Infection Ecology & Epidemiology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ziee20

Literature review on micro-organisms from domestic goats potentially causing human pneumonia

Wouter Lokhorst, Inge Roof, Marieke Opsteegh, Alex Bossers, Manon Swanenburg, Wim H. M. van der Poel, Thomas J. Hagenaars & Joke W. B. van der Giessen

To cite this article: Wouter Lokhorst, Inge Roof, Marieke Opsteegh, Alex Bossers, Manon Swanenburg, Wim H. M. van der Poel, Thomas J. Hagenaars & Joke W. B. van der Giessen (2024) Literature review on micro-organisms from domestic goats potentially causing human pneumonia, Infection Ecology & Epidemiology, 14:1, 2406835, DOI: 10.1080/20008686.2024.2406835

To link to this article: https://doi.org/10.1080/20008686.2024.2406835

INFECTION ECOLOGY & EPIDEMIOLOGY
2024, VOL. 14, 2406835
https://doi.org/10.1080/20008686.2024.2406835

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS Check for updates

Literature review on micro-organisms from domestic goats potentially causing human pneumonia

Wouter Lokhorst[a,b*], Inge Roof[c*], Marieke Opsteegh[c], Alex Bossers[a,d], Manon Swanenburg[a], Wim H. M. van der Poel[a,b], Thomas J. Hagenaars[a] and Joke W. B. van der Giessen[c]

[a]Department of Epidemiology, Bioinformatics & Animal Models, Wageningen Bioveterinary Research, Lelystad, The Netherlands; [b]Quantative Veterinary Epidemiology, Wageningen University, Wageningen, The Netherlands; [c]Centre for Infectious Disease Control, National Institute for Public Health and The Environment, Bilthoven, The Netherlands; [d]Department Population Health Sciences, Institute for Risk Assessment Sciences, Utrecht, The Netherlands

ABSTRACT

Background: In the Netherlands, living in proximity to goat farms has been consistently associated with an increased incidence of community-acquired pneumonia (CAP). The cause remains largely unknown though airborne microbial agents could play a role.

Objective: The aim of this study is to explore micro-organisms present in goats that can cause human pneumonia.

Methods: An extensive literature review was conducted to identify all micro-organisms detected in goats that are associated with human pneumonia. Additionally, the identified micro-organisms were prioritized using a self-developed scoring system and expert opinion.

Results: Through extensive literature review, 4309 references describing 302 different micro-organisms in goats or on goat farms were identified. Additional searches and reviews for human respiratory disease caused by each of these micro-organisms yielded a final list of 76 bacteria, 7 viruses, 7 fungi, and 6 protozoa. They were assigned scores based on pneumonia type, diagnosis of respiratory disease, patient immune status, and evidence strength. Based on these scores, the most likely potential causal micro-organisms included Moraxella spp. Chlamydia psittaci, Staphylococcus aureus, and Streptococcus pneumoniae. Subsequently, the list of micro-organisms was reviewed by external experts on their perceived likelihood of the organism causing this CAP.

Conclusion: Results of this literature study can give insight into the possible causes of pneumonia. Nonetheless, no unambiguous conclusion on the actual cause of the increased CAP risk around goat farms can be drawn solely based on these results.

ARTICLE HISTORY
Received 2 May 2023
Accepted 17 September 2024

KEYWORDS
Community-acquired pneumonia; aetiology; goats; respiratory disease; micro-organism; literature review

Introduction

From 2009 to 2019, epidemiological studies in the Netherlands on the effects of intensive livestock farming on nearby residents showed a consistent association between the incidence of community-acquired pneumonia (CAP) and living in close proximity of goat farms [1–8]. The cause of this increased incidence of CAP near goat farms remains largely unknown. For the years 2009–2010 there is an overlap with the Dutch 2007–2010 Q-fever epidemic, in which the transmission of *Coxiella burnetii* from infected goat farms caused human Q-fever cases with pneumonia as the predominant clinical presentation [9,10]. The increased CAP incidence near goat farms, however, remained for many years after the Q-fever epidemic had ceased in 2010 [11], and an obligatory Q-fever vaccination and monitoring of tank milk of dairy goats and sheep was introduced and is still ongoing [12]. Additional studies showed *C. burnetii* to be an unlikely cause, as the increased CAP incidence was also found near farms that remained Q-fever negative throughout the epidemic and there was no statistically significant association between having had pneumonia and seropositivity for *C. burnetii* among participants in a subsequent cross-sectional study in the south of the Netherlands [3,4,11,13].

A possible causal hypothesis would be the involvement of other airborne microbial agents, however, indications for specific micro-organisms are still inconclusive. In general, the causes of CAP are sparsely documented in the Netherlands. In primary care, the information on CAP aetiology is limited because CAP is mostly a clinical diagnosis and microbiological diagnostics are not included in the CAP guidelines of the Dutch

CONTACT Joke W. B. Van der Giessen joke.van.der.giessen@rivm.nl Centre for Infectious Disease Control, National Institute for Public Health and the Environment, P.O. Box 1, Bilthoven, BA 3720, The Netherlands

*Shared first authors.

Supplemental data for this article can be accessed online at https://doi.org/10.1080/20008686.2024.2406835

College of General Practitioners [14]. In an observational study on CAP aetiology in the Netherlands, *S. pneumoniae*, *Mycoplasma pneumoniae,* and *C. burnetti* were among the most frequently identified micro-organisms [15]. This study coincided with the Dutch Q-fever epidemic but was performed before the increased CAP incidence around goat farms was determined, and associations between the identified organisms and their presence on farms were not investigated. More recently, a retrospective study using routine laboratory diagnostic data of hospitalised patients with CAP specifically explored identified micro-organisms related to goat farm exposure [16]. Although a slightly (non-significant) higher percentage of *S. pneumoniae* positive antigen tests was found in the urine of patients living close to goat farms, this analysis did not yield clear leads towards a particular causative micro-organism [16].

