ORIGINAL ARTICLE

Evaluation of Patients with Community-Acquired Pneumonia Caused by Zoonotic Pathogens in an Area with a High Density of Animal Farms

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Impacts

- Intensive animal farming could be of potential influence on community-acquired pneumonia (CAP). By the use of geographic information system (GIS) techniques, we demonstrated that patients with CAP caused by *Coxiella burnetii* were more likely to live near sheep or in regions with high numbers of goats.
- In this study, CAP with unknown aetiology was not associated with the presence of animal farms.

Summary

Intensive animal farming could potentially lead to outbreaks of infectious diseases. Clinicians are at the forefront of detecting unusual diseases, but the lack of specificity of zoonotic disease symptoms makes this a challenging task. We evaluated patients with community-acquired pneumonia (CAP) with known and unknown aetiology in an area with a high livestock density and a potential association with animal farms in the proximity. Between 2008 and 2009, a period coinciding with a large Q fever outbreak in the Netherlands, patients with CAP were tested for the presence of possible respiratory pathogens. The presence and number of farm animals within 1 km of the patients' home address were assessed using geographic information system (GIS) and were compared between cases and age-matched control subjects. Of 408 patients with CAP, pathogens were detected in 275 (67.4%) patients. The presence of sheep and the number of goats were associated with CAP caused by *Coxiella burnetii* in a multiple logistic regression model ($P < 0.05$). CAP with unknown aetiology was not associated with the presence of animal farms ($P > 0.10$). The use of GIS in combination with aetiology of CAP could be potentially used to target diagnostics and to identify outbreaks of rare zoonotic disease.

Introduction

Community-acquired pneumonia (CAP) is one of the most common infectious diseases that clinicians face and usually caused by a range of well-known endemic pathogens, particularly *S. pneumoniae*, *H. influenzae* or *M. pneumoniae* (Lim et al., 2009; Woodhead et al., 2011). In addition, CAP cases may be caused by rare zoonotic or environmental pathogens. A well-known example is *Legionella*

pneumophila (Fields et al., 2002). *Legionella* is found ubiquitously in water and moist soil, and accounts for 0.5–15% of all CAP (Fields et al., 2002). *Chlamydia psittaci* is a zoonotic pathogen and infections occur primarily in bird owners, veterinarians and poultry workers, mainly through inhalation of aerosols from faeces of infected birds. *C. psittaci* outbreaks have also been described, mainly among visitors of bird fairs (Belchior et al., 2011). Cattle, sheep and goats are the most common reservoirs for

Coxiella burnetii. *C. burnetii* is responsible for Q fever, which has a wide variety of clinical manifestations, including pneumonia (Dijkstra et al., 2012).

Awareness of CAP cases caused by unusual pathogens not endemic to the area or caused by pathogens thought to be part of a cluster is important because of epidemiological implications or because these pathogens require unique therapeutic intervention. Initial treatment of CAP is empirical, but a thorough understanding of the likely pathogens may lead to different treatment decisions. Some guidelines recommend macrolide monotherapy for outpatient treatment, despite an increasing rate of resistance of *S. pneumoniae* for this antibiotic (Mandell et al., 2007; Woodhead et al., 2011). Other guidelines for non-severe pneumonia advocate initial therapy with amoxicillin, a treatment not suitable for atypical organisms such as *M. pneumoniae* or zoonotic organisms such a *C. burnetii* (Lim et al., 2009; Wiersinga et al., 2012).

Alterations in human living conditions, large-scale intensive animal farming or vaccination campaigns could have an important influence on the aetiology of CAP and subsequently on the empirical treatment of CAP. As environmental and especially zoonotic infections are rare causes of illness, these are not consistently included in diagnostic algorithms. Adding these routinely may not be cost-effective as using molecular diagnostics for testing a wide range of respiratory pathogens for each patient with CAP is costly. The use of spatial analysis to quickly detect cluster formation of an unusual elevation of cases could be very helpful in these circumstances. We therefore conducted a case–control study to investigate whether there is an association between CAP with known and unknown aetiology and living in an area with a high density of farm animals.

