Livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) colonisation and infection among livestock workers and veterinarians: a systematic review and meta-analysis

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ABSTRACT

Objectives Methicillin-resistant *Staphylococcus aureus* (MRSA) is an increasing public health concern worldwide. The objective of this study was to calculate a summary odds ratio (OR) of livestock-associated MRSA colonisation and infection in humans, and to determine specific risk factors in livestock production contributing to MRSA colonisation.

Methods We screened PubMed and Embase for studies published from 2005 to 2019 inclusive, reporting livestock-associated (LA)-MRSA colonisation and infection among livestock workers/veterinarians, their families, and community members not regularly exposed to livestock. The primary outcome of interest was the OR of LA-MRSA colonisation comparing exposed and control groups. Quality was assessed according to the Newcastle-Ottawa quality assessment scale. A meta-analysis using a random-effects model was conducted to calculate a pooled OR. The heterogeneity in the meta-analysis was assessed using the I^2 method, and publication bias was evaluated using funnel plots.

Results A total of 3490 studies were identified by the search, with 37 studies including 53 matched exposed-control groups and 14 038 participants eligible for the meta-analysis. The pooled OR for LA-MRSA among livestock workers and veterinarians is 9.80 (95% CI 6.89 to 13.95; p=0.000; I^2=73.4), with no significant publication bias (Egger's p=0.66). The OR for swine workers was highest at 15.41 (95% CI 9.24 to 25.69), followed by cattle workers (11.62, 95% CI 4.60 to 29.36), veterinarians (7.63, 95% CI 3.10 to 18.74), horse workers (7.45, 95% CI 2.39 to 23.25), livestock workers (5.86, 95% CI 1.14 to 30.16), poultry workers (5.70, 95% CI 1.70 19.11), and industrial slaughterhouse workers (4.69, 95% CI 1.10 to 20.0).

Conclusions Livestock workers, particularly swine farmers, are at significantly higher risk for LA-MRSA colonisation and subsequent infection. These results support the need for preventive practices to reduce LA-MRSA risk among those who handle and treat livestock.

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Key messages

What is already known about this subject?

- ► Methicillin-resistant *Staphylococcus aureus* (MRSA) carriage is prevalent in livestock farmers, veterinarians, slaughterhouse workers, and butchers. However, whether the MRSA strains were livestock associated (LA) was less well-understood.

What are the new findings?

- ► Livestock workers, particularly swine farmers (with an OR of 15.41), are at significantly higher risk for LA-MRSA colonisation and subsequent infection compared with control populations.

How might this impact on policy or clinical practice in the foreseeable future?

- ► Preventive practices to reduce LA-MRSA risk are recommended among those who handle and treat livestock. In addition, coordinated strategies along livestock supply chains are recommended in farms, especially from regions with high risk of LA-MRSA colonisation.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a major cause of antibiotic resistant infections and a broader public health concern worldwide. As one of the most common pathogens in hospital settings, healthcare-associated MRSA (HA-MRSA) is a major cause of skin and soft tissue infections (SSTIs) and severe diseases such as pneumonia and sepsis.[1] Twenty-nine per cent of MRSA carriers develop MRSA infection, which increases length of stay in hospitals, additional in-hospital costs and causes thousands of deaths worldwide.[2] In the USA, MRSA infections killed over 11 000 hospitalised patients in 2011.[3]

Since the 1990s, epidemiological characteristics of MRSA have changed greatly. New MRSA lineages have emerged, acquiring different types of the resistance genes responsible for infections occurring in the community (CA-MRSA, community-acquired MRSA).[4] MRSA has also become widely distributed among livestock due to routine antibiotic use in livestock farming.[5] Livestock-associated (LA)-MRSA strains are different from human MRSA strains, with a higher capacity of establishing and transmitting within livestock herds and potential for spreading and causing infections in humans.[6] International trade of livestock has further intensified transmission of LA-MRSA between animals and humans.[5] As global meat production and consumption have increased rapidly, farmers are facing pressures to produce livestock more efficiently to meet this demand. Often this involves administration of antibiotics worldwide, which can increase the risk of MRSA associated with livestock production.

LA-MRSA strains can be characterised by multilocus sequence typing, consist of *S. aureus* protein A (*spa*) and have a transmissible genetic element called staphylococcal cassette chromosome mec, which carries an element for beta-lactam antibiotic resistance.[7] An increasing body of evidence demonstrates that livestock workers are a high-risk population for LA-MRSA carriage due to regular close contact with animals, especially in farm-intensive regions. LA-MRSA has emerged in swine production globally. The prevalence of LA-MRSA colonisation varies widely among livestock workers throughout the world, with reported rate in pig workers of 24%%–86% in Europe, 25%%–45% in North America, and 6%%–19% in Asia.[8–11] The epidemiology of LA-MRSA strains differs in different geographic regions. In Europe, MRSA ST398 is the predominant clone complex found in livestock workers or veterinarians. Other clones such as ST1 (the USA), ST5 (the USA and Ireland), ST8 (the USA, Denmark and Switzerland), and ST22 (Ireland) were also identified at lower frequencies in livestock operations. In Asian countries, the presence of various clones of LA-MRSA such as ST9, ST63 and ST2359 were reported in livestock workers.[12–14]

LA-MRSA isolates have a strong adherence capacity to human keratinocytes, and humans working closely with livestock harbouring LA-MRSA isolates may become colonised.[15] LA-MRSA can cause severe SSTIs, which mainly occur in persons with occupational exposure to livestock. LA-MRSA is capable of being established in hospital settings via colonised or infected patients, which can lead to nosocomial infections, although the incidence of these infections is rare.[7]

A prior systematic review summarised the prevalence of MRSA carriage in livestock workers: farmers (18.2%), veterinarians (9.4%), slaughterhouse workers (2.6%) and butchers (5.7%).[16] However, whether the MRSA strains were human-associated or livestock-associated was not distinguished, and the extreme heterogeneity of the results (I^2=96.9%) called into question whether a pooled prevalence estimate such as they provided offered a meaningful statistic. In another study, a 760-fold higher risk of MRSA colonisation was found among a group of regional pig farmers compared with the general population.[17]

What has already been uncovered about the risk of livestock-acquired MRSA comes from individual studies examining, mostly, the impact of one type of occupation (eg, swine producer, cattle producer and veterinarian) on the risk of LA-MRSA colonisation. These studies range across multiple different species and multiple different occupations, providing a range of odds ratios (ORs) and relative risks when comparing the exposed population to a control population.

The objective of the current study is to calculate a summary OR of LA-MRSA colonisation and infection in humans who are occupationally exposed to livestock and to determine specific risk factors in livestock production contributing to MRSA colonisation. Our unique contribution in this manuscript is to bring together these studies in a systematic review and meta-analysis: to examine and quantify overall risk of occupational LA-MRSA from multiple different nations worldwide and to pool the data from existing studies on each type of occupation to determine that livestock-related occupations result in the highest LA-MRSA risk.

