MRSA risk assessment

Prepared by the MRSA expert group

December 2014

The Danish Veterinary and Food Administration

CONTENTS

PURPOSE OF THE EXPERT GROUP'S WORK

In August, the Ministry of Food, Agriculture and Fisheries of Denmark, in conjunction with the Ministry of Health, decided that an interdisciplinary expert group should be formed consisting of experts from the human and veterinary sides. The expert group should have the task of preparing a new risk assessment of the animal MRSA situation in light of the increasing occurrence of human cases.

The Ministry of Food, Agriculture and Fisheries of Denmark also decided in August 2014 that in addition to the ongoing screening studies of the occurrence of MRSA in 200 randomly selected finisher herds and the ongoing research which will shed light on many of the unknown conditions regarding the spread of MRSA in herds and the surrounding environment, there should be an ongoing screening of all pig herds at the breeding level.

The MRSA expert group was established in October 2014. The expert group is composed of representatives from the Danish Health and Medicines Authority, Statens Serum Institut (SSI), the Organisation of Danish Medical Societies, the Danish Veterinary and Food Administration, the Danish National Veterinary Institute, the Danish Veterinary Association and the Norwegian Veterinary Institute, which has been involved in the Norwegian MRSA efforts. The Danish Veterinary and Food Administration handles the Chair and Secretariat functions.

The expert group's task was to conduct a new assessment of the risk of animal MRSA based on the existing knowledge and the results of the two veterinary screening studies concluded in 2014 (MRSA in finisher herds and MRSA at the breeding level). Based on the risk, the experts should prepare recommendations for any efforts which could be made here and now with regards to reducing the spread of MRSA from the affected herds to the surrounding environment and community while waiting for new knowledge via the results of the research activities launched by the Danish National Veterinary Institute in cooperation with Statens Serum Institut. The risk of infection from meat should be included in the expert group's considerations.

It should be noted that the expert group's recommendations are prepared based on what, in the expert group's assessment, could contribute to reducing the spread of MRSA from herds to the surrounding environment without assessing the socio-economic consequences this could have for the parties involved.

The results of the research projects which will be implemented during the period of 2015-2017 will provide new knowledge regarding the spread of MRSA in pig herds and the surrounding environment which does not exist at the current time. This knowledge can be used for a more targeted approach to the problem in the future. It is therefore appropriate for the expert group to continue their work and continually assess the research results with regards to coming up with new recommendations for scientifically documented efforts which could reduce the MRSA problem in the future.

FACTS ABOUT METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

THE BACTERIA *STAPHYLOCOCCUS AUREUS*

Staphylococcus aureus is a bacteria which is widespread in many humans and animals. It is also able to survive in the environment for a long time.
S. aureus is part of normal nasal, mucosal and skin bacteria in about 50-70 % of the population, where it is not normally associated with discomfort or disease (asymptomatic colonisation, carrier). The nose is the primary place of colonisation, but the bacteria are also often found in the throat and on the skin, especially in moist areas such as the groin and perineum. About 20 % always have *S. aureus* as part of their normal flora, while 30-50 % only carry *S. aureus* at times. *S. aureus* is an opportunistic pathogen, which means that in addition to being part of the normal flora, it cause infections ”when the opportunity arises.” *S. aureus* can cause a wide variety of infections. Most common are inflammations of cuts, sores and other lesions in the skin, impetigo and abscesses. *S. aureus* can also cause deep infections such as bone infections, joint inflammation, pneumonia, sepsis and heart valve infections. Many interventions and procedures performed in hospitals, such as putting catheters in blood vessels, drainage tubes and operations increase the risk of staphylococcal infections.

S. aureus is a very hardy bacteria and can survive in the environment for several months (for example, on door handles, mobiles, keyboards and in dust).

S. aureus can be classified into subtypes through typing with, for example, MLST (Multilocus sequence typing), where 7 genes of vital significance to the bacteria's survival have been sequenced and compared. Because of their importance to the bacteria's survival, these genes are very stable and can thus be used to track development over time. The MLST subtypes (ST types)
can be divided into related families called clonal complexes (abbreviated CC). Typing of the *spa* gene is also used. This gene codes for a surface protein in *S. aureus*. It is therefore exposed to much greater impacts, which results in a higher degree of heterogeneity (diversity). These types are specified as T-types. The subcategorisation of certain CC, ST or *spa* types is crucial to contact tracing, but also to the characterisation of the individual *S. aureus* or outbreak strain, since the types are often associated with certain characteristics, such as toxin and virulence factors.

Mode of transmission for S. aureus
Transmission of *S. aureus* primarily occurs through close direct contact with humans (such as household contact) or animals who are positive for *S. aureus*.

There is also a risk of indirect transmission via contact with surroundings where there is *S. aureus* (such as bedding, furniture, floors, railings, keyboards, money and mobiles). Dust is also a source of infection, since *S. aureus* binds to skin cells and shed skin cells are a component of dust.

However, a person hardly becomes a carrier of the bacteria every time they are exposed to *S. aureus*. It is not completely understood what determines whether a person becomes a carrier of *S. aureus*, but it depends on a number of factors, including the amount of bacteria they are exposed to, the duration and frequency of the exposure and their own susceptibility. Individual susceptibility is also influenced by a number of risk factors, such as the presence of beard growth, smoking, blood sugar levels, immunological conditions and the composition of existing bacterial flora (microbiome) in the nose and throat.

Transmission via the hands is the most frequent mode of transmission and washing hands/using hand disinfectant is thus the most significant way to stop the mode of transmission.

METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

MRSA is *S. aureus*, which is resistant to antibiotics belonging to the penicillin group and similar antibiotics (= β-lactam antibiotics, which consist of pencillins, cephalosporins and carbapenems). The name comes from methicillin, which was the first anti-staphylococcal penicillin, developed in 1959. Methicillin resistance is coded by either the *mecA* or *mecC* gene. These two genes are not natural to *S. aureus*, but are transferred from other types of bacteria. As a result of this, the development of methicillin resistance requires the import of one of these genes. Therefore, the effect of antibiotics on *S. aureus* cannot in itself make it into an MRSA, but can promote the survival of already existing MRSA strains or other methicillin-resistant staphylococci (selection) and probably also promote the exchange of the gene between staphylococci.

The genes *mecA* and *mecC* are already placed in a so-called "cassette" of genes (Staphylococcal Cassette Chromosome *mec* = *SCC*mec). These cassettes can also contain other genes which code for resistance to other antibiotics and metals (such as zinc), which can in turn promote selection of MRSA (co-selection). To date, 11 different main types of these cassettes are described.

MRSA was first detected in 1961 in England. MRSA has since spread throughout the world. MRSA previously existed almost exclusively in the hospital environment, but in the late 1990s, the disease pattern changed significantly when the *mecA* gene became increasingly transferred to *S. aureus* bacteria, which thrives outside the hospital environment.
These bacteria are called community-acquired MRSA. MRSA was almost exclusively found in humans until mid-2000, when MRSA made a horizontal jump to animals, where a reservoir was established.

Monitoring in Denmark
In Denmark, MRSA has been monitored by Statens Serum Institut since MRSA was first discovered in 1961. Since 1988, an MRSA strain has been systematically collected from each person found positive with MRSA. Epidemiological data has been gathered on all persons with detected MRSA since 1999. Since 2006 (Guidelines on prevention of MRSA, Danish Health and Medicines Authority, 1st edition), MRSA has had mandatory notification for

laboratories and practicing doctors and hospitals. The mandatory notification includes not only persons with disease (infection), but also healthy persons where MRSA has been detected through screening, for example, household members of MRSA patients.

Household members of MRSA patients are included in order to be able to treat (remove) the carrier state and thus stop further infection. However, for MRSA CC398 it is recommended not to treat the carrier state for persons with daily/regular work on a pig farm, since they will be quickly reinfected and repeated treatments have a high risk of leading to development of resistance to the antibiotics (mupirocin) used to remove the carrier state. In contrast, persons with MRSA CC398 who are not regularly in pigsties, including household members of positive pig herders, are treated just as others with MRSA.

In Denmark, the first case of MRSA was found in a patient in 1962. In Denmark, as in other countries, MRSA had been closely linked to hospitals until the late 1990s, after which MRSA was increasingly caused by community-acquired MRSA and community-acquired MRSA currently constitutes the most common form of MRSA in Denmark. In Denmark, a reservoir was also established in animals in the mid-2000s (see below).

MRSA is spread in the same way as non-resistant *S. aureus* and in principle has the same reservoirs and modes of transmission. Close physical (household) contact with persons with MRSA is thus the most common mode of transmission and hand hygiene is the most important method of interrupting person-to-person transmission of MRSA. MRSA also causes the same types of infections as non-resistant *S. aureus*, but cannot be treated with β- lactam antibiotics (primarily anti-staphylococcal penicillins) which are the first choice for treatment of staphylococcal infections. This often means that proper treatment is not initiated until after microbiological culture and susceptibility testing. The antibiotics which work on MRSA can also cause side effects and hospitalisation may be required to treat the infection.

ANIMAL MRSA

MRSA in animals was first described in 1972. Until about 10 years ago, however, the discovery of MRSA in animals was infrequent and sporadic in nature. Based on the typing, it seems that the bacteria were of "human" types and it is believed that these findings are primarily due to transmission from humans to animals. This changed in 2005 when a new MRSA subtype, MRSA CC398, was described in both the Netherlands and France in both pigs and humans who work with pigs. MRSA CC398 has subsequently spread to animals in most parts of the world, including most of Europe, South and North America, Canada, Australia and Asia. In Asia, epidemiology of MRSA in animals is dominated by another subtype (CC9). In addition to CC398 and CC9, other CC types in pigs have been described in Europe (such as in Italy) and in the U.S. and Canada (CC5). Such CC types are known from

human cases in Denmark, but currently do not seem to originate from livestock to a significant degree.

