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Human–livestock contacts and their relationship to transmission of zoonotic pathogens, a systematic review of literature

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ABSTRACT

Background: Micro-organisms transmitted from vertebrate animals – including livestock – to humans account for an estimated 60% of human pathogens. Micro-organisms can be transmitted through inhalation, ingestion, via conjunctiva or physical contact. Close contact with animals is crucial for transmission. The role of intensity and type of contact patterns between livestock and humans for disease transmission is poorly understood. In this systematic review we aimed to summarise current knowledge regarding patterns of human–livestock contacts and their role in micro-organism transmission.
Methods: We included peer-reviewed publications published between 1996 and 2014 in our systematic review if they reported on human–livestock contacts, human cases of livestock-related zoonotic diseases or serological epidemiology of zoonotic diseases in human samples. We extracted any information pertaining the type and intensity of human–livestock contacts and associated zoonoses.
Results: 1522 papers were identified, 75 were included: 7 reported on incidental zoonoses after brief animal–human contacts (e.g. farm visits), 10 on environmental exposures and 15 on zoonoses in developing countries where backyard livestock keeping is still customary. 43 studies reported zoonotic risks in different occupations. Occupations at risk included veterinarians, culling personnel, slaughterhouse workers and farmers. For culling personnel, more hours exposed to livestock resulted in more frequent occurrence of transmission. Slaughterhouse workers in contact with live animals were more often positive for zoonotic micro-organisms compared to co-workers only exposed to carcasses. Overall, little information was available about the actual mode of micro-organism transmission.
Conclusions: Little is known about the intensity and type of contact patterns between livestock and humans that result in micro-organism transmission. Studies performed in occupational settings provide some, but limited evidence of exposure response-like relationships for livestock–human contact and micro-organism transmission. Better understanding of contact patterns driving micro-organism transmission from animals to humans is needed to provide options for prevention and thus deserves more attention.

Contents

Abbreviations: LA, Livestock-associated; MRSA, Methicillin-Resistant *Staphylococcus aureus*; PPE, Personal Protective Equipment; VTEC, VeroToxin-producing *Escherichia coli*.

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1. Introduction

Zoonotic infectious diseases – diseases transmitted from vertebrate animals to humans – account for an estimated 60% of all human infectious diseases [1]. The rise of zoonotic diseases in humans began after the introduction of agriculture and the domestication of animals when humans started living in large numbers together, in close contact with other vertebrate animals [2,3]. Nowadays, livestock associated infectious diseases are still a major threat to human health, as recently illustrated by the outbreak of pig origin H1N1 influenza A pandemic in 2009 or the emergence of camel-origin Middle-East Respiratory Syndrome Coronavirus [4–6]. The occurrence of a zoonotic disease may lead to large economic losses in the agricultural sector [7–14]. When it comes to recent emerging infectious diseases, zoonoses again account for the majority of the newly introduced infectious diseases to the human population. Although zoonoses with a wildlife origin dominate among emerging pathogens, livestock associated zoonotic diseases occur mainly in densely human populated areas in the world [15] and can therefore have a considerable public health impact. In developing countries humans often live close to their livestock [16–18]; in developed countries there are mainly occupational contacts with large numbers of live [19], ill [20] or dead animals [21–24], but there are also reports of micro-organism transmissions via the environment [25,26] or after brief contact [27,28].

Contact with livestock animals can lead to transmission of micro-organisms by inhalation, ingestion, via conjunctiva, or during incidents such as biting or other injuries inflicted by animals [29]. Furthermore, aerosols contaminated with micro-organisms from respiratory [30–34] or fluid sources [35], can play an important role in the transmission of micro-organisms between humans [30–35], but also from animals to humans. Aerosols have been suggested to play a role in micro-organism transmission over very short distances, sometimes as a parallel route to direct contact [30]. It is thus clear that for transmission of zoonotic diseases to occur, the presence of animals or some type of contact with (livestock-) animals is crucial. Initiatives to control livestock-associated zoonotic diseases are already in place, as reviewed by Zinnstag et al. [36] and others [37,38]. However, better understanding of contact patterns driving micro-organism transmission from animals to humans is needed to provide options for prevention and thus deserves more attention. Therefore, in this study we reviewed current literature on livestock-associated zoonotic diseases, to evaluate current knowledge regarding human–livestock contact patterns. We conducted a systematic review to identify papers reporting on livestock-related zoonoses. We searched the publications regarding reports of contact patterns between livestock animals and humans that led to a transmission of infectious diseases or micro-organisms from livestock to man.

2. Methods

We searched EMBASE and Medline for reports on livestock associated (LA) zoonoses combined with human–livestock interactions. Our search terms and selection steps are given in Appendix A. We also scrutinised references of the included publications. Publications until the 22nd of September 2014 were included.

We included publications reporting on zoonoses from livestock animals, human–livestock contacts, human–livestock contacts and infectious disease transmission, and in case of multiple human LA-zoonosis case reports, exact DNA matches between livestock and human isolates. Peer-reviewed, original research in English, Dutch or German language was included.

We excluded articles describing; vector borne diseases, experimental laboratory studies, xenotransplantation-related diseases, reports on diseases with livestock as a dead-end host (e.g. Rabies, Schistosomiasis, Malaria, and Trypanosoma), papers evaluating diseases linked to wildlife hosts (e.g. bat-related and primate (bushmeat)-related diseases), as well as papers discussing food related zoonosis outbreaks. These articles were excluded because these zoonotic pathogens, are not transmitted through direct contact between livestock and humans.

Selected papers were either articles or articles in press, other publication types were removed from the selection. Titles and abstracts of retrieved publications were evaluated regarding the inclusion and exclusion criteria by GK together with RAC.

3. Results

We included seventy-five articles (Fig. 1) and an overview is given in Table 1. Eighteen infectious agents were studied in the selected papers: Methicillin Resistant *Staphylococcus aureus* (MRSA) was studied most often (N = 20 papers), followed by Avian Influenza (AI, N = 19) and *Coxiella burnetii* (*C. burnetii*, N = 10). An overview of micro-organisms and their associated host animals is provided in Table 2. The results are divided in two sections; occupational contact and non-occupational contact. This division was based on the level of reported or assumed contact between humans and livestock, with the assumption that people in livestock handling occupations have greater exposure. Publications reporting on zoonoses from developing countries are classified within the non-occupational contact section, because occupations in these countries are difficult to specify and livestock exposure is not comparable to occupational livestock exposure in developed countries.