METHODS

Data sources and search strategy

We performed a systematic review and meta-analysis of the risk of livestock contact in increasing the incidence of MRSA colonisation in occupational workers and veterinarians. A literature search was conducted on PubMed and Embase databases from 31 October to 21 October 2019. The search terms included combinations of: ("methicillin-resistant *Staphylococcus aureus*" OR "MRSA") AND ("livestock" OR "pig" OR "swine" OR "hog" OR "cattle" OR "poultry" OR "farmer" OR "worker"). Retrieved publications were reviewed by examining titles and abstracts, and all potentially relevant articles were subsequently screened as full text. In addition, the search was extended by examining the reference lists of retrieved publications to find more relevant studies linking MRSA carriage with livestock farming or care. No study type or language restriction was imposed. The meta-analyses were conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (research checklist). The leading author (CC) screened the search results and identified relevant papers by reviewing retrieved studies. The quality assessment of included studies was conducted by both authors together. Any discrepancies on inclusion were resolved by joint reevaluation of the original full text by both authors. Studies reporting the occurrence of LA-MRSA colonisation among workers/veterinarians and control populations were included in the analysis. The microbiological method based on strain typing was a criterion for presence of LA-MRSA. Studies without control groups, or that did not differentiate between LA-MRSA and other types of *Staphylococcus aureus*, were excluded. This systematic review is registered with PROSPERO.

Data extraction

The primary outcome of interest was LA-MRSA colonisation among study participants who had close contact with livestock, determined by LA-MRSA strain isolation from nasal, oropharyngeal, or axillary samples. The participants in the eligible studies were divided into exposed and control groups according to their occupational contact with livestock. The exposed group includes the following populations who have direct contact with animals: livestock farmers and veterinarians (including veterinary students) with occupational exposure to various animal species, and slaughterhouse workers including butchers, industrial hog operation and industrial livestock operation workers. The control populations are those who have close proximity to colonised animals but no or minimal direct contact with them, including household and community members of farmers, employees working on farms (eg, salesmen and administrative personnel), antibiotic-free livestock operation workers, and employees not working on farms or treating livestock. These categories allowed the examination of OR of LA-MRSA colonisation among occupations with different levels of exposure to different livestock species.

The following data were extracted from each study: authors, year of publication, study location, study period and duration, study design type, population size, participants' gender and age (range), type of occupations, strain type and genotype identified, and LA-MRSA colonisation rate and infections among exposed and control participants. In addition, the details of the screening including sampling sites (nasal, oropharyngeal or axillary swabs), MRSA isolation method (culture or PCR), genotyping of isolates, carriage status definition and timeframe of the screening process were retrieved from the studies. Regarding detection methods of microbial isolates, two studies applied a culture method (enrichment broth, sheep blood and chromogenic medium) to screen for carriage of MRSA isolates, which is less sensitive than PCR assays to determine the genotype of MRSA. They were excluded from the analysis. When needed, authors were contacted via email to request additional information.

To ensure that only LA-MRSA strains are included in the meta-analysis, numbers of carriers with *spa* types not of animal origin

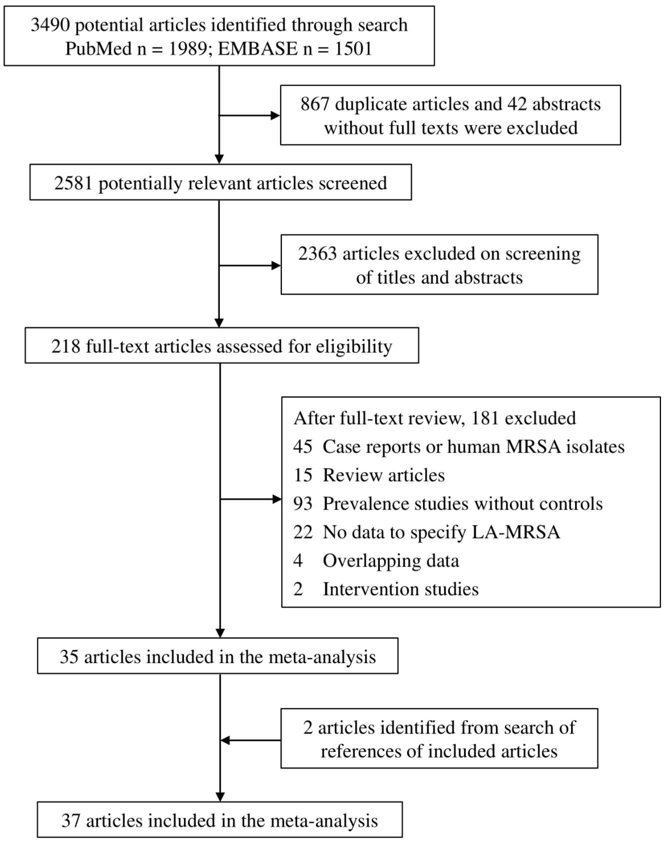

Figure 1 Study selection flow chart. LA-MRSA, livestock-associated methicillin-resistant *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

were subtracted from the LA-MRSA positive persons.[18–20] The secondary outcome of interest was the OR of developing MRSA infections among exposed and control populations. In addition, an index year of each eligible study was determined to model the time trend of LA-MRSA colonisation among participants.

Study quality assessment

Quality assessment of included studies was conducted by both authors according to the Newcastle-Ottawa Scale, a star-based scoring system. Studies that received at least five stars were considered of adequate quality for eligibility.

Data analysis

The OR is a comparison of the odds of an event after exposure to a risk factor (colonisation of LA-MRSA in this analysis) with the odds of that event in a control situation. For each study, matched exposed-control groups were identified, from which ORs and 95% CIs could be calculated between the different exposed and control groups. A random-effects model meta-analysis was conducted to calculate the pooled OR and the associated 95% CI from the eligible studies. Heterogeneity among the selected studies was evaluated using the Cochran's Q value calculated from the Mantel-Haenszel method and I^2 statistic. Sensitivity analyses were conducted by removing each study in turn, and the remaining studies were analysed to determine if the results were significantly impacted by a particular study. The effect of the index year of the study as a covariate on OR of LA-MRSA colonisation was explored through meta-regression analysis for each continent. P values for OR comparisons were calculated using the Fisher's exact test. Bias in meta-analysis was evaluated by asymmetry in funnel plot and related statistical analyses. All statistical analyses were conducted in Comprehensive Meta-Analysis Software V.2.0.

RESULTS

Our literature search retrieved 3490 studies based on our search terms (figure 1). After applying the eligibility criteria described above at the title and abstract level, 2363 studies were excluded. We then retrieved and read the full texts of the remaining 218 studies, from which 35 were selected for sufficient data for our systematic review and meta-analysis. Two of the contacted authors were able to provide information included in the analysis. Two additional articles were identified from search of the references of the 35 included studies. Finally, 37 studies were included in this systematic review and meta-analysis.[12–14 18 21–53] Six studies were of six stars, 32 received five stars (online supplemental material table S1).

An overview of the eligible studies is listed in table 1, including the year(s), location and study type; number and occupation of participants and their gender and age; sample type and measurement of colonisation; *spa* type; number of LA-MRSA carriers in exposed and control populations; and the number of MRSA infection cases. The 37 eligible studies on LA-MRSA colonisation and occupational livestock exposure consist of 26 cross-sectional studies, 5 prospective cohort studies, 3 case–control studies and 3 longitudinal studies published between 2005 and 2019 from nine countries, comprising 53 exposed-control groups and 14 038 participants. Twenty-one studies assessed the risk of MRSA carriage in occupational pig workers, 10 in veterinarians, 7 in cattle workers and 5 in poultry workers.

