007.

Results: Discriminant analysis showed that the two regions are characterised by different meteorological conditions. A multiple Poisson regression analysis identified region, temperature and vapour pressure during the month of infection as significant risk factors for legionellosis. The risk of developing LD was 129.5% (or 136.4% when considering vapour pressure instead of temperature in the model) higher in the Canton Ticino as compared to the Basle region. There was an increased relative risk of LD by 11.4% (95% CI=7.70-15.30) for each 1 hPa rise of vapour pressure or by 6.7% (95% CI=4.22-9.22) for 1 °C increase of temperature.

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.

Article summary

Article Focus

Identify meteorological factors that could be associated with an increased risk of community-acquired LD in two Swiss regions.

A link between community-acquired Legionnaires' disease (LD) and warm, humid weather is established. However, risk factors and epidemiology of LD are not well understood.

Compare 2 different regions (with different climatic conditions) and including vapour pressure for LD infection risk.

Key Messages

In Switzerland, there was an increased relative risk of LD of 11.4% (95% CI=7.70-15.30) for each 1 hPa rise of vapour pressure or of 6.7% (95% CI=4.22-9.22) for 1 °C increase of temperature.

In the southern Swiss region of Canton Ticino, the incidence during the period 2003-2007 was three-times higher than northern Swiss region. Our model revealed that the region has also an influence on the incidence of LD.

Strenghts and Limitations

The originality of this study is to use vapour pressure as variable instead of relative humidity for multivariable Poisson regression analysis to identify weather main risk factors for LD.

The main limitation of this study is the use of monthly mean of the month during which the LD case occurred because the incubation period of 14 days for every case cannot be determined exactly.

INTRODUCTION

Bacteria of the genus *Legionella* colonise natural and man-made aquatic environments, soils or free-living amoebae.[1] Some species may cause Legionnaires' disease (LD) and Pontiac fever.[2] Transmission occurs by inhalation of contaminated bioaerosols, generated by the aerosolization of water droplets from different reservoirs, such as air-conditioning units,[3, 4] cooling towers,[5] whirlpool spas,[6] soils,[7] sinks taps and shower heads.[8]

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] In the southern Swiss region of Canton Ticino, however, the incidence was three-times higher (approx. 6/100,000).[9] In Switzerland, community-acquired LD cases are not randomly distributed. So far, it is not clear why the incidence is so high in southern Switzerland and the sources of *Legionella* infections could rarely be identified.

Switzerland is divided in two parts by the Alps, with the mountains acting as a barrier that create two distinct climatic zones.[10] The northern part is characterised by rigid, rather dry winters and warm summers with frequent precipitations. The climatic conditions in the South are influenced by the geography, with lakes that favour dry and mild winters with a very low relative humidity. 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]

Previous studies showed that warm, wet weather and rainfalls were associated with an increased risk for legionellosis.[12-14] Therefore, in Switzerland, the climate could play an important role in the transmission of LD from sources located within the community.

The aim of this study was to investigate whether or not the occurrence of community-acquired LD could be associated with specific meteorological factors (such as temperature, relative humidity, vapour pressure, wind, radiation and precipitation) during the month of occurrence of the disease in two different Swiss regions characterised by two distinct climatic conditions.

METHODS

Study area and design

The Canton Ticino ("Ticino") and the region of Basle ["Basle": Cantons Basel-Stadt (BS), Basel-Land (BL), Aargau (AG) and Solothurn (SO)] were chosen to estimate the risk of occurrence of legionellosis. The Canton Ticino is located in southern Switzerland and is a mountainous region with valleys and lakes, as opposed to the region of Basle, located in the north-western part of the country on the Swiss Plateau, which is an almost flat region, covered with rolling hills, lakes and rivers. The climate in Canton Ticino is generally very warm in the summer, with some days of very high humidity.[10] The northern region was chosen to have a higher LD incidence than other Swiss cantons and thus to be comparable to Canton Ticino. Moreover, this group of Cantons was chosen due to their similar geography, population characteristics and proportion of urban/rural territory.