3.1. Occupational contact

The 42 selected papers in this section all originate from developed countries. Human–livestock contacts mainly occurred in occupational settings and concerned primarily veterinarians and veterinary medicine students, people culling animals for zoonotic outbreak control, hereafter named 'cullers', slaughterhouse workers and farmers and their family members. Publications discussed occurrence of: MRSA (N = 18 papers), Avian Influenza (N = 10), *C. burnetti* (N = 5), Swine Influenza (N = 3), Hepatitis E virus (N = 2), Antibiotic Resistant *E. coli*, Avian Metapneumovirus, *Brucella* spp., *Chlamydophila psittaci* (*C. psittaci*), and *Leptospira* spp. (all N = 1).

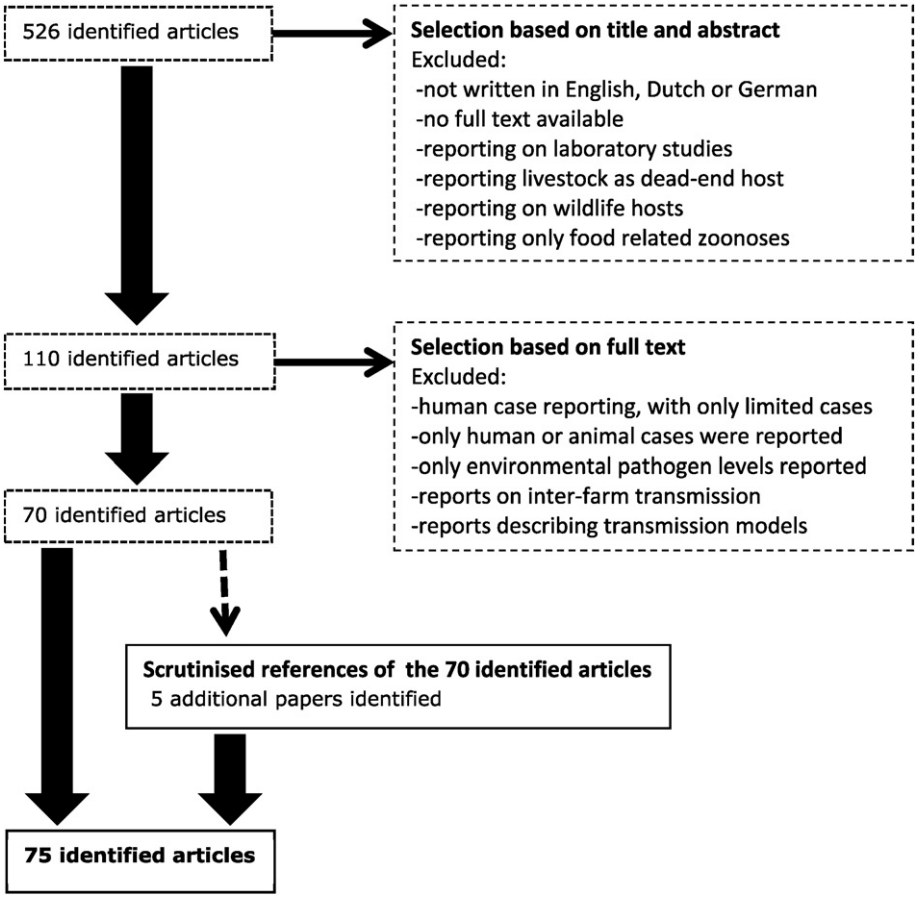

Fig. 1. Flowchart of the selection steps, after the Embase and Medline search and filtering procedures.

3.1.1. Veterinarians and veterinary medicine students

With respect to contact with infected animals, veterinarians and veterinary medicine students have an increased risk of acquiring infections. Veterinarians are the first people who come in contact with infected animals in case of an outbreak [39]. They are at increased risk to acquire a wide range of zoonotic infections, as was illustrated in a study among veterinarians from South-Africa [20]. In Denmark, 36% of veterinarians and 11% of other occupationally exposed people in contact with dairy cattle were found positive for serological markers of *C. burnetii*; these markers are indicative of (previous-) infection after exposure to infected animals [40]. Seroconversion for *C. burnetii* was found in 18.7% of students whom provided a blood sample in the study of De Rooij et al. A clear exposure–response relationship was found for the prevalence of converted sera which increased with every year the students advanced in their education within the study specialisation 'farm animals' [41]. In 44% of a cohort of Dutch veterinarians, LA-MRSA carriage was found on at least one of the repetitive measuring moments, 13% of all participants were persistent carriers of LA-MRSA. This makes MRSA carriage among veterinarians extremely high, because in the general Dutch population MRSA carriage is very rare (<0.1%) [42]. In veterinary medicine students MRSA carriage was detected after contact with MRSA carrying horses [43].

3.1.2. Cullers

After the first cases of a zoonotic outbreak are identified [39], control measure sometimes consists of the culling of the entire flock or herd on the affected farm. Cullers are usually equipped with personal protective equipment and receive personal hygiene instructions, although it has been shown that such measures can reduce exposure, but are not fully protective [44,45]. Secondary cases among contacts of cullers can also occur, as reported after a large outbreak of H7N7 Avian Influenza in Dutch poultry farms in 2003 [46]. After this outbreak, risk factors for the acquisition [39] and transmission [47] of an infection were 'clinical inspection of poultry in the area surrounding infected flocks' [39,47], and 'active culling during depopulation' [39]. A more quantitative relationship was reported by Whelan et al. during the large Q-fever outbreak in the Netherlands between 2007 and 2009 [48]. In cullers working on Q-fever infected goat farms, an exposure-response-like relationship between the 'total number of hours worked inside the farm perimeter' and 'working mostly inside stables' and the risk of seroconversion for *C. burnetii* markers was discovered [48].

3.1.3. Slaughterhouse workers

The most relevant observations in this occupational group are the exposure–response relationships for micro-organism carriage or transmission found in slaughterhouse personnel, in particular those individuals in close contact with live animals [21–24]. Four reports, three addressing MRSA and one *C. psittaci*, in both pig and poultry slaughterhouses, demonstrated clear relationships between the position of the workers on the slaughter line and carriage of micro-organisms or occurrence of disease [21–24]. This was supported by evidence for both temporal and spatial variations for micro-organism levels in air, on gloves and surface contamination. Temporal, because during the day an increase of MRSA and *C. psittaci* environmental levels were shown [22,24]. Spatial, because people at the start of the slaughter line working with live animals, were more often found to be carriers of MRSA, compared to people only working with carcasses [21–24].