The overall pooled OR of LA-MRSA carriage among exposed populations based on the random-effects model was 9.80 (95% CI 6.89 to 13.95; p=0.000; I^2=73.4) compared with control populations, among 53 exposed-control subgroups, indicating that livestock contact is a significant risk factor for LA-MRSA colonisation in humans. Stratifying the studies by geographical regions, the pooled OR from Asian countries (farm workers vs non-farm workers) was 4.03 (95% CI 1.44 to 11.29; p=0.15; I^2=46.9). Among European countries, the pooled OR was 9.56 (95% CI 6.90 to 13.25; p=0.000; I^2=76.5). A relatively lower OR (4.69, 95% CI 1.10 to 20.05; p=0.94; I^2=0.000) was found in the USA. Figure 2 shows classifications and population size of subgroups according to their occupational contact with livestock farming and the forest plots for the pooled OR and 95% CI of LA-MRSA colonisation among all exposed subgroups.

When stratifying occupations of the study participants by different animal species, the highest OR was seen in pig workers (15.41; 95% CI 9.24 to 25.69; p=0.000; I^2=68.7), followed by cattle workers (11.62, 95% CI 4.60 to 29.36; p=0.000; I^2=79.0), veterinarians (7.63, 95% CI 3.10 to 18.74; p=0.000; I^2=77.9), livestock workers (5.86, 95% CI 1.14 to 30.16; p=0.23; I^2=32.6), poultry workers (5.70, 95% CI 1.70 to 19.11; p=0.006; I^2=72.3) and industrial operation workers (4.69, 95% CI 1.10 to 20.0; p=0.94; I^2=0.000). Horse workers were 7.45 times (95% CI 2.39 to 23.25; p=0.17; I^2=47.6) more likely to be colonised by LA-MRSA compared with control participants based on two relevant studies. One study reporting risk of LA-MRSA colonisation among patients with sheep contact did not show a different risk (1.0, 95% CI 0.14 to 7.24) than control population.

Medium to substantial heterogeneity (I^2 ≥50) was observed in the subgroups of cattle farmers, veterinarians and poultry workers. The sensitivity analyses show that excluding the most

Table 1 Summary of studies included in the meta-analysis (n=37)

	Country	Study type	Period	Sex*	Age	Exposed population	Control population	Samples	Main *Spa* types of LA-MRSA	Non-LA-MRSA colonisation	Infection
Angen *et al*[21]	Denmark	One-week longitudinal study.	2016	27/7	–	48 volunteers visiting a swine farm.	46 passive observers.	Nasal and throat swabs.	LA-MRSA CC398 (t011).		
Bisdorff *et al*[18]	Germany	Cross-sectional study.	2009–2010	Non-OLC: 913/742; OLC: 58/132.	Non-OLC: 42.2; OLC 42.7.	1655 OLC group.	190 non-OLC group.	Nasal swabs.	ST398 (t034 and t011).	7 out of 25 non-OLC carried HA-MRSA.	
Bos *et al*[22]	The Netherlands	Longitudinal study	–	291/371	30.7 (0–83)	182 pig farmers and 67 cattle farmers.	286 family members of pig farmers and 127 of cattle farmers.	Nasal swabs.	ST398		
Cuny *et al*[23]	Germany	Cross-sectional study.	September 2007–January 2009	--	–	113 pig farmers; 49 veterinarians.	116 non-exposed family members of pig farmers; 44 non-exposed family members of veterinarians.	Nasal swabs.	ST398 (t011, t034, t2974 and t108).	–	
Denis *et al*[24]	Belgium	Cross-sectional.	April–July 2007	--	–	75 pig farmers.	27 persons without pig contact.	Nasal swabs and wound.	ST398 (t011, t034 and t567).	–	One LA-MRSA carrier had hand lesion infection.
Fang *et al*[12]	Taiwan	Cross-sectional study.	June–October 2012	16/84		52 pig farm workers.	32 auction market employers and 16 regular visitors.	Nasal swabs.	ST9 (t899 and t1939).	Three farmers carried CA-MRSA.	–
Geenen *et al*[27]	The Netherlands	Cross-sectional study.	July 2010–May 2011.	–	Mean: 36.	47 farmers.	89 family members and 9 employees.	Nasal swabs.	ST398 (t011, t034 and t0108).		
Gracia-Graells *et al*[26]†	Belgium, Denmark and The Netherlands	6 months longitudinal study.	2009–2010	–	–	15 pig farmers.	45 household members.	Nasal swabs.	ST398 (t011, t034, t0108 and t1451).		
Gracia-Graells *et al*[25]	Belgium	Cross-sectional study, Belgium.	February–April 2010	50/96	45.1	105 veterinarians working with livestock.	41 veterinarians not working with livestock.	Nasal swabs.	ST398 (t011, t034, t1451 and so on).	–	
Gracia-Graells *et al*[25]	Denmark	Cross-sectional study, Denmark.	February–October 2010	--	–	97 veterinarians working with livestock.	46 veterinarians not working with livestock.	Nasal swabs.	ST398 (t011, t034, t1451 and so on).	–	
Graveland *et al*[28]	The Netherlands	Cross-sectional study.	October 2007–March 2008	177/213	0–85	97 calf farmers.	259 family members and 34 employees.	Nasal swabs.	ST398 except four (t002, t015, t084 and t166).	1 HA-MRSA and 3 CA-MRSA carriers.	
Hatcher *et al*[29]	USA	Cross-sectional study.	2014	Adult: 252/148; children: 187/213.	–	198 IHO worker–child household pairs.	202 community referent adult–child household pairs.	Nasal swabs.	ST5 (t002), ST8 (t008 and t088).		
Huber *et al*[30]	Switzerland	Conference participants.	March–September 2009	–	–	148 pig farmers and 133 veterinarians.	179 slaughterhouse employees.	Nasal swabs.	All CC398 (ST8 t064, ST398 t011 and t034).		
Köck *et al*[31]	Germany	Case–control study.	January 2005–December 2008.	Case group: 23/77; control: 38/62.	Case group: 48; control: 54.	100 patients with LA-MRSA.	100 patients with other than LA-MRSA.	Nasal swabs.	ST398 (t011, t034, t108 and t1451).	–	
Lewis *et al*[32]	Denmark	Case–control study.	2004–2007	Case-patients: 13/8.	Median of case-patients 29 (8 monnths–80 years).	21 case patients with CC398 MRSA.	42 controls.	MRSA isolates from patients.	ST398 (t034, t108 and t1793).	–	10 case-patients had reported SSTI.
Moodley *et al*[33]	Denmark	Conference participants.	August 2006–February 2007	–	–	231 veterinarians, 72 veterinary students or nurses, 98 farmers.	301 unexposed persons.	Nasal swabs.	CC8 (t008), CC22 (t020 and t022), CC59 (t216), CC88 (t186) CC398 (t011 and t034).	Exposed: 6/9 were LA-MRSA carriers; unexposed: 1/2 was LA-MRSA carrier.	
Mutters *et al*[34]	Germany	Cross-sectional study.	June–October 2012	–	–	63 occupationally exposed individuals.	126 patients.	Nasal and rectal swabs.	Farmers CC398; 4/126 control inpatients CC398.		

