Prevalence of *lukPVL* and *lukMF'* genes in *Staphylococcus aureus* isolated from different host species and food samples: a meta-analysis

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Abstract

Staphylococcus aureus produces several leucocidins that cause cell lysis of neutrophils. Two of these leucotoxins are the bicomponent pore-forming complexes LukMF' and Panton-Valentine leucocidin (PVL). Both genes encoding these toxins, *lukMF'* and *lukPVL,* are located within the genomes of phages which can be transmitted horizontally between bacteria. The prevalence of both phage-encoded leucocidins strongly varies between populations. However, whereas host specificity is assumed, until now it remained unclear how much variation in prevalence exists between and within host species.

Scopus was searched for original research reporting the prevalence of *lukMF'* and *lukPVL* genes among *Staphylococcus aureus* strains of different animal species and food samples published before 16 January 2015. The estimated mean prevalence of both leucocidins per animal species was calculated by a random-effect meta-analysis.

Of 1300 articles found by the search strategy, 82 studies could be used for the meta-analysis. In total 30 prevalences were reported for *lukMF'* and 100 for *lukPVL.* It was shown that the prevalence of *lukMF'* varied between isolates from different animal species. The encoding genes were found most frequently in isolates associated with ruminants. The estimated mean prevalence of the luk*PVL* gene was low in most animal species but high in strains cultured from rabbits and rooks. The small number of isolates resulted in a large 95% CI. Therefore, the variation seen was not significant.

This meta-analysis shows a host association, suggesting a host specific activity of both phage-coded leucocidins.

Introduction

Staphylococcus aureus causes infections in humans and many animal species. For example, mastitis in cows caused by *S. aureus* has been a subject of many publications (reviewed by Barkema et al., 2006). Also, the prevalence of methicillin resistant *Staphylococcus aureus* (MRSA) was studied in many different animal species (Loncaric et al., 2013a; Pajic et al., 2014; Strommenger et al., 2006).

Neutrophils are seen as the most important effector cells to prevent *Staphylococcus aureus* infections in humans. *Staphylococcus aureus* is often the causative agent of recurrent infections in patients with disorders in neutrophil function (Spaan et al., 2013; Bogomolski-Yahalom et al., 1995). Also cows with subclinical mastitis developed a gangrenous mastitis after inducing neutropenia by treatment with anti-bovine leukocyte serum (Rainard et al., 2003b).

Staphylococcus aureus possesses several virulence factors that help the bacteria survive under the attack of the host's immune system (Spaan et al., 2013). A possibly important virulence factor of *Staphylococcus aureus* is the production of leucotoxins that cause cell lysis of neutrophils. In this way, phagocytosis or alternatively entrapment in a "neutrophil extracellular trap" may be prevented (Vrieling et al., 2015; Spaan et al., 2013). Two of these leucotoxins are the bicomponent pore-forming complexes LukMF' and Panton-Valentine leucocidin (PVL). These bicomponent complexes consist of an S and an F subunit that are co-transcribed from a single promotor (Alonzo et al., 2014). The S subunit attaches to receptors on the surface of the host cell and recruits the F subunit, followed by dimerization and oligomerization resulting in an octameric prepore. After a structural change the pore spans the host cell lipid bilayer, leading to cell death (Alonzo et al., 2014).

Both the *lukMF'* and the *lukPVL* genes are located within the genomes of temperate (pro-) phages which are transmitted horizontally between bacteria (Zou et al., 2000; Yamada et al., 2005). Plasmids, transposons and prophages offer an opportunity for the bacteria to vary its accessory genome. This part of the genome facilitates adaptation to different environments, such as different hosts or tissues and largely contributes to the extensive genetic and phenotypic variation of the pathogen (Deghorain et al., 2012; Moon et al., 2015).

Unlike the genes encoding the other bicomponent leucocidins produced by *S. aureus, lukPVL* is thought to be only present in a very limited range of lineages of *S. aureus* (McCarthy et al., 2014) and the estimated prevalence is 2-3% in human isolates (Kuehnert et al., 2006). Nevertheless, in humans this leucocidin is associated with necrotizing pneumonia and community associated disease (Lina et al., 1999; Naimi et al., 2003). A study by Löffler et al. (2010) showed that the PVL toxin causes cell death in human and rabbit neutrophils only and leaves the simian and murine neutrophils unharmed. Likewise, the LukMF' complex predominantly attaches to the CCR1 receptor specific for bovine immune cells and therefore specifically kills bovine neutrophils (Vrieling et al., 2015).

There is limited evidence regarding the clinical relevance of LukMF'. LukMF' was produced more by strains causing severe gangrenous mastitis compared to strains that cause subclinical mastitis in ewes in a study by Le Maréchal et al. (2011). Another study showed the presence of the *lukMF'* gene in virulent strains and its absence in less virulent strains (Guinane et al., 2008). Vrieling et al. (2015) showed *in vitro* that LukMF' should be seen as the most potent leucocidin produced by *S. aureus*.