That living animals were the main risk factor for carriage or infections with micro-organisms was also shown by Myers et al.: they reported that farmers showed the highest Swine Influenza H1N1 specific titres in their blood, compared to a pool of veterinarians, control subjects and slaughterhouse workers [49].

Table 1
Overview of the selected publications. The columns depict; first author, year of publication, country where the study was performed, study category, occupational exposure (YES/NO, YES versus NO) with N: number of people exposed, micro-organism studied, livestock involved if (YES): animals are screened for a micro-organism, description of the people involved, main study conclusion, reference number. There are three study categories; seroepidemiology reports on studies where blood samples were analysed for specific disease markers, risk analyses reports on specific risk factors for acquiring a micro-organism and source attribution, studies where the source of specific micro-organism is identified after human cases or carriage of the specified micro-organism. For occupational exposure (YES or NO) the number of either occupational exposed, non-occupational exposed or occupational versus non-occupational exposed people are given. The column with the description of people includes occupations and when available also descriptions of control groups.

Author	Year	Country	Study category	Occupational exposure (N=)	Micro-organism	Animals involved (screened?)	People involved	Main outcomes	Reference number
Al-Ani	2004	Jordan	Risk analyses	YES vs. NO (100 vs. 800)	*Brucella* spp.	Sheep, goats (YES)	Vets[a], sheepherders, lab technicians	More *Brucella* seroprevalence in human high risk group	[85]
Bos	2010	Netherlands	Source attribution	YES (872)	H7N7 Avian Influenza	Turkeys, layers, broilers	Cullers, cleaners, biosecurity managers	High infection probability for exposure infected poultry	[39]
Bosnjak	2010	Denmark	Seroepidemiology	YES (359)	*Coxiella burnetii*	Cattle	Farmers, vets[a], inseminators, Hoof-trimmers	34% in vets seroconverted for *C. burnetti*, 11% others	[40]
Buxton-Bridges	2002	Hong Kong	Seroepidemiology	YES (1525/293)	H5N1 Avian Influenza	Poultry	Poultry workers, government workers (cullers)	More poultry related tasks, more anti-H5 seropositivity	[61]
Castillo-Neyra	2014	USA, NC	Risk analyses	YES vs. NO (162 vs. 63, 111)	MRSA, MDRSA[b]	Pigs	Processing plant workers, family, residents	Processing workers, more MRSA, MDR-SA, than controls	[51]
De Marco	2013	Italy	Risk analyses	YES vs. NO (123 vs. 379)	Swine Influenza H1N1pandemic[c], H1N1swine[d]	Pigs	Swine workers, Non-exposed controls	Exposure H1N1sw gives cross-immunity for H1N1pdm	[63]
De Rooij	2012	Netherlands	Seroepidemiology	YES (674)	*Coxiella burnetii*	"Farm animals"[k]	Veterinary medicine students	18,7% of vet. Students seroconverted for *C. burnetii*	[41]
Di Trani	2012	Italy	Risk analyses	YES vs. NO (188 vs. 379)	H5 and H7 Avian Influenza	Poultry	Poultry workers, Non-exposed controls	Poultry workers more H7-AB positive, than controls	[60]
Dickx	2010	Belgium	Seroepidemiology	YES (53, 38)	*Chlamydophila psittaci*	Chickens, turkeys	Chicken and turkey slaughterhouse workers	Live animal contact risk, for *C. psittaci* seropositivity	[24]
Gaede	2008	Germany	Source attribution	YES (24)	*Chlamydophila psittaci*	Poultry (YES)	Poultry owners	Genotype *C. psittaci* similar in poultry and humans	[101]
Geenen	2013	Netherlands	Source attribution	YES (145)	MRSA	Broilers (YES)	Workers and residents poultry farm	People on MRSA positive farms, also MRSA carriers	[72]
Gilbert	2011	Netherlands	Source attribution	YES (341)	MRSA	Pigs (YES)	Pig slaughterhouse workers	Working with live animals, risk for human MRSA carriage	[21]
Gilpin	2008	New-Zealand	Source attribution	YES and NO (7)	*Campylobacter* spp.	Cattle (YES)	Dairy workers, resident children	Cattle found *Campylobacter* positive, after human cases	[102]
Gordoncillo	2011	USA, MI	Source attribution	NO	MRSA	Pigs (YES)	Hobby pig owners	Matched hobby pig farmers-pigs not both MRSA carriers	[73]
Graveland	2011	Netherlands	Seroepidemiology	YES (155)	MRSA	Veal calves	Veal calve farmers	Human MRSA carriage, reduced when cattle was absent	[19]
Gray	2008	USA, IA	Risk analyses	YES vs. NO (385 vs. 418, 66)	Avian Influenza	Poultry	Agricultural workers, University controls	Avian Influenza seropositivity in poultry workers	[58]
Gummow	2003	South-Africa	Interview study	YES (88)	All zoonotic diseases	"Farm animals"[k]	University employed vets[a]	Wide range of zoonoses reported by vets in their career	[20]
Hackert	2012	Netherlands	Risk analyses	YES vs. NO (26, 50, 14 vs. 253)	*Coxiella burnetii*	Goats	Farm residents/workers, visitors, household contacts	Seroconversion *C. burnetii* related to farm distance	[25]
Helmy	2013	Egypt	Source attribution	NO (165)	*Cryptosporidium parvum*	Cattle, buffalo (YES)	Farm children	LA-*Cryptosporidium* related to children's diarrhoea cases	[18]
Hoek	2008	United Kingdom	Source attribution	NO (20)	*Cryptosporidium parvum*	Sheep (YES)	Students and teachers camping on a farm	No pathway found for farm visit *C. parvum* infections	[93]
Huijbers	2013	Netherlands	Risk analyses	NO (1025)	ESBL[l]-*Enterobacteriaceae*	Poultry	Residents in a high and low poultry density area	5.1% ESBL-positive, lower risk ESBL carriage near poultry	[98]
Huijsdens	2006	Netherlands	Risk analyses	YES vs. NO (3 vs. 3)	MRSA	Pigs	Farmworkers and family members	Molecular analyses link human MRSA to pigs	[64]
Huo	2012	China (Jiangsu)	Seroepidemiology	YES (306)	H5N1 Avian Influenza	Poultry	Poultry workers	Poultry workers seropositive for Avian Influenza	[86]
Kandeel	2010	Egypt	Seroepidemiology	NO (6355)	H5N1 Avian Influenza	Poultry	All people having AI symptoms	Avian Influenza risk factors: rearing, slaughtering poultry	[80]
Kayali	2011	USA	Risk analyses	YES vs. NO (57, 38 vs. 82)	Avian Metapneumovirus	Turkeys	Turkey growers and processing workers, controls	Turkey slaughters Avian Metapneumo virus positive	[53]
Koopmans	2004	Netherlands	Seroepidemiology	YES (453)	H7N7 Avian Influenza	Poultry	Poultry farmers, farmworkers, family	Cullers and contacts seropositive for H7-antibodies	[46]
Köck	2012	Germany	Source attribution	YES (35)	MRSA ST398	Pigs	Pig farmers	59% farmers still MRSA carriers after holidays	[71]

