

**MRSA CC398 in humans and pigs in Norway: A “One Health” perspective on
introduction and transmission**

**Carl Andreas Grøntvedt^{1,*}, Petter Elstrøm^{2,*}, Marc Stegger^{3,4}, Robert Leo Skov³, Paal
Skytt Andersen^{3,4}, Kjersti Wik Larssen⁵, Anne Margrete Urdahl¹, Øystein Angen^{1,3},
Jesper Larsen³, Solfrid Åmdal⁶, Siri Margrete Løtvedt⁶, Marianne Sunde^{1,2,#}, Jørgen
Vildershøj Bjørnholt^{2,#}**

¹The Norwegian Veterinary Institute, P.O. Box 750 Sentrum, N-0106 Oslo, Norway

²The Norwegian Institute of Public Health, P.O. Box 4404 Nydalen, N-0403 Oslo, Norway

³Statens Serum Institut, 5 Artillerivej, DK-2300 Copenhagen S, Denmark

⁴Pathogen Genomics Division, Translational Genomics Research Institute (TGen), Flagstaff,
86001 Arizona, USA

⁵St. Olavs Hospital, The Norwegian Reference Laboratory for MRSA, P.O. Box 3250
Sluppen, N-7006 Trondheim, Norway

⁶The Norwegian Food Safety Authority, P.O. Box 383, N-2381 Brumunddal, Norway

Corresponding author: Carl Andreas Grøntvedt, The Norwegian Veterinary Institute, P.O.
Box 750 Sentrum, N-0106 Oslo, Norway, Tel: 00 47 23 21 63 87, Email: carl-
andreas.grontvedt@vetinst.no

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* contributed equally to this work

contributed equally to this work

Summary

The present study provides strong and novel evidence that humans may introduce MRSA CC398 into closed pig populations. Further, it demonstrates that stringent control and eradication measures were effective and prevented dissemination from pig farms to the general human population.

Abstract

Background Emerging livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) persist in livestock populations and represent a reservoir for transmission to humans. Understanding the routes of introduction and further transmission is crucial to control this threat to human health.

Methods All notified cases of LA-MRSA (CC398) in humans and pigs in Norway between 2008 and 2014 were included. Data were collected during an extensive outbreak investigation, including contact tracing and stringent surveillance. Whole-genome sequencing of isolates from all human cases and pig farms was performed to support and expand the epidemiological findings. The national strategy furthermore included a “search and destroy” policy at the pig farm level.

Results Three outbreak clusters were identified, including 26 pig farms, two slaughterhouses and 36 humans. Primary introductions likely occurred by human transmission to three sow

farms with secondary transmission to other pig farms mainly through animal trade and to a lesser extent via humans or livestock trucks. All MRSA CC398 isolated from humans without an epidemiological link to the outbreaks were genetically distinct from isolates within the outbreak clusters indicating limited dissemination to the general population.

Conclusions This study identified preventable routes of MRSA CC398 introduction and transmission: human occupational exposure, trade of pigs and livestock transport vehicles. These findings are essential for keeping pig populations MRSA-free and from a One Health perspective to prevent pig farms from becoming reservoirs for MRSA transmission to humans.

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Introduction

Staphylococcus aureus is one of the main causes of nosocomial and community-acquired infections, and methicillin-resistant *S. aureus* (MRSA) infections are associated with increased morbidity, mortality and costs [1, 2]. For a long time, MRSA was almost exclusively a healthcare-associated problem, but since the late 1990s, the epidemiology has changed significantly with dissemination of community-associated MRSA (CA-MRSA) and further from the mid-2000s by emerging MRSA strains with a primary reservoir in livestock [3, 4].

Livestock-associated MRSA (LA-MRSA) has now spread worldwide, especially in pig farms where it is transmitted to humans mainly by occupational exposure [5-7]. In countries with a low overall prevalence of MRSA in humans, like Denmark and the Netherlands, LA-MRSA has greatly impacted the notification rate of MRSA in humans and is increasingly found in people without livestock contact [8-10].