Research on the presence of the *lukMF'* gene in *Staphylococcus aureus* isolates showed large differences in prevalence between studies. According to Rainard et al. (2003a), for instance, only 10% of strains from bovine mastitis possessed the *lukMF'* gene whereas in samples from Ishikawa and Hokkaido the *lukMF'* gene was present in 62.5% and 86.1% of the isolates (Yamada et al., 2005).

The other leucocidins produced by *S. aureus,* LukED and LukAB*,* are encoded by genes located on the core genome of *S. aureus* (Kaneko et al., 2004; Kuroda et al., 2001; Alonzo et al., 2014). Hence, these genes are found at high prevalence in *S. aureus* isolates. However, as described above, the prevalence of both phage-encoded leucocidins strongly varies. Although many different prevalences of the *lukMF'* and *lukPVL* genes are found in previous studies it is not clear how much variation exists in the prevalence of both leucocidins between and within host species.

Therefore, in this study a systematic meta-analysis of the existing literature was done to estimate the prevalence of both phage-encoded leucocidins in *S. aureus* isolates from food samples and different animal species.

Material and methods

Search strategy and inclusion criteria

We searched for articles in Scopus (www.scopus.com) by using a combination of the following key words: aureus AND [panton-valentine leucocidin OR pvl OR leucocidin OR luk-pv OR luks-pv OR lukf-pv OR lukmf OR lukm]. The selection of articles was done by reading the abstracts of all articles that were identified with the above key words until 16 January 2015. Studies that only used human isolates were excluded, as well as studies for which the full text could not be accessed online or through the library of Utrecht University. Further inclusion criteria were the detection of the encoding genes for LukMF' and/or LukPVL, the presentation of unique data that was not published before by the same author and a prevalence differentiated between animal species.

Data extraction

In the full text of each selected article, information was collected about the country of study, the leucocidin type (LukMF' or LukPVL) targeted, the primers used, the number of strains tested and the number of strains positive for the leucocidin and the animal species or food type from which the strains were cultured. Also, a remark was made when only MRSA isolates were tested and the prevalence of both encoding genes in MRSA and MSSA strains was recorded separately. After the data extraction, all data were checked once for correctness by the same researcher.

Meta-analysis

A meta-analysis was performed using Comprehensive Meta-Analysis (Biostat, Englewood, USA). The data sets for LukMF' and PVL were analysed separately. Using a model for dichotomous values, the estimated mean prevalence and its 95% CI for both gene clusters was calculated stratified on animal species. Weight was assigned to the event rates of the used studies by a random effects model. To indicate the extent of heterogeneity between studies a Cochran's χ^2 test was used in the CMA software (Asmare et al., 2016; Odeyemi, 2016). This resulted in a *p*-value that was considered significant when it was lower than 0.05.

Results

With our search strategy, 1300 articles were found. After reviewing the abstracts, 85 studies remained eligible (Figure 1). Two studies presented the same data as other studies and were therefore excluded for further analysis. Wang et al. (2012) presented different observations in the tables compared to the text, hence, this article was excluded as well. A total of 82 Studies from 28 countries yielded 130 prevalence estimates, of which 30 for *lukMF'* based on 1908 isolates and 100 for *lukPVL* based on 3643 isolates (See Supplementary tables S1 and S2). As for bats, donkeys, guinea pigs, parrots and turtles only one isolate of *S. aureus* was tested for the presence of the *lukPVL* gene, for these host species the prevalence was not calculated.