Materials and Methods

This case–control study was performed between April 2008 and March 2009. All patients aged 18 years and older, attending the emergency ward of two hospitals in Tilburg, the Netherlands, with the suspicion of CAP were analysed. CAP was defined as the presence of a new or progressive infiltrate on a chest radiograph with clinical symptoms suggestive of a lower respiratory tract infection. Exclusion criteria included the following: (i) recent hospitalization (<2 weeks) or residence in long-term care facilities, (ii) known bronchial obstruction or a history of post-obstructive pneumonia (with exception of chronic obstructive pulmonary disease), (iii) primary lung cancer or another malignancy metastatic to the lungs, (iv) AIDS and/or known or suspected *Pneumocystis jirovecii* pneumonia and (v) known or suspected active tuberculosis. Patients aged 18 years and older who attended the emergency ward during the same period with either abdominal symptoms or chest pain were included as controls. To obtain a similar age distribution for the patients with CAP and control subjects, a 1 : 3 matching algorithm was used to match control subjects within a 5-year age range (SAS gmatch macro). The study was approved by the local medical ethics committee. Written informed consent was obtained from all participants in the study.

Metadata

A case report form was obtained from all patients, containing information on age, gender, current smoking, comorbidity, clinical symptoms, anti-microbial treatment prior to and at admission and blood analysis.

Samples for diagnostic evaluation

At the emergency ward, a throat swab ($n = 408$) was taken and two sets of blood samples ($n = 329$) were obtained and cultured according to standard microbiological procedures. When available, a sputum sample was evaluated by use of Gram staining, culture ($n = 203$) and quantitative polymerase chain reaction (qPCR) [for viruses ($n = 163$), for *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydia psittaci*, *Chlamydia pneumoniae* and *Coxiella burnetii* ($n = 167$) and for *Streptococcus pneumoniae* ($n = 169$)].

Urine samples ($n = 408$) were obtained to detect *Streptococcus pneumoniae* and *Legionella pneumophila* antigens. From some patients, paired serum samples were obtained.

Laboratory diagnostics

All respiratory samples were tested by reverse transcriptase (RT)-qPCR for the presence of respiratory pathogens including adenovirus (HAdV), human bocavirus, KI and WU polyomaviruses, human metapneumovirus, human rhinovirus, human coronaviruses (OC43, NL63, HKU1 and 229E), parainfluenza viruses (HPIV)1−4, influenza viruses A and B (InfA, InfB), respiratory syncytial virus (RSV), *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydia psittaci*, *Chlamydia pneumoniae* and *Coxiella burnetii*. Sputum samples were also tested by qPCR for *Streptococcus pneumoniae*.

Serum samples of 404 patients were tested for the presence of *Coxiella burnetii* DNA. Reverse transcriptase (RT)-qPCR procedures were performed as described previously (Greiner et al., 2001; Heddema et al., 2006; van de Pol et al., 2006, 2007, 2009; Diederen et al., 2008; Tilburg et al., 2010). Acute and convalescent serum samples (separated by at least 2 weeks) were analysed in parallel. In-house complement fixation tests were performed to detect antibodies to InfA, InfB, RSV, HPIV1-4, HAdV ($n = 61$), *M. pneumoniae* ($n = 90$), *L. pneumophila* ($n = 66$),

Chlamydia psittaci (n = 44) and *Coxiella burnetii* (n = 104). Urinary antigen detection test for *Streptococcus pneumoniae* and *Legionella pneumophila* was performed with the Binax NOW pneumococcal urinary antigen test and the Binax NOW *Legionella* urinary antigen test (both from Binax, Portland, ME, USA).

Classification of aetiology

Cases were considered to be caused by a specific pathogen, if one or more of the following criteria were met: (i) a pathogenic micro-organism was cultured from blood samples and/or the urinary antigen test was positive for *S. pneumoniae* or *L. pneumophila,* (ii) qPCR of the throat swab sputum sample or serum samples yielded a positive result, (iii) bacterial culture of sputum samples (presence of >25 polymorph nuclear leucocytes and <10 squamous cells per field) with a predominant organism and compatible results from Gram stain, (iv) IgM antibodies for *M. pneumoniae* were detected, and (v) a 4-fold increase in antibody titres for InfA, InfB, RSV, HPIV1-4, HAdV, *M. pneumoniae*, *L. pneumophila*, *Chlamydia psittaci* or *Coxiella burnetii* was detected.