LA-MRSA in pig holdings in Europe most commonly belong to the clonal complex (CC) 398, but the prevalence varies greatly among European countries, with up to 70% of all farms positive in Denmark and the Netherlands [8, 11]. In contrast, several surveillance programs conducted in Norway, including the 2008 EU baseline study and two more recent nationwide population surveillance programs found either an absence or a very low prevalence of LA-MRSA in pigs [12-14]. Trade in pigs has been identified as the major risk factor for inter-farm transmission of LA-MRSA [15, 16], including transboundary transmission [17]. In the period from 2000 to 2015, fewer than 80 live pigs were imported into the Norwegian commercial pig population, most of these in two separate imports of 49 and 20 high-health breeding animals from Finland and the Netherlands respectively [18]. In the latter the imported animals were

tested and confirmed to be negative for MRSA. Thus, the Norwegian pig population is de facto a “closed” production system.

The objective of the present study was to describe the first known introductions and transmission of MRSA CC398 in pig herds and the subsequent spread to humans in Norway. The study included all identified cases of MRSA CC398 in humans and pigs in Norway from 2008-2014.

Materials and methods

MRSA investigations in pigs

MRSA in the Norwegian pig population was first investigated in an EU baseline study in 2008, which did not detect LA-MRSA [12]. In 2011 and 2012, anonymized prevalence studies demonstrated MRSA CC398 in a few samples from a single slaughterhouse and a pig herd [13, 14]. In early 2013, two independent identifiable findings of MRSA CC398 in the Norwegian pig population initiated a public health risk assessment concerning the possible impacts of an increasing prevalence of LA-MRSA in pigs. This prompted an investigation to identify and control the transmission of MRSA CC398 to pig farms and humans. Norwegian authorities implemented a strategy including a farm level “search and destroy” policy to prevent the establishment of LA-MRSA in the Norwegian pig population. In 2014, a nationwide surveillance program of all sow farms (n=986) was initiated to investigate the prevalence of MRSA in the pig population [19].

The outbreak-related investigation collected epidemiological data from farmers by questionnaires (Table S1 in Supplementary Appendix) and included both human and animal contact tracing. Demographic information, farm characteristics, husbandry and production

details were collected. In total, 74 pig farms and five slaughterhouses were included and sampled in the outbreak investigation during 2013 and 2014 (Supplementary Appendix 1).

MRSA investigations in humans

Human MRSA infections have been notifiable to the Norwegian surveillance system for communicable diseases (MSIS) since 1995 and MRSA carriage has been notifiable since 2005 [20]. Humans are investigated for MRSA based on clinical signs of infection, admission screening in healthcare facilities, contact tracing and outbreak investigations [21]. All human MRSA CC398 cases notified to MSIS were included.

Epidemiological data on all persons occupationally exposed to pigs in the current outbreaks were collected (Table S2 in Supplementary Appendix). Household members were sampled if they were patients in healthcare institutions, worked as healthcare personnel, or if a farm or abattoir worker was found to be MRSA positive. MRSA screening samples from humans were collected from the vestibulum nasi, throat, and skin lesions (if present). In total, 272 persons were included.

Bacteriological analyses

All samples from animals and environment were investigated for MRSA using the protocol described by the European Food Safety Authority [22]. Human MRSA samples taken as part of the outbreak investigation were analyzed at seven medical microbiological laboratories using slightly different methodologies (Supplementary Appendix 2).

The national reference laboratory for MRSA confirmed presumptive MRSA isolates from human, animal and environmental samples by PCR detection of the genes *mecA*, *spa* and PVL using PCR protocols previously described [23, 24]. *Spa*-typing was performed on all isolates (<http://www.seqnet.org/downloads.html>). Multilocus sequence typing (MLST) was performed on new *spa*-types as described by Enright et al [25].

Whole-genome sequencing (WGS), detection of resistance and virulence markers, and phylogenetic analysis of MRSA CC398 from all pig farms and all human cases reported in Norway, as well as selected MRSA CC398 isolates was performed (Supplementary Appendix 3).

Statistical analyses

The data were collected with the objective of prevention and control of transmission of MRSA and not as a part of a planned scientific study. Stata Version 13 (Stata-Corp, College Station, TX, USA) was used to calculate attack rates (AR) and odds ratio (OR) of MRSA among persons distributed on occupational exposure and pig farms distributed on type of pig production.

Results

Overview of MRSA CC398 in Norway

The first human case of MRSA CC398 was notified in March 2009, and by the end of 2014, a total of 84 human cases had been reported, including human cases identified through outbreak investigations (Figure 1).