continued

Table 1 continued

	Country	Study type	Period	Sex*	Age	Exposed population	Control population	Samples	Main *Spa* types of LA-MRSA	Non-LA-MRSA colonisation	Infection
Nadimpalli *et al*[35]	USA	Cross-sectional study.	October 2013–February 2014	94/89	Mean: 30.	103 IHO workers.	80 family members.	Nasal swabs.	CC398		6 IHO and 6 of 80 household members had SSTI.
Neyra *et al*‡[36]	USA	Cross-sectional study.	September–November 2011	196/140	15–82	162 hog slaughter workers.	63 household members of plant workers and 111 community residents.	Nasal swabs.	ST1 (LA-MRSA), ST5 (HA-MRSA), ST8, 1 of ST72 (CA-MRSA) and ST398.		
Oppliger *et al*[37]	Switzerland	Cross-sectional study.	June 2008–July 2009	–	–	75 pig farmers and veterinarians.	128 persons without animal contact.	Nasal swabs.	CC398.	–	
Pletinckx *et al*[38]	Belgium	Cross-sectional study.	July 2009–October 2010	–	–	10 farmers and 10 veterinarians.	13 family members (living in farms).	Nasal swabs.	ST398 (t011 t034 t567).		
Richter *et al*[39]	Germany	Cross-sectional study.	June–October 2009	--		39 people with frequent contact with turkeys.	20 persons being rarely or never in turkey houses.	Nasal swabs.	ST398 (t011 and t034).		
Rinsky *et al*[40]	USA	Cross-sectional study.	May–December 2011	ILO: 59/40; AFLO: 46/59.	–	80 ILO workers.	19 household members of ILO workers, 92 AFLO workers and their 13 household members.	Nasal swabs.	CC398		
Sahibzada *et al*[41]	Australia	Cross-sectional study.	2015	12/40	–	37 piggery staff working in pig contact.	15 workers working in the agriculture or feedmill section.	Nasal swabs.	LA-MRSA ST398.	29 piggery staff carried ST93; two workers working in the agriculture or feedmill carried ST93.	
Schmithausen *et al*[42]	Germany	Cross-sectional study.	June–December 2012	–	–	79 pig farmers.	7 family members.	Nasal swabs.	ST398 (t011 and t034).		
van Cleef *et al*[44 45]†	The Netherlands	Prospective cohort study.	2010–2011	103/68	Median: 16 (0–70).	110 pig farmers.	171 household members.	Nasal swabs.	MLVA complex (MC) 398.		
van den Broek *et al*[46]	The Netherlands	Cross-sectional study.	January–October 2007	107/125	0–86	50 farmers.	171 family members and 11 coworkers.	Anterior nasal swabs.	ST398 (t108, t011 and t567 and others).	–	
Van Cleef *et al*[43]	The Netherlands	Cross-sectional study.	2008	16/233	Mean: 43.	207 slaughterhouse workers, 13 veterinarians and auxiliaries.	29 administrative and technical personnel.	Nasal swabs.	ST398 (t011 and t108).		
Vandendriessche *et al*[49]	Belgium	Cross-sectional study.	August 2009–May 2011	–	–	149 farmers: pig (25), veal (45), dairy (22), beef (21) and broiler (36).	42 farmers and family members living on horticulture farms.	Nasal swabs.	CC398 (t011, t034 and t567).		
van Duijkeren *et al*[47]	The Netherlands	Cross-sectional study.	November 2013–September 2014	–	–	11 turkey farmers.	32 family members and employees.	Nasal swabs.	ST398 (t011)		
van Loo *et al*[48]	The Netherlands	Case–control study.	2003–2005	56/55	Case: 42.7; control: 47.2.	35 case patients with CC398.	76 control patients with non-CC398 MRSA.	NT-MRSA isolates from patients.	ST398 (t108, t011, t034 and t571).	–	
Verkade *et al*[50]	The Netherlands	A 1-year prospective cohort study.	2009–2011	–	18–65.	135 livestock veterinarians.	386 non-exposed household members.	Anterior nares or oropharynx swabs.	MC398.		
Walter *et al*[51 52]	Germany	Prospective cohort study.	2011–2014	–	Median of 45 for LA-MRSA participants.	1435 participants of veterinary congresses.		Nasal swabs.	CC398 (t011, t034 and t571).		
Wang *et al*[13]	China	Cross-sectional study.	November 2013–November 2014	597/593	Workers: 39.3 controls: 36.4.	335 pig-related workers (including 178 slaughterhouse workers and 157 butchers).	855 control workers.	Nasal swabs.	Only 4 MRSA in workers and 3 in controls were LA.		

continued

Table 1 continued

	Country	Study type	Period	Sex*	Age	Exposed population	Control population	Samples	Main *Spa* types of LA-MRSA	Non-LA-MRSA colonisation	Infection
Wulf *et al*[53]	The Netherlands	Prospective surveillance study.	–	726/127	Mean: 36.9.	222 healthcare worker.	633 controls.	Throat and nasal swabs.	ST398 (t108).		
Ye *et al*[14]	China	Cross-sectional study.	November 2013–November 2014	669/1191	15–60	682 occupational livestock workers (224 farm workers, 20 veterinarians, 194 slaughterhouse workers and 244 butchers).	1178 controls	Anterior nasal swabs.	CC9 (ST9, ST63 and ST2359).	Farmers: 18/48 were LA-MRSA; controls: 2/16 were LA-MRSA.	–

*The number of female and male participants.
†LA-MRSA carriers were those who were colonised by LA-MRSA persistently or intermittently.
‡Tetracycline resistance was considered as the marker for livestock association among MRSA strains that showed resistance to cefoxitin.
AFLO, antibiotic free livestock operation; CA, community-associated; HA, healthcare associated; IHO, industrial hog operation; LA, livestock-associated; MLVA, multilocus variable-number-tandem-repeats analysis; OLC, occupational livestock contact; *Spa*, *Staphylococcus aureus* protein A; SSTI, skin and soft tissue infection.

heavily contributing study resulted in significantly reduced heterogeneity within these subgroups (figure 3).

The time trend plot (online supplemental material figure S1) on the basis of index year of the eligible studies indicated that a decreasing trend of LA-MRSA colonisation among livestock workers existed only in European countries (fixed effect, $p=0.046$), but not in North America ($p>0.5$) or Asia ($p>0.5$). Three of the selected studies recorded SSTI among the participants. The risk for MRSA infections based on these studies was 3.44 (95% CI 0.20 to 58.3; $p=0.015$; $I^2=76.1$) among occupational livestock workers. In hospital settings, infections with more serious symptoms and outbreaks caused by LA-MRSA among persons with occupational livestock contact have also been reported.

Publication bias was assessed by a funnel plot (online supplemental material figure S2). The associated statistical test (Egger's test $p=0.66$) of funnel plot asymmetry indicated that publication bias was not a serious limitation in our meta-analysis.

DISCUSSION

Our analysis indicates that livestock-exposed populations were 9.80-fold more likely to be colonised by LA-MRSA than the control population. In particular, pig farmers had the highest OR for LA-MRSA colonisation of 15.41. The differences in ORs for different livestock species may result from differences in basic facilities and operations across the species, or differences in transmissibility of LA-MRSA between each of these species and humans.