Krumbholtz	2012	Germany	Risk analyses	YES vs. NO (24, 14, 46, 22 vs. 116)	Hepatitis E virus	Pigs	Slaughterers, meat inspectors, farmers, vets[a], controls	Slaughterhouse workers more positive HEV antibodies	[52]
Leibler	2010	USA (MD, VA)	Risk analyses	YES vs. NO (24 vs. 75)	Avian Influenza	Poultry	Poultry workers, agricultural community members	No seropositivity Avian Influenza in US poultry workers	[57]
Liu	2008	China (Pearl river delta)	Descriptive study	n.a.	Avian Influenza, not focus[e]	Chickens, turkeys	Chicken owners	No epidemiology, overview poultry practises China	[16]
Lohiniva	2012	Egypt	Risk analyses	n.a.	H5N1 Avian Influenza	Poultry	Households with chickens	Overview post outbreak measures on poultry practises	[17]
López-Robles	2012	Mexico	Risk analyses	YES vs. NO (62 vs. 63)	Swine Influenza	Pigs	Swine workers, non-exposed controls	Swine workers compared with general public	[62]
Lyytikäinen	1998	Germany	Seroepidemiology	NO (239)	*Coxiella burnetii*	Sheep	All residents in a specific rural area	Specific sheep flock linked to human Q-fever cases	[99]
Manfredi-Selvaggi	1996	Italy	Seroepidemiology	NO (58)	*Coxiella burnetii*	Sheep	All residents in a specific rural area	Passing sheep flock causes human Q-fever outbreak	[100]
Meader	2009	United Kingdom	Seroepidemiology	YES (413)	Hepatitis E virus	Cat, chicken, deer, goat, horse, pig, sheep	UK Farmers Cohort	Animal contact risk factor HEV, pigs not specific	[56]
Milne	1999	United Kingdom	Source attribution	NO (3)	VTEC 0157[f] *Escherichia coli*	Goats, cattle (YES)	Children visiting recreational educational farm	Outbreak *E. coli* O157 linked to public accessible farm	[91]
Ming	2006	China	Source attribution	YES (100 exposed, 30 infected)	*Trichophyton verrucosum*	Cattle (YES)	Animal workers	Cattle and farm workers infected with *T. verrucosum*	[87]
Monno	2009	South-Italy	Risk analyses	YES vs. NO (128 vs. 280)	*Coxiella burnetii*, *Leptospira* spp., *Brucella* spp.	"Farm animals"[k]	Animal workers, vets*, blood donors	*C. burnetii* seroconversion found in Animal workers	[55]
Morgan	2009	United Kingdom	Seroepidemiology	YES (142)	H7N3 Avian Influenza	Poultry	People in contact with live or death infected animals	Incomplete PPE, resulted in significant infection risk	[45]
Mulders	2010	Netherlands	Source attribution	YES (466)	MRSA	Poultry (YES)	Poultry slaughterhouse personal	Working with live animals, risk for human MRSA carriage	[23]
Myers	2006	USA	Risk analyses	YES vs. NO (111, 97, 65 vs. 79)	Swine Influenza	Pigs	Farmers, meat processing workers, vets[a], controls	More SI seroprevalence in work-exposed, than controls	[49]
Okoye	2013	Nigeria	Risk analyses	YES vs. NO (316 vs. 54)	Avian Influenza	Poultry	Farmers, open market workers, controls	No risk factor identified for Avian Influenza transmission	[83]
Oppliger	2012	West-Switzerland	Source attribution	YES (67, 8)	MRSA	Pigs (YES)	Pig farmers, vets[a]	Pig and farmer/vet MRSA similar serotypes	[67]
Ortiz	2006	Nigeria (Kano)	Seroepidemiology	YES (295, 25)	H5N1 Avian Influenza	Poultry	Poultry workers, laboratory workers	No serological evidence for H5N1 infections identified	[82]
Osadebe	2012	USA (CT)	Source attribution	YES	MRSA	Pigs (YES)	Pig farmers	Pigs carried human MRSA serotypes, possible anthroponosis	[74]
Padungtod	2005	North-Thailand	Source attribution	YES and NO (197, 4 and 100, 205)	*Campylobacter*	Chickens, pigs, dairy cattle (YES)	Farm staff, slaughterers, community, diarrhoea patients	*Campylobacter* found in food animals and environments	[111]
Petersen	2012	Denmark	Seroepidemiology	NO	MRSA mecC gene positive[g]	Cattle, sheep	All MRSA samples from national databank	Cattle/sheep contact, possible risk factor mecC MRSA	[97]
Pletinckx	2012	Belgium	Source attribution	YES and NO (10, 10 and 13)	MRSA ST398[h]	Pigs, poultry, cattle, dogs, cats, rodents (YES)	Farmers, vets[a], family members of farmers	Farms LA-MRSA positive, environment, humans, animals	[65]
Puzelli	2005	Italy	Seroepidemiology	YES (983)	Avian Influenza; H7N1 HPAI[i], H7N3 LPAI[j]	Poultry	Poultry workers	Poultry workers H7N3 seropositive,after avian outbreak	[59]
Rabinowitz	2012	Egypt	Source attribution	n.a.	H5N1 Avian Influenza	Poultry, wild birds	All H5N1 confirmed human cases	Comparison animal and human H5N1 data bases	[84]
Radon	2007	Germany	Source attribution	NO (2425)	n.a.	"Farm animals"[k]	Neighbours confined animal feeding operations (CAFO)	Adverse-health effects residents with CAFO < 500 m home	[94]
Schimmer	2012	Netherlands	Seroepidemiology	YES (268)	*Coxiella burnetii*	Goats	People living or working on dairy goat farms	*C. burnetii* seroconversion in farmers, spouses, children	[54]
Schulze	2011	Germany	Source attribution	NO (457)	n.a.	"Farm animals"[k]	Non-farm residents	NH3 as proxy for exposure from CAFOs to residents	[95]
Scott	2005	USA	Source attribution	YES and NO (472)	Antibiotic Resistant *Escherichia coli*	Pigs (YES)	Consumers, pig workers, slaughter-plant workers	No similarity *E. coli* resistance profiles, pigs and humans	[50]
Siwila	2007	Zambia	Source attribution	YES (82, 207)	*Cryptosporidium parvum*	Cattle (YES)	Farm workers, household members	Similar *Cryptosporidium* found in humans and calves	[81]
Skowronski	2007	Canada	Seroepidemiology	YES (167)	H7N3 Avian Influenza	Poultry	Cullers, farmers, family members	PPE should be combined with vaccination, prophylaxis	[44]
Smit	2012	Netherlands	Risk analyses	NO (95,548)	*Coxiella burnetii*	Goats, poultry	Residents, general practitioners data	Poultry risk for pneumonia, goats risk for Q-fever	[26]
Spohr	2011	SW-Germany	Source attribution	YES (9)	MRSA	Cattle, pigs (YES)	People working on cattle farms	MRSA found in every section of the farm and on farmers	[69]