More research into the potential causes of the goat farm-associated CAP risk is needed. Although the Dutch national government already introduced several measures after the Q-fever period, in addition, a moratorium for new and existing goat farms has been active since 2017 in multiple Dutch provinces prohibiting the expansion of existing or the building of new goat stables [17–19] awaiting future research on the potential causes of this association. The objective of this study is to explore, by means of a literature review, which micro-organisms can be present on goat farms and have been reported to cause pneumonia and/or respiratory symptoms in humans. This work is intended to give direction to future studies on the increased CAP risk around goat farms.

Materials and methods

This literature study consisted of three different consecutive phases. The first phase aimed to identify all micro-organisms detected in goats and/or on goat farms by screening the literature. In phase 2, a literature search was conducted for each of the micro-organisms discovered in phase 1, aimed at studies describing human respiratory symptoms and/or pneumonia associated with the micro-organism. This resulted in a list of goat-related micro-organisms with evidence of causing human respiratory disease. The objective of the third phase was to prioritize the micro-organisms listed in phase 2 as a cause of the increased CAP risk among residents around goat farms in the Netherlands by using a self-developed scoring system applied to the literature and an additional expert opinion questionnaire. The methods applied in the three different phases are described in more detail below.

Phase 1: micro-organisms in goats

In the first phase, a literature search on micro-organisms detected in goats and/or on goat farms was conducted in Embase [20] by combining the following search terms and synonyms hereof: goat, infection, pathogen, micro-organism, zoonosis, virus, bacterium, fungus, parasite, and protozoa (complete search strategy phase 1 in Supplementary File 1). In view of the exclusion criteria listed in Table 1 and discussed below, pre-emptive exclusions from the search strategy of helminth infections (Category I), Schmallenberg orthobunyavirus (Category I and III), toxoplasmosis (Category II), brucellosis (Category IV), and *Coxiella burnetii* (Category IV) were made to avoid a large number of hits that would subsequently be excluded.

The literature search was performed on 11 July 2021, and all records were included in an Endnote database. The references were divided over four screeners, and the full-text was screened according to the following inclusion criterium: detection of a micro-organism in a goat and/or on a goat farm and/or from goat excreta by culture, PCR, sequencing, and/or serology. Studies describing an experimental infection model in goats were excluded. All micro-organisms described in goats in the included articles were listed, and organisms appearing under multiple names due to updated taxonomy were merged under the most recent name. Micro-organisms were listed according to the taxonomic level that was reported in the included articles, which was up to genus or species level.

The list of micro-organisms was narrowed down using the exclusion criteria described in Table 1. These exclusion criteria were formulated after careful deliberation by experts in the study team. In category I of the exclusions, micro-organisms that are primarily transmitted through a vector (e.g. ticks, mosquitos, fleas, and mites) are excluded. We consider it highly unlikely that the increased pneumonia incidence in neighbouring residents that was previously found can be driven by vector-borne transmission. We base this consideration on four assumptions: The spread of CAP would occur in a larger area than currently found, due to the fact that these vectors

Table 1. Exclusion criteria literature search phase 1.

Category I	Category II	Category III	Category IV
(1) Helminth infections (2) Micro-organisms with vector-borne transmission as their primary transmission route	Strictly meat- and foodborne pathogens	Pathogens that are strictly host-specific other than human	(1) Organisms not present in the Netherlands (tropical organisms) (2) Micro-organisms that are under national surveillance in goats in the Netherlands

usually spread over a larger area; the occurrence of CAP would most likely be more seasonal than observed, due to increased activity of vectors in summer; bites from several vectors would have been noticed and associated with the CAP by general practitioners; and for some of the micro-organisms the associated vector is not endemic in the Netherlands. Helminths and strictly meat- and food-borne pathogens (category I and II in Table 1) were excluded, because the focus was on micro-organisms with possible aerogenic transmission as this is hypothesized to be the main transmission route in the increased CAP incidence around goat farms. Organisms in category III have been proven to not be able to infect humans. Lastly, pathogens not present in the Netherlands and pathogens under Dutch national surveillance were also excluded (category IV in Table 1), because these are known to be absent through the current monitoring and are therefore not a potential cause of this CAP.

Phase 2: micro-organisms linked to human respiratory disease

In phase 2, separate literature searches of studies describing human respiratory disease or human respiratory symptoms associated with each of the micro-organisms from the final list of phase 1 were conducted. A narrow and broad literature search in the Embase database was performed for each micro-organism (complete search strategy phase 2 in Supplementary File 1). In the narrow literature search, the name of the micro-organism was combined with the search terms 'respiratory tract infection OR respiratory tract inflammation' and 'humans'. The broad search consisted of the name of the micro-organism and the search terms 'respiratory tract disease' and 'humans'. Changes in taxonomy were accounted for by including alternative or old names of each micro-organism in the narrow and broad searches. The retrieved citations per micro-organism were screened in two batches by the two lead authors to evaluate the evidence of human respiratory disease or symptoms associated with the micro-organism. Per micro-organism, the following evidence information was extracted from the articles: Evidence strength, type of respiratory disease, type of pneumonia and patient immune status (Table 2). The set of references from the narrow literature search was used as a starting point. When this yielded insufficient information on the evidence of human respiratory disease, the set of references from the broad searches were screened as well. Organisms that did not yield any references linking them to human respiratory disease in both the narrow and the broad search were excluded from the final organism list. The remaining micro-organisms and their taxonomy at phylum, class, order, and family level were included in the final organism list.