Our study has several limitations. The prevalence of LA-MRSA carriage in human population is associated with animal-to-human transmission, human-to-human transmission and airborne route.[54] Intensive contact with livestock allows LA-MRSA to persist in workers, and transmission events can occur on farms and beyond farms. Thus, the long-term persistence of the carriage is considered to play a key role in the transmission dynamics of LA-MRSA.[55] In this regard, a main limitation of our analysis is that the transmission dynamics of LA-MRSA was not taken into account when using the association between cause and effect in epidemiology. For the majority of the selected studies, whether the LA-MRSA carriage patterns were intermittent or persistent was not identified in studies that took cross-sectional nasal and/or throat samples; only six studies examined samples longitudinally at multiple time points in which occurrence of MRSA carriage over time is associated with the use of antibiotics and other determinants.[21 26 45 50 51] New evidence suggests that colonisation of ST398 in humans is potentially more persistent; the transmission from farm workers to their household members occurs at a low but consistent percentage.[2 23] Therefore, we assumed the carriage of LA-MRSA being in equilibrium, although this state is practically subject to change due to population dynamics and stochastic events in the transmission. Nonetheless, the weight of evidence shows that occupational livestock contact puts the workers at higher risk for LA-MRSA colonisation.[56]

We should take into account that a single nasal or throat swab is not a proof of colonisation of LA-MRSA, which has been shown to be a relatively weak coloniser in humans, where carriage of MRSA can disappear in the absence of animal exposure. However, in the majority of the selected studies, nasal and/or throat swab samples were collected for the detection of LA-MRSA carriage, except two studies in which the strain isolates were collected from patients infected with LA-MRSA, which may overestimate the number of positive individuals and

Study name	Subgroup within study	Livestock contact	Control	Odds ratio
Kock et al. 2009	Cattle	25 / 100	3 / 100	10.778
vandendriessche et al. 2013	Cattle	25 / 63	1 / 30	19.079
Bos et al. 2016	Cattle	18 / 67	12 / 127	3.520
Graveland et al. 2010	Cattle	31 / 97	27 / 293	4.627
van Loo et al. 2007	Cattle	7 / 29	1 / 63	19.727
Bisdorff et al. 2012	Cattle	18 / 59	18 / 1655	39.927
Lewis et al. 2008	Cattle	6 / 21	0 / 42	35.645
Subgroup (I^2 = 79.0, p = 0.000)				11.624
Kock et al. 2009	Horse	19 / 100	5 / 100	4.457
Bisdorff et al. 2012	Horse	3 / 22	18 / 1655	14.360
Subgroup (I^2 = 47.6, p = 0.167)				7.450
Nadimpalli et al. 2016	Industrial operation	1 / 103	0 / 80	2.356
Neyra et al. 2014	Industrial operation	1 / 162	0 / 174	3.241
Hatch et al. 2017	Industrial operation	2 / 198	1 / 602	6.133
Rinsky et al. 2013	Industrial operation	2 / 80	0 / 124	7.930
Subgroup (I^2 = 0.000, p = 0.943)				4.693
Moodley et al. 2008	Livestock	0 / 98	1 / 301	1.017
Wulf et al. 2008	Livestock	1 / 222	1 / 633	2.860
Ye et al. 2015	Livestock	18 / 682	2 / 1178	15.940
Subgroup (I^2 = 32.6, p = 0.227)				5.856
Angen et al. 2017	Pig	48 / 48	40 / 46	15.568
Sahibzada et al. 2018	Pig	5 / 37	0 / 15	5.246
Pletinckx et al. 2013	Pig	9 / 10	11 / 13	1.636
Kock et al. 2009	Pig	62 / 100	6 / 100	25.561
vandendriessche et al. 2013	Pig	9 / 16	1 / 30	37.286
Fang et al. 2014	Pig	7 / 52	3 / 48	2.333
Wang et al. 2017	Pig	4 / 335	3 / 855	3.432
Bos et al. 2016	Pig	116 / 182	29 / 286	15.576
van Cleef et al. 2010	Pig	12 / 207	0 / 29	3.772
Denis et al. 2009	Pig	35 / 75	4 / 27	5.031
Schmithausen et al. 2015	Pig	42 / 79	1 / 7	6.811
Cuny et al. 2009	Pig	97 / 113	5 / 116	134.588
van den Broek et al. 2009	Pig	28 / 98	5 / 134	10.320
van Cleef et al. 2014; 2015	Pig	88 / 110	45 / 171	11.200
van Loo et al. 2007	Pig	11 / 29	3 / 63	12.222
Bisdorff et al. 2012	Pig	39 / 104	18 / 1655	54.567
Oppliger et al. 2012	Pig	5 / 75	0 / 128	20.050
Gracia-Graells et al. 2013	Pig	14 / 15	16 / 45	25.375
Lewis et al. 2008	Pig	13 / 21	0 / 42	135.000
Mutters et al. 2016	Pig	24 / 38	4 / 126	52.286
Subgroup (I^2 = 68.7, p = 0.000)				15.407
vandendriessche et al. 2013	Poultry	1 / 29	1 / 30	1.036
Geenen et al. 2013	Poultry	4 / 47	4 / 98	2.186
Richter et al. 2012	Poultry	18 / 39	4 / 20	3.429
Duijkeren et al. 2016	Poultry	5 / 11	2 / 32	12.500
Bisdorff et al. 2012	Poultry	15 / 75	18 / 1655	22.736
Subgroup (I^2 = 72.3, p = 0.006)				5.704
Kock et al. 2009	Sheep	2 / 100	2 / 100	1.000
Subgroup (I^2 = 0.000, p = 1.000)				1.000
Huber et al. 2010	Veterinarians	4 / 133	0 / 179	12.475
Pletinckx et al. 2013	Veterinarians	9 / 11	11 / 13	0.818
Moodley et al. 2008	Veterinarians	6 / 303	1 / 301	6.061
Gracia-Graells et al. 2012b	Veterinarians	2 / 97	0 / 46	2.435
Walter et al. 2016; 2017	Veterinarians	64 / 695	35 / 963	2.689
van Cleef et al. 2010	Veterinarians	2 / 13	0 / 29	12.826
Cuny et al. 2009	Veterinarians	22 / 49	4 / 44	8.148
Gracia-Graells et al. 2012a	Veterinarians	11 / 105	0 / 41	10.101
Verkade et al. 2014	Veterinarians	59 / 135	16 / 389	18.098
Mutters et al. 2016	Veterinarians	15 / 25	4 / 126	45.750
Overall				7.627
I^2 = 73.4, p = 0.000				9.704