(continued on next page)

Table 1 (*continued*)

Author	Year	Country	Study category	Occupational exposure (N=)	Micro-organism	Animals involved (screened?)	People involved	Main outcomes	Reference number
Te Beest	2011	Netherlands	Source attribution	YES	H7N7 Avian Influenza	Poultry (YES)	People that visited farms during on H7N7 AI outbreak	Humans act as vector for H7N7 between poultry farms	[47]
Thorson	2006	Vietnam	Source attribution	NO (45,478)	Avian Influenza	Poultry	All residents in a specific rural area	Flu-like symptoms linked to handling live, death poultry	[77]
Tissot-Dupont	2005	France	Source attribution	NO (85)	*Coxiella burnetii*	Sheep	All people positive for IgG or IgM against *C. burnetii*	Specific pedagogical farm source Q-fever outbreak	[28]
Trevena	1999	United Kingdom	Source attribution	YES and NO (69)	VTEC 0157[f] *Escherichia coli*	Cattle, pony, dog (YES)	People working, living or visiting a farm	VTEC O157 infections after animal contact, food products	[92]
Uzel	2005	Turkey	Risk analyses	NO (9)	Orf virus	Sheep, goat	People illegally slaughtering animals	Sheep/goat related Orf cases, after feast-of-sacrifice	[90]
Van Cleef	2010	Netherlands	Risk analyses	YES vs. NO (49 vs. 534)	MRSA ST398[h]	Pigs	People living or working on farms, non-farm residents	MRSA ST398 in farm population (26.5%), controls (0.2%)	[96]
Van Cleef	2011	Netherlands	Risk analyses	YES (40)	MRSA	Veal calves	Fieldworkers	Short MRSA exposure leads to carriage, cleared after 24 h	[66]
Van Cleef	2010	Netherlands	Risk analyses	YES (249)	MRSA	Pigs	Pig slaughterhouse workers	Working with live animals, risk for human MRSA carriage	[22]
Van den Broek	2009	Netherlands	Source attribution	YES (50, 171, 11)	MRSA	Pigs (YES)	Farmers, family, farm workers	Only human MRSA carriage on farms with positive pigs	[70]
Van der Hoek	2011	Netherlands	Risk analyses	n.a.	*Coxiella burnetii*	Goats, sheep, cattle	All residents in a specific rural area	Protective factors human Q-fever; vegetation, moist soil	[120]
Van Duijkeren	2010	Netherlands	Source attribution	YES vs. NO (61, 106 vs. 64)	MRSA ST398[h]	Horses (YES)	Veterinary teaching hospital staff and students	Vet. students, staff and horses carried same MRSA ST398	[43]
Van Kerkhove	2008	Cambodia	Risk analyses	NO (3600)	H5N1 Avian Influenza	Poultry	Households with chickens	Model H5N1 risks, poultry contact as transmission proxy	[78]
Verkade	2013	Netherlands	Risk analyses	YES (137)	MRSA ST398[h]	Pigs, veal calves	Livestock vets[a]	Veterinarians often (persistent-) carriers MRSA ST398	[42]
Wang	2014	Australia, Cambodia	Source attribution	YES vs. NO (36 vs. 210)	Blastocystis	Pigs (YES)	Pig farm workers (Australia), Village people (Cambodia)	Blastocystis zoonotic Australia, non-zoonotic Cambodia	[76]
Whelan	2011	Netherlands	Seroepidemiology	YES (517 ≥ 246)	*Coxiella burnetii*	Goat, sheep	Culling workers	Exposure-response like seroconversion for C. burnetii	[48]
Wong	2012	USA (PA)	Seroepidemiology	NO (127)	H3N2 Swine Influenza	Pigs	Members of an agricultural club	Closeness contact pigs determines H3N2 seropositivity	[27]
Wulf	2011	Netherlands	Risk analyses	YES and NO (640)	MRSA ST398[h]	Pigs, veal calves	Study on screening data for MRSA	Work related LA-MRSA infections increased over years	[68]

n.a.: Not applicable
[a] Veterinarians.
[b] Multidrug-resistant *Staphylococcus aureus*.
[c] H1N1 2009 pandemic Influenza strain.
[d] H1N1 swine Influenza strain.
[e] The focus in this study was on poultry keeping practises, Avian Influenza was only briefly mentioned and therefore not the focus of the study.
[f] Verotoxin-producing *Escherichia coli*, strain O157.
[g] Specific livestock related *S. aureus* resistance gene.
[h] Sequence Type 398, livestock derived *S. aureus* substrain.
[i] High pathogenic Avian Influenza.
[j] Low pathogenic Avian Influenza.
[k] Livestock types not specified, all farm animals included to the study.
[l] Extended-Spectrum-β-lactamase producing.

Table 2
Overview of micro-organisms reported in selected publications. The columns depict; the micro-organisms reported in studies, animals involved carrying or infected with the micro-organism, transmission of a disease; excretion site of the micro-organism to uptake site, transmission pathway; mode of transmission of the micro-organism, number of identified studies, reference number. Transmission pathways as defined in indicated references.