MRSA CC398 is primarily found in pigs, but is also found in a number of other animals abroad, including veal calves, chickens, turkeys and horses, and more rarely in dairy cows. In Denmark, it is almost exclusively found in pigs (hence the nickname ”pig MRSA”), but in 2013 animal MRSA was found in 2 mink and was also found in some samples from cow's milk. There is very limited knowledge from Denmark on the prevalence of MRSA CC398 in types of animals other than pigs. The animals only very rarely get sick from the MRSA bacteria.

Reviews of both veterinary and human databases have not been able to demonstrate this type of MRSA before the years 2002-2003, either in Denmark or abroad. On the other hand, methicillin-sensitive *S. aureus* (MSSA) of this CC type is found from older dates. MSSA CC398 is currently one of the most common types of *S. aureus* in pigs.

Studies of the genome of MRSA CC398 and methicillin-sensitive *Staphylococcus aureus* (MSSA) CC398 show that MRSA CC398 in pigs originated from human MSSA CC398. After the transition from humans to pigs, the bacteria became resistant first to tetracyclines and the then to methicillin. MRSA CC398 is also usually resistant to several other groups of antibiotics. There have also been several other genetic changes which are believed to have significance for the bacteria's ability to resist the human immune system.

MRSA CC398 disappears by itself in human cases more quickly than other types of MRSA in humans.

Development in Danish pig herds and other livestock

In Denmark, the first case of MRSA CC398 in pigs was found in 2007. There is much to suggest that the prevalence in 2006-2007 was relatively modest, which is in contrast to the Netherlands, where between 60 and 80 % of herds were already positive at that time. A sampling in 2010 showed a prevalence in Danish pig herds of 16 % (DANMAP 2010). The new studies of the prevalence of MRSA conducted in 2014 show a prevalence of 63-70 % (Appendix 1). The presence of MRSA in chickens was studied in 2010, where MRSA was not found. The presence in other types of food animals was not systematically studied. MRSA CC398 was found in two mink (mink fed with offal from pigs and foreign poultry waste) and some milk tank samples from dairy cattle. The discovery of MRSA in humans with contact with horses may indicate that Danish horses may also carry MRSA CC398.

Relevant types of animal MRSA other than CC398 in Denmark

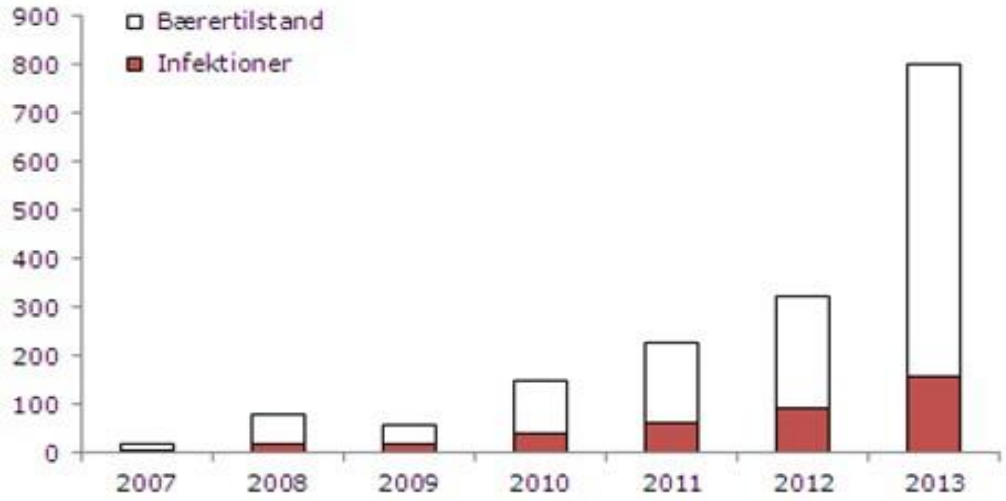
In 2011, a type of MRSA was also found in England and Denmark which seems to be linked to contact with animals, including cows and sheep. This type contains a variant of the *mecA* resistance gene - the so-called *mecC* gene. These bacteria have subsequently been shown to occur in humans all the way back to 1975, but still only constitute a minor part

(1-2 %) of new MRSA cases in Denmark. These bacteria do not seem to be increasing and are not further discussed in this text.

The prevalence of animal MRSA in humans

The first human cases of MRSA CC398 were found in Denmark in 2004. The number of new cases of MRSA CC398 have since increased sharply and MRSA CC398 constitutes 31 % of all new MRSA positive persons in 2013 and the most commonly occurring MRSA type (amongst 270 T-types from 24 different CC types). The increase has been particularly high from 2013 onwards. This is probably primarily a consequence of the revised MRSA guidelines from the Danish Health and Medicines Authority which came out in November 2012, with requirements on active questioning and screening upon hospitalisation if a person themselves or a household member works on a pig farm daily. This is supported by the fact that a large portion of the cases in 2013 were from healthy carriers. In spite of this, the absolute number of people with infections at the time of diagnosis is increasing, which suggests that there is an actual increase in prevalence (Figure 1). If only people with infection at the time of notification are taken into account, people with MRSA CC398 during the period of 2007-2010 amounted to: 4 %, in 2011: 9 %, in 2012: 11 % and in 2013: 17 %.

Figur 1. Antal MRSA CC398, 2007-2013



Demographic data

Because the screening activity is different in different parts of the country and has varied over time, the demographic data consists of people who have infections at the time of diagnosis.

In 2007-2013, Statens Serum Institut registered 1,279 people who had contracted MRSA CC398 and of these, 393 were cases of infection. Over the years, more cases have been found in men (239) than women (154). Most cases are found in people of working age.

They are distributed by age and gender as shown in Table 1.

Table 1. Age and gender distribution of people with MRSA CC398 infections in Denmark, 2007 - 2013

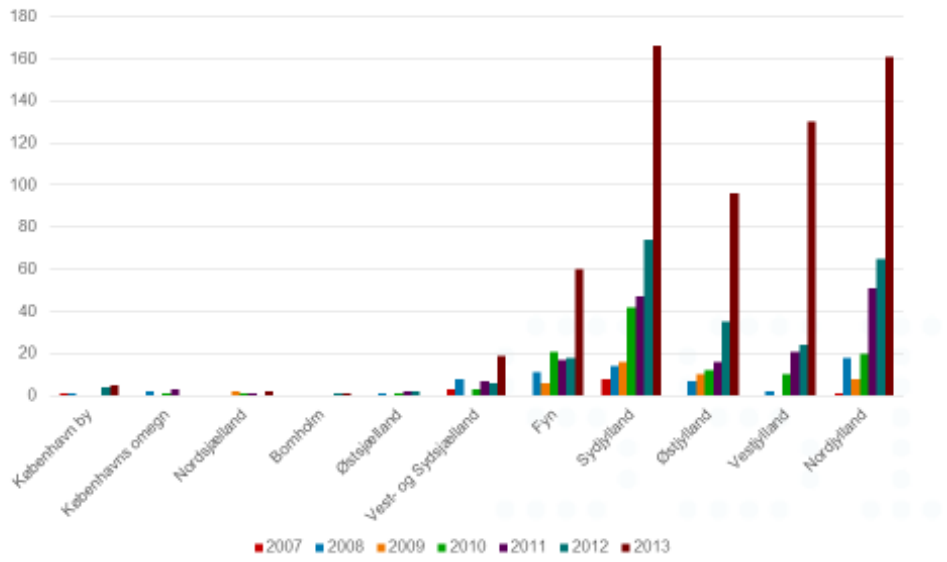
Age (years)	Women	Men	Total
<1	4	5	9
1-4	5	11	16
5-14	5	14	19
15-24	30	40	70
25-34	27	39	66
35-44	20	26	46
45-54	21	27	48
55-64	19	33	52
65-74	8	22	30
75-84	7	17	24
>85	8	5	13
Grand total	154	239	393

Geographically, there are major differences in the prevalence of diagnosed MRSA CC398 infections, with the highest prevalence in West Jutland, then South and North Jutland, followed by East Jutland and Funen. There is a low prevalence in West and South Jutland and Bornholm and infections are largely absent from the rest of Zealand, including in Copenhagen (Table 2 and Figure 2). This distribution reflects where pig farming is found in Denmark.

Table 2. The number and incidence per 100,000 inhabitants of MRSA CC398 infections in Denmark in 2013 (total number and incidence).

		2013	
		Number	Incidence
Capital	Copenhagen city	2	0.27
	Copenhagen area	0	-
	North Zealand	0	-
	Bornholm	1	0.14
Zealand	West and South Zealand	12	2.08
	East Zealand	0	-
Southern Denmark	Funen	20	4.11
	South Jutland	40	5.59
Central Denmark	West Jutland	30	7.05
	East Jutland	19	4.46
North Jutland	North Jutland	32	5.51
	unknown	4	-
	Grand total	160	2.85

Figure 2. Geographic development in the number of cases of MRSA CC398 from 2007-2013



Risk factors for infection by animal MRSA

The vast majority of the people who are found positive for MRSA CC398 either have direct contact with pigs or share a household with a person in contact with pigs (indirect contact), which about 15-20 % of cases have no known contact with pigs or other animals. In 2013, 87 % of the people who tested positive for MRSA CC398 had either direct or indirect contact with animals (primarily pigs).

In 13 (2.3 %) of the cases with animal contact in 2013, contact with minks was listed on the notification forms. In total, 36 people indicated contact with mink since 2009. In 10 of the 36 cases, the people also indicated that there had been contact with pigs and in 2 cases it was unclear whether there was also contact with pigs. The 24 people without contact with pigs had relations with at least 15 different mink farms.

The risk of infection from the environment

The risk of infection as a result of contact with contaminated environments is unclear. *S. aureus* can survive for a long time on inert surfaces. Foreign studies have shown that MRSA is found in very high quantities in air from livestock buildings (3.5x106 - 7x10 8/m3) and MRSA is found up to 300 m downwind from turkey and chicken flocks and 150 m from pig herds.