The first traceable finding of LA-MRSA in pigs occurred in February 2013, and by the end of 2014, outbreak investigations and surveillance had identified MRSA CC398 in 26 pig farms (Table 1), two slaughterhouses and 36 humans (Table 2). Epidemiological data placed these farms and persons in three clusters located in, or originating from, central eastern (outbreaks 1 and 3) and south-western (outbreak 2) Norway (Figure 2). MRSA isolates from animals, environment and humans in these three clusters belonged to the following CC398 associated *spa* types: t034 in outbreak 1, t034 and t12359 in outbreak 2 and t011 in outbreak 3. The findings were further supported by WGS-based phylogenetic analysis (Figure 3 and Supplementary Appendix 4). MRSA CC398 detected in samples from a slaughterhouse in the anonymized survey of 2011 (NORM-VET 2011) was shown by WGS to be related to isolates in outbreak 1 (Figure 3). Most pig farms in outbreak 1 regularly supplied this slaughterhouse. A single pig isolate from the 2012 survey and 48 human isolates not epidemiologically linked to the three outbreaks described were all genetically distinct from the isolates in the outbreak clades (Figure 3 and Supplementary Appendix 4). Based on information reported to MSIS, 25 (52%) of the human cases not linked to the outbreak clusters had likely acquired MRSA CC398 abroad.

Introductions of MRSA CC398 to the pig population

The index cases in the three outbreaks were identified through samples collected from a post-mortem examination of a fattening pig in February 2013 (outbreak 1), clinical infection in a farm worker in June 2013 (outbreak 2) and in a national surveillance program of sow farms in June 2014 (outbreak 3). Contact tracing identified two primary case sow farms having

supplied the index case farms in outbreaks 1 and 2. The index case farm in outbreak 3 was considered the primary case farm. All primary case farms had farm workers and/or consultants originating from other European countries. The use of foreign labor was common, as 24/62 (39%) and 4/63 (6%) of sow and finishing pig farm workers respectively, were of non-Norwegian nationality. The majority of foreign workers (25/28) were from Eastern Europe, while the remaining three were from Denmark (n=2) or the Netherlands (n=1). None of the farms investigated had imported pigs from abroad. WGS data from both human and pig isolates in outbreaks 1 and 2 demonstrated a close genetic relationship with isolates identified in Denmark, whereas isolates from outbreak 3 showed genetic relatedness to MRSA CC398 t011 strains from several European countries, including Denmark (Figure 3).

Further transmission

The trade of pigs was identified as the main route of MRSA CC398 transmission from the three primary case farms. This was considered the most likely route of transmission to 19 farms. In three farms, the most probable explanation for transmission was through the mutual use of farm workers or veterinary practitioners.

One farm had two separate introductions of MRSA CC398 (t034 and t011) based on epidemiological information supported by WGS data, and was involved in both outbreaks 2 and 3. The trade of pigs or contact through personnel was excluded as the route of re-introduction to this farm. A livestock transport vehicle had on two occasions transported pigs from a MRSA CC398 positive finishing farm to a slaughterhouse without subsequent disinfection shortly before transporting pigs to the farm involved and was considered the most likely transmission route.

Pigs from MRSA CC398 positive farms were slaughtered at five different slaughterhouses in southern Norway, and MRSA was detected in samples from pigs, personnel or the environment in two of these (Figure 2).

In total, 48 of 74 farms sampled during outbreak investigations were identified as MRSA negative. Twelve farms were sampled as they had supplied pigs to MRSA CC398 positive farms, and four farms had contact through MRSA CC398 positive veterinary practitioners. Of the 51 farms that had received pigs from MRSA CC398 positive farms, 32 were MRSA negative. Of these 32 farms, 14 had received pigs from farms in which MRSA CC398 had most likely only been recently introduced, 12 had been only sporadically supplied, and six had changed suppliers and had washed and disinfected the premises before the change of supplying herd.

Of the 36 human cases included in the outbreaks, 33 were detected through contact tracing. Three were identified through notification to MSIS, and subsequently linked to the outbreaks by epidemiological data, supported by WGS results (Figure 3 and Supplementary Appendix 4). All 36 persons had direct and regular contact with positive pigs (Table 2). No differences in the MRSA prevalence between different types of occupational exposure were observed.