Micro-organism	Animal involved	Transmission (Source→target)	Transmission pathway [27–29,90,91]	Number of papers	References
Antibiotic-resistant *Escherichia coli*	Pigs	Faecal→oral	Droplet, contact, aerosol	1	[50]
Avian influenza	Chickens, layer hens, broilers, turkeys, wild birds	Respiratory	Airborne, aerosol, droplet	19	[16,17,39,44–47,57–61,77,78,80,82–84,86]
Avian Metapneumo virus	Turkeys	Respiratory	Airborne, aerosol, droplet	1	[53]
Blastocystis	Pigs	Faecal→oral	Droplet, contact, aerosol	1	[76]
Brucella spp.	Sheep, goats, "farm animals"[a]	Urine/milk–oral/respiratory	Droplet, contact, aerosol	2	[55,85]
Campylobacter spp.	Cattle, dairy cattle, chickens, pigs	Faecal–oral	Droplet, contact, aerosol	2	[102,111]
Chlamydophila psittacosi	Poultry, chickens, turkeys	Respiratory	Airborne, aerosol	2	[24,101]
Coxiella burnetii	Goats, sheep, cattle, poultry, "farm animals"[a]	Faecal–respiratory	Airborne, aerosol, dust	11	[25,26,28,40,41,48,54,55,99,100,120]
Cryptosporidium parvum	Cattle, sheep, buffalo	Faecal–oral	Droplet, contact, aerosol	3	[18,81,93]
Extended-Spectrum-β-lactamase producing *Enterobacteriaceae*	Poultry	Faecal–respiratory/oral	Dust, aerosol, airborne	1	[98]
Hepatitis E virus	Pigs, cats, chickens, deer, goats, horses, sheep	Faecal–oral	Droplet, water	2	[52,56]
Leptospira spp.	"Farm animals"[a]	Urine–oral	Droplet, contact, water	1	[55]
Methicillin-resistant *Staphylococcus aureus*	Pigs, veal calves, poultry, cattle, broilers, sheep, horses dogs, cats, rodents	Dermal–respiratory	Airborne, aerosol, dust	20	[19,21–23,42,43,51,64–74,96,97]
Orf virus	Sheep, goats	Dermal, faecal, saliva, vector–dermal	Droplet, contact, airborne, aerosol, dust	1	[90]
Swine influenza	Pigs	Respiratory	Contact, airborne, aerosol	4	[27,49,62,63]
Trichophyton verrucosum	Cattle	Dermal–dermal	Contact, aerosol	1	[87]
Verotoxin-producing *Escherichia coli* O157	Cattle, goats, pony, dog	Faecal–oral	Droplet, contact, aerosol	2	[91,92]
Not applicable/all zoonotic infections	"Farm animals"[a]	All[b]	All[c]	3	[20,94,95]

[a] Livestock animals not specified, or all possible livestock animals studied.
[b] All transmissions possible, not specified in publications.
[c] All transmission pathways possible, not specified in publications.

Scott et al. found no relationship between antibiotic resistance patterns of *E. coli* isolated from pigs and isolates from slaughterhouse workers [50]. However, *S. aureus* isolates carried by slaughterhouse workers were found to be more extensively resistant to antibiotics compared to community controls [51]. An increased risk for Hepatitis E virus infection in people occupationally exposed to pigs was found, especially for slaughterhouse workers [52]. Also, meat-processing workers had been more often infected with avian Metapneumovirus compared to controls [53].

3.1.4. Farmers

Farmers face daily exposure to LA-micro-organisms in every aspect of their work. Still, it is very hard to determine which activity leads to transmission of micro-organisms. In this group, outbreaks are often investigated in a retrospective way, i.e. by performing serological epidemiology, analysing blood samples for antibodies against specific pathogens. This procedure does not allow distinguishing between past and more recent transmission events.

In the Netherlands, antibodies against *C. burnetii* were found in 73.5% of blood samples from farmers keeping dairy goats [54]. In an Italian study, animal workers were checked for blood markers against *C. burnetii*, *Leptospira* spp. and *Brucella* spp. Only for *C. burnetii* a higher sero-prevalence of 73.4% was found in animal workers, compared with 13.6% in controls [55]. For the evaluation of Hepatitis E virus, these links were not as clear as for Q-fever: serological epidemiology in a farmer cohort in the United Kingdom showed high Hepatitis E virus sero-positivity, but pig contact was not found to represent a risk factor [56]. In another study from Germany, however, increased Hepatitis E virus positivity in people with contact with pigs was shown, compared to age- and gender-matched controls [52].

The literature is also inconsistent for Avian Influenza. One study from the US indicated no human antibody sero-positivity of Avian Influenza subtypes prevalent in poultry among poultry workers [57], while other studies from the US and Italy did show similar Avian Influenza subtypes in poultry and poultry workers [58–60]. Evidence from Hong Kong even indicated an exposure–response-like relationship for H5N1 Avian Influenza transmission: more anti-H5 antibodies were found in poultry workers with more poultry-related tasks compared to community controls. Direct contact to poultry and butchering poultry was identified as risk factors carrying the highest infection risk [61]. For Swine Influenza studies are consistent, three studies reported serological antibody presence against swine influenza in pig farmers and workers [49,62,63]. Remarkably, the study of De Marco et al. reported cross-protective immunity against the 2009 human pandemic Influenza A in swine workers exposed to pigs and Swine Influenza [63].

Other research in farmers mainly focussed on antimicrobial-resistant zoonotic organism carriage. These studies often have a different design, utilising cross-sectional or cohort designs, occasionally with repeated measurements. LA-MRSA [64] can be transmitted between animal species [65] and from animals to humans [65–68], but also from animals to the farm environment, although the host preferences differ [65,69]. One study identified a correlation between the carriage prevalence in pigs and the likelihood of human LA-MRSA carriage [70]. Still, the prevalence of persistent LA-MRSA carriage among farmers is relatively low [71] and most individuals show relatively rapid clearing of LA-MRSA carriage [19,66]. In poultry farms, MRSA positivity was found to be less prevalent compared to veal calf and pig farms. This could explain the limited carriage in poultry workers [72] and among people who keep poultry at home [73]. In addition, the reverse transmission route has also been proposed, with the evidence for a reverse zoonosis/anthroponosis being pigs positive for healthcare associated-MRSA, thus indicating farmer-to-pig MRSA spread [74]. This theory is enhanced by evidence showing that LA-MRSA is less transmissible between people, compared to other MRSA types [75].

3.2. Non-occupational contact

Contact to livestock could also occur in non-occupational settings and may lead to transmission or infection with zoonotic micro-organisms. Both direct contact and dispersion through air can account for micro-organism transmission events. In this section 30 publications are discussed, focussing on: Avian Influenza (N = 9 papers), *C. burnetii* (N = 5), *Cryptosporidium parvum* (*C. parvum*, N = 3), MRSA (N = 2), Verotoxin producing *E. coli* (VTEC) O157 (N = 2), *Blastocytosis*, *Brucella* spp., *Trichophyton verrucosum* (*T. verricosum*), *Campylobacter* spp., Orf virus, *Salmonella* spp. and Swine Influenza (all N = 1).

