ANTIBIOTIC RESISTANT STAPHYLOCCUS AUREUS DISSEMINATION FROM HOG FARMS: A SYSTEMATIC REVIEW

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ABSTRACT

Chien-Hsiu Weng: Antibiotic resistant Staphylococcus aureus dissemination from hog farms: a systematic review
(Under the direction of Jacqueline MacDonald Gibson)

Research has identified antibiotic-resistant livestock-associated *Staphylococcus aureus* (LA-SA) in humans, suggesting that animal husbandry is contributing to the global spread of antibiotic resistance. However, the prevalence of antibiotic-resistant LA-SA organisms and the factors contributing to their spread are poorly understood. This review (1) summarizes the prevalence of antibiotic-resistant LA-SA in humans, hogs, and pork products and (2) identifies factors contributing to LA-SA spread. A systematic literature review identified 78 relevant studies. Together, these studies document high prevalence in farm hogs (pooled prevalence: 19%), farm workers (pooled prevalence: 32%), slaughterhouse hogs (pooled prevalence: 24%), and veterinarians (pooled prevalence: 20%). Major risk factors include amount of antibiotic used, frequency and duration of human contact with hogs, large herd sizes, summer season, location downwind from hog farms, and hog farm density. These findings may be useful for modeling antibiotic resistance transmission risks under different hog farming practices.

To my family and friends, I couldn't have done this without you. Thank you for all your support along the way.

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LISTS OF ABBREVIATIONS

AFLO	Antibiotic-free livestock operation
CI	Confidence interval
FDA	Food and Drug Administration
ILO	Industrial livestock operation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
MDRSA	Multidrug-resistant *Staphylococcus aureus*
MLVA	Multiple-locus variable-number tandem-repeat assays
MRSA	Methicillin-resistant *Staphylococcus aureus*
n.c.	not computable
OR	Odd ratio
PR	Prevalence ratio
USCDC	The United States in Centers for Disease Control and Prevention

CHAPTER 1: INTRODUCTION

Antibiotic resistance is a growing public health issue across the globe. Bacterial resistance to antibiotics can occur naturally, or can result from antibiotic use in human or veterinary medicine. In both human and veterinary medicine, up to 50% of the antibiotics used are not optimally prescribed, and are often prescribed unnecessarily, at incorrect doses or for an incorrect treatment duration [1]. Antibiotics are also commonly used in food animals to prevent, control, and treat disease, and to promote the growth of food-producing animals[2]. Despite the fact that (according to a new report by the FDA) approximately 80 percent of all antibiotics used in the United States are fed to farm animals[1], the number of studies on how antibiotic resistance in food animals spreads to human is relatively small compared to the number of studies on antibiotics use in humans.

Methicillin-resistant Staphylococcus aureus (MRSA) infections with strains circulating in hospitals (HA-MRSA) and communities (CA-MRSA) can be very serious and the number of infections is among the highest of all antibiotic-resistant threats in the United States, according to a Centers for Disease Control and Prevention (USCDC) report in 2013. MRSA is transmitted most frequently by direct skin-to-skin contact[3]. The USCDC estimates 80,461 invasive MRSA infections and 11,285 related deaths occurred in 2011. Although the early MRSA clones were hospital-associated MRSA (HA-MRSA), beginning in the late 1990s community-associated MRSA (CA-MRSA) clones emerged worldwide[4]. There is new evidence that antibiotic resistant *Staphylococcus* is moving from animal hosts to humans. The preponderance of the evidence suggests that the livestock-associated Methicillin-resistant Staphylococcus aureus

(LA-MRSA) strains originated from humans [5, 6]. Price et al.'s work indicates that a type of livestock-associated MRSA known as CC398 originated in humans before spreading to hogs and back to humans [6]. LA-MRSA strains have been found in food animals such as pigs, veal calves, turkeys, and chickens in countries throughout Europe, North America, and Asia[7-11]. However the ecology and virulence of these strains are not well understood. Both LA-MRSA and LA-MDRSA (where multidrug resistance is defined as intermediate or complete resistance to 3 or more antibiotic classes) have been documented in association with food animal production.

The first human LA-MRSA incident was reported in the Netherlands in 2004 and prompted studies on the prevalence of LA-MRSA and LA-MDRSA in food animals, meat products, farm workers, and other sample types. Several researchers have reported that LA-MRSA and LA-MDRSA are widespread in Europe and other regions. There appears to be an elevated exposure risk among farm workers and perhaps their household and community members, but infection risks are not clear. A study of 450 hospitals in Europe in 2006-2007 identified 12 cases of infections from MRSA ST398 (one of the MRSA strains frequently isolated from livestock) but none of these were caused by methicillin-resistant MRSA strains [12]. Studies of causalities of HA-MRSA or CA-MRSA are abundant, whereas the causality of transferring LA-MRSA and LA-MDRSA from hogs to humans is still poorly understood. Also, potential LA-MRSA and LA-MDRSA transmission routes and transmission factors are not fully developed in the literature [13], although reports suggest that air, water, and food may be among the transmission routes. Most previous systematic reviews have focused separately on occupational direct exposures, environmental factors, or food contaminations, but these reviews are not comprehensive enough and do not present all transmission routes and factors together.

The diversity of LA-MRSA and LA-MDRSA and the transferability of antibiotic-resistance genes complicate any examination of LA-MRSA and LA-MDRSA arising from hog farms. My objectives in this review are to: 1) identify the potential methods of LA-MRSA and LA-MDRSA transport or transmission and risk factors contributing to LA-MRSA and LA-MDRSA presence; and, 2) summarize the prevalence of livestock-associated antibiotic-resistant *Staphylococcus aureus* in humans, livestock, and livestock production facilities.

CHAPTER 2: METHODS

2.1 Research questions and review protocol

My research objectives are focused on the topic of the prevalence of LA-MRSA and LA-MDRSA in humans and animals and intended to identify the potential transmission routes and related factors influencing transmission. My review adheres to the principles established in the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) protocol (http://www.prisma-statement.org/).

2.2 Search strategy and data abstraction

I used the PubMed (http://www.ncbi.nlm.nih.gov/pubmed) database for my research. I included papers published up to January 2016. To assemble the most comprehensive set of relevant papers, I used 24 different advanced search approaches, combining the following terms in all relevant fields: (livestock associated MRSA, MRSA, MDRSA, antibiotic AND resistant AND staphylococcus AND livestock) AND (community, pig, swine, worker, pork chain, risk). I also used the following algorithm in PubMed to ensure I obtained all relevant articles: ((("livestock"[MeSH Terms] OR "livestock"[All Fields]) AND associated [All Fields] AND ("methicillin-resistant staphylococcus aureus"[MeSH Terms] OR ("methicillin-resistant"[All Fields] AND "staphylococcus"[All Fields] AND "aureus"[All Fields]) OR "methicillin-resistant staphylococcus aureus"[All Fields] OR "mrsa"[All Fields])) AND ("residence characteristics"[MeSH Terms] OR ("residence"[All Fields] AND "characteristics"[All Fields]) OR "residence characteristics"[All Fields] OR "community"[All Fields])) AND ("risk"[MeSH Terms] OR "risk"[All Fields]). The full search algorithm is shown in Supplemental Table S1. To minimize the risk of missing (updates to) relevant studies, I subscribed to the "Create Alert" feature of the PubMed database until January 2016.

2.3 Data management and chart creation

I screened the titles and abstracts of possibly relevant articles using six inclusion criteria and six exclusion criteria (Table 1). I excluded papers that focused on only HA-MRSA or HA-MDRSA or CA-MRSA or CA-MDRSA. Since my research question concerned livestock-associated antibiotic-resistant *Staphylococcus aureus* in humans and livestock, I focused on studies relevant to the following factors: hog and hog production facilities, LA-MRSA or LA-MDRSA tests on hog farms, farm workers and their household members, veterinarians, slaughterhouses, slaughterhouse workers, patients in hospitals, pork products, and environment samples from hog farms. I excluded lab studies to maintain a focus on real world transmission factors, and I excluded case reports because they only reported an outbreak or a new strain finding, not an investigation of routine farm operating conditions.

I compared PubMed IDs to identify and remove duplicated papers from different searches in the initial pool of papers. I imported citations identified via the search into Endnote X7 and used an extraction form in Microsoft Excel (2003 edition) (http://libguides.sph.uth.tmc.edu/excel_SR_workbook) to summarize the screening process. Relevant papers cited in the papers I found by my search were also included.

I extracted from articles in the final set of papers the prevalence of LA-MRSA or LA-MDRSA in pig-related populations, herds, environments, and products. I summarized the data using Microsoft Excel's (2011 edition) descriptive table and frequency chart tools; I used the descriptive table tool to create the summaries of the papers presented in Tables 2 to 9. If a given category (farm hogs, farm workers, slaughterhouse hogs, slaughterhouse workers, household members, veterinarians, pork products, and patients in hospitals) of prevalence data had more than three source papers, I calculated a pooled prevalence for the category using MetaXL (an add-in tool in Microsoft Excel).