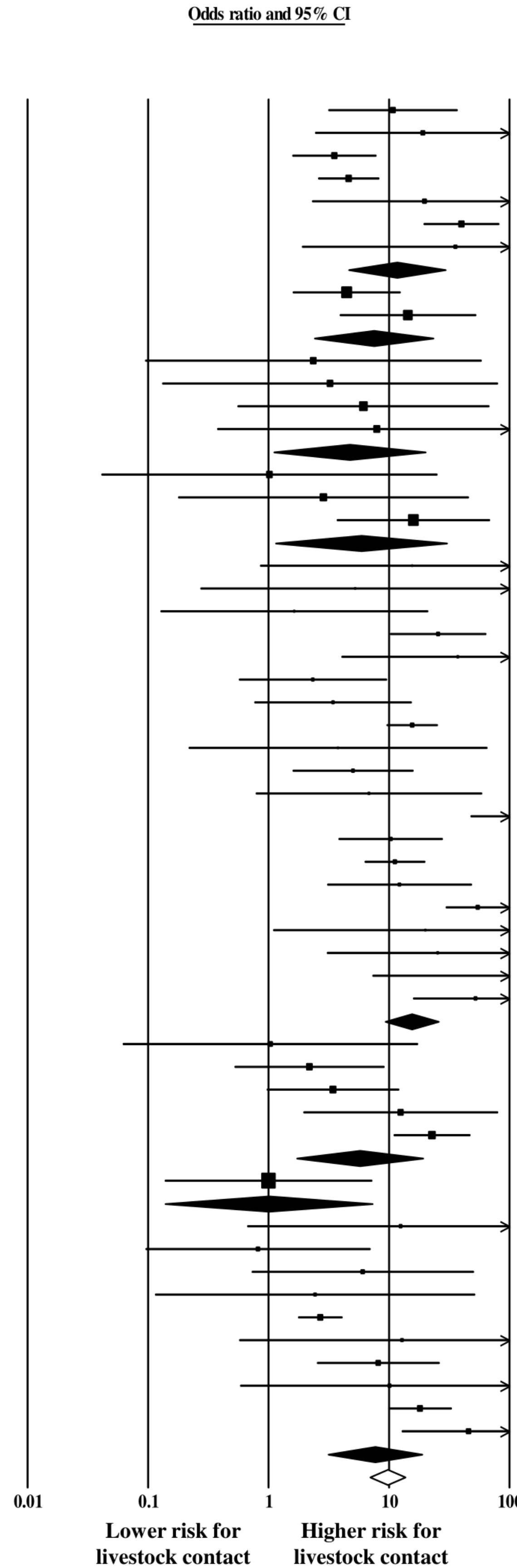

Figure 2 Forest plots of the OR and 95% CI for studies of LA-MRSA colonisation among subgroups who have contact with different animal species. The squares indicate or estimate within each subgroup; the diamond at the bottom indicates the pooled OR estimate in the meta-analysis according to the random-effects model.

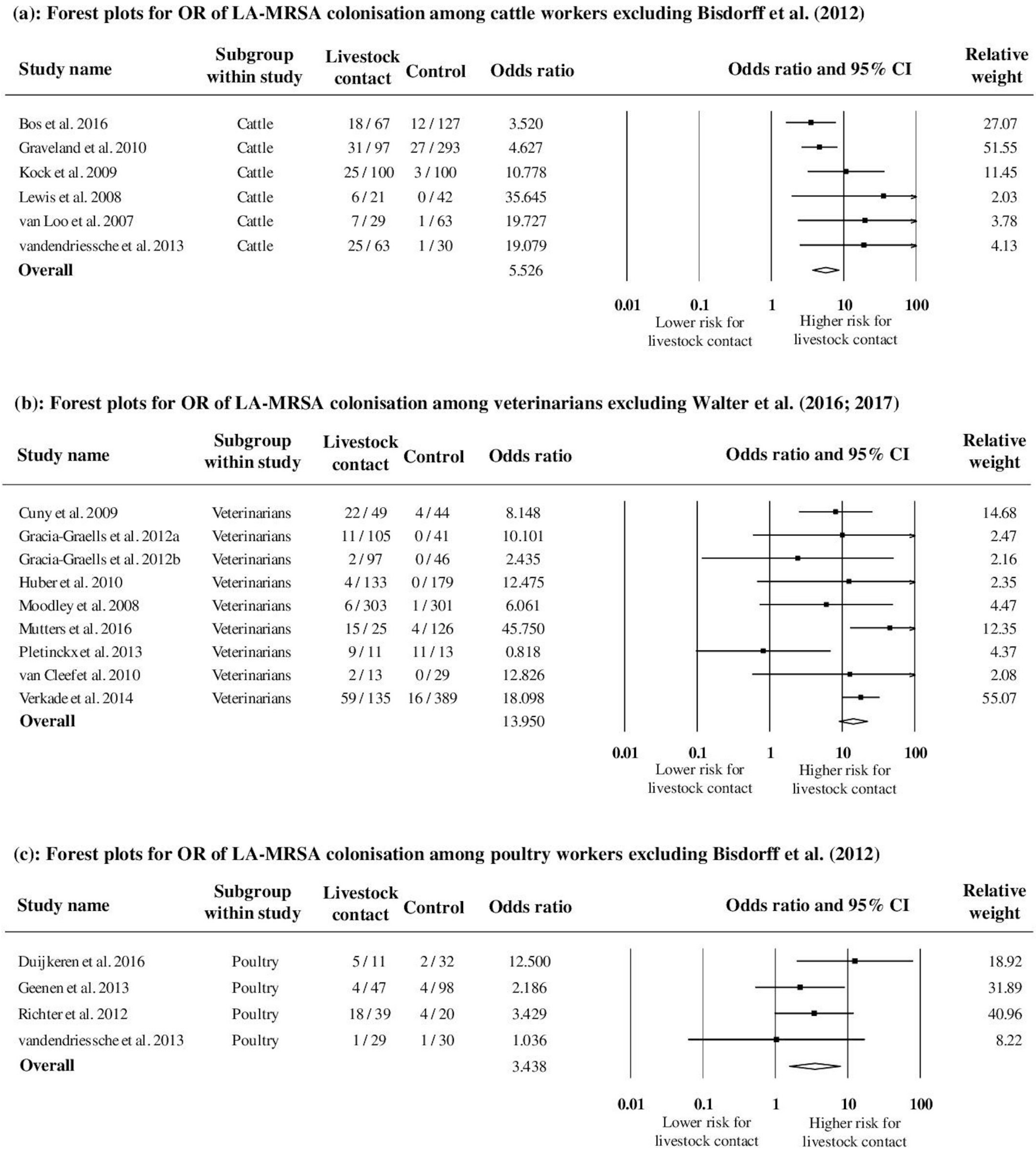

Figure 3 Forest plots for one-study-removed meta-analysis of OR among cattle workers (A), poultry workers (B) and veterinarians (C). The plots show the OR estimate when each study is removed from the meta-analysis. The deviation from the full analysis indicates the sensitivity of the full analysis with respect to each study, indicating the weight a particular study contributes to the meta-analysis. LA-MRSA, livestock-associated methicillin-resistant *Staphylococcus aureus*.

therefore is another limitation of our study. Moreover, colonisation of ST398 in humans has the potential to be more persistent and a strong link exists between occupational animal contact and persistent LA-MRSA colonisation.[2 44] Participants in the studies reviewed here generally have long-term repetitive contact with livestock, which is a major risk factor for persistent LA-MRSA carriage in humans.

Because no associations of the risk of LA-MRSA colonisation were found for demographic information (dietary preferences, exposure to raw meat, smoking, contact sports and travel) and medical history (exposure to healthcare facilities and antibiotic usage),[12 23 26] these variables were not considered as risk factors in our meta-analysis. In intensive farming, some livestock workers take preventive measures during work to reduce the risk of bacterial infection. Unfortunately, these measures have not been broadly successful for preventing occupational acquisition of LA-MRSA. For example, the majority of industrial hog operators wear protective footwear, long sleeves, long trousers or coveralls when working in operation areas.[35] However, the OR (4.69) of LA-MRSA colonisation among this group was still significantly higher than control population. Moreover, implementing nationwide eradication programmes has proven difficult.[54] Although the majority of LA-MRSA colonisation cases in occupationally exposed persons may be asymptomatic, a quantitative association between LA-MRSA carriage and infection still needs to be investigated in the future research.