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We defined a case as a patient with laboratory confirmed case of LD when, in addition to the clinical diagnosis of pneumonia, at least one of the following criteria were met: a) isolation in culture and identification of *Legionella* in secretions from the respiratory tract, lung tissue or blood; b) at least a four-fold increase in antibody titer against *Legionella pneumophila* serogroup 1 (Lp1); c) detection of specific *L. pneumophila* antigen in urine.[9]

Only autochthonous cases with sporadic community-acquired LD, for which a travel-associated or nosocomial origin could be excluded and for which the date of onset was known and occurred between 1 January 2003 and 31 December 2007, were included in the study.

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Meteorological data were obtained from three main weather stations in Ticino (covering the most populated areas) and two in Basle. The meteorological data evaluated in this investigation were the monthly means of daily average relative humidity, vapour pressure, mean temperature, global

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A canonical discriminant analysis was performed to assess differences in meteorological conditions between the two regions. The analysis was carried out using monthly means of daily average data for relative humidity, vapour pressure, mean temperature, global radiation, wind speed and daily amount of precipitations recorded in Ticino and Basle. The analysis was carried out with SPSS version 17.0 (SPSS Inc., Chicago, Illinois, USA).

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A multivariable Poisson regression was used to identify the main risk factors for LD. The cases are the prevalence of LD per 100,000 inhabitants grouped by month of onset and for each meteorological variable a monthly average was calculated using data from the closest weather station. For those months with no case reported, the monthly mean of each variable was used in the model.

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The final model included only those variables that reached a *P* value of <0.05 in the preliminary model with all the variables. To quantify the effects of meteorological variables, we computed the influences (e^{β}-1), which virtually correspond to the relative risks. These analyses were carried out using SAS (version 8.01, SAS Institute, Cary, NJ, USA). Data are presented as relative risk and corresponding 95% confidence intervals (95% CI). *P* values < 0.05 were considered statistically significant. Goodness of fit of the final model was tested using the GOF Chi square test applied to the deviance values shown in the SAS output.

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Canonical discriminant analysis carried out using daily average data for relative humidity, vapour pressure, mean temperature, global radiation, wind speed and daily amount of precipitations revealed that the Basle data can be grouped consistently according to their meteorological characteristics and were well separated from Ticino (Figure 2). The first three canonical discriminant functions explain 95.8% of the variance of the model. When the four cantons grouped in the Basle region were considered separately, the predictive values based on the new canonical variables were only moderately concordant with the original grouping, because only 53.3% of all cases were correctly classified in their original categories (Table 1). The two regions, Ticino and Basle, however, could be clearly separated, with 91% of the cases correctly classified. Thus, discriminant analysis has confirmed that the two regions investigated have clearly distinct climatic situations, with the four northern Cantons being meteorologically quite similar. The most important variable that influenced the first function of the model was the temperature; vapour pressure was determining the second and third functions.

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	Basel-Land	4.0	**70.0**	2.0	14.0	10.0
	Basel-Stadt	2.5	**60.0**	5.0	15.0	17.5
	Solothurn	0.0	**65.6**	9.4	9.4	15.6
Ticino	Ticino	1.0	3.0	4.0	1.0	**91**

Influence of meteorological factors on LD

The study of correlations between the independent variables at the regional and global level revealed a nearly perfect correlation (r > 0.96) between vapour pressure and average temperature, and vapour pressure and minimal and maximal temperature. Therefore, to avoid collinearity problems, we decided to explore the relationship of temperature and vapour pressure with LD cases by using two different models, including either temperature or vapour pressure together with all other predictors. In the two models, temperature ($P = 0.0002$) and vapour pressure ($P = 0.0014$) were highly significant; year and region were also significant in both models (Table 2).