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Language: English	Language: any language other than English
Included non hospital-associated MRSA or MDRSA or community-associated MRSA or MDRSA study	Hospital-associated MRSA or MDRSA only or community-associated MRSA or MDRSA study only
Population or target: LA-MRSA or MDRSA tests on hog farms workers and household members, veterinarians, slaughterhouse workers, patients in hospital, pork products, environment samples from hog farms (air, dust, and water) are conducted	Population or target: LA-MRSA or MDRSA tests on hog farms workers and household members, veterinarians, slaughterhouse workers, patients in hospital, pork products, environment samples from hog farms (air, dust, and water) are NOT conducted
Not lab experiments	Lab experiments
Original report or reviews associated with hog-MRSA or MDRSA	Non-original report, editorial, and comment
Period: pre-January, 2016	None

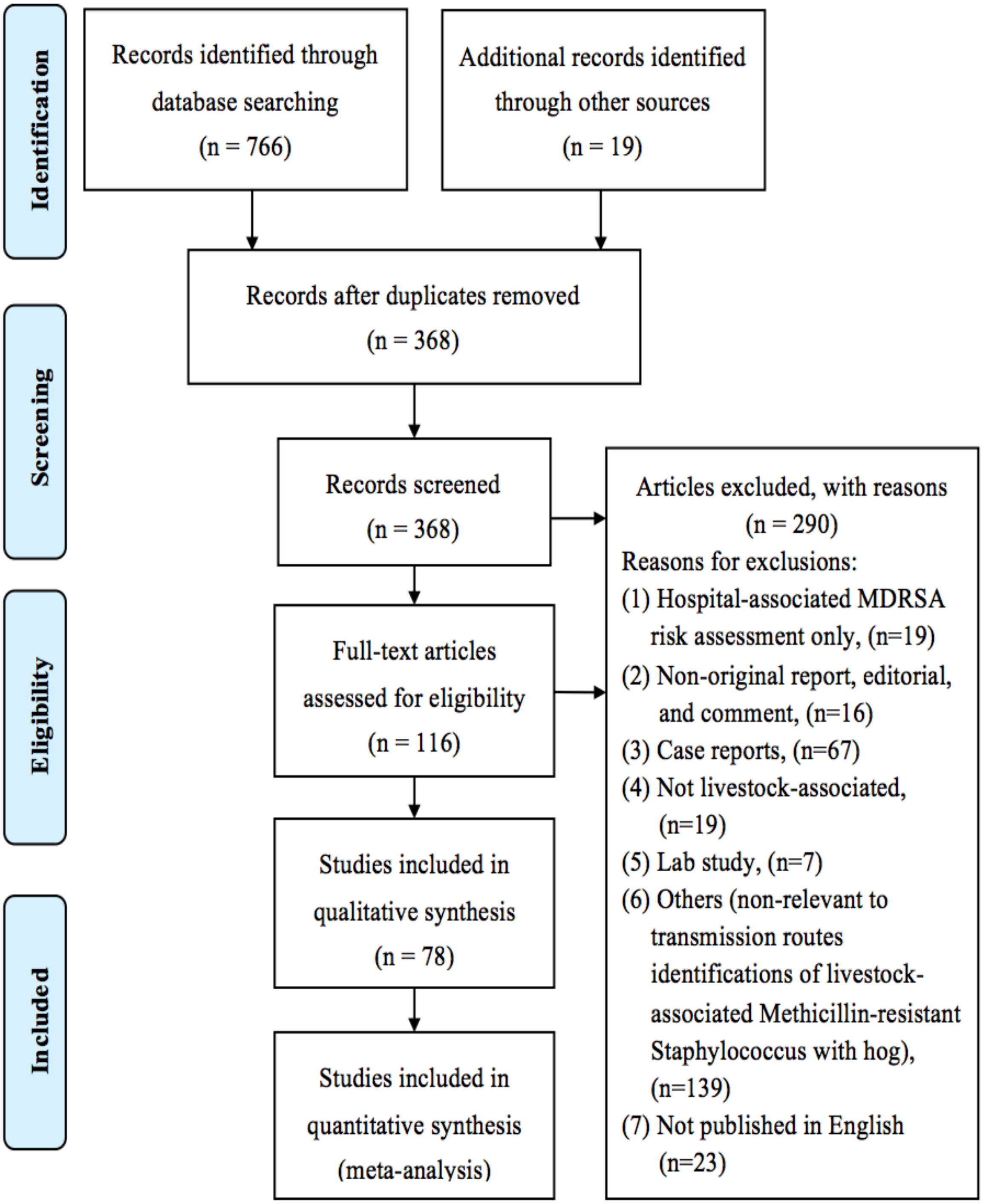

Figure 1. Flowchart of the literature search and screening process

CHAPTER 3: RESULTS

The 24 combination searches resulted in an initial set of 785 papers; applying the inclusion and exclusion criteria yielded a final set of 78 relevant papers (Figure 1). My goals in this paper were to identify the LA-MRSA and LA-MDRSA hog-to-human transport factors and routes and also to summarize the LA-MRSA and LA-MDRSA prevalence in different populations and vectors. Table 2 shows the risk factors I found for LA-MRSA and LA-MDRSA transmission, categorized by source location, and the papers supporting each finding

Table 2. Risk factors for LA-MRSA and LA-MDRSA, by source location

Location of Transmission	Risk factors	Supporting studies
Hog farm	Operation type	[14-20]
	Frequency and duration of exposure to livestock	[21, 22]
	Herd size	[23-25]
	Hog age or herd type	[23, 26, 27]
Air	Wind direction	[28]
	Season	[28]
Soil	Wind direction	[28]
	Season	[28]
	Time of day	[29]
Slaughter/processing plants	Location on slaughterline	[29-32]
	Use of scalding other heat treatments	[30, 33]
	Recontamination via machinery	[34]
	Recontamination by surfaces	[34]
	Recontamination by human handling	[34]
Households of workers	Worker hog contact rate	[18, 35-37]
	Time since last worker contact with hogs	[36, 38]
	Worker contact with sows	[38]
	Worker contact with antimicrobials	[38]
Community	Hog farm density	[37, 39-42]
	Visits to farms	[23, 43]
	Contact with hog farm workers	[37, 39, 40, 43]
	Veterinarians	[18, 29, 44-50]
	Household members of veterinarians	[18]
Food chain	Type of preservation	[51]
	Fresh or Frozen	[51, 52]
Hospitals	Contact with hogs	[53-55]
	Contact with other animals	[53]
	Unknown exposure	[53]
	Hog farm density	[56]

3.1 Hog farms

The prevalence and isolate type of LA-MRSA or LA-MDRSA among hog farms vary (Figure 2 and Table 3). The prevalence of LA-MRSA or LA-MDRSA may be greater than 45% [57, 58]. ST398 (sequence type) predominates in Europe and North America whereas ST9 is more common in Asia (Table 3). The pooled prevalence for farm hogs was 19% (95% CI: 11%-27%) and the pooled prevalence for farm workers was 32% (95% CI: 11%-52%).

The hog farm is one source of LA-MRSA and LA-MDRSA transmission. The type of hog farm operation has been reported as a likely risk factor for LA-MRSA and LA-MDRSA infection for both hogs and workers. Rinsky et al. showed that in North Carolina, LA-MRSA and LA-MDRSA prevalences in hogs are higher in industrial hog farms using antibiotics than in antibiotic-free farms [14]. Other studies have found that, farm workers are at higher risk of carrying MRSA than non-farmers[7, 59]. The presence of MRSA in farmers was strongly related to duration of animal contact and was strongly reduced in periods without animal contact (26% vs. 11%) in Graveland's study[21]. Van Cleef et al. showed a strong association between hogs and farm workers for MRSA (88% shared the same MLVA [multiple-locus variable-number tandem-repeat assays]-type or a single-locus variant) and reported the following occupational influencing factors: working in stables more than 40 hours/week (prevalence ratio [PR]: 1.89, 95% CI: 1.19–3.0, p=0.01), giving birth assistance to sows in the last 7 days (PR: 2.26, 95% CI: 1.10–4.67, p=0.03), removing the manure of finisher pigs in the last 7 days (PR: 0.48, 95% CI: 0.26–0.87, p=0.02), and continuously wearing a facemask when working in the stables (PR: 0.13, 95% CI: 0.02–0.76, p=0.02) [22].

Studies also have shown that hog herd size is a significant risk factor for MRSA prevalence among pigs and workers as well. Although the definition of a "large-scale" herd varies by study, the MRSA carriage rate for hogs in large-scale herds has been shown to be significantly higher than that in small-scale herds, and the carriage rate for hog farm workers in large-scale farms was significantly higher than that in small-scale farms. For example, a German study showed odds ratio (OR) of MSRA of 5.4 (95% CI: 2.7-11.2, $p < 0.05$) for large-scale farms compared to small-scale operations, and an Italian study showed a similar OR of 3.67 (95% CI: 1.04–112.91%)[23-25].