Experiences from hospitals show that infection as a result of contaminated environments is limited compared to the risk of infection of direct human to human contact. In agriculture, in stables and on machines, however, the dust and pollution levels are much higher than in hospitals, so immediate parallels cannot be drawn.

People without direct contact with pigs or other livestock have a greater risk of being positive for MRSA CC398 if they live in a community where there are MRSA positive farms. The staphylococcus laboratory at SSI is finalising studies which look at

the risk of being positive if there is contact with pigs. The studies show that people who live in municipalities where there is a person with MRSA CC398 as a result of working with pigs have a 2.5 greater risk of being positive for MRSA CC398 than people who live in municipalities where there is no one with MRSA CC398 as a result of contact with pigs. However, the studies do not produce a response to whether this increased risk is due to infection via the environment, for example, as a result of MRSA in ventilation air from farms or MRSA in manure which is spread on fields or whether this is due to people in the communities having greater likelihood to be infected by a person positive for MRSA CC398.

The risk of infection from meat

A number of studies have shown MRSA CC398 in pork and other types of meat both in Denmark and abroad. In a Dutch study of over 2,000 meat samples from retail, MRSA was found in 11 %, of which 84 % was CC398 (turkey 31 %, chicken 27 %, veal
17 % and pork 10 %).

In Denmark, during the period of 2009 to 2011, about 1,000 samples of Danish and imported pork, beef and chicken were studied for the presence of MRSA. The highest prevalence of MRSA was found in imported chicken meat in 2011 (31 %). The next highest prevalence was found in Danish pork (10 %). Some positive samples were found in beef, while only a few samples of Danish chicken meat were positive for MRSA. However, it was not studied whether it was CC398 or another type of MRSA. In all types of meat, MRSA was predominantly CC398. Because it is CC398 in most cases, it is most likely that MRSA in the meat primarily originates from animals rather than human contamination. The studies are qualitative and say nothing about the concentration of MRSA in the meat.

Meat for human consumption (food products)

Although meat from pigs and especially foreign poultry can have animal MRSA CC398 on the surface, the risk of infection via meat is assessed to be limited. Because spreading through the gastrointestinal tract cannot be considered to be a natural mode of transmission for S. aureus, it is in the handling of raw meat that there can be a risk of either acquiring an infection (for example, by getting the bacteria in an open sore) or becoming a carrier of the bacteria (for example, in the nose). It is unknown how many people become carriers via the meat.

The assessment is supported by the epidemiology of the human cases, which shows that almost no MRSA CC398 is found in, for example, Copenhagen, North and East Jutland, where there is a high population density with no relation to agriculture.

Handling of meat in slaughterhouses and by butchers

A Dutch study examined slaughterhouse workers and exposure during the slaughtering process and concluded that slaughterhouse workers have an increased risk of becoming carriers of MRSA, especially with contact with live pigs. There have been no corresponding systematic studies conducted in Denmark. Based on the notifications, it seems that in some cases (a few per year) handling meat is suspected as the cause of infection. However, there is nothing to suggest that handling meat, for example, in slaughterhouses or other

food product operations, is a dominant risk factor. However, it should be mentioned that in a few cases, handling meat was mentioned as a possible source of infection in the clinical reviews. In addition, a follow-up phone interview of a patient with MRSA CC398 infection further clarified meat handling as a source of infection, since the person, who did not have contact with livestock, worked in a meat department of a supermarket.

Infection in people without direct or indirect contact with pigs

In 2013, there were 82 people who were positive for MRSA CC398 who did not report contact with pigs. For these 82 cases, there is information on the suspected place of infection/mode of transmission in 29 of the cases based on the information which the reporting doctor has listed on the notification form or from a subsequent follow-up from the general practitioner.

Community-acquired cases of animal MRSA

The number of cases acquired in a nursing home or hospital are shown in Table 4. It should be noted that contact with pigs was not asked about upon admission to hospitals or being moved into a nursing home until December 2012. Because a person can carry staphylococci and thus MRSA for a long time without symptoms, it cannot be excluded that some of the cases in 2013 were acquired before admission/moving in.

Table 3. MRSA CC398 as a result of infection in nursing homes or hospitals, 2007-2013

Number of MRSA CC398 infections in nursing homes

	2007	2008	2009	2010	2011	2012	2013
All CC398	0	0	0	2	0	1	1
Infections	0	0	0	2	0	1	0

Number of MRSA CC398 infections in hospitals

	2007	2008	2009	2010	2011	2012	2013
All CC398	0	2	0	1	3	6	1
Infections	0	2	0	1	3	4	1

As shown in Table 3, community-acquired cases of MRSA CC398 are very rare.

Disease burden of MRSA CC398

MRSA, including MRSA CC398, can, as with other *S. aureus* - mentioned in the introduction - cause a wide variety of infections. The type and severity of the infections are highly dependent on the person's immune state and whether the person is susceptible to infection.

For example, patients who have been recently operated on, have bone prostheses, intravenous catheters, etc. are at risk of getting serious infections of MRSA. Patients who do not have chronic illnesses or are not being treated for other diseases are most commonly affected by infections in the skin and these are usually not of a serious nature.

Carriers of *S. aureus* (including MRSA) are at an increased risk of getting infections compared with people who do not carry *S. aureus*. In two major studies it was shown that up to 80 % of blood poisoning with S. aureus was caused by the patient's own carrier strain - self-infection.

The vast majority of infections which occur as a result of MRSA CC398 are skin and blood infections. This fits in with the fact that it is primarily working age 15-64 year old people who carry MRSA CC398 and it generally corresponds to the situation seen in Denmark for community-acquired human MRSA.

In Denmark, MRSA is nationally monitored only at the time of diagnosis and in the event of any subsequent blood poisoning. Therefore, there is no knowledge (other than blood poisoning) on the overall disease burden, because the diseases which arise after MRSA is first found are not registered, either for MRSA CC398 or for other types of MRSA. The percentage with infections and, to a certain extent, the type of infections at the time of diagnosis, are shown in the clinical reports and, together with the monitoring of blood poisoning, form the background for the following figures.

The number of people with infections as a result of MRSA CC398 at the time of diagnosis has increased throughout the period of 2007-13 (Figure 1). The number of infections and the percentage in relation to the total number of newly diagnosed people with MRSA is significantly lower for MRSA CC398 compared to other types of human MRSA (Table 4), but this can largely be attributed to the active screen for MRSA amongst people who have contact with pig herds. Out of the 82 without contact with pigs, 51 had infections at the time of diagnosis (62 %), while the corresponding figures for people with contact with pigs were 561 in total, of which 106 (19 %) had infections.

Table 4. MRSA total number and clinical infections, 2007 - 2014*

Year	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014***
Number of MRSA	14	65	42	111	164	232	643	694
- of which had	6	16	16	38	63	92	156	-
infections %	43	25	38	34	38	40	24	-
Other types of	647	781	775	987	1129	1334	1451	1047
- of which had	364	430	470	611	681	746	775	-
infections %	56	55	61	62	60	56	53	-

*until 30 August

A total of 7 people were found positive for MRSA CC398 with bacteremia during the period of 2007-2013, of which 3 were dead within 30 days. In the first 9 months of 2014, 6 additional cases of bacteremia were found, of which 2 people were dead within 30 days (Table 6). The five deceased patients with CC398 MRSA bacteremia all had a number of serious underlying diseases. During the same period, there were 167 cases caused by MRSA other than CC398, of which 39 died within 30 days. For comparison, in the same period (2007-2013) there were a total of 10,426 bacteremia cases from S. aureus bacteremia,

whether MRSA or not. In total, about 300-350 deaths were registered as a result of staphylococcal sepsis per year in Denmark

Table 5. The total number with MRSA, bacteremia and deaths after bacteremia from MRSA CC398, compared with other types of MRSA, 2007 - 3rd quarter 2014

	Number of MRSA			
	Regardless of manifestatio	With infection	(%) with bacteremia	(%) deaths within 30 days
CC398	2130	553	13 (2.4)	5 (38)
Other types	8300	4657	167 (3.6)	39 (23)

RISK ASSESSMENT FOR LIVESTOCK - MRSA

Transmission from animal to animal

Infection between herds is known to occur when trading pigs, which is shown from Norwegian outbreaks of MRSA CC398 in pig herds, amongst other things, which is largely spread through the moving of pigs. Pigs which carry MRSA CC398 thus take the bacteria to new herds where the bacteria can spread and establish itself in a new herd. This is also documented in Dutch studies. However, there are also examples of herds being free of MRSA, even if they have received pigs from infected herds. The dynamics of how MRSA is transmitted between pigs within the same herd is still unclear. Transmission between pigs can occur via direct contact, but it is unknown to what extent transmission via dust in the air or via contaminated equipment, tools and machines occurs. It is known that antibiotics and zinc exert a selective effect for MRSA, but there is no concrete knowledge as to the extent to which this means that MRSA is more easily established and spread in pig herds.

The European baseline study in 2007 showed that there was a correlation between the size of the herd and the likelihood that it was infected. Large herds were more frequently infected than small herds. In general, breeding herds and finisher herds were infected equally often, which was interpreted as a sign that transmission often occurs via trading pigs.

In principle, it is conceivable that introduction of MRSA CC398 from other animals could occur, including farm animals and pets as well as insects, birds and rodents. Insects such as flies would be able to act as passive vectors analogous to how flies and wild birds can introduce campylobacter into poultry flocks and how ESBL-carrying bacteria are found in bird droppings. There is only a little data in this area.

Transmission from human to animal

There are examples of closed herds which do not receive pigs from other herds being able to be infected with MRSA. There must therefore be other ways a herd can be infected than via infected pigs. Norwegian experiences show that

such introduction can occur from people who have access to the stables. Such people could be employees who previously worked in other pig herds or guests such as veterinarians and craftspeople.