The final model showed that vapour pressure and temperature, respectively, are highly significant factors that influence the risk of LD (both $P < 0.0001$). Each 1 hPa raise of vapour pressure corresponds to an increase in the number of cases by 11.4% (95% CI=7.70%-15.30%); likewise, a raise of 1 °C corresponds to an increase of 6.7% (95% CI=4.22%-9.22%). The results show that in Ticino the risk of being infected by *Legionella* is much higher than in Basle (129.5% or 136.4%, depending on the variable considered in the model; see Table 2). The variable year is also significant using either vapour pressure ($P = 0.0034$) or temperature ($P = 0.0073$) as independent variables. During the period 2003-2007, the relative risk of LD has been increasing in both regions

at an annual rate of approximately 16%, after adjusting by region and vapour pressure or temperature effect (Table 2).

Table 2 Poisson regression model of meteorological factor associated with risk of LD. Multiple Poisson regression model for legionellosis without temperature (A) and without vapour pressure (B). Final models without temperature (C) and without vapour pressure (D).

A)		**β**	**(e^{β}-1) = RR**	***P* value**
	Intercept	-356.746		0.0027
	relative humidity	0.0051	0.51%	0.8161
	vapour pressure	0.1220	12.98%	0.0014*
	region	0.7665	115.22%	0.0036*
	radiation	-0.0011	-0.11%	0.7130
	Foehn	-0.0189	-1.87%	0.4660
	wind	0.0224	2.27%	0.8311
	precipitation	0.0260	2.63%	0.3804
	year	0.1766	19.32%	0.0030*
B)				
	Intercept	-347.822		0.0031
	relative humidity	0.0189	1.91%	0.3207
	temperature	0.1036	10.92%	0.0002*
	region	0.7985	122.22%	0.0021*
	radiation	-0.0030	-0.30%	0.3357
	Foehn	-0.0193	-1.91%	0.4608
	wind	0.0361	3.68%	0.7329
	precipitation	0.0272	2.76%	0.3532
	year	0.1717	18.73%	0.0035*
C)				
	Intercept	-321.042		0.0032*
	vapour pressure	0.1083	11.44%	<0.0001**
	region	0.8603	136.39%	<0.0001**
	year	0.1587	15.87%	<0.0034*
D)				
	Intercept	-299.281		0.0069*
	temperature	0.0647	6.68%	<0.0001**
	region	0.8309	129.54%	<0.0001**
	year	0.1481	15.96%	0.0073*

* *P* values < 0.05 were considered statistically significant. ** *P* values < 0.0001 were considered statistically highly significant. RR: relative risk.

DISCUSSION

Our study indicates that temperature and vapour pressure during the month of disease are the meteorological factors that influence most the occurrence of sporadic community-acquired LD.

The two regions studied, Ticino and Basle, can be separated using meteorological parameters. Multiple Poisson regression identified vapour pressure and temperature as important contributing factors influencing the occurrence of legionellosis in both regions.

Association of weather factors with legionellosis has been described in previous studies that identified relative humidity and temperature as the most important risk for infection,[12, 13, 15] but to date the role of vapour pressure has not been investigated.

The relative humidity is the ratio between the partial pressure of water vapour in the air-water mixture to the saturated vapour pressure of water at the same conditions of temperature and pressure. Thus, relative humidity explains how far the air is from a saturated condition. In contrast, the vapour pressure is the measure of the partial pressure of water vapour in air-water mixture saturated with water and decreases non-linearly with temperature.[12] Vapour pressure increases with increasing relative humidity.

Our analysis indicates that vapour pressure is the most important factor that influences the increase in number of cases of legionellosis in both regions. The two regions investigated in this study differ from each other by their geographic and climatic features. Summers in Ticino are characterised by days with very high vapour pressure, for example after thunderstorms,[11] as opposed to the northern Swiss regions.[10] In general, throughout the year, the relative humidity is higher and the temperature is lower in Basle as compared to Ticino. By contrast, the vapour pressure is higher in Ticino than in Basle during summer.[10]

In Ticino the risk of being infected is much higher than in Basle; this is confirmed by the much higher incidence of cases in Ticino than in northern Switzerland. The risk of being infected in Canton Ticino rises by 11.4% for each 1 hPa increase in vapour pressure: this is in accordance with clinical observations that set the highest incidence of LD in the summer months, when in Ticino the

vapour pressure is higher (e.g., the monthly mean of August 2007 for Ticino was 16.9 hPa vs. 15.2 hPa of region Basle).[10]

LD in Switzerland exhibits a strong seasonality, with a summer-early autumn increase of notified LD cases, as noted also in America[13-15] and Europe.[16, 17] No cases were reported for 17 months in Ticino and for 12 months in Basle region.