Other risk factors for MRSA carriage identified in prior studies include hog age and herd type. Fang et al. reported that the MRSA carriage rate for young hogs (younger than 3 months) was significantly higher than for older hogs (25.38% vs. 5.84%, $p<0.001$)[23]. Friese and colleagues found that hogs from fattening farms had a significantly higher MRSA prevalence than those from breeding farms due to higher hog exchange and hogs from different suppliers being housed together (99.4% vs. 69.2%, $p<0.01$)[26].

With regard to routes of transmission, within-pen transmission (compared to between-pen transmission and transmission through environmental exposure) was associated with increased transmission rates [60]. MRSA may also spread to other species (e.g., chickens and cattle) in the same farm— Pletinckx et al. demonstrated that MRSA ST398 spread between hogs, other animals, and people residing on the same farm [61].

Table 3. Summary of hog farm studies, by category of risk factor and exposure group

Author and publication year	Country	Occupation of the participants or targets	No. of participants	No. of participants carrying LA-MRSA or LA-MDRSA	LA-MRSA or LA-MDRSA prevalence (%)	Type of Organism/ Note	Reference
Hogs							
Schmithausen et al., 2015	Germany and Netherlands	Hogs	241	37	15.35	LA-MRSA	[27]
Schulz et al., 2012	Germany	Hogs	24	4	16.67	LA-MRSA	[28]
Cui, 2009	China	Hogs	509	58	11.39	73.33% (44/60) isolates are LA-MDRSA	[62]
Crombé, 2012	Belgium	Hogs	1500	663	44.20	13.27% (15/113) isolates are LA-MDRSA	[57]
Habrun, 2011	Croatia	Hogs	68	24	35.29	LA-MRSA	[63]
Lewis, 2008	Denmark	Hogs	50	23	46.00	LA-MRSA	[58]
Köck, 2009	Germany	Hogs	1600	169	10.56	LA-MRSA	[54]
Van Duijkeren, 2008	Netherlands	Hogs	310	35	11.29	65.71% (23/35) isolates are LA-MDRSA	[64]
Khanna, 2008	Canada	Hogs	285	71	24.91	59.15% (42/71) isolates are LA-MRSA	[65]
Weese, 2011	Canada	Hogs	460	21	4.57	76.19% (16/21) isolates are ST398	[66]
Tsai, 2012	Taiwan	Hogs	74	5	6.76	8.11% (6/74) isolates are LA-MDRSA	[67]
Anukool, 2011	Thailand	Hogs	40	4	10.00	10% isolates are LA-MDRSA	[68]
Farm workers							
Cuny et al., 2009	Germany	Farm workers exposed to MRSA positive hogs	113	97	85.84	LA-MRSA	[18]
		Farm workers exposed to non exposition to MRSA positive hogs	116	5	4.31		
Voss et al., 2005	Netherlands	Farm workers	26	6	23.08	(>760 × higher than in the general Dutch population)	[59]
Armand-Lefevre et al., 2005	France	Farm workers	44	25	56.82	LA-MRSA	[69]

Author and publication year	Country	Occupation of the participants or targets	No. of participants	No. of participants carrying LA-MRSA or LA-MDRSA	LA-MRSA or LA-MDRSA prevalence (%)	Type of Organism/ Note	Reference
Liu et al., 2015	China	Farm workers			18.2		[47]
Dahms et al., 2014	Germany	Farm workers	36	20	55.56	LA-MRSA; 15/20 are LA-MDRSA	[70]
Khanna, 2008	Canada	Farm workers	25	5	20.00	LA-MRSA	[65]
Cui, 2009	China	Farm workers	13	2	15.38	LA-MDRSA	[62]
Huber, 2010	Switzerland	Farm workers	460	0	0		[50]
Van Cleef, 2014	Netherlands	Farm workers	110	42	38.18	LA-MRSA	[22]
Livestock operation type							
Rinsky et al., 2013	USA	Farm workers and household members	41	3	7.32	LA-MRSA, ILO*	[14]
			42	3	7.14	LA-MRSA, AFLO[1]	
			41	15	36.59	LA-MDRSA, ILO[2]	
			42	8	19.05	LA-MDRSA, AFLO	
Smith et al., 2013	USA	Hogs in ILO (1)	588	50	8.50	LA-MRSA	[15]
		Hogs in AFLO (2)	497	0	0		
Smith et al., 2009	USA	Hogs	299	147	49.16	LA-MRSA, conventional farm	[16]
		Farm workers	20	9	45.00		
Osadebe et al., 2013	USA	Non-conventional hog farms	35	1	2.86	1/5 is LA-MRSA	[17]
		Farm workers in non-conventional farms	9	2	22.22	0/2 is LA-MRSA (HA-MRSA)	
Cuny et al., 2009	Germany	Conventional farms	57	45	78.95	LA-MRSA	[18]
Cuny et al., 2012	Germany	Hogs in alternative farms[3]	178	0	0		[19]

[1] ILO, industrial livestock operation

[2] AFLO, antibiotic-free livestock operation

[3] Alternative farms: small farm (fewer than 600 hogs versus at an average of 3,000 hogs in conventional farms), and hogs are kept on floors with straw bedding, with sufficient room for running of the animals. There is no administration of antibiotics to hogs with body mass > 25 kg [19].

Author and publication year	Country	Occupation of the participants or targets	No. of participants	No. of participants carrying LA-MRSA or LA-MDRSA	LA-MRSA or LA-MDRSA prevalence (%)	Type of Organism/ Note	Reference
		Farm worker in alternative farms	89	1	1.12	LA-MRSA	
Van de Vijver et al., 2014	Netherlands	Hogs in organic farms	240	8	3.33	LA-MRSA	[20]
Hog age							
Schmithausen et al., 2015	Germany	Young farrowing piglet /newly weaned piglet	75	12	16.00	LA-MRSA	[27]
		Farrowing/nursery	75	20	26.67		
		Early finisher	205	64	31.22		
		Finisher	205	19	9.27		
Fang et al., 2014	Taiwan	Age<3 months	264	67	25.38	LA-MRSA	[23]
		Age>3 months	377	22	5.84		
Friese et al., 2012	Germany	Pooled nasal swabs among hogs in fattening farms Pooled nasal swabs among hogs in Breeding farms	180 120	179 83	99.40 69.20	17/22 isolates are LA-MRSA	[26]
Hog farm size							
Alt, K. et al., 2011	Germany	Large-scale herd (>1000) Small-scale herd (<500)	116 83	63 30	54.31 36.14	LA-MRSA/	[24]
Fang et al., 2014	Taiwan	Large-scale herd (>=10000)	181	62	34.25	83/89 isolates are LA-MRSA	[23]
		Small-scale herd (<10000)	355	25	7.04		
		Farm worker in large-scale herd	19	7	36.84	99/102 isolates are LA-MRSA	
		Farm worker in small-scale herd	33	3	9.09		
Battisti et al., 2010	Italy	Hog Holding	118	33	27.97	Larger herd size (>9000) is more likely MRSA positive than small her size (<9000). OR: 3.67, 95% CI: 1.04–112.91%	[25]
Other animals in farms							
Pletinckx et al.,	Belgium	Dog	6	4	66.67	LA-MRSA	[61]

Author and publication year	Country	Occupation of the participants or targets	No. of participants	No. of participants carrying LA-MRSA or LA-MDRSA	LA-MRSA or LA-MDRSA prevalence (%)	Type of Organism/ Note	Reference
2013	and Denmark	Cat	13	3	23.08		
		Rate-mice	17	12	70.59		