3.2.1. Developing countries

Especially in developing countries, transmission of micro-organisms can occur from live animals or via blood products from slaughtering practises within the home setting, but the actual transmission pathways are often unknown. In these countries livestock keeping is common practise for many families and animals are frequently kept in the home backyard for egg, milk or meat production [16,17,76–80,18,81–85]. Backyard poultry keeping has been linked to Avian Influenza transmission on many occasions. This was found by Thornson et al. performing interviews in Vietnam, asking for poultry contact and flulike illness [77], modelled by Van Kerkhove et al. in Cambodia after interviewing people regarding their poultry contacts [78], and shown among Egyptian women by Kandeel and colleagues performing a risk factor analysis of all suspected Avian Influenza cases in Egypt [80].

China knows a broad diversity in livestock farming practises, ranging from poultry farming with people involved in all stages of the production cycle [86], to large industrially managed cattle herds [87]. In both of these situations zoonotic disease transmissions have been described from livestock to humans, Avian Influenza and *T. verricosum*, respectively [86,87]. In summary, literature to date is not informative regarding which livestock–human contact pattern leads to zoonotic disease transmission in developing countries.

3.2.2. Brief contact

In some instances, very brief exposure may be sufficient for transmission of micro-organisms, especially when the infectious dose of a pathogen is very low [88]. This was shown in Germany in a study focussing on LA-MRSA carriage among farmers and residents in an area with a high density of livestock farms. Farmers were mainly at risk when they had pig contact, but the authors also found that regular visits to farms – e.g. to buy eggs or milk – increased the chance of becoming a LA-MRSA carrier among non-farm residents [89]. In Turkey, preparing freshly slaughtered sheep led to transmission of Orf virus during the feast of sacrifice, an Islamic tradition, among non-occupationally exposed people [90]. Visits to an agricultural fair in the US resulted in transmission of Swine Influenza between displayed pigs and human visitors [27]. Visitors of a pedagogical farm in France were reported to be infected with Q-fever [28] and gastrointestinal infections with VTEC O157 occurred on a farm open to the public in the UK [91]. VTEC O157 infections were also observed among 'holidaymakers', 'farm visitors', 'farming families' and 'farm workers' [92]. Still, the actual pathway of an infection was not specifically ascertained in most papers. This was illustrated by an outbreak of *C. parvum* among children camping on an adventure farm in the UK [93].

3.2.3. Environmental transmission

This section summarises reports where people indicated that they had no direct contact to livestock animals, but experienced adverse-health effects due to livestock in their immediate surroundings. These articles indicated that close contact to livestock animals was not necessary for a transmission event to occur, but that already living in close vicinity of livestock could be enough for the occurrence of adverse health effects among residents.

Respiratory health can be affected by many sources, including livestock farming in the vicinity of a residence. In Germany, reduced respiratory health of residents was linked to the presence of Confined Animal Feeding Operations, industrially managed livestock stables, near their home address. Although these studies did not focus on infectious diseases, they did indicate effects of livestock keeping on the health of nearby residents [94,95]. In a Dutch study investigating LA-MRSA presence in a rural population, only direct animal contact was found as a risk factor [96]. When the Danish national human MRSA database was checked for a livestock-associated MecC resistance gene, this was mainly found in samples from people living in rural parts of the country and animal contact was an important risk factor. Still, the gene was also discovered in human MRSA samples from people living in rural areas, but having no livestock contact [97]. An attempt to identify risk factors for Extended-Spectrum Beta-Lactamase (ESBL) *Enterobacteriaceae* carriage among people living in high- and low-poultry density areas in the Netherlands showed no elevated risk between the distance of positive poultry farms from the home and ESBL carriage of residents [98]. For Q-fever, however, the link between living close to infected farms and human cases of the disease is well established [25,26,88]. In the Netherlands, a large outbreak occurred in recent years and an exposure–response-like relationship was found for the number of goats within 5 km of the home address and human cases [26]. In Germany, a specific flock of sheep could even be identified as the source of a human Q-fever outbreak in a village [99]. In Italy, where in some areas free-range sheep herding is still common practise, the passing of three flocks of infected sheep through a village led to an outbreak of Q-fever [100].

4. Discussion

This review is a first attempt to summarise what is currently known regarding the nature of livestock–human interactions in the transmission of infectious diseases between livestock and humans. We performed a systematic procedure to identify current literature applying predefined criteria regarding livestock-associated zoonoses and tried to distinguish contact patterns between livestock and humans leading up to this zoonosis event. Zoonotic events can be reported in three ways. First, an outbreak is noticed in animals, followed by cases in humans [101]. Second, a cluster of human zoonosis cases appears, after which possible animal sources are identified [64,102]. The third way is retrospective, comparing blood samples from animal-exposed and non-exposed people for infectious disease markers [54], these are mainly cross-sectional studies, which may be subject to selection bias.

We identified 75 articles discussing micro-organism transmission or infections due to livestock associated micro-organisms. For people with occupational contact with livestock, the risk of acquiring micro-organisms from livestock was especially elevated, since transmission of infections seems to be possible during all phases of the livestock production cycle; from stables until the slaughterhouse [103]. Among the papers discussing occupational exposure to livestock, we found only two studies that assessed livestock contact quantitatively. These papers crudely estimated the number of hours spent among infected animals [48], or the number of tasks for handling infected animals [61]. A more detailed exposure assessment tackling concentration, exposure duration and frequency [104], however, is lacking.

Four studies were identified that showed spatial exposure relationships within slaughterhouses [19–22], and two of these also showed a temporal variability in environmental levels of micro-organisms [21–24]. Although these papers gave an indication of how transmission of micro-organisms from livestock to humans occurred, transmission routes were not specifically mentioned in the studies. The measured exposure proxies and related health effects can therefore not be specified for the potential transmission pathways.

For non-infectious disease studies, a detailed framework has been defined for possible exposure routes [105]. Such a framework is also

of potential importance for infectious disease studies because it describes all potential direct and indirect transmission routes. Therefore for LA-substances such as; particulate matter, gases, environmental micro-organisms and non-infectious (micro-)organism lysis products called endotoxins [106–110], time-weighted averages [106–108], or even task specific levels of endotoxins [110] are available. This enables exposure assessment for these substances within the farm environment.