Discussion

The present study encompasses all identified cases of MRSA CC398 in humans and pigs in Norway, between 2008 and 2014. All the traceable detections of MRSA CC398 in pig farms and slaughterhouses clustered in three separate outbreaks. Furthermore, 43% (36/84) of all human MRSA CC398 cases in the period were related to these outbreaks. The study strongly suggests that the outbreaks were caused by human introduction of MRSA. Phylogenetic

analysis revealed that the introduced MRSA strains were closely related to strains isolated in other European countries. The isolates from the primary case farms in outbreaks 1 and 2 showed close genetic relatedness to MRSA CC398 isolates from Denmark, and persons linked to the two farms had known contact with pig farms in Denmark. Further, the primary case farm in outbreak 3 involved farm workers from abroad, although without confirmed livestock contact outside Norway.

To our knowledge, the present study is the first to describe the importance of the human introduction of MRSA CC398 to livestock populations. Since there is virtually no import of live pigs to Norway, human transmission of LA-MRSA should be regarded as the most important route of introduction into the Norwegian pig population. Our findings are therefore highly relevant for the future prevention of LA-MRSA introduction to pig populations, at both the national level and farm level.

Based on other studies, the trade of pigs has been shown to be the predominant route of transmission of MRSA CC398 among pigs [15, 16], including transboundary transmission [17]. Domestic trade in pigs was found to be the main route of inter-farm transmission of MRSA after primary introductions, indicating that limiting the number of farms connected through trade is important in preventing MRSA transmission. In addition, we found humans and in one case a livestock truck to be the most likely explanation for MRSA transmission to farms not connected through the trade of pigs. These transmission routes may further constitute routes of dissemination to other segments of the animal population.

Our results show that 32 of 51 pig farms which had purchased pigs from MRSA positive suppliers were found to be MRSA negative at the time of sampling. This may be explained by the supplying farms not being MRSA positive at the time of delivering the animals or that management practices and hygiene routines prevented MRSA from becoming established in

the recipient farms, the latter being the most likely explanation in at least six farms. This indicates that changing to a supplier with a MRSA negative herd (all in – all out) combined with good routines for washing and disinfecting facilities may be effective measures to prevent MRSA establishment on finishing pig farms. These findings are supported by results from the Norwegian control strategy for LA-MRSA in the pig population, and may be relevant also for pig farms in other countries [26].

Other studies have identified direct contact, and to a lesser extent indirect contact to positive animals as a major risk factor for MRSA CC398 in humans [5, 27, 28]. In addition, an increased incidence rate of MRSA CC398 in the general public without contact with pig farms has been described from areas with a high density of pig herds [8, 9, 29]. In the present study, we did not observe the transmission of MRSA CC398 from the outbreaks to the general public. This may be partly explained by the relatively short exposure times, as all pigs on MRSA CC398 positive farms were slaughtered and the holding facilities thoroughly washed and disinfected.

Public health surveillance data from Norway show that more than one third of all notified human MRSA cases have acquired MRSA abroad [12, 30]. An increased prevalence of MRSA on Norwegian pig farms could change this epidemiological situation by constituting a new domestic reservoir for MRSA, leading to an increase of the total public health burden of MRSA. Such a development has been described in Denmark, where the rapid spread of MRSA CC398 in the pig population has led this to be the dominant clone found in humans [8]. The rapid increase of MRSA CC398 in humans in other low endemic countries and the results from the present study, highlights the importance of control measures to prevent the introduction and further transmission of MRSA CC398 in pig populations. The present Norwegian control strategy includes targeted screening of personnel before working in pig herds, annual national surveillance of the pig population and contact tracing with eradication

measures, resembling a “search and destroy” strategy. The preliminary results of testing in herds following the implementation of MRSA eradication measures show that this has largely been an effective strategy [26].

Some of the data described here were collected in order to control outbreaks and, although extensive, were not fully comprehensive. Only household contacts of MRSA CC398-positive occupationally exposed humans were screened, thus bias may have been introduced regarding the detection of further spread. The WGS analysis was compared to available sequences primarily from Denmark, thus the relatedness to isolates from other countries was explored to a lesser extent. The major strengths of the study are the extensive outbreak investigations and the active surveillance programs in the pig population together with mandatory notification of all human MRSA diagnoses, giving a near-complete description of MRSA CC398 in Norway.