The time trend analysis shows a decreasing risk of LA-MRSA colonisation among livestock workers in European countries. This may be due to multiple different phenomena. Farming practices may be improving to reduce LA-MRSA transmission risk, including methods to keep animals healthy without the need for antibiotics; such as the use of vaccines, nutritional supplements, prebiotics, probiotics or synbiotics, and waste management strategies.[57] Veterinarians are more informed than ever about the risks of antimicrobial resistance; hence, they are careful in their own use of antibiotics with animals as well as the advice that they provide to livestock and poultry farmers. However, changes in the prevalence in control populations may also contribute to the change in risk of colonisation over time. We calculated the time trend of the risk difference of LA-MRSA carriage between populations with intensive animal contact and those in the control population and found that the risk difference remains stable over time ($p>0.1$) based on a meta-regression analysis, which might suggest an equilibrium of prevalence of LA-MRSA between the exposed and control groups.

Most (28 out of 37) of the selected studies are originated from European countries, but the risk of LA-MRSA colonisation varied widely among countries. This may be because of different regulations or enforcement of regulations regarding animal operations (including antibiotic use) across countries or because of differences in climate (temperature and precipitation) that could affect MRSA transmission rates. Trading colonised animals between countries is a vehicle and considered as another major risk factor for transmission of LA-MRSA between humans and pigs.[58] In MRSA-free areas, livestock imports should be considered an important route of introduction of LA-MRSA into livestock populations.[59] The LA-MRSA strains in pig supplying farms from regions with high risk of LA-MRSA colonisation can highly affect the MRSA status of the recipient farms. In addition, associations have been observed between MRSA infections and high-density livestock production.[7] Coordinated strategies along livestock supply chains are recommended to control and prevent LA-MRSA in livestock farming and trade.

The source of heterogeneity in the meta-analysis is also a limitation. Many studies providing the prevalence of LA-MRSA among livestock workers without a control population were excluded, prohibiting a calculation of an OR. Currently, there is lack of consensus on validated markers for detecting livestock-associated *S. aureus*, which may be a source of heterogeneity in our analysis. Absence of *scn*, positivity of *mec*A and tetracycline resistance are recognised as main indicators of livestock association among MRSA isolates.[35] However, these characteristics have also been found in other lineages. Some strains of LA-MRSA appear to be phylogenetically originated in humans and evolved a variety of adaptations via transmission and spread among hosts.[60] As a result, some strains of LA-MRSA may be human associated. Second, no selected studies originated from Africa or South Asia, which influences the representativeness of our analysis but highlights the need for further research in these regions.

The risk of developing LA-MRSA colonisation among livestock workers and veterinarians is also affected by other risk factors: livestock density and the type of farm or stage of animal production (eg, LA-MRSA transmission risk was higher in sows than finishing pigs), antimicrobial use history, hospital admission, working on farms with MRSA-positive animals, herd size and sanitary conditions.[23 46 56] These factors vary among individuals and different geographical regions, representing additional source of heterogeneity. However, these variables have not been measured in the majority of the selected studies. Our analysis summarised a combined estimate of the OR but was not able to identify the contributions of these risk factors to LA-MRSA colonisation among study participants.

The principal strength of our study is the analysis of the OR of LA-MRSA colonisation and infection among livestock workers and veterinarians as the main outcomes of the occupational contact with livestock. The pooled OR indicates a high risk and major burden of LA-MRSA colonisation and infection currently involved in livestock contact, which underscores the importance of this clone for global occupational health. Occupational exposure to pigs is the most important factor for LA-MRSA carriage, which underscores the importance of this clone for global occupational health. Future studies should focus on implementing interventions in livestock farming and operation and veterinary settings and determining the effectiveness of these interventions in reducing LA-MRSA colonisation among occupational workers and veterinarians.

CONCLUSION

The review shows that livestock workers, particularly swine farmers, are at significantly higher risk for LA-MRSA colonisation and subsequent infection. These results support the need for preventive practices to reduce LA-MRSA risk among those who handle and treat livestock. In addition, coordinated strategies along livestock supply chains are recommended in farms, especially from regions with high risk of LA-MRSA colonisation, to control and prevent LA-MRSA in livestock farming.

Contributors FW conceived and designed the study. CC did the literature review and data extraction. Both authors evaluated the studies. CC was involved in the data synthesis and statistical analysis. CC and FW contributed to the interpretation of the data and writing of the manuscript. Both authors agreed with its content and approved the final submitted version.

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Supplemental Material

Livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) colonization and infection among livestock workers and veterinarians: a systematic review and meta-analysis

Chen Chen, Felicia Wu

Chen C, Wu F. *Occup Environ Med* 2020;0:1–11. doi: 10.1136/oemed-2020-106418

Table S1: Quality assessment of eligible studies.

Study	Selection				Comparability	Outcome			Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Angen et al (2017)	★	★	★	NA	NA	★	★	★	6
Bisdorff et al (2012)	★	★	★	NA	NA	★	★	NA	5
Bos et al (2016)	★	★	★	NA	NA	★	★	★	6
Cuny et al (2009)	★	★	★	NA	NA	★	★	NA	5
Denis et al (2009)	★	★	★	NA	NA	★	★	NA	5
Fang et al (2014)	★	★	★	NA	NA	★	★	NA	5
Geenen et al (2013)	★	★	★	NA	NA	★	★	NA	5
Gracia-Graells et al (2012)	★	★	★	NA	NA	★	★	NA	5
Gracia-Graells et al (2013)	★	★	★	NA	NA	★	★	★	6
Graveland et al 2010	★	★	★	NA	NA	★	★	NA	5
Hatcher et al (2017)	★	★	★	NA	NA	★	★	NA	5
Huber et al 2010	★	★	★	NA	NA	★	★	NA	5
Köck et al (2009)	★	★	★	NA	NA	★	★	NA	5
Lewis et al (2008)	★	★	★	NA	NA	★	★	NA	5
Moodley et al (2008)	★	★	★	NA	NA	★	★	NA	5
Mutters et al (2016)	★	★	★	NA	NA	★	★	NA	5
Nadimpalli et al (2016)	★	★	★	NA	NA	★	★	NA	5
Neyra et al (2014)	★	★	★	NA	NA	★	★	NA	5
Oppliger et al (2012)	★	★	★	NA	NA	★	★	NA	5
Pletinckx et al (2013)	★	★	★	NA	NA	★	★	NA	5

Richter et al (2012)	★	★	★	NA	NA	★	★	NA	5
Rinsky et al (2013)	★	★	★	NA	NA	★	★	NA	5
Sahibzada et al. (2018)	★	★	★	NA	NA	★	★	NA	5
Schmithausen et al (2015)	★	★	★	NA	NA	★	★	NA	5
van Cleef et al (2010)	★	★	★	NA	NA	★	★	NA	5
van Cleef et al (2014; 2015)	★	★	★	NA	NA	★	★	★	6
Vandendriessche et al (2013)	★	★	★	NA	NA	★	★	NA	5
van den Broek et al (2009)	★	★	★	NA	NA	★	★	NA	5
van Duijkeren et al (2016)	★	★	★	NA	NA	★	★	NA	5
van Loo et al (2007)	★	★	★	NA	NA	★	★	NA	5
Verkade et al (2014)	★	★	★	NA	NA	★	★	★	6
Walter et al (2016; 2017)	★	★	★	NA	NA	★	★	★	6
Wang et al (2017)	★	★	★	NA	NA	★	★	NA	5
Wulf et al (2008)	★	★	★	NA	NA	★	★	NA	5
Ye et al (2015)	★	★	★	NA	NA	★	★	NA	5

NA=not applicable.
*The Newcastle-Ottawa Scale (NOS) consists of three parameters to evaluate the quality of individual studies: selection (four stars), for comparability (two stars) and exposure/outcome (three stars).