Phase 3: prioritization of micro-organisms

In phase 3, a scoring system was developed to prioritize the micro-organisms for which there was evidence of human respiratory disease in phase 2 similar to the goat-related CAP. The scoring system consisted of (a) the type of pneumonia, (b) the diagnosis of respiratory disease, (c) the immune status of the patient, (d) the strength of the evidence, as described in Table 2. Each micro-organism was scored by the two lead authors by applying this scoring system to the found literature from phase 2. For pathogens with an equal total score, the highest score on type of pneumonia, followed by diagnosis of respiratory disease, immune status of the patient, and strength of the evidence, determines the order in which the organisms appear on the final organism list.

Further prioritization was achieved through an expert panel from different scientific domains such as veterinary (goat) health, human respiratory medicine, epidemiology, and medical and veterinary microbiology including bacteriology, parasitology, mycology, and virology. This expert panel comprised of external experts not directly involved in the design and analysis of this study. Specifically, experts were asked whether the listed micro-organism could in their opinion be responsible for the increase in pneumonia risk among citizens living near goat farms and

Table 2. Description of scoring system used to rank micro-organisms associated with human respiratory disease in phase 3.

	Score		
Factor	High (3)	Medium (2)	Low (1)
Pneumonia type	Community-acquired pneumonia	Hospital-acquired pneumonia	Ventilation-associated pneumonia
Type of respiratory disease	–Lower respiratory tract infection Pneumonia Necrotizing pneumonia Empyema	–Pleurisy Organizing pneumonia	Higher respiratory tract infection
Patient immune status		Immunocompetent (including organisms with both immunocompetent and immunocompromised patients)	Immunocompromised
Evidence strength	Larger studies/reviews with evidence of the micro-organisms causing respiratory disease	Multiple case reports	Single case report

to clarify their reasons. For each organism, they could give a score ranging from 1 (highly improbable) to 4 (highly probable) and were allowed to skip in case the micro-organism was not their expertise. The answers of all experts were summarized by calculating the mean score and variance for each micro-organism from the experts that gave a score on that organism and these summary scores were included in the final organism list. The mean score was also used to order the final organism list among organisms that have equal scores after the scoring described in Table 2.

Results

Phase 1

The search strategy from phase 1 yielded 4309 references which were screened for eligibility. This screening resulted in a total of 302 different micro-organisms (classified up to genus and/or species level) detected in goats, excreta from goats, and/or on a goat farm. The micro-organisms consisted of 80 bacteria, 13 fungi, 60 protozoa, and 49 viruses (Figure 1). By applying the exclusion criteria (Table 1), 79 micro-organisms were excluded (Figure 1, $n = 21$ bacteria, $n = 1$ fungus, $n = 42$ protozoa and $n = 15$ viruses). The complete list of 302 micro-organisms found in phase 1 with reason for exclusion (if applicable) can be found in Supplementary File 2.

Phase 2

In total 223 micro-organisms from phase 1 were included in the search strategy at the start of phase 2. For 79 micro-organisms ($n = 54$ bacteria, $n = 2$ fungi, $n = 9$ protozoa and $n = 14$ viruses) the search strategy in phase 2 yielded zero references and was excluded from the list (Figure 1, Supplementary File 2). The number of references found in the narrow and broad search per micro-organism are listed in Supplementary File 3. The reference sets for the remaining 144 micro-organisms were screened for evidence of human respiratory disease. Another 48 micro-organisms ($n = 29$ bacteria, $n = 3$ fungi, $n = 3$ protozoa, $n = 13$ viruses) were excluded based on this screening, because no association of human respiratory disease was described in the found references (Figure 1, Supplementary File 2). This led to a final list (up to genus or species level) of 76 bacteria, 7 viruses, 7 fungi, and 6 protozoa that were detected in goats and have been associated with human respiratory disease. The list can be found in Supplementary File 4. Figures 2–5 give an overview of the different classes, orders, families, and genera per kingdom that were present in the final list of micro-organisms. Among the final list of bacteria, the Gammaproteobacteria are the most abundant, comprising of several known intestinal and extra-intestinal human pathogens, including *Pseudomonas* species, *Proteus* species, *Acinetobacter* species, *Klebsiella* species, and *Escherichia coli* (Figure 2). In second place comes Bacilli, of which *Streptococcus* species and *Staphylococcus* species form the largest group. Among the other kingdoms, there is less grouping possible (Figures 3–5).

Phase 3

The final organism list of 96 micro-organisms with scores per organism including the expert opinion scores can be found in Supplementary File 4. The top scoring organisms for each kingdom are depicted in Table 3. Mean and variance of expert scores were calculated from those experts that gave a score on that particular organism.

When combining the literature scoring system and the expert scores, *Moraxella* species, *Chlamydia psittaci, Staphylococcus aureus, Streptococcus pneumoniae,*

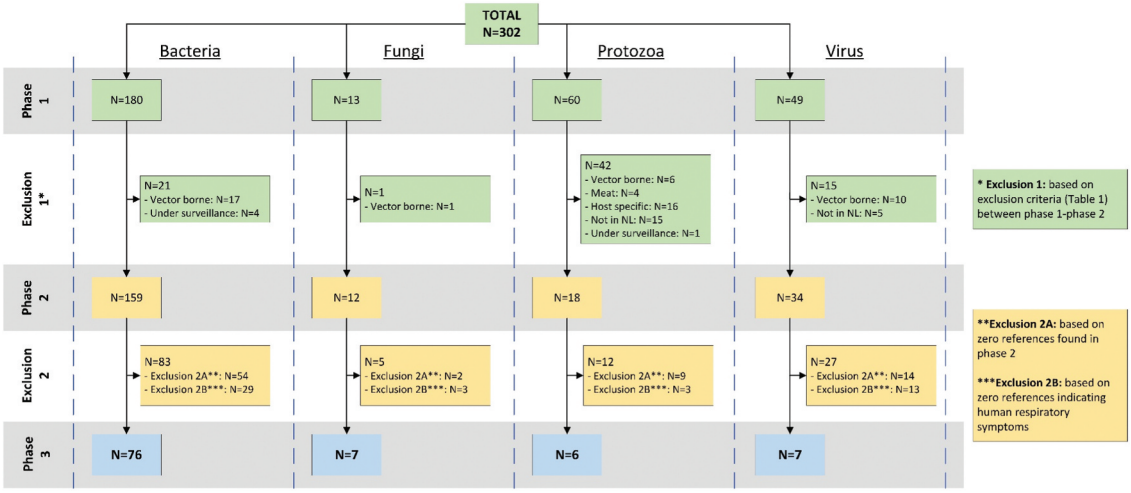

Figure 1. Flowchart of the number of micro-organisms related to goats and human pneumonia during the different phases of the literature study.