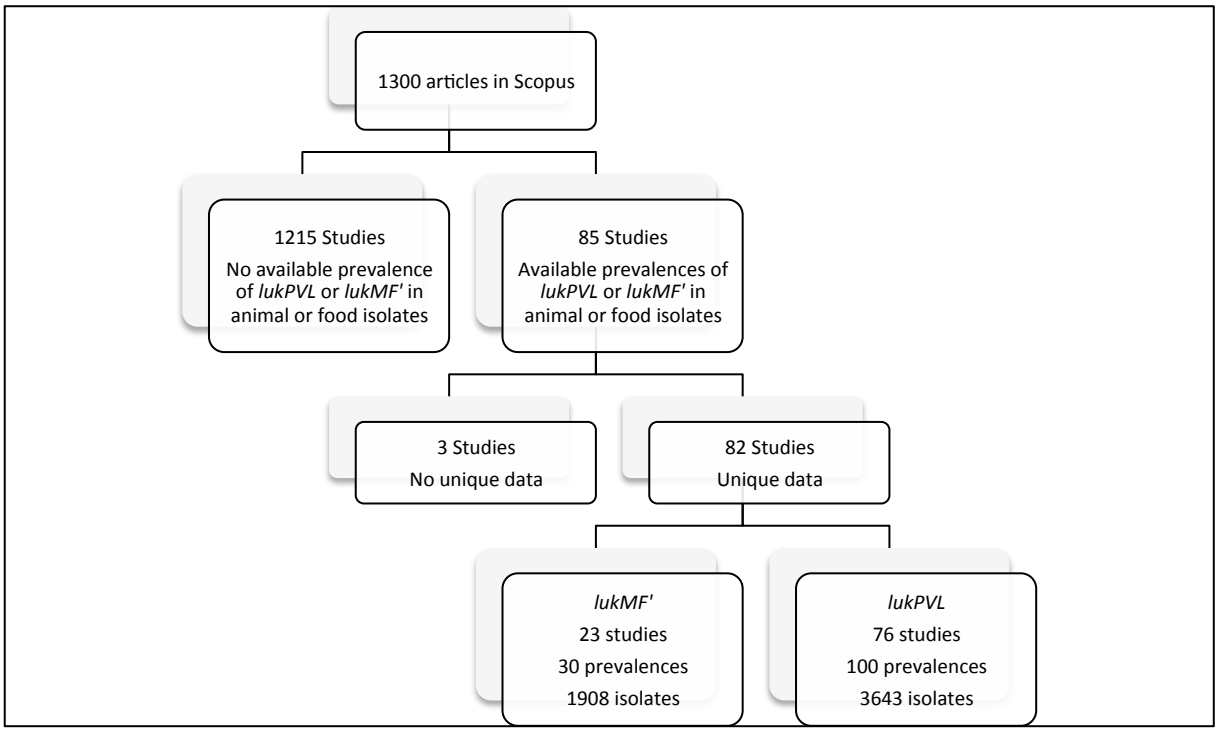


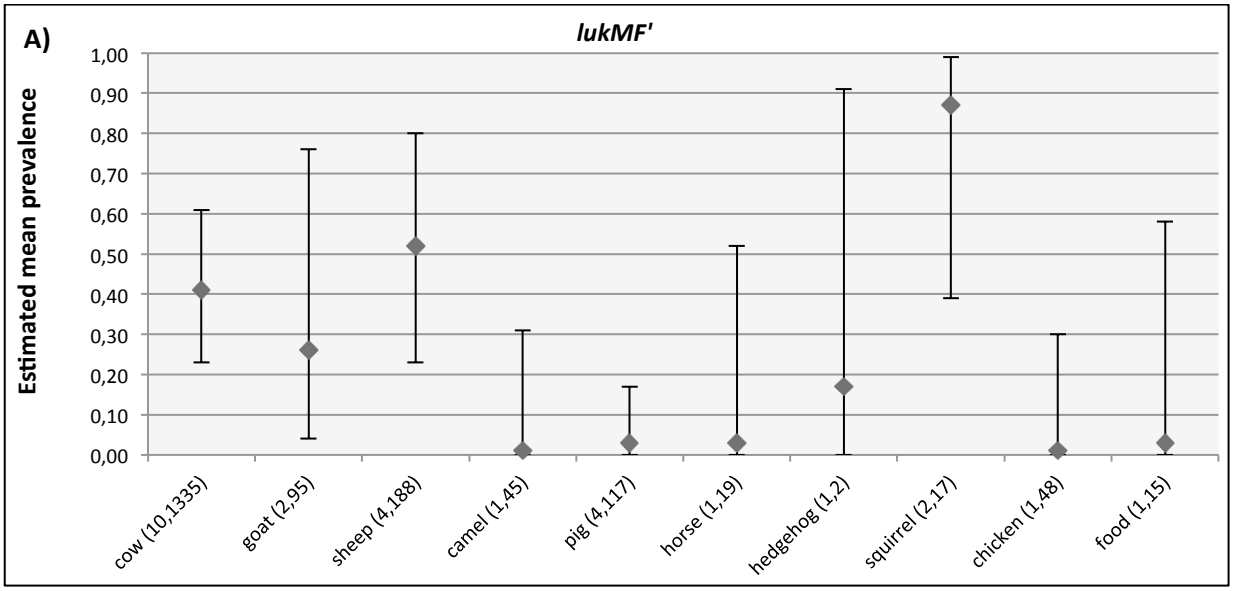
Figure 1: Flowchart representing the selection strategy for studies in this systematic meta-analysis.

lukMF'

The average prevalence of the *lukMF'* gene in *Staphylococcus aureus* isolates could be calculated for food samples and 9 animal species: cow, goat, sheep, camel, pig, horse, hedgehog, squirrel and chicken (Figure 2). The *lukMF'* gene was found in *S. aureus* isolates of cows, goats, sheep and squirrels. In the studies in this meta-analysis the *lukMF'* gene was not found in isolates from camels, pigs, horses, hedgehogs, chickens and food samples. The studies that tested for the presence of *lukMF'* in MRSA isolates only did not find the gene.