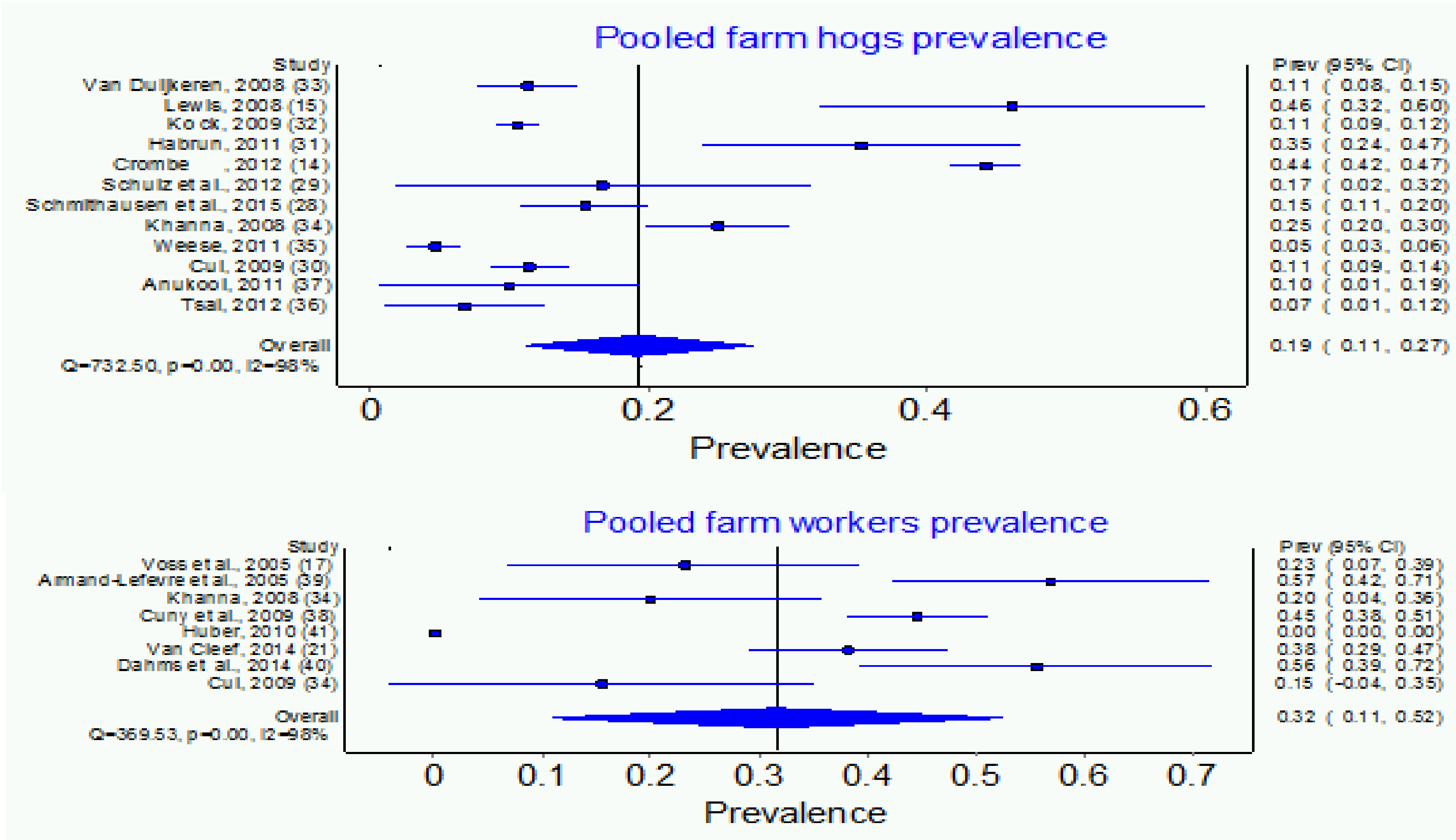

Figure 2. Summary of LA-MRSA prevalence in farm hogs and farm workers

3.2 Environmental factors

According to Dahms et al., environmental transmission routes for LA-MRSA and LD-MRSA include air, dust, soil, and farm wastewater [70]. Table 4 summarizes associations between these transmission routes and the prevalence of LA-MRSA or LA-MDRSA. The airborne transmission of LA-MRSA within hog herds suggests that it may also act to contaminate the barn environment [26] as well as the vicinity of LA-MRSA-positive hog barns [71]— the former was indirectly confirmed by Bos et al., who showed that exposure to ST398 MRSA in barn air is an important risk factor for nasal carriage, especially in those who worked over 20 hours per week in LA-MRSA positive air in barns (pooled OR: 2.25, 95% CI: 1.57-3.22)[72]. Reports indicate that airborne LA-MRSA transmission and deposition are influenced by wind direction and season—while positive LA-MRSA samples were detected upwind of hog barns sporadically, LA-MRSA could be detected on soil surfaces at distances of up to 300 m downwind from barns[28]. LA-MRSA also could be detected in air samples in low concentrations at distances of 50 and 150 meters downwind of hog barns[28]. With regard to season, a greater number of positive LA-MRSA samples were found both in air and soil samples in summer compared to other seasons (19/35 in summer vs. 9/35 in spring, p=0.0039; 21/37 in summer vs. 15/37 in autumn, p=0.0209; 21/39 in summer vs. 14/39 in winter, p=0.0196) [28]. A European Food Safety Authority report indicated that the prevalence of LA-MRSA ST398 in dust samples in hog production facilities ranged from 0% to 51.2% [73].

Table 4. Summary of environmental factor studies, by sample type

Author and publication year	Country	Occupation of the participants or targets	No. of participants	No. of participants carrying LA-MRSA or LA-MDRSA	LA-MRSA or LA-MDRSA prevalence (%)	Type of Organism/ Note	Reference
Air							
Schmithausen et al., 2015	Germany	Farm	70	60	85.71	LA-MRSA	[27]
		Slaughterhouse	14	13	92.86	LA-MRSA	
Friese et al., 2012	Germany	Hog barns	27	23	85.19	LA-MRSA	[26]
Schulz et al., 2012	Germany	Downwind air (50 and 150 m)	47	5	10.64	LA-MRSA	[28]
		Upwind air (100 m)	20	0	0		
		Air inside the barn	24	21	87.50		
Dust							
Van de Vijver et al., 2014	Netherlands	Hog farm	120	1	0.83	LA-MRSA, in organic farms	[20]
Dahms et al., 2014	Germany	Dust in conventional farm	17	6	35.29	LA-MRSA; 4/6 are LA-MDRSA	[70]
Schulz et al., 2012	Germany	Downwind soil (50, 150, and 300 m)	67	49	73.13	LA-MRSA	[28]
		Upwind soil (100 m)	18	6	33.33		
		Floor inside the barn	24	24	100.00		
Van Cleef BA et al., 2010	Netherlands	Start of the day	59	10	16.95	LA-MRSA	[29]
		End of the day	59	20	33.90		
		Live hog areas at end of the day	24	16	66.67		
		Dirty hog areas at end of the day	35	4	11.43		

3.3 Hog slaughter/processing plants

Hog slaughter facilities are another potential LA-MRSA transmission route. Table 5 and Figure 3 show the prevalence of LA-MRSA and LA-MDRSA in hogs and workers in hog slaughter/processing plants. The pooled prevalence of MRSA in slaughterhouse hogs was 24% (95% CI: 0.16-0.32). The pooled prevalence of MRSA in slaughterhouse workers was 5% (95% CI: 0.01-0.09).

Broens and colleagues suggested that MRSA prevalence in hogs was higher in slaughterhouses than in farms due to the transmission of MRSA during transport—they found that the prevalence was 0% at hog loading but increased to 10.26% on hog arrival [31]. The prevalence of MRSA in slaughter hogs in slaughter facilities varied: Yan et al. reported a prevalence of 6.44% (38/590)[74], but Ho et al. indicated a prevalence of 39.3% (157/400)[75]. The prevalence of nasal MRSA carriage in employees of hog slaughterhouses also varied, from 5.6% (14/249)[29] to 11.3% (34/300)[76]. Neyra et al. found that slaughterhouse workers had a higher prevalence of LA-MDRSA (OR: 1.96, 95% CI: 0.71-5.45) and a higher average number of antibiotic classes to which S. aureus isolates responded than community residents (1.96 times)[41].

Although MRSA positive environmental samples have been found throughout the slaughter process, studies have shown that occupational exposure to MRSA decreases along the slaughterline. In one study, MRSA-positive workers identified as nasal MRSA carriers were predominantly found at the start of the slaughter process (11.11% among workers in lairage area and 23.52% among workers in scalding and dehairing area)[30]. Narvaez-Bravo et al. corroborated this finding and reported that the initial steps of slaughter and processing showed a significantly higher MRSA prevalence (61.93%) than pork products from the same plants (1.21%

at the end of the slaughterline)[33]. However, although heat treatments such as scalding and flaming during the slaughter process can significantly reduce the burden of MRSA on the carcasses, studies have shown that MRSA recontamination can recur via surface treating machinery, as a result of fecal contamination at evisceration, or via increased human handling during meat processing [34]. Beneke et al. demonstrated that MRSA could be introduced to final pork products in the slaughterhouse by carcass surfaces or staff members even though no MRSA was found in the processing areas [32]. In addition, wastewater from hog slaughterhouses can be a risk factor for the dissemination of LA-MDRSA, potentially affecting not only workers but also the general public [77].