Class	Family	Genus	Species
Actinomycetia (n=10)	Actinomycetaceae (n=2)	Actinomyces (n=1)	*Actinomyces spp.*
		Trueperella (n=1)	*Trueperella pyogenes*
	Corynebacteriaceae (n=2)	Corynebacterium (n=2)	*Corynebacterium pseudotuberculosis*
			Corynebacterium ulcerans
	Micrococcaceae (n=2)	Micrococcus (n=2)	*Micrococcus luteus*
			Micrococcus spp.
	Mycobacteriaceae (n=1)	Mycobacterium (n=1)	*Mycobacterium spp.*
	Nocardiaceae (n=3)	Nocardia (n=2)	*Nocardia farcinica*
			Nocardia spp.
		Prescottella (n=1)	*Prescottella equi*
Bacilli (n=23)	Bacillaceae (n=1)	Bacillus (n=1)	*Bacillus cereus*
	Enterococcaceae (n=3)	Enterococcus (n=3)	*Enterococcus faecalis*
			Enterococcus faecium
			Enterococcus hirae
	Listeriaceae (n=1)	Listeria (n=1)	*Listeria monocytogenes*
	Staphylococcaceae (n=9)	Mammaliicoccus (n=1)	*Mammaliicoccus lentus*
		Staphylococcus (n=8)	*Staphylococcus aureus*
			Staphylococcus capitis
			Staphylococcus cohnii
			Staphylococcus epidermidis
			Staphylococcus haemolyticus
			Staphylococcus intermedius
			Staphylococcus lugdunensis
			Staphylococcus saprophyticus
	Streptococcaceae (n=9)	Lactococcus (n=1)	*Lactococcus cremoris*
		Streptococcus (n=8)	*Streptococcus agalactiae*
			Streptococcus dysgalactiae
			Streptococcus equi
			Streptococcus intermedius
			Streptococcus pluranimalium
			Streptococcus pneumoniae
			Streptococcus suis
			Streptococcus uberis
Betaproteobacteria (n=2)	Burkholderiacceae (n=2)	Burkholderia (n=2)	*Burkholderia cepacia*
			Burkholderia pseudomallei
Chlamydiia (n=2)	Chlamydiaceae (n=2)	Chlamydia (n=2)	*Chlamydia abortus*
			Chlamydia psittaci
Clostridia (n=5)	Clostridiaceae (n=3)	Clostridium (n=3)	*Clostridium botulinum*
			Clostridium cadaveris
			Clostridium perfringens
	Peptostreptococcaceae (n=2)	Clostridioides (n=1)	*Clostridioides difficile*
		Paeniclostridium (n=1)	*Paeniclostridium sordellii*
Epsilonproteobacteria (n=3)	Campylobacteraceae (n=2)	Campylobacter (n=2)	*Campylobacter fetus*
			Campylobacter lari
	Helicobacteriaceae (n=1)	Helicobacter (n=1)	*Helicobacter pylori*
Erysipelotrichia (n=1)	Erysipelotrichaceae (n=1)	Erysipelothrix (n=1)	*Erysipelothrix rhusiopathiae*
Fusobacteriia (n=2)	Fusobacteriaceae (n=2)	Fusobacterium (n=2)	*Fusobacterium necrophorum*
			Fusobacterium nucleatum
Gammaproteobacteria (n=26)	Aeromonadaccae (n=1)	Aeromonas (n=1)	*Aeromonas spp.*
	Enterobacteriaceae (n=10)	Citrobacter (n=2)	*Citrobacter diversus*
			Citrobacter freundii
		Cronobacter (n=1)	*Cronobacter sakazakii*
		Enterobacter (n=1)	*Enterobacter cloacae*
		Escherichia (n=1)	*Escherichia coli*
		Klebsiella (n=2)	*Klebsiella oxytoca*
			Klebsiella pneumoniae
		Salmonella (n=1)	*Salmonella enterica*
		Shigella (n=2)	*Shigella sonnei*
			Shigella spp.
	Francisellaceae (n=1)	Francisella (n=1)	*Francisella tularensis*
	Moraxellaceae (n=4)	Acinetobacter (n=3)	*Acinetobacter baumannii*
			Acinetobacter haemolyticus
			Acinetobacter lwoffii
		Moraxella (n=1)	*Moraxella spp.*
	Morganellaceae (n=4)	Morganella (n=1)	*Morganella morganii*
		Proteus (n=2)	*Proteus mirabilis*
			Proteus vulgaris
		Providencia (n=1)	*Providencia stuartii*
	Pasteurellaceae (n=1)	Pasteurella (n=1)	*Pasteurella multocida*
	Pseudomonadaceae (n=2)	Pseudomonas (n=2)	*Pseudomonas aeruginosa*
			Pseudomonas putida
	Xanthomonadaceae (n=1)	Stenotrophomonas (n=1)	*Stenotrophomonas maltophilia*
	Yersiniaceae (n=2)	Serratia (n=1)	*Serratia marcescens*
		Yersinia (n=1)	*Yersinia enterocolitica*
Mollicutes (n=1)	Mycoplasmataceae (n=1)	Mesomycoplasma (n=1)	*Mesomycoplasma hyorhinis*
Spirochaetia (n=1)	Leptospiraceae (n=1)	Leptospira (n=1)	*Leptospira spp.*

Figure 2. Bar chart of the taxonomy for the bacteria present in the final list of micro-organisms.