The number of LD cases notified in Switzerland is increasing yearly in both regions, as is in whole Europe.[2] This is why we inserted the variable year in the Poisson model to control for additional confounding unknown factors and indeed, in both models, the variable year was highly significant.

Poisson regression models are often not suitable to study infectious disease because of the non-independence of events caused by person-to person transmission: it is, however, appropriate for LD because contagion occurs mainly through aerosol.

Some methodological limitations must be acknowledged for this study: the incubation period of 14 days for every case cannot be determined exactly and this is why we choose to use monthly mean of the month during which the LD case occurred; the use of aggregate or average meteorological data, which are approximations for each daily and monthly value or the aggregation of LD cases for months; the direction of these approximations, however, are likely to be random, suggesting that our risk estimates are reliable. Moreover, with this set up we cannot evaluate short-term effect of the weather on LD. We also used clinical data provided to the Swiss Federal Office of Public Health by several laboratories: we cannot exclude that our dataset can be incomplete because of lack of case notifications or by missing or wrong bacterial identifications: undercounting of legionellosis cases, on the other hand, is a bias that should not influence the outcome of the analysis. Our study was performed only for the period 2003-2007 because more recent, updated data were not easily available. Finally, this investigation being an ecological study, we cannot exclude that we could not identify and consider some potential confounding variables.

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.[9]

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.

In conclusion, high vapour pressure and temperature were associated with a higher risk of community-acquired LD in two regions of Switzerland, characterised by two distinct climatic conditions. These findings strongly support the hypothesis that climatic factors in general and vapour pressure and temperature in particular are risk factors for the transmission of community-acquired LD and should increase awareness of the increased risk of LD after days with humid and warm weather conditions.

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COMPETING INTEREST

None.

CONTRIBUTORSHIP

LC, SC, VG, CL conception and design, or analysis and interpretation of data.

LC drafting the article.

SC, VG, CL revising it critically for important intellectual content.

LC, SC, VG, CL final approval of the version to be published.

DATA SHARING

There is no additional data available.

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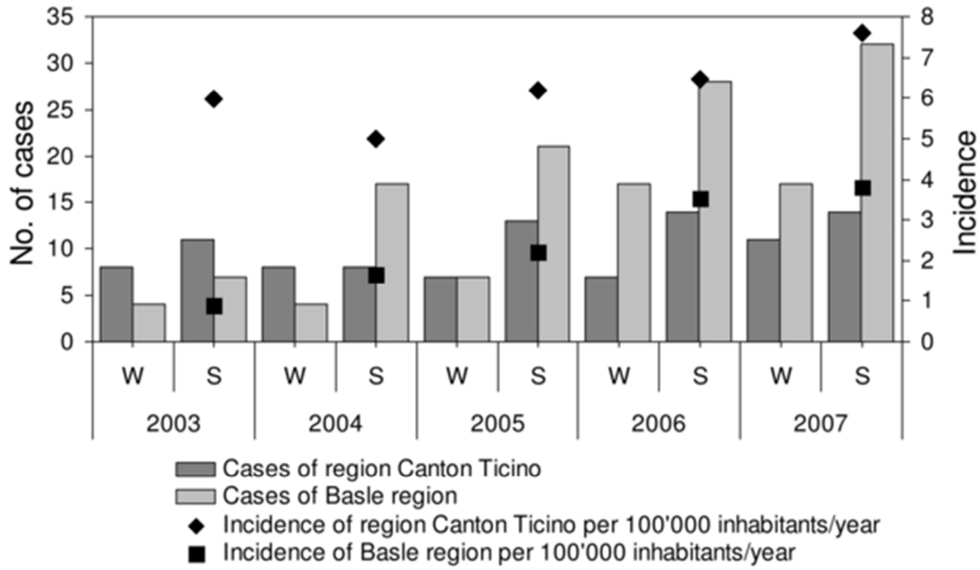
Figure 1 **Seasonal distribution and incidence of LD cases according to onset date in Ticino and Basle from 2003-2007.[9]** W: winter (October-March), S: summer (April-September).