For cow isolates we found an estimated mean prevalence of 0.41 by a random-effect meta-analysis of 10 different studies from 7 different countries. The test for heterogeneity between

studies gave P = 0.37 (See Supplementary table S3). The prevalence of *lukMF'* in goat isolates was 0.26 based on two studies in Taiwan and France (test for heterogeneity P = 0.35) and in sheep isolates 0.52 within four different studies. The high outcome for squirrels (0.87) was based on two studies. The between-study heterogeneity (P = 0.11) was not significant. These reports, published by Simpson et al. (2013a; 2013b), included four out of four positive isolates in one study and eleven out of thirteen positive isolates in the other study. Both studies were done in the United Kingdom.



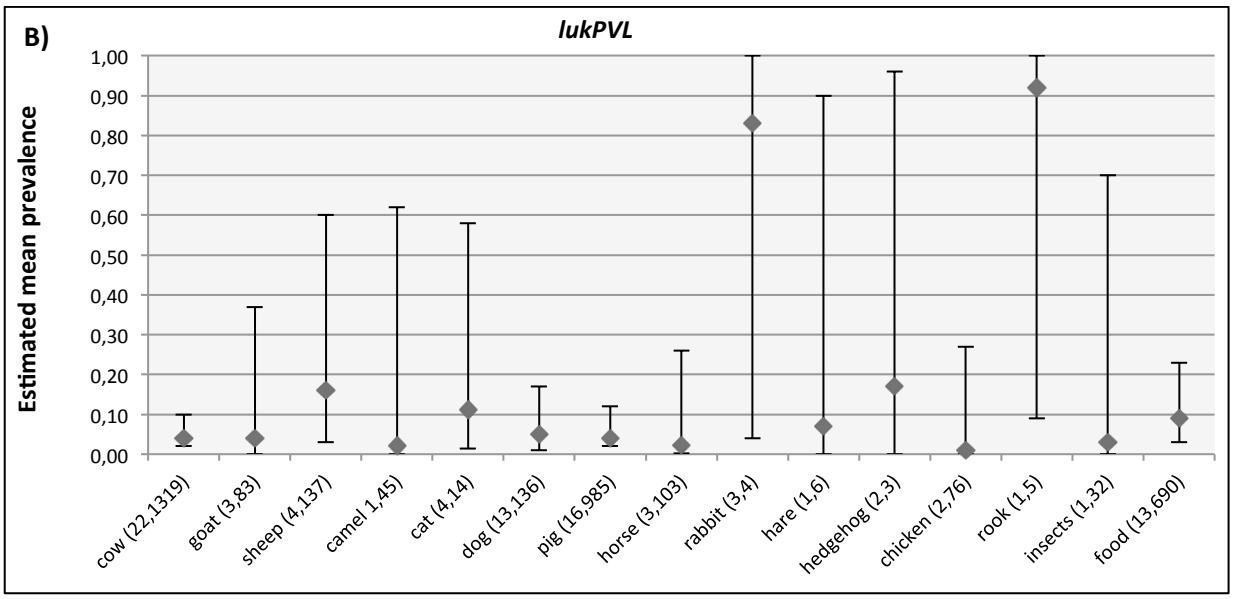


Figure 2a & b The estimated mean prevalence, including the 95% confidence interval, of the *lukMF'* (A) and *lukPVL* (B) genes in isolates from different animal species and food calculated by a random-effects meta-analysis. The x-axis represents the findings per animal-species (number of studies, number of isolates).

lukPVL

The prevalence of the *lukPVL* gene in *S. aureus* isolates from food samples and several animal species is summarized in Figure 2. The *lukPVL* gene was not found in isolates of cats, chickens, goats, hares, hedgehogs and horses. Also, the studies that tested a guinea pig, a parrot and a turtle did not find the encoding gene for PVL. The studies that tested for the presence of *lukPVL* in MRSA isolates only found a very low prevalence, on average 0.06.

The presence of *lukPVL* was studied most in cow isolates. We found 22 studies with 1319 cow isolates. However, the estimated mean prevalence is very low. The highest estimated prevalence of the *lukPVL* gene was found in rooks, but based on only one study, where all 5 isolates were found positive. Similarly, in rabbits the estimated prevalence was 0.83 based on three studies (confidence interval 0.04-1.00). The four tested isolates were classified as MRSA. The test for heterogeneity was significant in chickens, cows, dogs, horses, pigs and food samples (See Supplementary table S4).

Discussion

In this study, we aimed to describe the prevalence of both phage-encoded leucocidins in *S. aureus* isolates from different animal species and food samples. In accordance with our hypothesis, it was shown that the prevalence was associated with the animal species from which *S. aureus* was isolated.