Class	Family	Genus	Species
Duplopiviricetes (n=1)	Picobirnaviridae (n=1)	Picobirnavirus (n=1)	*Picobirnavirus spp.*
Herviviricetes (n=1)	Herpesviridae (n=1)	Simplexvirus (n=1)	*Simplexvirus spp.*
Insthoviricetes (n=1)	Orthomyxoviridae (n=1)	Deltainfluenzavirus (n=1)	*Deltainfluenzavirus influenzae*
Monjiviricetes (n=2)	Paramyxoviridae (n=1)	Respirovirus (n=1)	*Respirovirus pneumoniae*
	Pneumoviridae (n=1)	Orthopneumovirus (n=1)	*Orthopneumovirus bovis*
Stelpaviricetes (n=1)	Astroviridae (n=1)	unclassified Astroviridae (n=1)	*Caprine astrovirus*
Tectiliviricetes (n=1)	Adenoviridae (n=1)	Mastadenovirus (n=1)	*Mastadenovirus spp.*

Figure 3. Bar chart of the taxonomy for the viruses present in the final list of micro-organisms.

Class	Family	Genus	Species
Ascomycota (n=2)	Ascomycota (n=2)	Aspergillus (n=1)	*Aspergillus spp.*
		Candida (n=1)	*Candida albicans*
Basidiomycota (n=2)	Basidiomycota (n=2)	Cryptococcus (n=2)	*Cryptococcus gattii*
			Cryptococcus neoformans
Microsporidia (n=2)	Microsporidia (n=2)	Encephalitozoon (n=1)	*Encephalitozoon cuniculi*
		Enterocytozoon (n=1)	*Enterocytozoon bieneusi*
Zoopagomycota (n=1)	Zoopagomycota (n=1)	Conidiobolus (n=1)	*Conidiobolus spp.*

Figure 4. Bar chart of the taxonomy for the fungi present in the final list of micro-organisms.

Class	Family	Genus	Species
Apicomplexa (n=2)	Apicomplexa (n=2)	Cryptosporidium (n=2)	*Cryptosporidium hominis*
			Cryptosporidium parvum
Ciliophora (n=1)	Ciliophora (n=1)	Balantioides (n=1)	*Balantioides coli*
Euglenozoa (n=1)	Euglenozoa (n=1)	Leishmania (n=1)	*Leishmania donovani*
Mesomycetozoea (n=1)	Rhinosporidiaceae (n=1)	Rhinosporidium (n=1)	*Rhinosporidium seeberi*
Parabasalia (n=1)	Parabasalia (n=1)	Pentatrichomonas (n=1)	*Pentatrichomonas hominis*

Figure 5. Bar chart of the taxonomy for the protozoa present in the final list of micro-organisms.

Table 3. Highest-scoring micro-organisms, sorted by pneumonia score, respiratory disease type score, immune status score, strength of evidence and expert score, in that order.

Organism	Pneumonia type score (max. 3)	Respiratory disease type score (max. 3)	Immune status score (max. 2)	Evidence strength score (max. 3)	Expert Score Mean (max. 4)	Expert Score Variance	N of experts that scored organism
Kingdom bacteria							
Moraxella spp.	3	3	2	3	2.75	1.58	4
Chlamydia psittaci	3	3	2	3	2.67	1.07	6
Staphylococcus aureus	3	3	2	3	2.60	1.30	5
Streptococcus pneumoniae	3	3	2	3	2.60	1.80	5
Escherichia coli	3	3	2	3	2.40	1.80	5
Klebsiella pneumoniae	3	3	2	3	2.20	0.70	5
Pseudomonas aeruginosa	3	3	2	3	2.00	0.50	5
Listeria monocytogenes	3	3	2	3	1.83	1.37	6
Prescottella equi	3	3	2	3	1.67	0.33	3
Mycobacterium spp.	3	3	2	3	1.67	0.33	3
Clostridioides difficile	3	3	2	3	1.60	0.80	5
Aeromonas spp.	3	3	2	3	1.33	0.33	3
Acinetobacter baumannii	3	3	2	3	1.25	0.25	4
Kingdom viruses							
Orthopneumovirus bovis	3	3	2	3	2.17	0.57	6
Mastadenovirus *spp.*	3	3	2	3	2.00	0.00	3
Kingdom gungi							
Cryptococcus neoformans	3	3	2	2	1.80	0.20	5
Aspergillus spp.	3	3	1	3	2.00	0.50	5
Kingdom protozoa							
Pentatrichomonas hominis	1	3	1	1	1.00	0.00	2
Cryptosporidium parvum	1	1	2	2	1.75	2.25	4

Escherichia coli, and *Klebsiella pneumoniae* are among the highest scoring bacteria. These micro-organisms have the maximum score on all four categories of the scoring system from Table 2 and have a mean expert score of above 2.00 (Table 3). Within the viruses, Orthopneumovirus bovis and Mastadenovirus species were the highest scoring organisms. In general, the scores for bacteria and viruses were higher than the scores for the micro-organisms within the kingdom of protozoa and fungi (Table 3, Supplementary File 4). The gram-negative bacterium *Chlamydia abortus*, which scored low in terms of evidence strength (score of 1), received the highest mean score by the experts (mean score of 2.83) out of all included organisms (Supplementary File 4). The list also included organisms such as Picobirnavirus, of which nearly all questioned experts could not give an opinion about infection risks (Supplementary File 4).

Discussion

The objective of this literature review was to explore which micro-organisms have been described in goats, can be present on goat farms and have been reported to cause pneumonia and/or respiratory symptoms in humans. This literature study was intended as the first step to give direction to further prospective study designs elucidating the etiology of the increased CAP risk around goat farms in the Netherlands.