In conclusion, this study confirms that the trade of pigs and occupational exposure are the major risk factors for transmission of MRSA CC398 between humans and pigs. However, the primary introductions leading to the three outbreak clusters cannot be explained by the trade of animals. In these cases, both the epidemiological and the WGS data indicate that these introductions were the result of human-to-animal transmission. In addition, further transmission likely occurred via humans and livestock transport vehicles to farms not connected to MRSA CC398 positive farms through the trade of live animals. These findings have important implications for risk management to prevent the dissemination of MRSA CC398 among farms. In Norway, we believe that the prevention of human introduction of LA-MRSA is of the utmost importance for the current ambitious strategy to control LA-MRSA to prove feasible and successful in the longer term.

Contributors

Outbreak investigations (PE, MS, AMU, JVB, SÅ, SML), data collection (CAG, PE, MS, AMU, JVB, SÅ, SML, JL, KWL, ØA), data analysis and interpretation (CAG, PE, MS, AMU, JVB, KWL, RLS, JL, PSA, MSt, ØA), preparing tables and figures (PE, CAG and MSt). CAG and PE contributed equally as shared first authors with the primary responsibility of writing and revising the manuscript. MS and JVB contributed equally as shared senior authors. All authors contributed to revising the manuscript and approved the final version.

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and interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflicts of interest

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Figure Legends:

Figure 1. Notified cases of human MRSA involving CC398 in Norway, from the first case in March 2009 until December 2014.

Figure 2. Geographical distribution of (A) MRSA CC398 positive farms (circles), slaughterhouses (triangles), and (B) MRSA CC398 positive farm or slaughterhouse workers in outbreak one (red), two (blue) and three (yellow). In A, negative farms and slaughterhouses are indicated in green. Insert in A depicting Norway in Europe with box highlighting focus area in A and B.

Figure 3. Phylogenetic analysis for understanding diversity and spread of CC398 MRSA isolates in Norway. The phylogenetic relationship was inferred using maximum likelihood based on 4,854 SNPs in 271 isolates. The human-adapted (HuA) and livestock-associated (LA) clades are highlighted. Identified outbreaks in relation to Norwegian livestock were identified and highlighted; Outbreak 1 (red), outbreak 2 (blue), and outbreak 3 (yellow). Genotypic and epidemiological data are represented encircling the topology. Inner circle represent Norwegian isolates (solid), Danish pig-production isolates (empty), and others (blank). Middle circle represent the sample environment with livestock, meat and environmental samples (solid) and human isolates (empty). Outer circle depicts the occurrence of specific fluoroquinolone-associated resistance mutations in *gyrA* (Ser84Leu) and *parC* (Ser80Tyr).

Table 1: MRSA outbreaks: The number and type of pig farms sampled and results from MRSA analysis.

	Outbreak 1			Outbreak 2			Outbreak 3			Total			OR ⁴	(95% CI)
	N ¹	Pos ²	AR(%) ³	N ¹	Pos ²	AR(%) ³	N ¹	Pos ²	AR(%) ³	N ¹	Pos ²	AR(%) ³		
Sow farms	7	3	(42.9)	16	3	(18.8)	1	1	(100.0)	24	7	(28.0)	Ref.	
Finishing pig farms	19	9	(47.4)	28*	8*	(28.6)	3*	2*	(66.7)	49	18	(36.7)	1.26	(0.50 – 3.57)
Total	26	12	(46.2)	44	11	(25.0)	4	3	(75.0)	74	26	(35.1)		

¹Number of pig farms sampled (one farm included in both outbreak 2 and 3)

²Number of pig farms found positive of MRSA (*one farm included in both outbreak 2 and 3)