Unfortunately, comparable sampling methods were not applied in the aforementioned studies on *C. burnetii* and Avian Influenza [48,61]. This could be due to lack of experience with these methods or technical difficulties due to micro-organism features, such as difficulty to catch and culture pathogenic strains. With the rise of molecular techniques, in future outbreaks concentrations of pathogens could be quantified, when combined with information on the duration and frequency of exposure, exposures can be assessed and exposure-response models can be developed for these pathogens.

For people not working in an occupation with livestock, the exposure to zoonotic micro-organisms is much lower compared to people with an occupation in the livestock sector. In developing countries it is often impossible to distinguish transmission pathways of micro-organisms since people are exposed to animals in both occupational settings and at home [16,17,76–80,18,81–84,111].

We found several papers reporting brief exposure to livestock animals that resulted in zoonotic disease transmission to people who were not occupationally exposed to livestock. Remarkably, brief contact in these studies was sufficient to transfer micro-organisms to susceptible persons, still the nature of these contacts remain elusive [27,28,66,90–93]. Perhaps the contact moment was not even necessary for disease transmission, but the environmental presence of high levels of micro-organisms surrounding infected animals, shown in other studies [112–119], was sufficient for a transmission event.

Environmental presence of LA-micro-organisms and other LA-emissions is the explanatory factor for the occurrence of LA-adverse health effects in people that did not have any contact with livestock, but were nevertheless affected by livestock in the vicinity of their home [25,26,94–97,99,100,120]. For both transmissions due to brief contact and environmental transmission of micro-organisms, micro-organism transmission pathways are hard to distinguish. Generally, people with adverse health effects from livestock in the vicinity of their homes are residents of rural areas, therefore (brief) livestock–human contact cannot be completely excluded in these studies.

Since there are so many unknown factors in the knowledge about livestock contact and zoonotic micro-organism transmission, it is very hard to optimise interventions, minimising effects of a future outbreak on public health. However, some suggestions on intervention can be given. For the occupational setting: In case of an animal outbreak, Personal Protective Equipment (PPE) use by cullers should be reinforced, especially in case of infectious micro-organisms that can be inhaled [30]. For slaughterhouse workers, PPE appears to be especially relevant for people working on the start of the slaughter line, since they seem to be exposed to the highest levels of zoonotic micro-organisms [21–24]. Since the protective abilities of PPE have been shown to not always be optimal [30,44–46], vaccination, if available, of cullers and slaughterhouse workers [44,121] may be considered, as well as usage of prophylactic drugs for cullers during their work [44]. For farmers, PPE can be used when they enter the stables, combined with a standardised general on-farm hygiene protocol [122]. When it comes to protecting the general public, in case of zoonotic outbreaks, there is always a risk of spread of micro-organisms from an infected farm to the direct environment [112–119], and farm-emissions are difficult to control [26,94,95,110]. The possible solution to control (infectious-)farm-emissions is complete closure of stables, combined with effective air filtering or washing systems [123], also manure should be handled with outmost care, since this can contain several micro-organisms [41,43,80–83].

Additional to the suggested measures regular and close surveillance of farms and both human and livestock health databases for LA-micro-organisms could be implemented to identify a zoonotic disease outbreak as early as possible.

The limitation of our study was that in most reports on zoonotic disease occurrence in humans, the intensity and the type of contacts between livestock and humans leading to the actual disease or micro-organism transmission were only implicitly cited. Therefore, it is virtually impossible to identify specific livestock–human interactions that lead to infectious disease transmission. This makes it very difficult to avert these interactions and even more challenging to design tailor-fit transmission preventive interventions.

4.1. Conclusions and future perspectives

Although, we found a significant body of evidence that described zoonotic transmissions of micro-organisms, little is known about the intensity and type of contact patterns leading to transmission, and thus the exact transmission pathways of micro-organisms from livestock to humans usually remains unclear. Human–livestock contacts were merely implicitly cited in the literature, and commonly, contact intensity was defined by the occupational status of the person carrying or infected with a LA-micro-organism. Studies performed in an occupational setting provided some evidence of exposure response relationships between the intensity of livestock–human contacts and the transmission of micro-organisms. Using methods that are already in place in the exposure assessment sciences [110], exposure to LA-zoonotic micro-organisms through contact patterns between livestock and humans, can be better quantified both in the occupational and the non-occupational setting. This will be crucial in the development of effective interventions to prevent transmission of micro-organisms from livestock to humans.

Authors contribution

GK, AH, DJJH and RAC designed the study, GK wrote the paper, GK and RAC reviewed the selected papers, AH, DJJH and RAC revised it critically for important intellectual content. All authors approved the submitted version of the article.

Conflicts of interest

None.

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Appendix A. Search terms and filter settings

A.1. Search terms

The following Boolean search statement was used in EMBASE, set to 'search as broadly as possible'; [(zoonoses'/exp./mj OR 'zoonoses' OR 'zoonosis'/exp./mj OR 'zoonosis' OR 'infectious disease' OR 'human infection' OR 'human case') AND ('livestock'/exp./mj OR 'livestock' OR 'farm animal'/exp./mj OR 'farm animal' OR 'cow'/exp./mj OR 'cow' OR 'cattle'/exp./mj OR 'cattle' OR 'cattle' OR 'chicken'/exp./mj OR 'chicken' OR 'poultry'/exp./mj OR 'poultry' OR 'turkey' OR 'duck'/exp./mj OR 'duck' OR 'sheep'/exp./mj OR 'sheep' OR 'goat'/exp./mj OR 'goat' OR 'ruminants'/exp./mj OR 'ruminants' OR 'small ruminants' OR 'pig'/exp./mj

OR 'pig' OR 'pigs' OR 'swine'/exp./mj OR 'swine') AND ('contact' OR 'contact intensity' OR 'bioaerosol' OR 'environmental' OR 'exposure'/exp./mj OR 'exposure' OR 'occupational' OR 'work' OR 'work related' OR 'workers' OR 'culling' OR 'residents' OR 'residential') AND ('transfer' OR 'exchange' OR 'transmission') NOT ('toxicity'/exp./mj OR 'toxicity' OR 'microextraction' OR 'tick'/exp./mj OR 'tick' OR 'rabies'/exp./mj OR 'rabies' OR 'schistosoma'/exp./mj OR 'schistosoma' OR 'transplant')].

A.2. Filter settings

Date preferences were set to <1966 to 2014, so no data restrictions were applied to the search. Filters were set for; *study types* (human, nonhuman, questionnaire, case report, cross-sectional study, interview, case control study and cohort analysis) and *floating subheadings* (epidemiology, aetiology, prevention, diagnosis, complication, drug resistance and disease management).

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