The different phases from this literature study resulted in a final list of 96 micro-organisms (76 bacteria, 7 viruses, 7 fungi, and 6 protozoa) related to goats and human respiratory disease. Among the most commonly typical-identified causes of CAP in general literature [21,22], there are many that occur also in the high-scoring regions of our list (even without the additional ranking of the expert opinions), such as *Streptococcus pneumoniae, Moraxella spp.* and *Staphylococcus aureus*. Gammaproteobacteria and Bacilli were the most abundant classes of bacteria in our final organism list. They both contain typical CAP-inducing organisms, despite both classes being known for pathogens more related to other infectious diseases besides CAP. The top-scoring micro-organisms also include atypical CAP causes. For example, *Chlamydia psittaci* is the second highest scoring bacterium when combining both the literature scoring system and the external expert score. This bacterium is the cause of human psittacosis, a zoonosis with CAP as the most important clinical presentation. Transmission occurs mainly through infected bird species. Goats have been reported as a potential source of human psittacosis, although the strength of evidence was considered very low [23]. The related pathogen *Chlamydia abortus* received the highest mean score from the expert panel out of all included micro-organisms but scored low on the evidence strength score as the bacterium was only reported as a human cause of pneumonia in a single case report. Noteworthy is that in this case report of human pneumonia, aerogenic transmission of *Chlamydia abortus* by infected goats was considered as a likely causal scenario [24]. Among the fungi and protozoa, there were pathogens on our final organism list that are more commonly associated with other diseases as well, such as the meningitis-inducing *Cryptococcus spp.* and Simplexviruses [25,26], the diarrhoea-associated *Enterocytozoon bieneusi* [27,28], and the eukaryotic pathogen responsible for rhinosporidiosis, *Rhinosporidium seeberi* [29]. It should be noted that a goat micro-organism could either directly cause disease (pathogenic) or alternatively trigger a dysbiosis allowing opportunistic human pathogens to cause disease. The latter might be the case for some of the atypical and rarer micro-organisms in this list.

Though the top-scoring organisms shown in Table 3 are the most likely organisms to cause CAP in humans according to the searched literature and experts, the full list of organisms in Supplementary file 4 should be considered when performing additional investigations. Moreover, apart from the exclusion criteria, the scores given here only serve to prioritize organisms, not to rule out any one of them. It should also be noted that the approach used here only documents already described organisms, not pathogens not described before or identified very recently, or organisms that thus far have been described in only one of the two hosts (human or goat). The strategy used in this research can therefore create a blind spot. As a validation step, we presented our list of micro-organisms to an expert panel in which they could give their opinion about the likelihood of the organism being the cause of CAP. These expert opinions can be a valuable asset when literature description of a disease is limited. Additionally, differences between published literature and expert views could indicate a disbalance between published literature and current knowledge. However, we did not explicitly ask the experts to identify any micro-organisms that in their opinion could be the cause of CAP around goat farms, but that were not in the final list based on the literature. We used the expert opinion scores to further prioritize the organisms based on the literature scoring system. Still, there were discrepancies between the expert judgements as some of the organisms had a large variance in scores between the experts. For example, the largest variance was seen in *Cryptosporidium parvum*, with a variance of 2.25. Here, there was 1 expert that scored a 4 and there

were 3 experts that scored a 1. This is likely at least in part due to the different expertise fields of the experts. The frequency at which an organism is encountered and the importance of that organism in their expertise field may significantly influence their view on the likelihood of it being the causative organism, and differs between, for example, veterinarians and clinical virologists. We did ask the experts to motivate their assigned score based on aspects such as the prevalence, clinical disease picture, and aerogenic transmission possibility, however, this was not always answered in great detail. Since it was not possible to determine whether an outlier answer was based e.g. on more detailed knowledge or a lack of expertise, all answers were considered equally, and the literature-based criteria were considered first in the ranking of the micro-organisms.

In phase 1, no quality assessment was performed for the publications as it was considered better not to be strict in the initial selection of micro-organisms for phase 2. This means that in some articles found in phase 1, the laboratory methods for isolation and identification of organisms were not of the highest standards, and in some cases additional clinical information about the animals was lacking. In exceptional cases, this could mean that the authors of these articles have erroneously reported an organism. In phase 2, rather than a quality assessment for each individual paper, the authors chose to add a score on the overall scale of evidence presented in the articles linking the micro-organism to human respiratory disease (i.e. a distinction between review and large studies, case reports describing multiple cases and single-case reports). Another factor impacting quality is the description and availability of causative organism determination in articles. One-to-one patient and pathogen data can generally only be found in supplementary files, if available at all. More clearly linked metadata can help discover patterns in pathogen occurrence. Furthermore, laboratory determination methods of causative organisms vary greatly between articles, as well as the human tissue used for the determination. Both among the high-scoring reviews (top of the final organism list) and the low-scoring articles (bottom of the final organism list) data about causative pathogen identification was often incomplete. On the low end, this could suggest false determination, especially if the researchers relied on a single technique for diagnostics and the result was a pathogen previously not associated with pneumonia. A standard practice with multiple types of diagnostics (e.g. culture and PCR or culture and sequencing) based on multiple types of patient material (e.g. BAL and sputum or BAL and blood) could provide more reliable diagnosis and help further epidemiological research into the etiology of CAP.