Farm animals around the home address

The presence and number of farm animals around the home address was compared between cases and control subjects. Full postal codes (six characters, generally representing part of a street) of patients' residential addresses were available; postal code centroids were geocoded. The precise coordinates (centroids of stable complexes) of all animal farms in the study area and numbers of commercially kept swine, poultry, cattle, goats and sheep were obtained from the database of mandatory environmental licences for keeping livestock in the province of Noord-Brabant in 2009. This database does not specify the purpose for which animals are kept (e.g. dairy or meat). Distances between coordinates of patients' home addresses and all animal farms within a 1 km radius were calculated using geographic information system (ARCGIS 9.3.1, Esri, Redlands, CA, USA). Binary and continuous variables indicating the presence (yes: at least one animal of a specific species present on a farm within 1 km, no: no animals of that species on a farm within 1 km) and the total number of specific farm animal species present on farms within 1 km from the home address were created.

Statistical analysis

Data were analysed using SAS statistical software version 9.2 (SAS Institute, Cary, NC, USA). Three definitions of case status were studied: (i) (any) CAP, (ii) CAP with unknown aetiology and (iii) CAP caused by *C. burnetii*. The presence of one or more farms (all types) or specific farm animal species within 1 km from the home address (present yes/no) was compared between cases and controls by means of the chi-square test. To assess whether the number of animals near the home address was a risk factor for CAP, we further compared the number of animals within 1 km from the home address between cases and controls by means of a nonparametric test (Wilcoxon). These comparisons were restricted to subjects who were living within 1 km of at least one specific animal. Variables that were associated with case status in the univariate tests for the presence or the number of animals (P < 0.10) were included in a multiple logistic regression model with backward variable selection to evaluate potential independent farm-related risk factors of CAP. The presence of a specific farm animal (yes/no) was included in the model together with the number of animals. To allow direct interpretation of the adjusted odds ratio for the presence of a specific animal, the number of animals was mean-centred, while keeping 0 for those with 0 of those animals (Leffondre et al., 2002). This provides interpretable odds ratios in one model of (i) the qualitative effect of the presence of a specific animal and (ii) the quantitative effect of the number of these animals among subjects with >0 of those animals around their home. Odds ratios for an interquartile range increase in the number of animals were calculated.

Results

Characteristics of patients

In total, 408 patients with CAP and 1096 control subjects were included. The mean age of the patients was 65 years (range 20–94), and 61.3% of them were male. The mean age of the controls was 63 (range 20–94), and 52.1% of them were male. Comorbidity was scored in 252 (61.8%) of the 408 patients with CAP. Respiratory pathogens were found in 275 (67.4%) of the 408 patients with CAP.

L. pneumophila was detected in 15 (3.7%) patients, *C. psittaci* in 7 (1.7%) patients and *C. burnetii* in 50 (12.3%) patients. In 133 (32.6%) patients, no pathogen was detected. The number of patients with CAP caused by *C. psittaci* and *L. pneumophila* was too low to perform any analysis.

Association between the presence and number of farm animals and CAP

Around 60% of the patients with CAP and controls were living within 1 km of at least one animal farm (cases: 59.3%, controls: 62.7%; P = 0.23). Only CAP caused by *C. burnetii* was associated with the presence of animal farms within 1 km from the home address (Table 1).

Patients with CAP caused by *C. burnetii* were more often living within 1 km from poultry ($P = 0.09$) or sheep ($P = 0.02$) than controls (Table 1). We further studied whether animal density was a risk factor for CAP among subjects who were living within 1 km of a specific species (Table 2). The median number of goats within 1 km from the home address was higher in patients with CAP caused by *C. burnetii* (1330 goats) than in controls (696 goats; $P = 0.06$). There was no statistically significant association between the number of other farm animals within 1 km and *C. burnetii* infection (Table 2). Farm animal densities around the home address did not increase the risk of any CAP, or CAP with unknown aetiology (data not shown).