Because animal MRSA is most likely a mutated human MRSA strain which has adapted to animals, human to animal transmission must be considered as a possible mode of transmission. In Norway, it is considered to be a genuinely possible source of infection of animal MRSA. Norway has also discovered MRSA bacteria other than CC398 in their herds.

The Danish breeding herds are closed herds with very high infection protection standards. The Danish study of breeding herds in 2014 shows that 63 % have MRSA. This observation suggests that modes of transmission other than trading pigs affects the prevalence of MRSA. These modes of transmission are not prevented with existing infection protection measures Examples of such modes of transmission can humans or spreading via dust in the air.

Transmission from animals to humans who work in the stable daily
Staying in MRSA positive stable environments leads to a significant risk of becoming positive for MRSA CC398. Based on foreign studies, it must be assumed that at least 70 % of people with daily contact with MRSA positive animals in stables are positive.
The dynamics of infection from animals to humans for MRSA are unknown and it is unclear the role that physical contact with animals plays in relation to the prevalence of MRSA in dust in the air or contact with the many surfaces which can contain large quantities of MRSA. It should be added that the quantity of MRSA in dust in the air in contaminated conventional stables is very high.

There is no knowledge on whether the use of protective equipment, particularly dust masks, can reduce the percentage of carriers. It is also unclear whether measures to reduce MRSA in the air can reduce the risk of colonisation. Ventilation systems which reduce the content of dust in the air and thus the content of MRSA in the air must be expected to be able to reduce the risk of colonisation.

Transmission from animals to humans who regularly work in the stable environment
Based on foreign experiences, the percentage of MRSA positive veterinarians is somewhat less than 70 %, probably 20-40 % for pig veterinarians. Those who transport pigs also have increased risk, but it is somewhat less and also determined based on studies abroad. The risk of becoming infected seems to be significantly less if one works with/handles dead pigs (slaughterhouses).
The production conditions in Denmark are more intensive than in most other countries. Therefore, foreign data cannot immediately be used for comparison under Danish conditions.

Transmission from animals to humans with single visits to the stable
In connection with the initial studies of livestock-associated MRSA, the risk of becoming a carrier after a short-term visit in herds has been studied (in connection with

sampling). In over 90 % of the cases, the people lost the MRSA bacteria spontaneously after just 24 hours.

Therefore, based on this there is assessed to be only a small risk in practice of becoming a carrier through single visits to a pig herd. However, the assessment is based on few studies.

The risk of infection from animals other than pigs
The extent to which other livestock are significant reservoirs for MRSA in Denmark is unclear. Poultry is a significant reservoir in several European countries, but it is unclear whether there is MRSA in Danish poultry production. The same applies to Danish beef and dairy cattle.

Contact with mink seems to be an independent risk factor, though significantly less than for pigs. Staphylococcal infections in mink are very common, but are usually of a different type, *Staphylococcus delphini*, while *S. aureus* is less common. Mink are handled in connection with moving from one cage to another, handling sick animals and skinning. Since the animal bites, such handling must always occur with tongs, traps or thick gloves. It is known that mink feed which contains offal from pigs and poultry products may be contaminated with MRSA CC398. Whether the infected persons were infected through contact with the animals or contact with the feed is unknown. It not known the extent to which MRSA is found in mink farms or which risk factors are linked to becoming MRSA positive.
Studies conducted by Copenhagen Fur have shown that MRSA could not be detected in the nose and throat in mink.

Discovery of MRSA in veterinarians who primarily work with horses indicates that there is an unknown reservoir amongst horses in Denmark.

There is currently nothing, either in Denmark or abroad, which suggests that dogs and cats constitute a significant reservoir.

Risk of infection from the environment
The significance of this mode of transmission is unclear and it should be studied whether transmission via contaminated environments is a significant mode of transmission, including ventilation air and slurry.

Based on general knowledge of staphylococci's mode of transmission, it is highly likely that the vast majority of people without contact are infected as a result of contact with another person with MRSA CC398, but transmission via the environment cannot be ruled out at the current time.

Risk of infection human to human
Transmission of MRSA CC398 between humans is assumed to have the same mode of transmission as other MRSA / S. aureus, which is to say, primarily through close direct contact between humans, but indirect transmission via contaminated objects must also be assumed to occur to some extent. Several studies show that MRSA CC398 does not transfer between humans as well as other types of human MRSA.

Infection - future scenarios

It is Statens Serum Institut's expectation that without further intervention, there will be an increase in the number of colonised persons who have contact with pig herds. Since most of the herds are already infected and the number of employees in the pig production industry is limited, we will reach a saturation point in the course of a few years. However, the prevalence will continue to increase for a period after this saturation point has been reached, since people with MRSA CC398 who work daily in a pig herd are not treated for the carrier state.

Amongst people who do not have contact with pigs, there will also eventually be an increased prevalence. This is due in part to the number (prevalence) of infected employees in the pig industry continuing to increase, which is why there will be more secondary cases and these individuals will cause further infection.

Genetic changes in the form of increased adaptation of MRSA CC398 to humans can increase the spread of infection. The more people who carry MRSA CC398, the more the risk of this occurring increases. It should also be mentioned that MRSA CC398 can be replaced by other types of staphylococci after a number of years, which could change the picture again. It is not possible to predict how the development will go.

In particular, the increase in secondary cases is expected to contribute to more serious cases of the disease. The more infected people there are, the more those with reduced immune systems or other risk factors will be infected. However, in any case, the development will be partially counteracted by the applicable guidelines, since secondary cases without direct contact with pig herds, cf. MRSA guidelines, will be treated for the carrier state and thus the further infection and risk of serious infections will be reduced.

CONCLUSION OF RISK ASSESSMENT OF ANIMAL MRSA

Conclusions on the assessment of the disease risk, etc. that animal MRSA

(MRSA 398) MRSA CC 398 will constitute a health and resource problem:

- For ill and infirm people and for people who have had operations or similar interventions. These people have an increased risk of getting serious staphylococcal infections and if the infection is caused by a MRSA staphylococci, including MRSA CC 398, the course of the disease will be more prolonged and the risk of death will be significantly higher.
- For some people who show MRSA CC 398 and their families, who must deal with the transmission of MRSA, which currently particularly applies to people who work in pig herds and their families.
- For health care, which currently uses increasing resources to prevent the spread of MRSA 398 and on treating patients with MRSA 398. If MRSA 398 becomes sufficiently widespread in the community, the primary efforts can no longer be specially limited to people (and their household members) who work with pigs. As a consequence of this, the spread of infection, resources

for treatment, etc. may be greatly increased and there will probably also be an increase in mortality. Specification of this increased risk and quantification of extra resource consumption in health care is presently a difficult task due to a number of uncertainties.

For the population as a whole, MRSA 398 constitutes a very minor health problem.

THE STRUCTURE OF DANISH PIG PRODUCTION

Danish pig production can be viewed as a pyramid, where breeding herds are at the top, multiplier herds are in the middle and the production herds are at the bottom.

In brief, the breeding herds provide breeding animals (boars) for AI stations (AI = artificial insemination) and purebred females for multiplier herds. Many of the breeding herds are also multiplier herds.

The multiplier herds have purebred females, for example, Landrace or Yorkshire (LL or YY) which are crossed with a purebred boar. For example, a Landrace sow is inseminated with a purebred Yorkshire boar and the offspring will then be YL females or YL boars.
The females are then sold to production herds as gilts. In production herds, these are used as dams, i.e. regular sows. YL males are either fattened in multiplier herds or in finisher herds.

The production herds then often inseminate the sows with semen from a Duroc boar, whereby the offspring will be a YLD cross. The crossbreeds are the ones there are clearly the most of and those which are sold as 30 kg pigs for export or slaughter in Denmark.

Data on the number of animals which ”go down through the pyramid” for the first 10 months of 2014 has been provided by Dansk Svineavl.

5,200 purebred boars have been sold from Denmark. 4,846 boars (93.2 %) were exported, while in Denmark, 354 boars were sold (6.8 %). In Denmark, Duroc boars were mainly sold to production herds which have their own boar and thus do not purchase semen from AI stations. The Duroc boars only come from one herd, so far as is known.

The sale of purebred females in the first 10 months was 21,519 females. Of these, 16,506 females (76.7 %) were exported, while 5,013 (23.3 %) were sold in Denmark. The
5,013 are divided into 3,774 females (75.3 %) for multiplier herds and 1,239 females (24.7 %) for production herds.

When evaluating how many animals go from breeding herds down to production herds, where the major production is, it is thus only the 1,239 females (5.8 %) out of the total 21,519 females.

The second most trades occur from multiplier herds (females) down to production herds with sows.

By far the most trades occur between the production herds. Primarily through production herds with sows selling 7 or 30 kg pigs for fattening in finisher herds in the local area or in other parts of the country. About 18.5 million finishers are slaughtered in Denmark per year.

In total, there are about 8,900 herds registered with pigs.

PREVIOUS EFFORTS

THE MRSA ACTION GROUP

In autumn 2012, the Ministry of Food, Agriculture and Fisheries of Denmark and the Ministry of Health and Prevention established a MRSA CC398 action group which had the purpose of proposing initiatives for limiting MRSA CC398. There was a requirement that the initiatives could be launched in the short term.

The action group's recommendations resulted in three initiatives being launched. These are:

- The forum for animal MRSA was established as a permanent interdisciplinary ministerial cooperation group. The group still exists and holds several meetings a year.
- The advisory service for animal MRSA was established in order to raise awareness of animal MRSA in the Danish community. The advisory service also still exists and advises farmers, concerned citizens and eventually also plans to advise healthcare professionals. See under the five-point plan.
- Hygiene project. See under the five-point plan.

The last two are included in the ministry's five-point plan.