We showed that the prevalence of *lukMF'* varied between different animal species. Comparing the point estimates with their 95% confidence intervals it can be concluded that the prevalence of *lukMF'* in cows and sheep is higher than in pigs. The estimated mean prevalence of the gene in squirrel strains is higher than in strains of chickens and pigs. However, even though the presumption of a difference between the other species exists, the meta-analysis does not show a significant difference since the confidence intervals overlap.

Similar to McCarthy and Lindsay (2013) the encoding genes were found most frequently in ruminant isolates. Nevertheless, substantial variation was seen between studies that tested ruminant isolates (See Supplementary table S1). In cows, the prevalence varied from 0.04 (Chu et al., 2013) up to 0.80 (Schlotter et al., 2012). Different ways of typing strains were used in the studies. However, among different clonal complexes (CC), pulsotypes and sequence types the prevalence of *lukMF'* turns out to be highly variable. Strains from mastitis milk compared to strains from random milk samples do not seem to possess the *lukMF'* gene more frequently as, for example, Haveri et al. (2008) used mastitis milk and found *lukMF'* in only 14% of the isolates compared to the 80% in the random milk samples taken by Chu et al. (2013).

Although Vrieling et al. (2015) suggest a geographical explanation could exist for the variation in prevalence, the meta-analysis does not show a clear geographical distribution. For example, the prevalence differs considerably between two studies in Japan (Yamada et al., 2005; Hata et al., 2010) and between studies in Germany and Switzerland (Monecke et al., 2007; Moser et al., 2013; Schlotter et al., 2012). However, the horizontal gene transfer by phage φPV83 makes a pattern in geographical distribution on a smaller scale plausible.

The estimated prevalence of *lukMF'* in sheep and goat isolates was based on less studies than the estimate for bovine isolates. Positive caprine isolates were only found by Vautor et al. (2009). They found a high prevalence in ovine isolates as well. Strikingly, none of the MRSA strains tested by Gharsa et al. (2012) were *lukMF'* positive whereas the prevalence was 0.90 in the other strains tested. These five MRSA strains possessed the *lukPVL* gene.

Interestingly, we demonstrated that the estimated prevalence of *lukMF'* is also high in squirrel isolates. In squirrels *lukMF'* positive *Staphylococcus aureus* is associated with fatal exudative dermatitis (FED) (Simpson et al., 2013a; Simpson et al., 2013b). Vrieling et al. (2015) assumed a role for the LukMF' binding receptor CCR1 might as well exist in some rodents, since mice are known to

express CCR1 on the neutrophils (Tokuda et al., 2000). The high prevalence in squirrel isolates makes this hypothesis more plausible. However, this is only based on two studies that likely tested squirrels from the same population. Noteworthy, the same MLST clonal complex (CC49) was found in all FED cases and all these isolates were *lukMF'* positive. Only one of three *Staphylococcus aureus* strains from squirrels in other cases than FED turned out positive suggesting a role of LukMF' in the pathogenesis of FED.

The prevalence of the other phage-encoded leucocidin, luk*PVL*, did not show significant differences between animal species and food samples. The estimated mean prevalence only was high in rabbits and rooks. The 95% CI however has a very wide range due to the small number of isolates that were studied, 4 and 5 respectively. In food samples and the other animal isolates the prevalence of *lukPVL* seems to be very low. In goats, cats, horses, hares, hedgehogs and chickens the gene encoding PVL was not found in any *Staphylococcus aureus* isolate (See Supplementary table S2).

The high prevalence of *lukPVL* in rabbits strains makes sense, given the findings by Löffler et al. (2010), as their study showed that this leucocidin was able to kill both human and rabbit neutrophils, while the number of alive murine and simian neutrophils did not significantly decrease. It is therefore assumed that the Panton-Valentine leucocidin is host specific for humans and rabbits. Correspondingly, we found a high estimated prevalence in rabbits and a low prevalence in all other animals, except for the rooks. The five rook isolates were typed as MRSA ST1 and ST22. These sequence types have been associated with both humans and animals (Loncaric 2013c).

For cows, six of a total of 22 studies contained *lukPVL* positive isolates. A prevalence higher than 0.5 was found in studies by Kwon et al. (2005), Wang et al. (2014) and Zecconi et al. (2006) in Korea, China and Italy. However, of 1319 isolates only 64 were tested positive. A possible explanation could be human contamination as Wang et al. (2012) found *lukPVL* positive isolates on cow skin and in cow milk but none of the *Staphylococcus aureus* isolates retrieved from the nasal cavity carried the gene. Similarly, fourteen of the fifteen tested isolates in the study by Kwon et al. (2005) were classified as one sequence type of CA-MRSA that carried the *lukPVL* gene. Unfortunately, we do not know whether the strains found by Wang et al. (2014) are of human or bovine origin. The high prevalence found by Zecconi et al. (2006) is striking too and indicates that *lukPVL* can be found in other hosts than humans and rabbits.