Table 5. Summary of the hog slaughter/processing plant studies, by exposure group

Author and publication year	Country	Occupation of the participants or targets	No. of participants	No. of participants carrying LA-MRSA or LA-MDRSA	LA-MRSA or LA-MDRSA prevalence (%)	Type of Organism/ Note	Reference
Hog in Slaughterhouse							
Schmithausen et al., 2015	Germany and Netherlands	Hog	241	30	12.45	LA-MRSA	[27]
Morcillo et al., 2012	Spain	Hog	300	247	85.67	LA-MRSA	[76]
Yan et al., 2014	China	Hog	590	38	6.44	LA-MRSA	[74]
Ho et al., 2012	Hong Kong	Hog	400	157	39.25	LA-MRSA	[75]
Gomez-Sanz, 2010	Spain	Hog	106	37	34.91	91% isolates are LA-MRSA; 18.92% (7/37) are LA-MDRSA	[78]
Porrero, 2012	Spain	Hog	263	160	60.84	80.56% (29/36) are ST398. LA-MDRSA	[79]
Overesch, 2011	Switzerland	Hog	797	31	3.89	64.52% (20/31) are ST398. LA-MDRSA.	[80]
Huber, 2010	Switzerland	Hog	800	10	1.25	All are ST398 and LA-MDRSA	[50]
de Neeling, 2007	Netherlands	Hog	540	209	38.70	All are ST398. 36.36% (16/44) are LA-MDRSA	[81]
Baba, 2010	Japan	Hog	115	1	0.87	LA-MDRSA	[82]
Lim, 2012	Korea	Hog	657	12	1.83	57.14% (12/21) are LA-MRSA	[83]
Agerso, 2012	Denmark	Hog	789	101	12.80	93.07% (94/101) are LA-MRSA	[84]
Slaughterhouse workers							
Van Cleef BA et al., 2010	Netherlands	Slaughterhouse worker	249	14	5.62,	LA-MRSA	[29]
		Livestock transport worker	41	9	21.95	LA-MRSA	
		Official veterinarian and auxiliary	13	2	15.38	LA-MRSA	
		Lairage worker	32	2	6.25	LA-MRSA	
		Dirty area worker	7	1	14.29	LA-MRSA	
		Worker in dead pig area	127	0	0	LA-MRSA	
		Other	29	0	0	LA-MRSA	
Gilbert et al., 2012	Netherlands	Lairage area	36	4	11.11	73% are LA-MRSA	[30]
		Scalding and dehairing area	34	8	23.53		
		Evisceration area	94	4	4.26		

Author and publication year	Country	Occupation of the participants or targets	No. of participants	No. of participants carrying LA-MRSA or LA-MDRSA	LA-MRSA or LA-MDRSA prevalence (%)	Type of Organism/ Note	Reference
		Intestine cleaning	22	0	0	n.c[4].	
		Cutting area	109	0	0	n.c.	
		Technical service	15	1	6.67		
		Other	46	0	0	n.c.	
Morcillo et al., 2012	Spain	Slaughterhouse workers	300	34	11.33	LA-MRSA	[76]
Neyra et al., 2014	USA	Slaughterhouse workers	162	9	5.56	LA-MRSA	[41]
			162	13	8.02	LA-MDRSA	
Huber, 2010	Switzerland	Slaughterhouse workers	179	0	0		[50]
Hog in slaughterline							
Broens et al., 2011	Netherlands	Hog at loading (transportation)	117	0	0	LA-MRSA	[31]
		Hog on arrival	117	12	10.26		
		Hog at stunning	117	70	59.83		
Beneke et al., 2011	Germany	Hog at stunning	133	86	64.66	LA-MRSA	[32]
		Slaughterline environment	50	6	12.00		
		Carcasses at slaughterline	150	9	6.00		
		Processing area environment	44	0	0		
		Meat at processing	144	6	4.17		
		Final pork products	71	2	2.82		
Narvaez-Bravo et al., 2015	Canada	Nasal swab samples after bleeding	662	410	61.93	LA-MRSA	[33]
		Nasal swabs after scalding or skinning	658	187	28.42		
		Carcass swabs after pasteurization or washing	660	50	7.58		
		Retail pork (final products)	660	8	1.21		

[4] n.c.: not computable

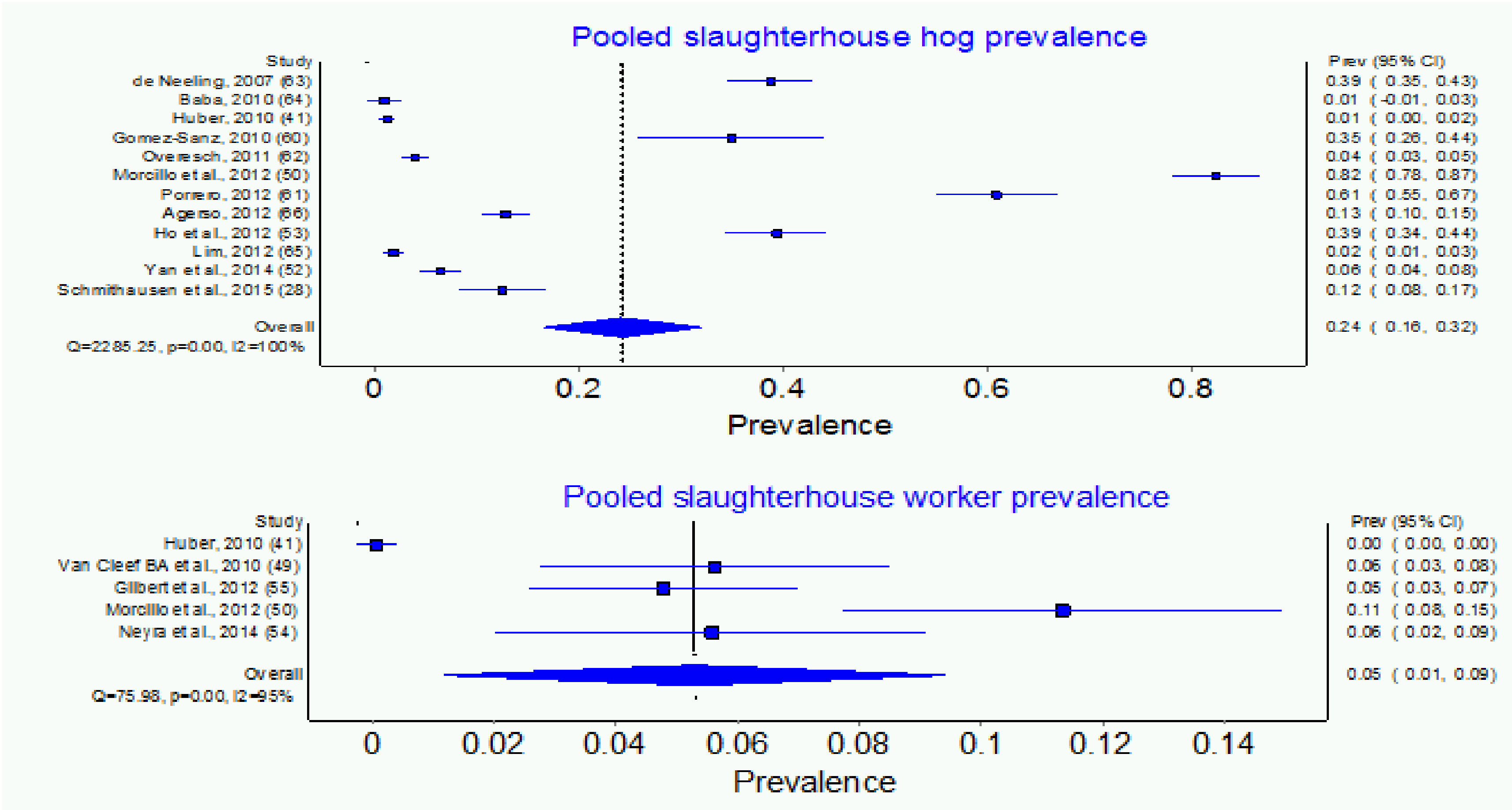

Figure 3. Summary of LA-MRSA prevalence in slaughterhouse hogs and slaughterhouse workers

3.4 Household members

Several studies indicate that MRSA could be transmitted to hog farm workers' household members. Table 6 and Figure 4 show the prevalence for household members of hog farm workers, by type of exposure. The pooled prevalence among household members was 10% (95% CI: 4%-16%)(Figure 4).

Nadimpalli et al. showed that the nasal carriage of LA-MRSA and LA-MDRSA could persist among industrial hog operation workers over a two-week period, even in the workers off duty for more than 96 hours [35]. Although the proportion of persistent carriers was significantly higher among farmers than among household members (87% vs. 11%, $p<0.0001$) [38], Garcia-Graells et al. pointed out that the risk factors of MRSA acquisition also applied to MRSA carriage among household members, including pig contact rate (prevalence: 85.71% with 10-30 hours per week duration vs. 26.32% with <10 hours per week duration), exposure to hogs within the last 7 days (prevalence: 70% vs. 8% no exposure to hogs within the last 7 days), contact with sows ($p<0.04$), and handling antimicrobial drugs for hogs ($p<0.03$). However, even in both livestock and farmers with high carriage rates of MRSA, the risk for household members to acquire MRSA is limited and still depends strongly on hog exposure among the workers [38].