FORUM FOR ANIMAL MRSA

The ”Forum for animal MRSA” was established in August 2013 in order to ensure a better cooperation between the authorities. The group has the purpose of ensuring an exchange of knowledge and experiences with the prevalence of animal MRSA in animals and humans with and
without contact with animals. The work should help ensure that the authorities' work on animal MRSA is as resource-efficient as possible.

The ”Forum for animal MRSA” is composed of representatives from the Danish Working Environment Authority, the Danish National Food Institute the Danish National Veterinary Institute, the Danish Health and Medicines Authority and Statens Serum Institut. The group can convene experts ad hoc.

The Danish Veterinary and Food Administration handles the Chair and Secretariat functions. There are 3-4 annual meetings as a starting point.

THE MINISTRY'S 5-POINT PLAN

In June 2014, the Ministry of Food, Agriculture and Fisheries of Denmark introduced a five-point plan with the purpose of containing animal MRSA to the stables:

Point 1: Hygiene measures – barriers out of the stable
As a barrier to reduce the risk of animal MRSA coming out of the stable, requirements were introduced on infection protection when people leave pig herds.
The requirement will minimise the risk of pathogens being introduced, including resistant bacteria, from the stable out to the rest of the community.

The hygiene rules came into effect on 1 September 2014 via Executive Order Amendment no. 949 of 27 August 2014 relating to the amendment to the Executive Order relating to health advisory agreements for pig herds being inserted into Executive Order no. 534 of 27 May 2014 relating to health advisory agreements for pig herds. With the Executive Order, a requirement is introduced that clothing and footwear must be changed or washed and footwear disinfected, along with hand washing and disinfection when leaving a pig stable.

In addition, in cooperation with the industry, a hygiene project has been initiated which will measure the effect of various hygiene measures in relation to limiting the transmission from
pig MRSA from the stables. The project includes a practical aspect which includes taking samples from animals and people from pig herds.

Point 2: Requiring a zoonotic infection protection plan
As part of the health advice for all pig herds with mandatory health advisement, it is a requirement that the person responsible for the herd must prepare a zoonotic disease prevention plan when advised by their veterinarian. The plan is specifically designed to reduce the risk of MRSA being transmitted from pig herds. In addition to requirements for hand washing, changes of clothing and changes of footwear or disinfection of footwear when leaving the stable, the infection protection requirement involves the farmer and the veterinarian once a year together discussing further measures to reduce the spread of bacteria and diseases from the stable. The measures will be set out in an infection protection plan prepared for the herd in question.

The person responsible for the herd must also ensure that employees and all other persons who have permanent or occasional errands in the herd comply with the infection prevention measures contained in the herd's infection protection plan. These requirements came into effect on 1 September 2014 via Executive Order Amendment no. 949 of 27 August 2014 relating to the amendment to the Executive Order relating to health advisory agreements for pig herds being inserted into Executive Order no. 534 of
27 May 2014 relating to health advisory agreements for pig herds.

Point 3: Routine flock medication is stopped
In order to ensure a low and correct use of antibiotics, special requirements for pig herds where group medication is used came into effect on 1 June 2014. The requirements include laboratory studies, multiple veterinarian visits in the herd and shorter prescription periods for medication prescribed for flock treatment. The requirements are intended to discourage inappropriate use of group medication and are part of the efforts to ensure responsible use of antibiotics which causes a low level of antibiotic resistance. Sick animals have to be treated, but treating an entire herd with medicine is not always necessary.

The requirements established in Executive Order no. 537 of 27 May 2014 on health advisement in pig herds, as well as in Executive Order no. 533 of 27 May 2014 on veterinary use, dispensation and prescription of medicines for animals.

Point 4: Establishing a MRSA advisory service
The purpose of a MRSA advisory service is improved advice on animal MRSA for farmers and employees of MRSA crews so that they know how to avoid becoming carriers and thus further transmit MRSA.

The advisory service was established on 1 July 2014. The service has already gotten going and is helping increase the level of information about animal MRSA in Denmark through advisement at the request of farmers, veterinarians, doctors, agricultural schools and unions.

The service gives advice on animal MRSA to farmers and employees in pig herds, amongst others, so that they know how to avoid becoming carriers of animal MRSA and avoid transmitting animal MRSA. It is important to have correct and adequate information to reduce animal MRSA infection in the community, while avoiding uncertainty due to incorrect or insufficient information.

The advisory service includes a "hotline" and "mailbox" for responses to these topics and answers questions from citizens and health care professionals. In addition to this, the advisory service contributes to the development of information and educational materials and organises informational and educational meetings. Finally, the service/Statens Serum Institute (SSI) collects data from infected persons in order to monitor new risks of infection for humans.

Point 5: Study of the fee structure of antibiotics
An evaluation of the fee structure of antibiotics has been initiated which has the purpose of finding new solutions which can strengthen the incentives to choose alternatives to antibiotic treatment, such as preventive vaccinations.

This study is awaiting the collection of sufficient data in order to analyse whether the fees have the desired effect.

GENERAL ANTIBIOTICS-REDUCING MEASURES

Denmark has a long tradition of active efforts to reduce the use of antibiotics. There are a number of initiatives running under the auspices of Veterinærforlig II. The initiatives are briefly discussed below.

LIMIT VALUES AND YELLOW CARD SYSTEM

In December 2010, the government introduced limit values for antibiotics and the so-called "Yellow card" system.

The scheme was introduced after several years of increasing antibiotic consumption in production animals and resulted in a significant decrease in the consumption of antibiotics for pigs. The reduction was initially up to 25 percent and has since stabilised at approximately 15 percent lower than in 2009. The decrease in the consumption of antibiotics for pigs resulted in an overall decrease in antibiotic use for all species of approximately 10% (measured in kg compared to the consumption in 2009).

The scheme's limit values have subsequently been adjusted twice, most recently with effect from the end of November 2014.

In addition, the establishment of Animal Daily Dose (ADD), which lays the groundwork for the entire scheme, was changed to a more solid model. This change will also be effective from the end of November 2014. Both initiatives were announced in February 2014.

STRICTER RULES FOR FLOCK MEDICATION

As part of Veterinærforlig II, the Danish Veterinary and Food Administration tightened the rules for flock medication in pig herds in June 2014. With the strictures, intensive laboratory diagnoses and frequent vet visits are required to use flock treatment on pig herds. The incentive for flock medication was thus reduced.

DIFFERENTIATED FEES ON ANTIBIOTICS

As part of Veterinærforlig II, it was agreed that a differentiated fee structure on antibiotics should be established. The purpose is to strengthen the incentive to choose alternatives to antibiotics such as preventive vaccinations or - when antibiotic treatment is required - to choose the antibiotics which are least critical and which have the least risk of resistance development. The conciliation text also shows that the economic framework for the fee structure is DKK 8.3 million per year and its revenue will be used to fund initiatives with regards to responsible use of antibiotics.

The fee structure was established in cooperation with the Danish Health and Medicines Authority and the Danish Veterinary and Food Administration in September 2013. The Danish Health and Medicines Authority is responsible for collecting the relevant fees.

The current rates are shown in Table 6.

Table 6. Overview of fees on veterinary medicines

Group of medicines	Fee
Vaccines	0 %
Simple, narrow-spectrum penicillins	0.77 %
Other antibiotics for animals	4.99 %
Critically important antibiotics	10.77 %
(3rd and 4th gen. Cephalosporins and	
Other drugs for animals (non-antibiotic)	0.77 %

EFFORTS IN OTHER COUNTRIES

NORWAY

In Norway, animal MRSA (CC398) was detected in samples from pigs for the first time in 2011. Surveys from 2008, 2011 and 2012 showed a very low incidence of all types of MRSA in pig herds in Norway. In 2008, human strains of MRSA were only found in a single herd, where the infection came from humans.

In 2013/2014 however, outbreaks of animal MRSA were detected in Norwegian pig herds. A comprehensive mapping study of all herds with more than 10 sows per year (986 sow herds plus 9 sow herds studied as part of the discovery of the outbreak) was conducted in the spring of 2014. In Norway, one sow herd was found to be infected with animal MRSA. At discovery of the outbreak, the Norwegians found 25 infected herds. The veterinary authorities of Norway believe it is likely that there had originally been 3-4 infected farms and the rest were infected by the purchase of infected animals.

Norway uses reorganisation of infected herds. In total, 26 herds were reorganised during the period of 2013 - 2014. Follow-up samples taken after the reorganisation indicate that the reorganisation was successful in 20 herds during the first reorganisation. Out of the 26, three of the herds were reorganised recently, so it is not known whether they are still negative. Of the reorganised herds, only 3 herds now have animal MRSA again. For one of the herds, the infection was reintroduced via the purchase of an animal MRSA positive pig. For the other two, the explanation is not known. They were all reorganised a second time, one of them became positive again with unknown cause.

Norway generally has a very comprehensive sampling program. In addition to samples from the pigs, environment samples are also taken. However, Norway has entirely different pig production than Denmark, with a total of approximately 2,000 herds of pigs in Norway (Denmark has approximately 8,900 herds). Of these, there are about 1,200 sow farms averaging 80

sows per year (Denmark has an average of 651 sows per year (2012)). There is annual production in Norway of approximately 1.6 million finishers (Denmark has, in comparison, an annual output of 18.5 million finishers).

THE NETHERLANDS

The Netherlands was one of the first countries to be aware of a very high prevalence of MRSA CC398 in their herds. It is currently assumed that the majority of Dutch herds are positive, including veal calves. The Dutch authorities' main priority is on ESBL, which they regard as a larger public health problem than animal MRSA. There is monitoring of ESBL in the animals, but not animal MRSA.

In the Netherlands, where the focus is on ESBL, pig slaughterhouses have introduced an additional side-oven at the slaughter line, which is expected to contribute positively to reducing the prevalence of animal MRSA and other resistant bacteria on the surface of carcasses.

POSSIBLE FOCUS AREAS

INTRODUCTION OF ANIMAL MRSA INTO THE HERD

Introduction via humans

People who have been in a MRSA positive pig stable are at risk of being carriers of MRSA and could therefore transmit the bacteria to other herds or humans and animals outside the stable.