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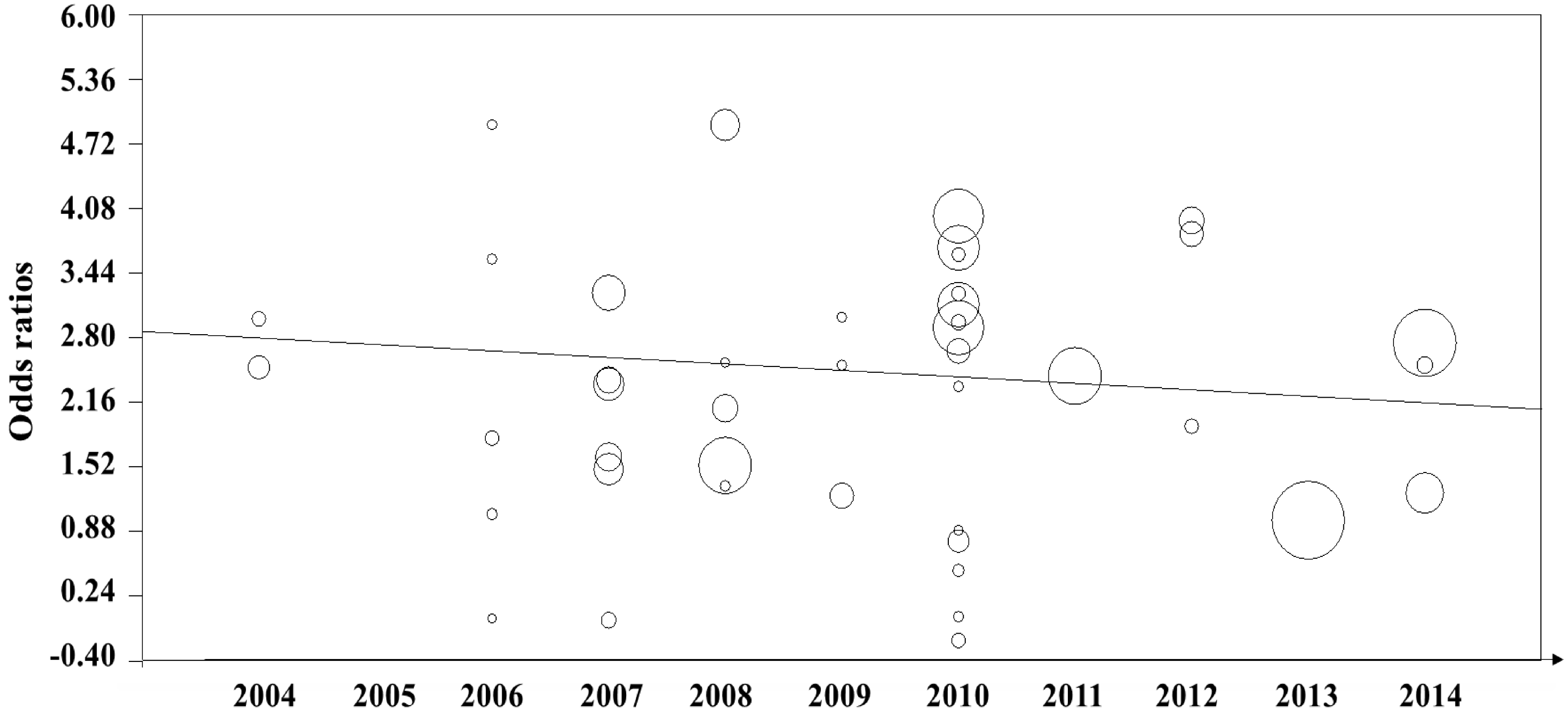
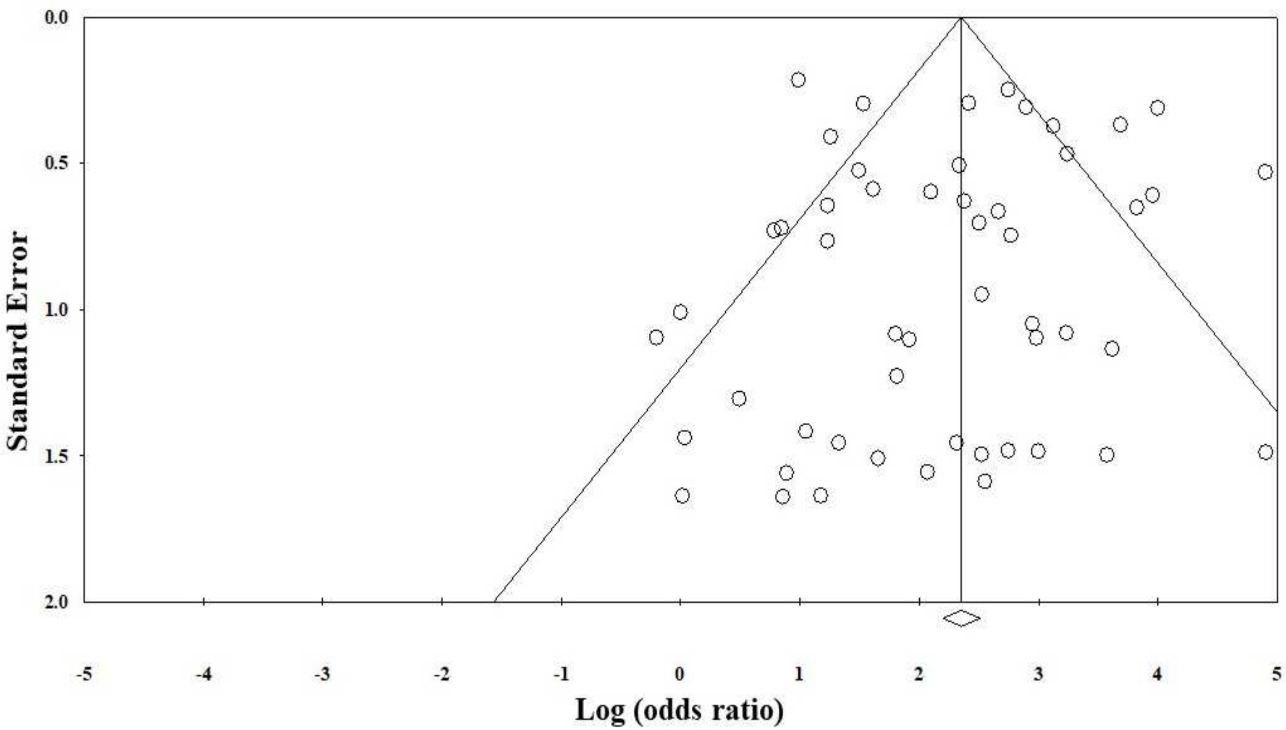
Figure S1. Meta regression analysis of index year of odds ratio for eligible studies in Europe.



Circles represent the OR and size of circles is proportional to the precision of each study. The fitted regression line is depicted by the index year of the study. We used the index year that the study was conducted rather than the year of publication. If the study extended beyond one calendar year, the year that the sampling took place was assumed to be the index year. For studies that did not report the time frame, we assumed that the study period was two years before the publication year.

Chen C, Wu F. *Occup Environ Med* 2020;0:1–11. doi: 10.1136/oemed-2020-106418

Figure S2. Funnel plot to assess publication bias for the association between livestock exposure and LA-MRSA carriage.



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