The gene encoding PVL was encountered only once in dog isolates. Van Duijkeren et al. (2005) published a case report in which three family members and their dog carried a *lukPVL* positive MRSA. Therefore it seems likely the family might have transmitted the bacteria to the dog in this case, making the dog a spillover host of this strain.

Interestingly, the studies that tested for the presence of *lukMF'* and *lukPVL* in MRSA isolates only found a very low prevalence, on average 0.07 for *lukMF'* and 0.06 for *lukPVL* respectively. This is

in contrast to the fact that PVL is seen as an important virulence factor of CA-MRSA (Vandenesch et al., 2003). However, the few studies that tested MRSA strains only for the presence of *lukMF'* did not find positive strains from hedgehogs, dogs, horses, sheep and pigs. It is not known whether MSSA strains from horses and hedgehogs carry *lukMF'.* For dogs and pigs the limited data show the absence of *lukMF'* in MSSA strains. If the prevalence of *lukPVL* and *lukMF'* is indeed lower in MRSA strains, this could possibly be explained by the fact that some strains seem to be more restrictive in the uptake of foreign DNA than other strains caused by differences in restriction-modification systems (Goerke et al., 2009; Waldron et al., 2006).

The fact that many studies only used the MRSA isolates for further analysis, including detection of *lukMF'* and *lukPVL,* might have caused an underestimation of the true prevalence of both genes. Also, the CMA software does not offer an estimated prevalence of zero when the genes are not detected in any isolate. Unfairly, an estimated prevalence higher than zero is calculated. Besides, the most important bias in this study might be the fact that all studies used for the meta-analysis had different protocols and many different primers were used with a possible difference in sensitivity.

In this meta-analysis a random effects approach was chosen, because it was assumed that the true prevalence could vary from study to study (Borenstein et al., 2007). As noted before, geographical distribution and variation between sequence types possibly cause variation. An I_2 test and Egger regression test were not performed to support the choice for a random approach, because the model choice should not be dependent on heterogeneity tests when the number of studies is low (Hardy and Thompson, 1998).

Overall, the number of studies was low and the heterogeneity between studies within one animal species was mainly high for PVL. This resulted in a large 95% CI for most animal species for both *lukMF'* and *lukPVL*. As described by Higgins and Thompson (2002) the power of the used test for heterogeneity is limited when a small number of studies is available. Possibly therefore, the heterogeneity between studies targeting *lukMF'* was only significant in pigs.

This meta-analysis showed a significant host association of LukMF'. The *lukMF'* gene is present most frequently in isolates of ruminants and squirrels, animal species whose neutrophils have been shown to be or are likely to be susceptible to LukMF'. Significant host association was not seen for PVL. However, the *lukPVL* gene has the highest prevalence in rabbit isolates, whose neutrophils are susceptible to the Panton-Valentine leucocidins. This suggests that *Staphylococcus aureus* indeed adapts to its hosts by acquiring the genes that makes it more fit in that environment.

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Supplementary table S1: LukMF' prevalence per publication in various animal species and food

Study name	MRSA/MSSA	Animal	Tested samples	Positive samples	Prevalence
Monecke et al., 2011	Unknown	Camel	45	0	0.00
Yamada et al., 2005	Unknown	Chicken	48	0	0.00
Chu et al., 2013	Unknown	Cow	28	1	0.04
Fueyo et al., 2005	Unknown	Cow	84	42	0.50
Hata et al., 2010	Unknown	Cow	110	32	0.29
Haveri et al., 2007	Unknown	Cow	116	31	0.27
Haveri et al., 2008	Unknown	Cow	284	41	0.14
Monecke et al., 2007	Unknown	Cow	128	68	0.53
Moser et al., 2013	Unknown	Cow	78	56	0.72
Schlotter et al., 2012	Unknown	Cow	189	151	0.80
Vautor et al., 2009	Unknown	Cow	21	4	0.19
Yamada et al., 2005	Unknown	Cow	297	218	0.73
Wedley et al., 2014 MRSA	MRSA	Dog	7	0	0.00
Wedley et al., 2014 MSSA	MSSA	Dog	20	0	0.00
Li et al., 2015	Unknown	Food	15	0	0.00
Chu et al., 2013	Unknown	Goat	73	0	0.00
Vautor et al., 2009	Unknown	Goat	22	16	0.73
Monecke et al., 2013	MRSA	Hedgehog	2	0	0.00
Walther et al., 2009b	MRSA	Horse	19	0	0.00
Franco et al., 2011	MRSA	Pig	2	0	0.00
Huijsdens et al., 2006	MRSA	Pig	8	0	0.00
Van Duijkeren et al., 2008	MRSA	Pig	35	0	0.00
Yamada et al., 2005	Unknown	Pig	72	0	0.00
Almeida et al., 2013	Unknown	Sheep	18	0	0.00
De Santis et al., 2005	Unknown	Sheep	32	8	0.25
Gharsa et al., 2012 MRSA	MRSA	Sheep	5	0	0.00
Gharsa et al., 2012 MSSA	MSSA	Sheep	68	61	0.90
Vautor et al., 2009	Unknown	Sheep	65	58	0.90
Simpson et al., 2013a	Unknown	Squirrel	4	4	1.00
Simpson et al., 2013b	Unknown	Squirrel	13	11	0.85