The consistent association between increased CAP incidence and a shorter residential distance to goat farms suggests that there are one or more unique factors present on goat farms compared to other livestock farms. Dutch domestic goat farms harbour a large variety in housing types, feed and bedding materials, supply and amount of feed and bedding, walkways, as well as goat breeds. Furthermore, differing mechanisms and machines used in the regular and irregular activities on these farms add to the complexity of Dutch goat farming. It may be reasonable to assume that goats and their excreta are the only unique factors that are not also present on other animal farms and therefore the most likely source of a micro-organism potentially causing CAP. As such, this research focused on micro-organisms found in goats and goat excreta only. However, micro-organisms causing goat farm-related CAP in humans could also come from non-goat materials if goat farm specific management practices allow for an increase in emission of the micro-organism compared to other livestock farms. Non-infectious causes, such as particulate matter emissions and endotoxins, might also play a role in the explanation of the increased pneumonia risk around goat farms. These farm emissions might act as predisposing factors, as previous studies demonstrated that inhalation of fine dust and particulate matter can lead to increased susceptibility for airborne infections [30–33]. However, these non-infectious causes were beyond the scope of this literature study.

The organisms that are currently subject to active monitoring in small ruminants were excluded in this research. The Dutch laws, based in part on EU law [34], for notifiable diseases and pathogens causing them, have some overlap between humans [35] and small ruminants [36,37], but not all disease are notifiable in the two domains. The following pathogens listed here differ between animal and human notifications: *Campylobacter spp*., *Leptospira spp*., *Listeria spp*., *Mycoplasma mycoides*, *Salmonella spp*. and *Yersinia* species. Consequently, future studies may not reflect the results given from phase 2 onwards, due to changes in the monitoring programmes.

Conclusion

The final list of 96 micro-organisms depicts a comprehensive overview of the currently known micro-organisms occurring in goats which can cause human respiratory symptoms. On this list, bacteria are far more numerous than viruses, fungi, and protozoa combined. Furthermore, the scores assigned are generally higher for bacteria and viruses than those for fungi and protozoa. No unambiguous conclusion on the cause of the increased CAP risk around goat farms can be drawn solely based on these results. Further research is currently being carried out adopting a broad approach that includes analysing samples from goat farms, patients with CAP and from healthy neighbouring residents.

Acknowledgments

We would like to thank Rob van Spronsen (National Institute for Public Health and the Environment) for his assistance with the search strategies and performing the literature search. We thank the participants in our expert panel: Barry Rockx (Wageningen Bioveterinary Research), Daan Notermans (National Institute for Public Health and the Environment), Ferry Hagen (Westerdijk Fungal Biodiversity Institute), George Sips (formerly National Institute for Public Health and the Environment), Jos Houbraken (Westerdijk Fungal Biodiversity Institute), Jos Rooijackers (Netherlands Expertise Centre for Occupational Respiratory Disorders), Karianne Peterson (Royal Animal Health Services), Mariet Feltkamp (Leiden University Medical Center), Wim van der Hoek (formerly at National Institute for Public Health and the Environment), and Yvette de Geus (Utrecht University). We also thank Piet Vellema (Royal Animal Health Services), Herman van Roermund (Wageningen Bioveterinary Research), Ed van Klink (Wageningen Bioveterinary Research), and Kees van Maanen (Royal Animal Health Services) for their advice in the first phase of this literature review.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This study is part of the Veehouderij en Gezondheid omwonenden (VGO-III) study (Dutch acronym for Livestock Farming and Neighbouring Residents' Health) funded by the Ministry of Health, Welfare and Sports and the Ministry of Agriculture, Nature and Food Quality of the Netherlands.

References

[1] Heederik D, Yzermans J, Opstal - van Winden A, et al. Mogelijke effecten van intensieve veehouderij op de gezondheid van omwonenden: onderzoek naar potentiele blootstelling en gezondheidsproblemen. IRAS, Utrecht University, Nivel, RIVM; 2011.

[2] Maassen K, Smit L, Wouters I, et al. Veehouderij en Gezondheid Omwonenden. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu (RIVM); 2016.

[3] Freidl GS, Spruijt IT, Borlée F, et al. Livestock-associated risk factors for pneumonia in an area of intensive animal farming in the Netherlands. PLOS ONE. 2017;12(3):e0174796. doi: 10.1371/journal.pone.0174796

[4] Kalkowska DA, Boender GJ, Smit LAM, et al. Associations between pneumonia and residential distance to livestock farms over a five-year period in a large population-based study. PLOS ONE. 2018;13(7):e0200813. doi: 10.1371/journal.pone.0200813

[5] IJzermans CJ, Smit LAM, Heederik DJJ, et al. Longontsteking in de nabijheid van geiten- en pluimveehouderijen; actualisering van gegevens uit huisartspraktijken 2014–2016. Utrecht: Nivel; 2018.

[6] IJzermans J, Smit L, Dückers M, et al. Longontsteking in de nabijheid van geitenhouderijen in Noord-Brabant en Limburg: actualisering van gegevens uit huisartspraktijken 2017 - 2019. Utrecht: Nivel; 2021.

[7] Smit L, Huss A, Jacobs J,et al. Veehouderij en Gezondheid Omwonenden III: longontsteking in de nabijheid van geiten- en pluimveehouderijen in Gelderland, Overijssel en Utrecht 2014–2017. Utrecht: IRAS; 2019.

[8] Smit LAM, van der Sman-de Beer F, Opstal-van Winden AWJ, et al. Q fever and pneumonia in an area with a high livestock density: a large population-based study. PLOS ONE. 2012;7(6):e38843. doi: 10.1371/journal.pone.0038843

[9] Dijkstra F, van der Hoek W, Wijers N, et al. The 2007–2010 Q fever epidemic in the Netherlands: characteristics of notified acute Q fever patients and the association with dairy goat farming. FEMS Immunol Med Microbiol. 2012;64(1):3–12. doi: 10.1111/j.1574-695X.2011.00876.x

[10] Roest HIJ, Tilburg JJHC, Van Der Hoek W, et al. The Q fever epidemic in the Netherlands: history, onset, response and reflection. Epidemiol Infect. 2011;139(1):1–12. doi: 10.1017/S0950268810002268

[11] Hagenaars T, Hoeksma P, de Roda Husman AM, et al. Veehouderij en Gezondheid Omwonenden (aanvullende studies): Analyse van gezondheidseffecten, risicofactoren en uitstoot van bio-aerosolen. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu (RIVM); 2017 2017 06 16.