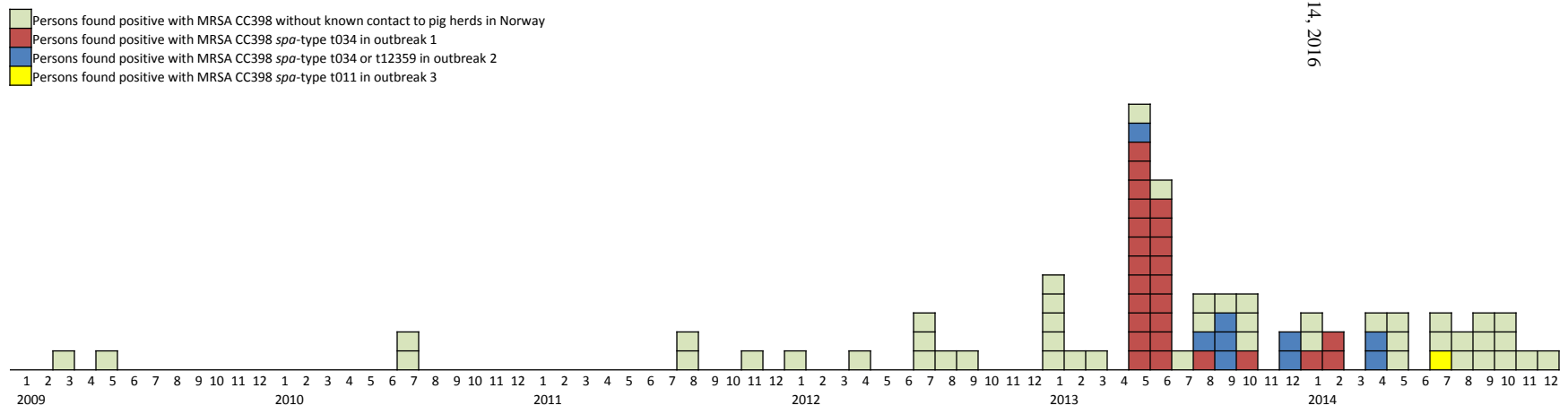
³Attack rate

⁴Odds ratio

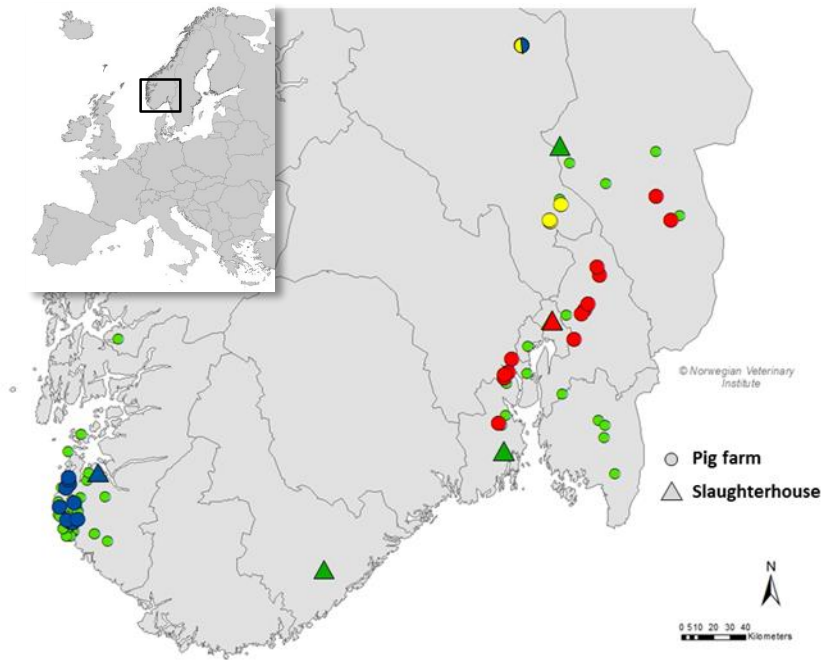
Table 2: Results of case tracing of persons, distributed by the type of known exposure to MRSA

	Outbreak 1			Outbreak 2			Outbreak 3			Total			OR ⁴	(95% CI)
	N ¹	Pos ²	AR(%) ³	N ¹	Pos ²	AR(%) ³	N ¹	Pos ²	AR(%) ³	N ¹	Pos ²	AR(%) ³		
Working in sow pig farm	19	10	(52.6)	39	3	(7.7)	4	1	(25.0)	62	14	(22.6)	Ref.	
Working in finishing pig farm	29	5	(17.2)	34	4	(11.8)	-	-	-	63	9	(14.3)	0.63	(0.24 – 1.57)
Veterinary practitioner	11	2	(18.2)	4	1	(25.0)	-	-	-	15	3	(20.0)	0.89	(0.16 – 3.17)
Working in slaughterhouse	107	9	(8.4)	17	1	(5.9)	-	-	-	124	10	(8.06)	0.36	(0.14 – 0.86)
Household members	5	0	(0.0)	3	0	(0.0)	-	-	-	-	-	-	-	-
Total	171	26	(15.2)	97	9	(9.3)	4	1	(25.0)	272	36	(13.2)		

¹Number of humans sampled²Number of humans found positive of MRSA³Attack rate⁴Odds ratio



A



B