Reducing the contamination levels of individual employees through bathing, changing clothes and changing footwear or disinfecting footwear (from working suits to private clothes) and applying meticulous hand hygiene when leaving the stable area can reduce the risk of further infection. However, it should be noted the MRSA cannot be removed in this way, it is carried in the nasal cavity, for example, and that these bacteria can subsequently be a source of contamination of hands and can lead to further infection in the same way as seen with the spread of other types of MRSA.

MRSA CC398 disappears by itself in human cases more quickly than other types of MRSA in humans.

In connection with the implementation of the minister's five-point plan, requirements have been introduced for hand washing, changes of clothes and changes of footwear upon leaving the stable. Some of the initiated research projects will address the effect of these conditions.

Introduction via import of live pigs into the herd

Sale of animals
It could be considered in the future to only exclusively introduce animals from animal MRSA negative herds and in this way reduce the disease burden. This way, the infection may slowly die out. However, there is no immediate evidence that this can be done. With a MRSA prevalence of 63-70% and insufficient knowledge of each herd's status, this is unrealistic.

In Denmark, the breeder level supplies the next segment – the multipliers - with animals and so on down the system. However, there are still herds that do not buy animals, but have their own sows and even fatten up their piglets.

To keep MRSA negative herds free of MRSA, it will be necessary to exclusively buy animals from MRSA negative herds. A prerequisite for this is that the status of all herds must be identified and those that are MRSA-free should be continuously monitored. Experience from Norway shows that it is possible to keep MRSA negative herds free from infection. The degree to which the same applies under Danish conditions is uncertain, since the number of pigs per herd is larger, the number of infected herds is significantly higher than in Norway, and in Denmark there is much more sale of animals as a result of much greater production.

The results of animal MRSA studies in 200 randomly selected herds in Denmark do not give a clear indication that there may be areas in Denmark which show less prevalence of animal MRSA than others. If future studies find the existence of low prevalence areas, the possibility of establishing low-prevalence or free zones could be studied, cf. the *S. Dublin* Action Plan, which was developed for cattle.

The *S. Dublin* action plan divided the country into areas of high and low prevalence of *S. Dublin.* It was not permitted to move animals from a high-prevalence zone to a low-prevalence zone in order to avoid spreading the infection. After the prevalence of *S. Dublin* falls in high-prevalence areas, the areas with low prevalence will be expanded. This way, it is believed that the infection can be forced out area by area.

This requires more intensive study on the prevalence of animal MRSA in areas that could have potential as low-prevalence areas.

Reorganisation – physical
In Norway, the political decision was made to completely reorganise MRSA positive herds. The reorganisation was implemented through the release of all animals with subsequent cleaning and disinfection.
Only then were animal MRSA-negative animals introduced. The Norwegian state pays part of the cost of the reorganisation.

In Denmark, pig production, as mentioned, is much more intensive with much larger herds than in Norway. The basis for Danish pig production success is the quality of breeding that takes place in the few herds at the breeding level. Elimination through reorganisation of a large part of the herds at the breeding level will have major genetic

consequences and breeding will be set back, resulting in major consequences for Danish pig production.

Due to the high negative consequences, solid knowledge should be secured on how to effectively reorganise for MRSA CC398 in Danish pig herds before any decision is made to reorganise breeding herds with MRSA CC398. Therefore, it may be worth studying reorganisation opportunities for sow herds in small scale studies. In Denmark, complete reorganisation of sow herds as a result of production diseases is only implemented annually. The vast majority of reorganisations are implemented as partial reorganisations in stages or as "medical reorganisations" using antibiotics and/or vaccines.

Before deciding to initiate a reorganisation strategy, conditions which could discourage re-infection with MRSA CC398 with should be clarified through research.

Based on experience from combating other diseases in pig production, it is estimated that reorganisation is not realistic at the present time, because there is insufficient knowledge about the modes of transmission for animal MRSA. If only animal MRSA-free animals are added in the future, there is a need for more knowledge of the modes of transmission of the bacteria, including the prevalence and survival in the stable, in order to prevent re-infection. There is knowledge that the bacteria is found in dust, because some studies have detected the bacteria via dust. The lack of knowledge includes the bacteria's survival on different surfaces in the stable and where it can be found other than in dust. These conditions will be addressed in the ongoing research projects.

Reorganisation using antibiotics

Infectious diseases, such as virulent pneumonia and lawsonia-related intestinal inflammation, are occasionally fought through reorganisation with antibiotics. The expert group is not aware of any attempted reorganisation of herds for animal MRSA using antibiotics ("medical reorganisation"). If such a reorganisation was done, it would be expected that critically important antibiotics would be used. The expert group assesses that an increased use of these types of antibiotics would not be appropriate due to the risk of developing further resistance.

Introduction via other production animals or dogs, cats and rodents including rats and mice as well as insects and wild animals

Because other animals are likely to be able to act as reservoirs for animal MRSA, it could be considered to recommend that people with daily contact with pigs should not handle other animals such as poultry, horses, cattle, sheep, goats and possibly even dogs and cats. However, such a recommendation is not appropriate, because knowledge of the spread of MRSA CC 398 in these animals in Denmark is sparse, while at the same time, some herds have multiple types of animals. The extent to which these animals constitute a reservoir will be important to address.

Knowledge of this can be achieved by initiating screening of the prevalence of animal MRSA in herds with other types of production animals such as cattle, mink, poultry and horses.

Mice and rats can constitute a risk and should be controlled. The Danish Ministry of the Environment has rules on rat control in Denmark.

Dogs and cats should be refused access to pig stables, which is already the case in the herds enrolled in the agricultural Specific Pathogen Free scheme (SPF herds), cf. SPF regulations. However, this does not apply to farm cats, which only come into the stable and are a tool for controlling mice.

However, there is no knowledge of the prevalence of animal MRSA in dogs and cats, which could be obtained by screening them.

The collection site for dead pigs before retrieval for destruction could also constitute a risk for the spread of animal MRSA to pets and wild animals if the cadavers are not properly covered. The requirement for proper storage already exists in the current legislation. This should be controlled by a campaign against improper and illegal storage of dead animals.

SELECTION PRESSURE WITHIN THE HERD

Reducing the use of antibiotics

Use of antibiotics and other antimicrobial agents in any context will result in an undesirable development of resistance.

In order to avoid development of resistance, it is crucial to ensure efforts aimed at reducing the use of antibiotics while simultaneously maintaining good animal welfare. Denmark has a long tradition of active efforts to reduce the use of antibiotics. Most recently, the Danish Agriculture & Food Council announced that they want to cut the use of tetracyclines in half by the end of 2015. Such a reduction could be expected to have a favourable effect on the development of the prevalence of MRSA.

There is no scientific documentation on the extent to which a reduction in antibiotics consumption will reduce the prevalence of animal MRSA. Research initiatives should in the future be able to be document the significance of the reduction of antibiotics on the prevalence of animal MRSA.

The following elements can contribute to reducing the consumption of antibiotics:

Increased use of vaccines

When effective vaccines are used, it is likely that the consumption of antibiotics can be reduced, because the animals do not develop symptoms of the disease against which they are vaccinated. Therefore, it can have a beneficial effect if the use of vaccines is promoted.
Marketing of new vaccines can also contribute to the desired effect.

Flock medication should be further limited in pig production.

When experience has been gained with the already introduced measures against flock medication (cf. the minister's 5-point plan), these should be evaluated with regards to an assessment of whether they have led to the desired reduction in the prevalence of animal MRSA. Depending on the results of this, it should be assessed whether there is a need to initiate further measures.

Differentiated yellow cards should be introduced.
As part of the government's future antibiotics strategy, Nationale Antibiotikaråd (*the Danish National Antibiotics Council*) planned to initiate and fund a pilot project where a model for a differentiated yellow card would be developed and assessed. In yellow cards, a herd's antibiotics consumption is assessed in relation to the number of standard doses (ADD) used in the herd per animal and per day. What is in ”a differentiated yellow card” is so that each medicine can also be assessed independent of the degree to which the medicine is the cause of resistance development in the human sector.

Termination or restriction of the use of critical antibiotics
Critically important antibiotics such as fluoroquinolones and cephalosporins should be avoided in pig production, because they are particularly important in the treatment of serious infections in humans caused by resistant bacteria and should constitute a final and only treatment option.

Currently, the use of fluoroquinolones is highly restricted via Danish regulations. In practice, other than individual clinical trials, the use has been terminated.

The consumption of cephalosporins in the pig industry was completely phased out in 2010. This is because the pig industry imposed a voluntary ban on the use of these medicines in 2010.

Zinc and other metals
Zinc (like copper) is primarily an essential trace element and without these trace elements, animals cannot survive. Zinc is also used in pharmaceutical form (zinc oxide) for the prevention of diarrhoea in piglets during the first 14 days after weaning.

Initiatives against high use of zinc may be considered. Zinc is currently used in the form of zinc oxide as an approved medication for diarrhoea in connection with weaning piglets. It is believed to cause relatively large problems in Danish pig production if the prescription of zinc oxide as a medication becomes very restrictive, which is supported by the other EU member states using a lot less zinc oxide, but significantly more antibiotics in the weeks after weaning.

At Aarhus University, there is an ongoing three-year project specifically designed to address the physiological conditions regarding the need for further prescription of zinc and copper at various weaning intervals. The research project is expected to be concluded in 2017.

Weaning age
EU's rules prescribe a weaning age of 28 days, though with some exceptions allowing a weaning age down to 21 days.

It is not possible to specify the exact weaning age, i.e. the age at which the piglets are weaned from their own sow, because many piglets are weaned from their own sow to a nursing sow. However, it is possible to specify the average weaning age, i.e. the age at which piglets are weaned from their own or from a nursing sow. The average weaning age is 31 days according to the Danish Pig Research Centre's latest production figures from 2013.