[12] Dutch ministry of agriculture nature and food quality. Available from: https://www.rijksoverheid.nl/onderwerpen/diergezondheid/vraag-en-antwoord/kleine-herkauwers

[13] Pijnacker R, Reimerink J, Smit LAM, et al. Remarkable spatial variation in the seroprevalence of Coxiella burnetii after a large Q fever epidemic. BMC Infect Dis. 2017;17(1):725. doi: 10.1186/s12879-017-2813-y

[14] ThJM V, Hopstaken RM, Prins JM, et al. NHG-Standaard Acuut hoesten (Eerste herziening). 2011 Available from: https://richtlijnen.nhg.org/standaarden/acuut-hoesten

[15] van Gageldonk-Lafeber AB, Wever PC, van der Lubben IM, et al. The aetiology of community-acquired pneumonia and implications for patient management. Neth J Med. 2013;71(8):418–425.

[16] Roof I, van Gageldonk-Lafeber Ab, Zomer TP, et al. Identified micro-organisms in hospitalized community-acquired pneumonia patients living near goat and poultry farms. Pneumonia. 2021;13(1):13. doi: 10.1186/s41479-021-00091-w

[17] Limburg P. Omgevingsverordening [Available from: https://www.limburg.nl/onderwerpen/omgeving/omgevingsverordening/

[18] Noord-Brabant P. Tijdelijke stop op nieuwe geitenstallen. 2017 [Available from: https://www.brabant.nl/onderwerpen/landbouw-en-voedsel/veehouderij/beleid-veehouderij/tijdelijke-stop-op-nieuwe-geitenstallen

[19] ANP. Ook Overijssel zet rem op geitenboerderijnen [Overijssel puts a stop on goat farms as well. Binnenlands Bestuur Sijthoff Media Groep Amsterdam. 2018.

[20] Embase. [Available from: https://www.embase.com/

[21] Ieven M, Coenen S, Loens K, et al. Aetiology of lower respiratory tract infection in adults in primary care: a prospective study in 11 European countries. Clin Microbiol And Infect. 2018;24(11):1158–1163. doi: 10.1016/j.cmi.2018.02.004

[22] Shoar S, Musher DM. Etiology of community-acquired pneumonia in adults: a systematic review. Pneumonia. 2020;12(1):11. doi: 10.1186/s41479-020-00074-3
[23] Hogerwerf L, Roof I, de Jong Mjk, et al. Animal sources for zoonotic transmission of psittacosis: a systematic review. BMC Infect Dis. 2020;20(1):192. doi: 10.1186/s12879-020-4918-y
[24] Imkamp F, Albini S, Karbach M, et al. Zoonotic chlamydiae as rare causes of severe pneumonia. Swiss Med Wkly. 2022;152(102):w30102. doi: 10.4414/SMW.2022.w30102
[25] Li Y, Zou M, Yin J, et al. Epidemiological, and clinical characteristics of patients with cryptococcal meningitis at a tertiary hospital in China: a 6-year retrospective analysis. Front Microbiol. 2020;11:1837. doi: 10.3389/fmicb.2020.01837
[26] Reichman RC. Herpes simplex virus infections. Eur J Clin Microbiol. 1984;3(5):399–405. doi: 10.1007/BF02017359
[27] Thellier M, Breton J. Enterocytozoon bieneusi in human and animals, focus on laboratory identification and molecular epidemiology. Parasite. 2008;15(3):349–358. doi: 10.1051/parasite/2008153349
[28] Wanke CA, DeGirolami P, Federman M. Enterocytozoon bieneusi infection and diarrheal disease in patients who were not infected with human immunodeficiency virus: case report and review. Clin Infect Dis. 1996;23(4):816–818. doi: 10.1093/clinids/23.4.816
[29] Arias AF, Romero SD, Garcés CG. Case report: rhinosporidiosis literature review. Am J Trop Med Hyg. 2020;104(2):708–711. doi: 10.4269/ajtmh.20-0291
[30] Liu D, Mariman R, Gerlofs-Nijland ME, et al. Microbiome composition of airborne particulate matter from livestock farms and their effect on innate immune receptors and cells. Sci Total Environ. 2019;688:1298–1307. doi: 10.1016/j.scitotenv.2019.06.217
[31] Zelikoff JT, Chen LC, Cohen MD, et al. Effects of inhaled ambient particulate matter on pulmonary antimicrobial immune defense. Inhal Toxicol. 2003;15(2):131–150. doi: 10.1080/08958370304478
[32] Sahlander K, Larsson K, Palmberg L, et al. Daily exposure to dust alters innate immunity. PLoS One. 2012;7(2):e31646. doi: 10.1371/journal.pone.0031646
[33] Smit LAM, Boender GJ, de Steenhuijsen Piters WAA, et al. Increased risk of pneumonia in residents living near poultry farms: does the upper respiratory tract microbiota play a role? Pneumonia. 2017;9(1):3. doi: 10.1186/s41479-017-0027-0
[34] Commission implementing regulation (EU) 2018/1882 of 3 December 2018 on the application of certain disease prevention and control rules to categories of listed diseases and establishing a list of species and groups of species posing a considerable risk for the spread of those listed diseases [Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02018R1882-20220705
[35] Wet publieke gezondheid [Available from: https://wetten.overheid.nl/BWBR0024705/2022-10-10
[36] Regeling diergezondheid [Available from: https://wetten.overheid.nl/BWBR0045053/2022-04-30#Hoofdstuk2_Artikel2.1
[37] Regeling houders van dieren [Available from: https://wetten.overheid.nl/BWBR0035248/2023-01-01#Hoofdstuk3a