Table 6. Summary of studies on household prevalence, by exposure focus

Author and publication year	Country	Occupation of the participants or targets	No. of participants	No. of participants carrying LA-MRSA or LA-MDRSA	LA-MRSA or LA-MDRSA prevalence (%)	Type of Organism/ Note	Reference
Household members vs. workers							
Garcia-Graells et al., 2013	Belgium, Denmark, and Netherlands	Farm workers	15	13	86.67	LA-MRSA	[38]
		Household members	45	5	11.11		
Cuny et al., 2009	Germany	Farm workers	113	97	85.84	LA-MRSA	[18]
		Household members	116	5	4.31		
Van Cleef BA et al., 2015	Netherlands	Household members	168	45	26.79	LA-MRSA	[36]
Wardyn et al., 2015	USA	Farm worker and household member in hog farm	1342	34	2.53	LA-MRSA	[85]
			351	68	19.37	LA-MDRSA	
Hog contact							
Garcia-Graells et al., 2013	Belgium, Denmark, and Netherlands	Hog contact duration: 10~30 HRs/week Hog contact duration: <10 HRs/week	7 38	6 10	85.71 26.32	LA-MRSA	[38]
		Exposure to hogs within last 7 days Not exposure to hogs within last 7 days	20 25	14 2	70.00 8.00		
Van Cleef BA et al., 2015	Netherlands	Hog contact duration: per 10 hours/week			PR: 2.11 (p<0.0001)	LA-MRSA	[36]
		Exposure to hogs within last 7 days			PR: 1.97 (p<0.0001)		
Household members							
Van Cleef BA et al., 2015	Netherlands	Household members with MRSA-positive farm workers			PR: 4.63(p<0.02)	LA-MRSA	[36]
Cuny et al., 2009	Germany	Household members with MRSA-positive farm workers	116	5	4.31	LA-MRSA	[18]

		Veterinarians' household members	44	4	9.09	LA-MRSA	
Bisdorff et al., 2012	Germany	Household members with occupational livestock contact among residents without livestock contact			MRSA+(8/25) vs. MRSA-(468/1630)		[37]
		Household members had private visits to farms among residents without livestock contact			MRSA+(15/25) vs. MRSA-(124/1630)		
Neyra et al., 2014	USA	Slaughterhouse workers' household members	35	3	8.57	LA-MRSA	[41]
			35	4	11.43	LA-MDRSA	

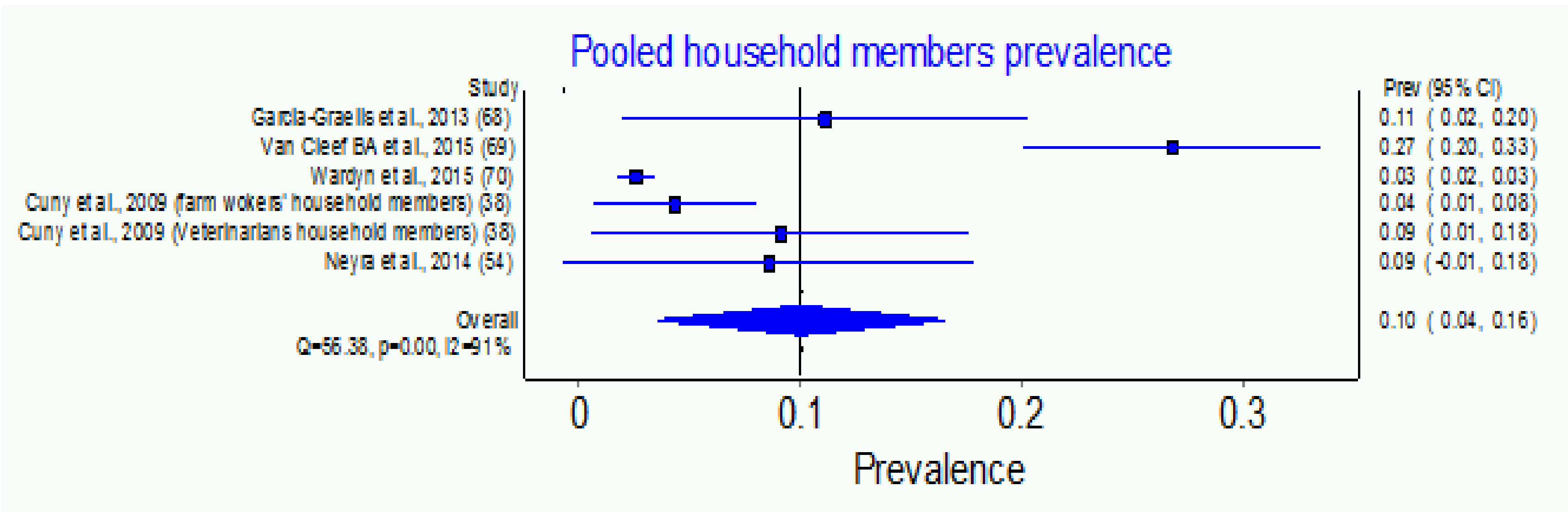

Figure 4. Summary of LA-MRSA prevalence in household members

3.5 Community and visitors

At the community level, a greater hog density on a farm is a potential risk factor for MRSA acquisition for neighboring residents. Table 7 and Figure 5 show the prevalence of MRSA for local communities, non-veterinary visitors, and visiting veterinarians (the pooled prevalence of MRSA in veterinarians was 20% [95% CI: 11%-29%]). Residents in medium-density hog farming areas (1-149 hogs per square mile) had a greater risk for MRSA acquisition (OR: 4.76, 95% CI: 1.36-16.69)[42]. Private farm visits (OR: 3.2, 95% CI: 1.4–7.4) or contact with persons who are directly exposed to livestock (OR: 3.8, 95% CI: 1.5–9.3) may also increase the risk for LA-MRSA acquisition[43]. Garcia-Graells et al. reported a strong direct association (OR: 12.1, 95% CI: 1.6-548.5, p=0.01) between exposure to live hogs and LA-MRSA acquisition for visitors such as veterinarians [45]. Wulf et al. suggested that the average world-wide MRSA prevalence among veterinarians is 12.5% [44]. Cuny et al. found a relatively high prevalence among veterinarians' household members even though they did not have direct contact with livestock [18]. Frana et al. demonstrated that MRSA can be recovered from persons with only short-term exposures to contaminated farms, e.g., pre-visit MRSA-negative veterinary students conducting diagnostic investigations [46].

Table 7. Summary of the studies on community and visitors, by type of exposure

Author and publication year	Country	Occupation of the participants or targets	No. of participants	No. of participants carrying LA-MRSA or LA-MDRSA	LA-MRSA or LA-MDRSA prevalence (%)	Type of Organism/ Note	Reference
Visitors							
Fang et al., 2014	Taiwan	Visitors	16	1	6.25	LA-MRSA	[23]
Veterinarians							
Wulf et al., 2008	Worldwide	Veterinarians	272	34	12.50	LA-MRSA	[44]
Cuny et al., 2009	Germany	Veterinarians	49	22	44.90	LA-MRSA	[18]
Van Cleef BA et al., 2010	Netherlands	Veterinarians in slaughterhouse	13	2	15.38	LA-MRSA	[29]
Garcia-Graells et al., 2012	Belgium and Denmark	Veterinarians	289	16	5.54	LA-MRSA	[45]
		Veterinarians working with livestock	202	13	6.44	LA-MRSA; 11/13 are LA-MDRSA	
Frana et al., 2013	USA	Veterinary student	27	6	22.22	MRSA; Acquired MRSA after visiting hog farms	[46]
Liu et al., 2015	China	Veterinarians			9.40(Pooled)	LA-MRSA	[47]
Wulf, 2006	Netherlands	Veterinarians	99	5	5.05	LA-MRSA	[48]
		Veterinary student	80	2	2.50		
Verkade, 2013	Denmark	Veterinarians	137	60	43.80	LA-MRSA	[49]
Huber, 2010	Switzerland	Veterinarians	133	4	3.01	LA-MDRSA	[50]
Community							
Feingold et al., 2012	Netherlands	LA-MRSA positive residents in rural area	27	12	44.44	LA-MRSA	[39]
		Non-LA-MRSA positive residents in rural area	60	4	6.67		
		LA-MRSA positive residents with contact to hog	27	0	37.04	LA-MRSA	
		Non-LA-MRSA positive residents with contact to hog	60	3	5.00		
Van Cleef BA et al., 2010	Netherlands	Residents contact with hogs in high hog-densities area	49	13	26.53	LA-MRSA; 7/13 are LA-MDRSA	[40]
		Residents without livestock contact in high hog-densities area	534	1	0.19	LA-MRSA	

Author and publication year	Country	Occupation of the participants or targets	No. of participants	No. of participants carrying LA-MRSA or LA-MDRSA	LA-MRSA or LA-MDRSA prevalence (%)	Type of Organism/ Note	Reference
Bisdorff et al., 2012	Germany	Residents contact with hogs in high hog-densities area	190	46	24.21	LA-MRSA	[37]
		Residents without livestock contact in high hog-densities area	1655	25	1.51		
Neyra et al., 2014	USA	Residents near slaughterhouse	111	4	3.60	LA-MRSA	[41]
			111	6	5.41	LA-MDRSA	