There are no grounds to assume that a change in the age at which piglets are weaned from their own or from a nursing sow will result in a significant decrease in the need for the use of medical zinc supplements, because the greatest need for zinc is probably within the first 10 days after weaning, regardless of whether this is 3 or 4 weeks.

The abovementioned research project at Aarhus University addresses the topic.

Weaning diet
When the piglets are weaned from the sow, the sow gets weaning feed. The quality of the weaning feed on the market is very different. In order to give the piglets a good start when they are weaned, when they are vulnerable to infections, it is important to have sufficiently high quality feed which ensures optimal nutrition and builds a stable stomach flora, which prevents the need for treating diarrhoea. It should therefore be recommended that farmers always ensure that the weaning feed is of high quality.

Reducing MRSA in pigs
Reducing the amount of dust in stables via spraying options
Since 1999, there have been requirements for a device which, for example, allows for spraying of boars and gilts so they can regulate their body temperature.

There are no known experiences of spraying to reduce the amount of dust in the stables. It should be part of the interventions which could be tested in a future project.

General washing of animals is assumed to be unrealistic, but it could be studied whether a form of spraying of the pregnant sows with a disinfectant solution when they are moved from the sow stable to the farrowing stable could reduce the prevalence of animal MRSA in the piglets.

Focusing on reducing the use of antibiotics as dry matter
Attention should be called to the use of antibiotics as dry dusting. This has to do with reducing flock medication, because flock medication can be used as dry matter. The percentage of flock medication which is used as dry matter is decreasing. At the moment, the percentage is about 17.5 % for 2014 through September. Measures in this area should be seen in context with the other measures initiated in the antibiotics area.

Reducing the amount of dust in the stables via optimisation of ventilation There is no knowledge as to whether there are quantitative differences in the prevalence of MRSA in herds with different ventilation systems.

Reducing MRSA in pigs through increased use of sectioning in stables At the current time, there is no specific knowledge as to whether special organisation of stables would be able to reduce the amount of animal MRSA CC398. Such knowledge should be generated through implementation of comparative studies of different types of stables.

What is believed to mean something is the introduction of general hygiene measures in connection with employees switching from one section to another, so that MRSA CC398 cannot be transferred via people from pigs from one section to another.

The problem is that the pigs definitely encounter the bacteria in the farrowing stable, because the sow is probably also carrying it. If this is the case, it would not mean much to section, because the pigs would be brought from the farrowing stable to the climate stable with the bacteria. It is unclear whether enough cleaning can be done (sows, environment, equipment, etc.) to be able to reduce or eliminate the bacteria when transferring animals between the sections.

In order to get more knowledge of special equipment in stalls, etc., it is suggested to perform small scale experiments in practice via MRSA ambassadors.

Management - MRSA ambassadors – small scale experiments in practice.
As part of the general strategy for reducing MRSA, it is being considered to establish "bottom up" efforts so that proactive farmers can be the spokespeople for methods which in practice can reduce or remove MRSA CC398 in pig herds – so-called MRSA ambassadors. In order to be successful, it is important that ideas which emerge from veterinary practice and in pig production can be tested without having to go through a long and complicated application process. For example, this could be achieved by setting up a smaller pool of development resources which can be applied for by practicing veterinarians in cooperation with farmers.

BARRIER FUNCTION – REDUCE THE RISK OF MRSA COMING FROM THE STABLE ENVIRONMENT

Below is a list of hygiene measures which are expected to be able to reduce the risk of MRSA coming out from the stable to the surrounding environment.

- Introducing a requirement for a shower at the exit of the stable area at the end of the work day or before entering the farmhouse in addition to a change of clothing and footwear and hand washing and hand disinfection.
- Washing work clothes should occur in the barn and not in the farmhouse.
- Correct storage of dead animals so that pets or wild animals will not have access to dead pigs or waste from the stable, cf. existing legislation. This should be controlled via campaigns for proper storage of dead animals, as previously mentioned.

The possibility of studying whether there are quantitative differences in the prevalence of MRSA in herds with different ventilation systems was previously mentioned. These studies should also assess the possibilities for optimising ventilation so that MRSA is kept in the stable. Below are specified considerations which are part of the considerations regarding the above hygiene efforts.

For humans
As already mentioned under "Introduction to the herd - via humans", people who have been in a MRSA positive pig stable are at risk of becoming carriers of

MRSA and can thus spread the bacteria to other people. It is the same mechanisms that apply to both preventing infection getting into the herd and out of the herd. Therefore, it is important to keep the infection in the stable. See also the point ”Introduction to the herd - via humans”.

As a result of the high prevalence of MRSA-contaminated dust in stables, people will be significantly contaminated with MRSA both on their body and on their clothes after being in a conventional MRSA-positive pig stable. Therefore, protection is required in the form of closed coveralls, gloves and filtered air (P3 masks) to completely avoid being contaminated with MRSA. It is therefore considered to be completely unrealistic to prevent people who work in pig stables from becoming temporary carriers of MRSA. The already introduced hygiene measures can thus contribute to reducing the amount of animal MRSA being brought out of herds.

It is not known whether the risk of contamination is directly due to contact with pigs with regards to contamination via dusty air or whether protective equipment in the form of gloves, hat and basic face mask/mask could reduce the degree of contamination.

Reducing the contamination levels of individual employees through bathing, changing clothes and changing footwear or disinfecting footwear (from working suits to private clothes) and applying meticulous hand hygiene when leaving the stable area can reduce the risk of further infection.

It is recommended, in order to minimise transmission out of the herd, to wash work clothes in the stable area and not in the farmhouse or in the employee's private home.

There is insufficient knowledge of the prevalence of animal MRSA in humans with professional contact with pigs and it should be studied in order to obtain knowledge on the risk people with more occasional contact constitute.

The same applies to people without contact with pigs, where the prevalence should also be studied in rural and urban environments.

For the environment

Infection through contamination of the surroundings through ventilation air and possibly through the spread of manure are potential sources of infection, though the importance is still unclear.

When bacteria leaves a stable with ventilation air, both ultraviolet light from the sun and the so-called ”open air factor” affect a significant reduction of the amount of bacteria in this air. However, MRSA has been measured up to 300 m downwind from stables. Infection via inhalation of this air or via contact with objects which are contaminated via the air is thus a possibility. However, the extent to which this plays a significant role is uncertain.

Similarly, there is a possible risk through the spread of manure from a MRSA-positive herd. There is a also a risk of infection here through contact with MRSA-contaminated surfaces. Pets can constitute a mode of transmission by sniffing/licking contaminated surfaces and spreading the bacteria to humans from there.

MRSA in meat

The prevalence of MRSA in meat has most recently been studied by the Danish Veterinary and Food Administration in 2011, where a MRSA prevalence in Danish pork of about 10 % was found.

Because staphylococci/MRSA do not have a natural niche in the gastrointestinal tract, in contrast to other genuinely food-borne bacteria, it is assessed that infection via meat, both through professional handling and general consumption, does not constitute a significant mode of transmission. Therefore, there is no need for additional measures for meat other than the already existing recommendations regarding good general kitchen hygiene.

Socio-economic analysis

Handling MRSA CC 398 constitutes a large and growing burden on the health care industry
– for hospitals, general practice and municipalities, particularly in the areas of Denmark where there is intensive pig production. There is also a need for significant advisory efforts for both handling the infection control and human aspects of this situation. The economic consequences of this burden are not currently known, but are important to discover in order to be able to get perspective on the efforts in both sectors from a socio-economic point of view.

MRSA RECOMMENDATIONS FROM THE EXPERT GROUP

The report has presented the available knowledge on animal MRSA, described the principles of Danish pig production, described existing measures against MRSA in Denmark and included experiences from Norway and the Netherlands. Considerations are then made regarding various efforts. Based on this, the expert group comes up with a number of recommendations.

It should again be pointed out that the expert group's recommendations are prepared based on what from the expert group's assessments could contribute to reducing the spread of MRSA from herds to the surrounding community. Any economic consequences on industry and the public and not intentional.

In general, an animal MRSA action plan should be introduced with annual milestones, as is known from the Salmonella action plans for pigs and poultry. This will involve establishing a technician group and a management group which sets an overall 4-year plan with initiatives and goals for political approval. As with the Salmonella action plans, the MRSA action plans should be for 4 years. It must be expected that there will be a need for multiple animal MRSA action plans, since, for example, we are now on Salmonella action plan 5 for pigs.

RECOMMENDATIONS FOR TOOLS

INTRODUCTION OF ANIMAL MRSA INTO THE HERD

Introduction via humans

- Until more knowledge is gained, people should implement the already prescribed hygienic measures for contact with pigs and contact with other animals such as cattle, mink, horses and poultry. These measures could be optimised by simultaneously bathing.

Introduction via import of live pigs into the herd

- The possibility of establishing MRSA low-prevalence areas in parts of Denmark should be studied in order to assess whether MRSA low-prevalence or free zones can be established, cf. the *S. Dublin* action plan.

Introduction via other production animals or dogs, cats and rodents including rats and mice as well as insects and wild animals

- The presence of animal MRSA in production animals other than pigs, such as cattle, mink, poultry and horses, should be studied.
- This can be considered through studying the prevalence of animal MRSA in dogs and cats. Dogs and cats (except farm cats, which only come into the barn to control mice) should be refused access to the barn.
- Mice and rats should be controlled.

SELECTION PRESSURE WITHIN THE HERD

Reducing the use of antibiotics

- The overall total consumption of antibiotics for pigs must continue to be reduced. There should be more ambitious targets set for the total consumption of antibiotics. The following suggestions should be considered:
  - Increased use of vaccines should be promoted in order to avoid disease requiring treatment.
  - Flock medication should be further limited in pig production.
  - Differentiated yellow cards should be introduced.
  - Critically important antibiotics such as fluoroquinolones and cephalosporins should continue to be avoided in pig production.
  - Zinc should be used more restrictively - the use of zinc from sources other than approved drugs should be stopped (for example, in-feed zinc). Campaigns should be established.
  - Weaning should be a minimum of 28 days in all herds.
  - There should be increased focus on the quality of feed at weaning.