Supplementary table S2: PVL prevalence per publication in various animal species and food

Study name	MRSA/MSSA	Animal	Tested samples	Positive samples	Prevalence
Walther et al., 2008	MRSA	Bat	1	0	0.00
Monecke et al., 2011	Unknown	Camel	45	1	0.02
Loncaric et al., 2014a	MRSA	Cat	4	0	0.00
Strommenger et al., 2006	MRSA	Cat	3	0	0.00
Walther et al., 2008	MRSA	Cat	4	0	0.00
Weese et al., 2006	MRSA	Cat	3	0	0.00
Wendlandt et al., 2013	MRSA	Chicken	28	0	0.00
Yamada et al., 2005	Unknown	Chicken	48	0	0.00
Bardiau et al., 2013	MRSA	Cow	19	0	0.00
Benhamed et al., 2013	Unknown	Cow	11	1	0.09
Chu et al., 2013	Unknown	Cow	28	0	0.00
Erdem et al., 2013	MRSA	Cow	12	0	0.00
Feßler et al., 2010	MRSA	Cow	25	0	0.00
Fueyo et al., 2005	Unknown	Cow	84	0	0.00
Hata et al., 2010	Unknown	Cow	110	3	0.03
Kwon et al., 2005	Unknown	Cow	15	15	1.00
Lim et al., 2013	MRSA	Cow	19	0	0.00
Monecke et al., 2007	Unknown	Cow	128	0	0.00
Moser et al., 2013	Unknown	Cow	78	0	0.00
Pajiç et al., 2014	Unknown	Cow	75	5	0.07
Prashanth et al., 2011	Unknown	Cow	34	0	0.00
Pu et al., 2014	MRSA	Cow	28	0	0.00
Schlotter et al., 2012	Unknown	Cow	189	0	0.00
Tavakol et al., 2012	MRSA	Cow	14	0	0.00
Türkyilmaz et al., 2010	MRSA	Cow	16	0	0.00
Van Duijkeren et al., 2014	MRSA	Cow	16	0	0.00
Wang et al., 2014	Unknown	Cow	53	40	0.75
Yamada et al., 2005	Unknown	Cow	297	0	0.00
Zecconi et al., 2006	Unknown	Cow	50	28	0.56
Stastkova et al., 2009b	MRSA	Cow	18	0	0.00
Boost et al., 2007	MRSA	Dog	6	0	0.00
Corrente et al., 2014	MRSA	Dog	1	0	0.00
Davis et al., 2014	Unknown	Dog	11	0	0.00
Grönlund et al., 2014	MRSA	Dog	13	0	0.00
Loncaric et al., 2014	MRSA	Dog	5	0	0.00

Rubin et al., 2011	Unknown	Dog	27	0	0.00
Strommenger et al., 2006	MRSA	Dog	13	0	0.00
Van Duijkeren et al., 2005	MRSA	Dog	1	1	1.00
Vanderhaeghen et al., 2012	MRSA	Dog	2	0	0.00
Walther et al., 2008	MRSA	Dog	18	0	0.00
Walther et al., 2009a	MRSA	Dog	7	0	0.00
Wedley et al., 2014 MRSA	MRSA	Dog	7	0	0.00
Wedley et al., 2014 MSSA	MSSA	Dog	20	0	0.00
Weese et al., 2006	MRSA	Dog	5	0	0.00
Loncaric et al., 2014	MRSA	Donkey	1	0	0.00
Boost et al., 2013	MRSA	Food	127	3	0.02
Hammad et al., 2012	Unknown	Food	175	0	0.00
Hanson et al., 2011	Unknown	Food	27	1	0.04
Jackson et al., 2013	MRSA	Food	7	1	0.14
Kraushaar et al., 2014	Unknown	Food	28	7	0.25
Li et al., 2015	Unknown	Food	15	5	0.33
Ogata et al., 2014	MRSA	Food	4	0	0.00
Pu et al., 2009	MRSA	Food	22	3	0.14
Rodriguez-Lazaro et al., 2014	Unknown	Food	6	5	0.83
Siriken et al., 2013	Unknown	Food	41	0	0.00
Song et al., 2015	Unknown	Food	142	30	0.21
Velasco et al., 2014	Unknown	Food	63	0	0.00
Vestergaard et al., 2012	MRSA	Food	5	0	0.00
Young et al., 2014 MSSA	Unknown	Food	25	1	0.04
Young et al., 2014 MRSA	MRSA	Food	3	0	0.00
Chu et al., 2013	Unknown	Goat	73	0	0.00
Stastkova et al., 2009a	MRSA	Goat	5	0	0.00
Stastkova et al., 2009b	MRSA	Goat	5	0	0.00
Walther et al., 2008	MRSA	Guinea Pig	1	0	0.00
Loncaric et al., 2013a	MRSA	Hare	6	0	0.00
Loncaric et al., 2013a	MRSA	Hedgehog	1	0	0.00
Monecke et al., 2013	MRSA	Hedgehog	2	0	0.00
Loncaric et al., 2014	MRSA	Horse	78	0	0.00
Schwaber et al., 2013	MRSA	Horse	6	0	0.00
Walther et al., 2009b	MRSA	Horse	19	0	0.00