Figure 2 **Graphical plot of the discriminant model.** The centroids of the data of Basle (1-4) are grouped and well separated from Ticino (5). 95.8% of the total variance is explained by the first tree discriminant functions.

There is no additional data available.



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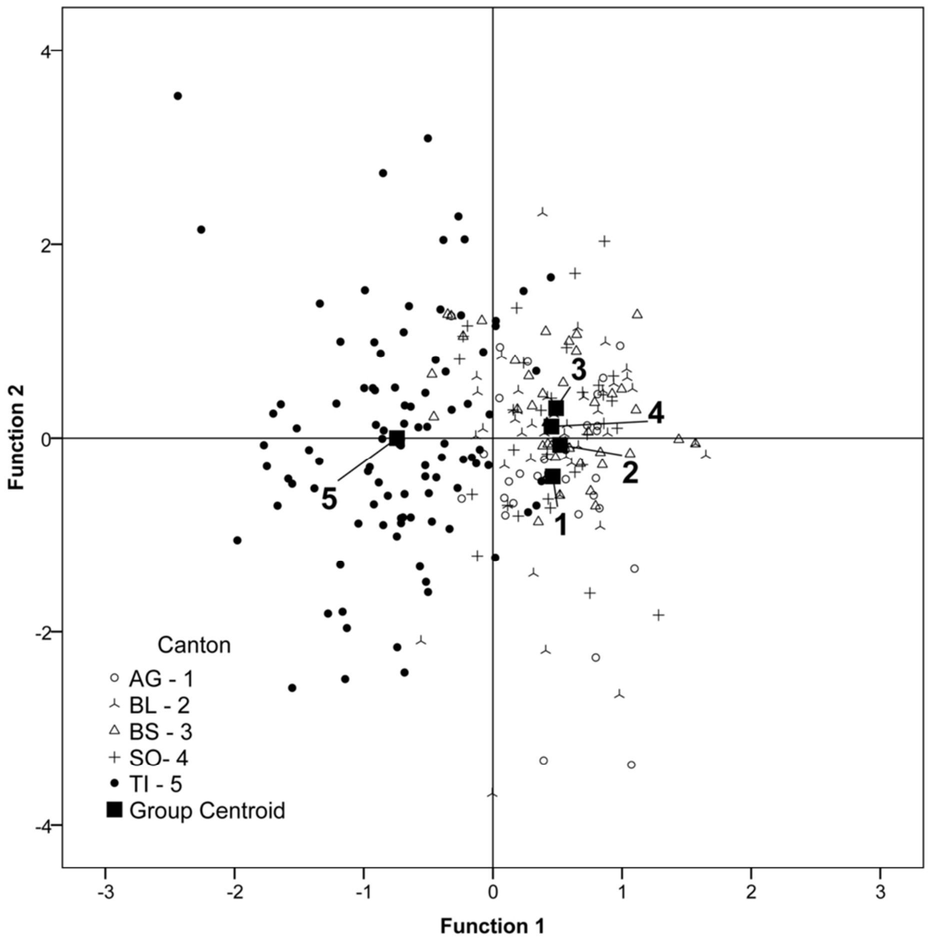

Figure 2 Graphical plot of the discriminant model. The centroids of the data of Basle (1-4) are grouped and well separated from Ticino (5). 95.8% of the total variance is explained by the first tree discriminant functions.
91x93mm (300 x 300 DPI)