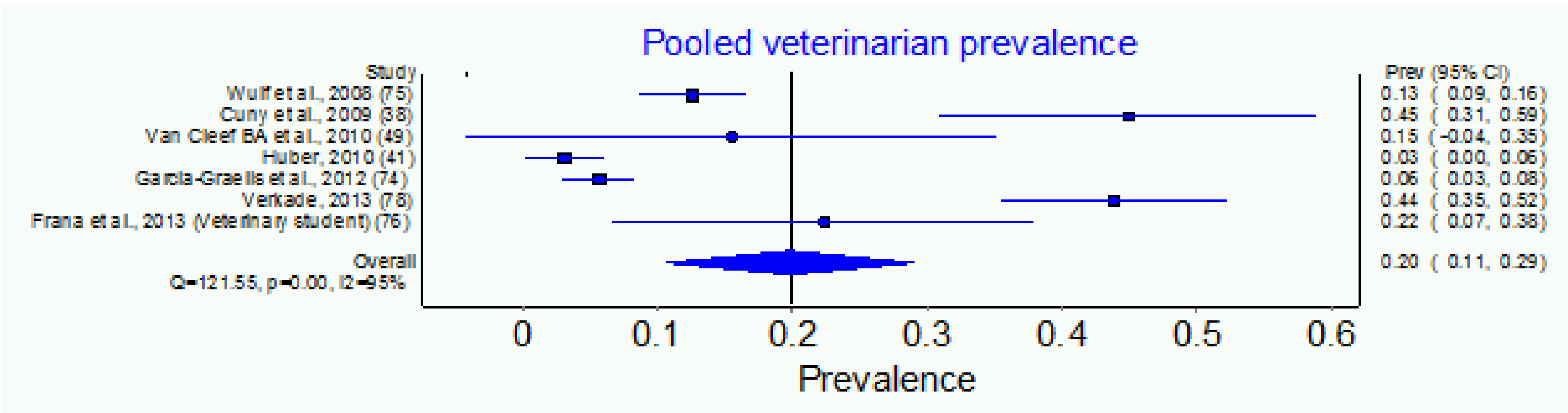

Figure 5. Summary of LA-MRSA prevalence in veterinarians

3.6 Food chain

Table 8 and Figure 6 show the LA-MRSA and LA-MDRSA prevalence in the food chain. The pooled prevalence of LA-MRSA in the food chain was 7% (95% CI: 5%-9%).

The food chain is a known LA-MRSA transmission route, but the prevalence and strains are product-dependent and vary with the region of production. Verhegghe et al. suggested that the observed genetic diversity of the isolates is an indication that MRSA can be transmitted to the human population through cross-contaminated meat [86]; this was corroborated by Wang et al., who found LA-MRSA and LA-MDRSA from both animal and human origin in pork products [87].

Table 8 also shows that the prevalence of LA-MDRSA in pork products varies with the type of preservation and the form of the pork products; fresh pork tends to have a higher prevalence (46.67%, per Boost et al.) but that of frozen pork was much lower (0.56%, from the same study) [52], and the prevalence of MRSA in raw pork (37.5%, per Costa et al.) was higher than that in pork products (6.7%, from the same study) [51]. The similar MRSA prevalence in conventional pork and alternative pork (labeled ‘‘raised without antibiotics’’ or ‘‘raised without antibiotic growth promoters’’) suggests that cross-contamination could occur in the processing facilities [88], which is at least partly corroborated by the work of Buyukcangaz et al., who demonstrated that meat could be contaminated in the meat production chain by documenting the presence of LA-MRSA and LA-MDRSA and comparing the genetic similarity between strains of porcine origin (meat and animals) [89].

Table 8. Summary of the food chain studies

Author and publication year	Country	Occupation of the participants or targets	No. of participants	No. of participants carrying LA-MRSA or LA-MDRSA	LA-MRSA or LA-MDRSA prevalence (%)	Type of Organism/ Note	Reference
Pork products							
Verhegghe et al., 20	Belgium	Pork	137	98	71.53	97% (143/147) isolates are LA-MRSA	[86]
		Ear	23	23	100.00		
		Forelimb	24	21	87.50		
		Rib	24	20	83.33		
		Minced meat	18	11	61.11		
		Bacon	24	12	50.00		
		Chop	24	1	4.17		
Wang et al., 2014	China	Pork	160	1	0.63	2 isolates are LA-MDRSA	[87]
Boost et al., 2013	Hong Kong	Pork	355	78	21.97	LA-MDRSA	[52]
		Fresh pork	165	77	46.67		
		Chilled pork	10	0	0		
		Frozen pork	180	1	0.56		
Costa et al., 2015	Brazil	Raw pork	24	9	37.50	LA-MRSA	[51]
		Prepared pork product	15	1	6.67		
Hanson et al., 2011	USA	Pork	55	2	3.64	LA-MRSA	[90]
O'Brien et al., 2012	USA	Conventional pork	300	19	6.63	LA-MRSA	[88]
		Alternative pork[5]	95	7	7.37	LA-MRSA	
Hiroi et al., 2012	Japan	Raw pork	100	4	4.00	LA-MRSA	[91]
Buyukcangaz et al., 2013	USA	Raw pork	71	5	7.04	4/5 are LA-MDRSA	[89]
Agerso, 2012	Denmark	Pork	153	7	4.58	LA-MRSA	[84]
Lozano, 2009	Spain	Pork	55	1	1.82	LA-MDRSA	[92]
de Boer, 2009	Netherlands	Pork	309	33	10.68	96.68% (32/33) are LA-MRSA	[93]
Weese, 2010	Canada	Pork	230	0	0	Neither LA-MRSA nor LA-MDRSA was detected	[94]
Weese, 2010	Canada	Pork	402	10	2.48	32.26% (10/31) are LA-MRSA	[95]
Waters, 2011	USA	Pork	26	7	26.92	7/11 are LA-MDRSA	[96]
Pu, 2009	USA	Pork	90	0	0	Neither LA-MRSA nor LA-MDRSA was detected	[97]

[5] Alternative pork: labeled "raised without antibiotics" or "raised without antibiotic growth promotants"[88].

Lim, 2010	Korea	Pork	56	0	0	Neither LA-MRSA nor LA-MDRSA was detected	[98]

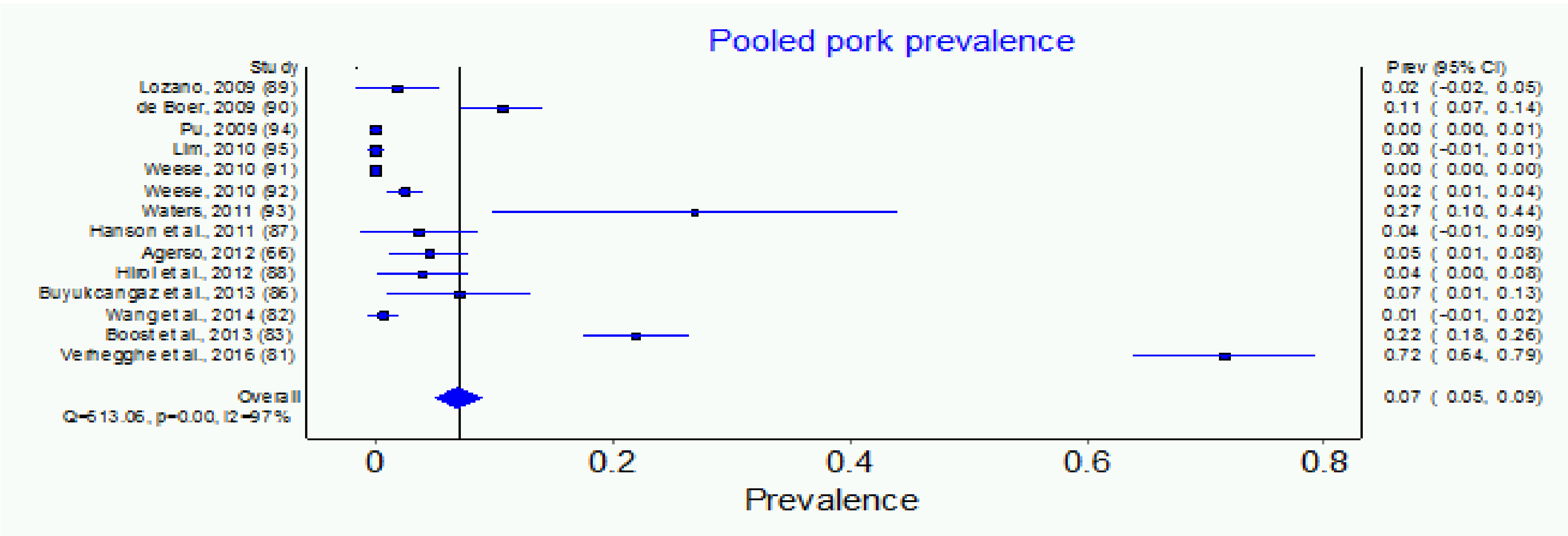

Figure 6. Summary of LA-MRSA prevalence in pork products

3.7 Prevalence in hospital patients

Table 9 and Figure 7 show the prevalence of MRSA in hospital patients. The pooled prevalence of LA-MRSA in hospital patients was 12% (95% CI: 9%-15%).