Oliveira et al., 2014	Unknown	Insects	32	1	0.03
Walther et al., 2008	MRSA	Parrot	1	0	0.00
Cui et al., 2009	MRSA	Pig	58	0	0.00
Fall et al., 2012	Unknown	Pig	57	36	0.63
Fang et al., 2014	MRSA	Pig	89	0	0.00
Franco et al., 2011	MRSA	Pig	2	0	0.00
Gordoncillo et al., 2012	MRSA	Pig	2	0	0.00
Ho et al., 2012	MRSA	Pig	170	0	0.00
Huijsdens et al., 2006	MRSA	Pig	8	0	0.00
Kadlec et al., 2009	MRSA	Pig	54	0	0.00
Lo et al., 2012	MRSA	Pig	166	0	0.00
Osadebe et al., 2013 MSSA	MSSA	Pig	22	4	0.18
Osadebe et al., 2013 MRSA	MRSA	Pig	8	7	0.88
Smith et al, 2009	MRSA	Pig	15	0	0.00
Van Duijkeren et al., 2008	MRSA	Pig	35	0	0.00
Velasco et al., 2014	Unknown	Pig	21	0	0.00
Vestergaard et al., 2012	MRSA	Pig	6	0	0.00
Yamada et al., 2005	Unknown	Pig	72	0	0.00
Yan et al., 2014 MRSA	MRSA	Pig	38	0	0.00
Yan et al., 2014 MSSA	MSSA	Pig	162	3	0.02
Loncaric et al., 2013b	MRSA	Rabbit	1	0	0.00
Walther et al., 2008	MRSA	Rabbit	1	0	0.00
Wardyn et al., 2012	MRSA	Rabbit	2	2	1.00
Loncaric et al., 2013c	MRSA	Rook	5	5	1.00
De Santis et al., 2005	Unknown	Sheep	32	0	0.00
Gharsa et al., 2012 MSSA	MSSA	Sheep	68	0	0.00
Gharsa et al., 2012 MRSA	MRSA	Sheep	5	5	1.00
Ünal et al., 2012	Unknown	Sheep	21	14	0.67
Velasco et al., 2014	Unknown	Sheep	11	0	0.00
Walther et al., 2008	MRSA	Turtle	1	0	0.00

Supplementary table S4: Meta-analysis results LukMF'

	Number of studies	Number of isolates	Event rate	Lower limit 95% CI	Upper limit 95% CI	P-value
Cow	11	1141	0,41	0,23	0,61	0,37
Goat	2	95	0,26	0,04	0,76	0,35
Sheep	4	183	0,52	0,23	0,80	0,90
Camel	1	45	0,01	0,00	0,31	0,02
Pig	3	115	0,03	0,00	0,17	0,00
Horse	1	19	0,03	0,00	0,52	0,06
Hedgehog	1	2	0,17	0,00	0,91	0,42
Squirrel	2	17	0,87	0,39	0,99	0,11
Chicken	1	48	0,01	0,00	0,30	0,02
Food	48	15	0,03	0,00	0,58	0,07

Supplementary table S4: Meta-analysis results PVL

	Number of studies	Number of isolates	Event rate	Lower limit 95% CI	Upper limit 95% CI	P-value
Cow	22	1319	0,04	0,02	0,10	0,00
Goat	3	83	0,04	0,00	0,37	0,02
Sheep	4	137	0,16	0,03	0,60	0,11
Camel	1	45	0,02	0,00	0,62	0,08
Cat	4	14	0,11	0,01	0,58	0,09
Dog	13	136	0,05	0,01	0,17	0,00
Pig	16	985	0,04	0,02	0,12	0,00
Horse	3	103	0,02	0,00	0,26	0,01
Rabbit	3	4	0,83	0,04	1,00	0,52
Hare	1	6	0,07	0,00	0,90	0,29
Hedgehog	2	3	0,17	0,00	0,96	0,52
Chicken	2	76	0,01	0,00	0,27	0,01
Rook	1	5	0,92	0,09	1,00	0,32
Insects	1	32	0,03	0,00	0,70	0,12
Food	13	690	0,09	0,03	0,23	0,00