Finally, risk factors identified in the univariate models (Tables 1 and 2; $P < 0.10$) were mutually adjusted in a multiple logistic regression model. The number of goats and the presence of sheep remained significantly associated with *C. burnetii* pneumonia, whereas the presence of poultry was not an independent risk factor and therefore not included in the final model (Table 3). The risk of *C. burnetii* pneumonia increased 1.8-fold for every 1171 goats (interquartile range) within the 1 km radius, while the presence of sheep resulted in a 2-fold increase of the risk (Table 3). In addition, we explored the number of goats as tertiles, showing that only the upper tertile (>1210 goats) was associated with an increased risk of *C. burnetii* pneumonia (OR: 3.14, 95%CI: 1.17–8.41).

Discussion

We conducted an exploratory analysis on 408 patients with CAP and found that patients with CAP caused by *Coxiella burnetii* were more likely to live near sheep or in regions with high numbers of goats. CAP with unknown aetiology was not associated with the presence of animal farms.

Table 1. Association between the presence of farm animals within 1 km from the home address and CAP

	Controls	Any CAP	CAP with unknown aetiology	CAP caused by *C. burnetii*
n	1096	400	130	50
One or more farms within 1 km, *n* (%)	687 (62.7)	237 (59.3)	72 (55.4)	33 (66.0)
Presence of farm animals within 1 km, *n* (%)				
Swine	455 (41.5)	156 (39.0)	50 (38.5)	25 (50.0)
Poultry	259 (23.6)	99 (24.8)	32 (24.6)	17 (34.0)*
Cattle	593 (54.1)	213 (53.3)	65 (50.0)	29 (58.0)
Goats	170 (15.5)	74 (18.5)	23 (17.7)	9 (18.0)
Sheep	189 (17.2)	81 (20.3)	30 (23.1)	15 (30.0)**

Residential addresses were geocoded for 400/408 patients with CAP.
*$P < 0.10$; **$P < 0.05$, CAP cases versus controls.

In general, Q fever is considered to be an occupational disease of workers who are in close contact with farm animals such as cattle, goats and sheep or processing their products; however, it is not solely an occupational disease as it may occur also in persons without direct contact. Infection may occur through inhalation of dust particles or aerosols containing *C. burnetii* (Tissot-Dupont et al., 2004). In our study, *C. burnetii* was detected more often in patients with CAP, in contrast with published literature. This was due to a large Q fever outbreak in the Netherlands between 2007 and 2010 which coincided with the enrolment of our study population (Delsing et al., 2010). Previous studies have suggested an airborne spread of *C. burnetii* in this outbreak (Schimmer et al., 2010; Dijkstra et al., 2012). Pneumonia was the most frequent diagnosis (61.5%) among the notified Q fever patients in the epidemic in the Netherlands (Dijkstra et al., 2012). We confirmed previous findings that dairy goats were a source of infection, but in our study, also living near sheep was associated with CAP caused by *C. burnetii* (Dijkstra et al., 2012; van der Hoek et al., 2012).

Table 2. The number of farm animals within 1 km from the home address among controls and patients with CAP caused by *C. burnetii*

Type of farm animal	Controls		CAP caused by *C. burnetii*	
	n	Median number of animals within 1 km (IQR)	*n*	Median number of animals within 1 km (IQR)
Swine	455	3061 (551–5752)	25	4372 (587–8524)
Poultry	259	770 (20–25 000)	17	240 (40–11 550)
Cattle	593	360 (110–781)	29	529 (363–859)
Goats	170	696 (39–1210)	9	1330 (1078–3275)*
Sheep	189	65 (42–100)	15	50 (30–88)

Data are shown for subjects who were living within 1 km of at least one specific animal. IQR, interquartile range.
*$P < 0.10$.

Table 3. Multiple logistic regression models of association between the presence and number of farm animals within 1 km from the home address and CAP caused by *C. burnetii*

Risk factor	OR (95% CI)	*P*
Presence of goats*	0.79 (0.34–1.86)	0.59
Number of goats*	1.79 (1.03–3.12)	0.04
Presence of sheep	2.08 (1.07–4.04)	0.03

OR: odds ratio, 95% CI: 95% confidence interval.
*By including the presence of goats and mean-centred number of goats together in the models, an OR for the number of goats in subjects with >0 goats within 1 km of the home address is obtained. The OR for the increase in risk for every 1171 goats in the 1 km radius (interquartile range) was calculated.