Several researchers have documented the transmissibility of LA-MRSA in hospitals [55, 99, 100]. Van de Sande-Bruinsma et al. suggested that the major risk factor categories in LA-MRSA-positive patients were contact with hogs, contact with other animals, and unknown source [53]. Kock et al. conducted a case-control study of LA-MRSA positive patients and found that contact with hogs was a crucial risk factor for LA-MRSA carriage (OR: 20.455, 95% CI: 7.831-64.386, $p<0.001$)[54]. Carrel et al. found that living near a high-density hog operation area (>1,000 hog animal units within 1 mile, where a mature hog of >55 pounds equals 0.4 animal units) increased the MRSA carriage in patients (OR: 2.76, 95% CI: 1.27-5.99, $p=0.0101$) [56].

Table 9. Summary of the studies on hospital patients

Author and publication year	Country	Occupation of the participants or targets	No. of participants	No. of participants carrying LA-MRSA or LA-MDRSA	LA-MRSA or LA-MDRSA prevalence (%)	Type of Organism/ Note	Reference
Köck et al., 2013	Germany	Patients	14036	2771	19.74	LA-MRSA	[101]
			14036	2603	18.57	CC398	
			14036	1	0.01	CC30	
			14036	142	1.01	CC5	
			14036	1	0.01	CC97	
			14036	20	0.14	CC9	
Van de Sande-Bruinsma et al., 2015	Netherlands	Patients	3856	292	7.57	LA-MRSA	[53]
Benito et al., 2014	Spain	Patient with livestock contact history	25	19	76.00	LA-MDRSA	[55]
		Patient without livestock contact history	42	21	50.00	LA-MDRSA	
Köck et al., 2011	Germany	MRSA CC398 positive patients	834	149	17.87	LA-MRSA	[100]
		MRSA non-CC398 positive patients	834	442	53.00		
Köck et al., 2010	Netherlands	MRSA carriage among inpatients	19458	18	0.09	Almost 40% are LA-MRSA	[102]
		MRSA infection among inpatients	19458	4	0.02		
Köck et al., 2009	Netherlands and Germany	MRSA positive patients	25540	390	1.53	18.71(73/390) are LA-MRSA	[103]

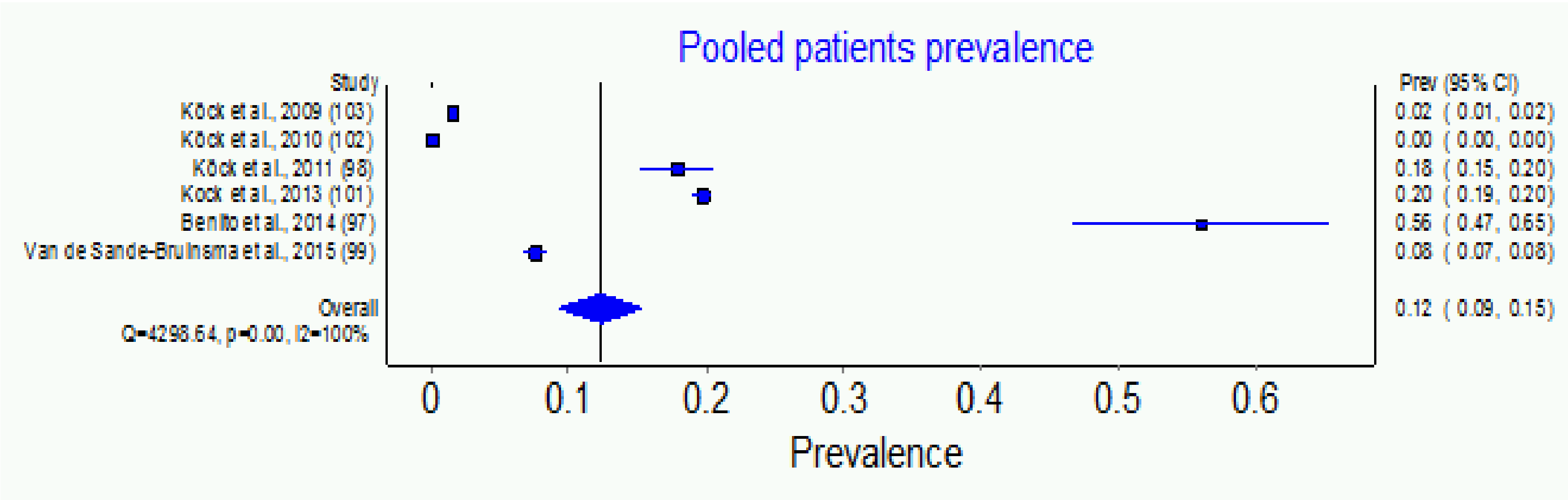

Figure 7. Summary of LA-MRSA prevalence in patients in hospitals

CHAPTER 4: DISCUSSION

In this literature review, I have presented the prevalence of LA-MRSA and of LA-MDRSA, as reported by 78 eligible studies in humans, livestock, and livestock production facilities, together with pooled prevalence estimates where applicable. My findings are consistent with other reviews with regard to the populations at direct risk (farm hogs, farm workers, and veterinarians [104] [105]) and the major risk factors for LA-MRSA transmission to humans (contact with livestock, exposure frequency and duration [106-108]). I also identified other risk factors for LA-MRSA or LA-MDRSA transmission, including the hog farm operation type (industrial rather than antibiotic-free operation), herd size (large-scale herd size), hog age, and hog type.

4.1 Study Limitation

I may have underestimated the frequencies of multidrug resistant *Staphylococcus aureus* strains if the eligible papers presented only results for the major antibiotics resistance tests or the resistance frequency of each antibiotic. If a paper did not explicitly mention terms such as “pig,” “LA-MRSA” or “MDRSA”, my database searches would not have found it; however, I attempted to minimize such omissions by reviewing the reference lists in the included papers and reviews.

Misclassification bias may have also occurred, resulting in underestimates of the prevalence of LA-MRSA and LA-MDRSA, due to category inconsistency in the eligible studies, although I attempted to minimize the impact of misclassification through the use of the inclusion/exclusion criteria. Bias could also be present from analyses using small study sample sizes or if an LA-MRSA investigation did not test for resistance to additional antibiotics. Lastly, because much of the LA-MDRSA data comes from studies on LA-MRSA, HA-MDRSA or CA-MDRSA data may underestimate in this study.

CHAPTER 5: CONCLUSION

In this review, I have documented multiple LA-MRSA and LA-MDRSA transmission routes and risk factors. LA-MRSA and LA-MDRSA can be transmitted from hog farms to other locations and populations via hogs, workers, air, water, and pork products. I have also summarized the prevalence of LA-MRSA and LA-MDRSA in different populations and transmission vectors. Although direct contact with livestock is the greatest risk factor for acquiring LA-MRSA or LA-MDRSA, contamination can occur via air (greater concentrations were found downwind of hog farms), water, soil (where MRSA may linger), and human activity (MRSA present at slaughter may be carried to other locations). I determined that there were other transmission factors within the hog farm environment, including the hog farm operation type, contact with livestock (exposure frequency and duration), large-scale herd size, and hog age. I also found that seasonality (summer) also had a role in airborne LA-MRSA. Lastly, I documented that high-density hog farming is a risk factor for LA-MRSA carriage in household members of farm workers and farm visitors, at the community level and in hospital patients. My findings provide the sources of prevalence datasets needed to estimate the risk of hog-to-human transmission and thus may be useful in the construction of LA-MRSA and LA-MDRSA comprehensive risk assessment models.

APPENDIX: TABLE OF COMBINATION OF SEARCH TERMS

Term 1	Term 2	Term 3
livestock associated mrsa	community	risk
livestock associated mrsa	pig	risk
MRSA	swine	
livestock associated mrsa	community	pig
livestock associated mrsa	worker	risk
livestock associated mrsa	pork chain	
livestock associated mrsa review		
livestock associated mrsa	risk	
MDRSA	community	risk
MDRSA	pig	risk
MDRSA	swine	
MDRSA	community	pig
MDRSA	worker	risk
MDRSA	pork chain	
MDRSA review		
MDRSA	risk	
antibiotic AND resistant AND staphylococcus AND livestock	community	risk
antibiotic AND resistant AND staphylococcus AND livestock	pig	risk
antibiotic AND resistant AND staphylococcus AND livestock	swine	
antibiotic AND resistant AND staphylococcus AND livestock	community	pig
antibiotic AND resistant AND staphylococcus AND livestock	worker	risk
antibiotic AND resistant AND staphylococcus AND livestock	pork chain	
antibiotic AND resistant AND staphylococcus AND livestock	review	
antibiotic AND resistant AND staphylococcus AND livestock	risk	

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