Results of this study are in accordance with a previous study demonstrating a significant relationship between increasing numbers of goats around the home address and suspected Q fever and pneumonia in general practitioners' registrations (Smit et al., 2012). We did not confirm the higher risk of pneumonia observed among patients with clinically confirmed CAP living in the vicinity of poultry (Smit et al., 2012). However, pneumonia registered by general practitioners includes cases with relatively mild symptoms compared with the patients with clinically confirmed CAP in the present study. As shown in the present analysis, specific pathogens causing CAP may depend on environmental risk factors.

While these observations are interesting, they are retrospective observations that currently do not influence case ascertainment, diagnostic triaging or patient management decisions. GIS with residence locations of cases and farm locations in combination with early notification of human clusters by health care professionals could be a powerful tool to detect outbreaks or to detect the source of the outbreak (Schimmer et al., 2010; Smit et al., 2012), particularly when performed in real time. Earlier identification of clusters could lead to a faster mitigation of an outbreak and a better understanding of the disease aetiology, and awareness of an outbreak could lead to the use of targeted diagnostics and, if necessary, antibiotics. van den Wijngaard et al. (2011) demonstrated that the use of syndromic surveillance such as pneumonia or lower respiratory infection combined with GIS on hospitalizations leads to the detection of Q fever clusters, but again, this was based on retrospective analysis. For practical applicability, real-time cluster detection should be combined with algorithms that target diagnostic work-ups to patients with increased risk of a zoonotic infection (van der Have and van der Lubben, 2011). Such an approach could also be extended to treatment guidance.

Not only *C. burnetii* is a potential farm pathogen but individuals living near animal farms may be exposed to other pathogens such as influenza viruses or resistant bacteria (e.g. MRSA) and to increased levels of air pollutants such as particulate matter or bio-aerosols (Just et al., 2012). Epidemiological studies have shown that exposure to particulate matter could be a risk factor for pneumonia (Neupane et al., 2010). Reedijk et al. (2013) suggested that particulate matter could play a role in the transmission of *C. burnetii* from infected animals to humans. Moreover, animal studies have observed that exposure to ambient particulate matter compromised host ability to handle ongoing pneumococcal infections (Zelikoff et al., 2003). However, in this study, CAP with unknown aetiology was not related to the presence of animal farms near the home address.

We used farm licence data to estimate the total number of farm animals in an arbitrary 1 km radius circle around the home address. Licence data may overestimate the number of animals actually present at a facility, and this database does not specify whether animals are kept for dairy or meat production or for other purposes. Nevertheless, in a previous study that used this database, strong associations between the presence of livestock and infectious diseases were reported (Smit et al., 2012).

It could be argued that the risk of infection may depend on the distance between a farm and a patient's home. To take this into consideration, we also computed the inverse distance weighted number of goats. For each farm with goats within 1 km, we divided the number of goats on that farm by the squared distance between the farm and the patients' home address. We summed these weighted numbers of goats for all farms with goats within 1 km. Nonparametric analysis (Wilcoxon) showed that the weighted number of goats within 1 km of the home was significantly higher in cases than in controls (*P*-value of 0.03), showing similar results as for the (unweighted) number of goats. For clarity, we decided to present the unweighted number of animals.

The present study did not shed more light on the question whether neighbouring residents of animal farms are at increased risk of infection with *C. psittaci* or *L. pneumophila*. Patients with CAP caused by *L. pneumophila* were often living within 1 km of one or more farms (85.7%, versus 62.7% of controls), but numbers of patients infected with *L. pneumophila* (or *C. psittaci*) were deemed too low to justify a further in-depth statistical analysis. A potential risk factor for infection with *L. pneumophila* is air scrubbers. Air scrubbers are increasingly applied to reduce ammonia emissions from animal housing, and it could be hypothesized that the presence of air scrubbers may be linked to *L. pneumophila* infection in neighbouring residents of animal farms. This question, however, needs to be addressed in studies with larger number of patients.

In conclusion, using geographic information system in combination with aetiology of CAP, we found that patients with CAP caused by *Coxiella burnetii* were more likely to live near sheep or in regions with high numbers of goats. CAP with unknown aetiology was not associated with the presence of animal farms.

Disclosure Statement

No competing financial interests exist.

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