Reducing MRSA in pigs

- Reducing the amount of dust in barns:
  - The effect of spraying options for animals should be studied.
  - Focus on reducing distribution of antibiotics as dry material, because distribution as dry material gives off dust – along with the reduction of flock medication and other antibiotics-reducing measures.
  - The effect of optimising ventilation should be studied
- Increased use of stable sectioning with effective hygiene or infection protection barriers in consultation with the veterinarian.

BARRIER FUNCTION – REDUCE THE RISK OF IT COMING FROM THE STABLE ENVIRONMENT

Improving hygiene

- Introducing a requirement for a shower at the exit of the stable area at the end of the day or before entering the farmhouse in addition to a change of clothing and footwear and hand washing and hand disinfection.
- Washing work clothes should occur in the barn and not in the farmhouse.
- Correct storage of dead animals so that pets or wild animals will not have access to dead pigs or waste from the stable, cf. existing legislation. This should be controlled via a campaign aimed at proper storage of dead animals.

RECOMMENDATIONS FOR GENERATING GREATER KNOWLEDGE

The report has shown a need for more knowledge regarding animal MRSA, which is why the MRSA expert group has a number of research proposals to further generate increased beneficial knowledge in the area so that future efforts can be implemented based on solid scientific evidence. The suggestions relate to introduction into the herd, the selection pressure in the herd and barrier functions.

INTRODUCTION OF ANIMAL MRSA INTO THE HERD

Introduction via humans

- It will be studied whether people with more sporadic contact (for example, craftspeople and slaughterhouse workers) carry MRSA and whether they constitute a risk group. This point is also mentioned under barriers, since it generates knowledge in both places.

Introduction via import of live pigs into the herd

- Monitoring programs for live pigs to be established at appropriate intervals.
- Reorganisation possibilities for sow farms should be examined in small scale studies to see whether a goal of gradual reduction of MRSA prevalence through reorganisation is possible and thereby gain more knowledge of barriers which can be transferred to other levels of pig production.

Introduction via other production animals or dogs, cats and rodents including rats and mice as well as insects and wild animals

- Survey/mapping of animal MRSA in other types of production animals such as cattle, mink, horses and poultry.
- Study of the prevalence of animal MRSA in dogs and cats should be conducted.
- Study of the prevalence of animal MRSA in rodents such as mice and rats as well as wild birds and insects should be conducted.

SELECTION PRESSURE WITHIN THE HERD

Analyses of animal MRSA data from pig farms should be studied:

- Focus on breeding companies that have both positive and negative farms and further out into the production herds.
- Focus on herds negative for animal MRSA.
- Possible links between labour and animals as well as antibiotics consumption and weaning age.

Significance of spread through a contaminated environment should be studied:

- Infection opportunities through ventilation air and slurry should be studied.
- Dust,
  - Risks for employees, both those with daily work in the stable and people with short-term visits, should be studied, including studying the effect of protective equipment.
  - Risks for pigs should be studied.

Research into alternatives to antibiotics should be considered:

- Probiotics
- New vaccines
- Cost-benefit analysis of the use of zinc in pig production.
- MRSA ambassadors – small scale experiments in practice.

BARRIER FUNCTION – REDUCE THE RISK OF IT COMING FROM THE STABLE ENVIRONMENT

- The presence of animal MRSA in people with professional contact with pigs should be studied to obtain knowledge about whether individuals with more sporadic contact (for example, craftspeople and slaughterhouse workers) carry MRSA and whether they constitute a risk group.
- The prevalence of animal MRSA in humans with no contact with pigs should be studied in rural and urban environments.

RECOMMENDATIONS ON INCREASED ADVISEMENT AND INFORMATION FOR CITIZENS AND PROFESSIONALS

- Strengthening of the MRSA advice service. Hygiene

courses for people who handle pigs should be introduced.

RECOMMENDATION FOR IMPLEMENTATION OF SOCIO-ECONOMIC

ANALYSIS

- Study of the economic health costs of MRSA CC398 for health services (hospitals, municipalities, general practice).
- Study of the agriculture costs of implementing the proposed actions.

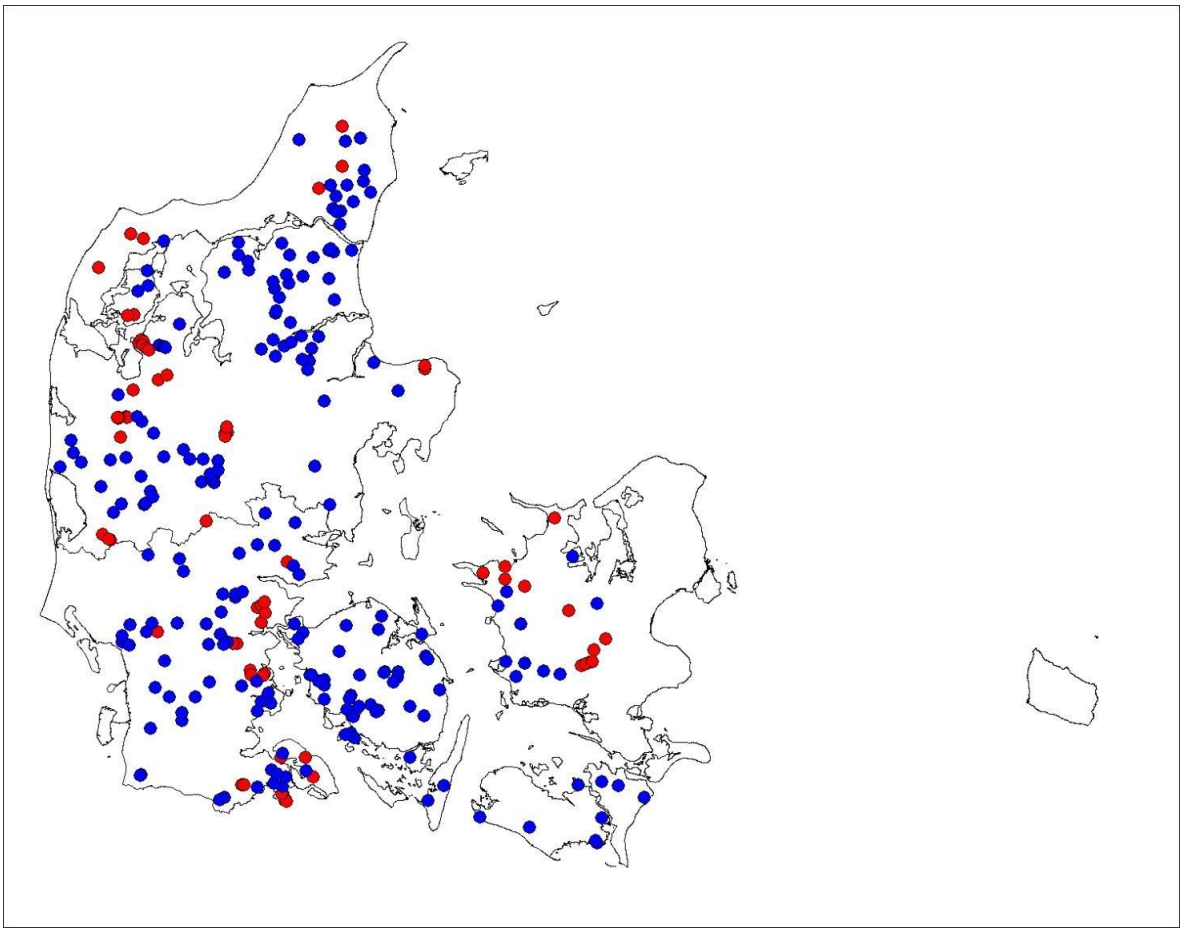
APPENDIX 1. RESULTS OF DANISH ANIMAL MRSA STUDIES IN 2014

Results of studies in 2014 of 205 randomly selected finisher herds and 70 herds in Danish pig production at the breeding level.

Table. MRSA CC398 results for 2014 in 70 breeding herds and 205 finisher herds

	Number of herds studied	Prevalence
Breeding herds	**70**	**63%**
Finishers - Denmark	**205**	**68%**
Finishers - Jutland	147	70%
Finishers - Funen	39	69%
Finishers - Zealand	19	53%

Figure. Localisation of herds studied for MRSA CC398. Finisher herds (total 205) are represented by a blue dot. Breeding herds (total 70) are represented by a red dot.



APPENDIX 2. NORWEGIAN EXPERIENCE WITH MRSA IN PIG HERDS

Veterinærinstituttet
Norwegian Veterinary Institute

Norwegian experience with LA-MRSA in pig herds

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In Norway, there were found to be 1,250 sow herds and 800 finisher herds with an annual production of 1.6 million finishers in 2013. On average, herd size in 2013 was 114 yearlings when sows are included or 80 yearlings when sows are left out. The Norwegian pig population is organised into a breeding and fitness pyramid, the top of the pyramid is made up of 40 finisher herds with purebred breeding animals. The production of hybrid sows occurs in 58 multiplier herds.
The remaining herds are breeding herds with either piglet production, combined piglet and finisher production or specialised finisher production.

In Norway, LA-MRSA (CC398) was detected in samples from pigs for the first time in 2011. Surveillance programs implemented in 2008, 2011 and 2012 indicated very low prevalence of MRSA-positive pig herds in the country.

However, in 2013/14, an outbreak of LA-MRSA was discovered in Norwegian pig herds in Eastern Norway and in Rogaland. A comprehensive mapping program was also initiated, where all herds with more than 10 sows (986 herds, plus 9 herds studied as a part of the detection of the outbreak) were studied. This mapping program was implemented in the spring of 2014 and identified one positive herd. Reorganisation of this was implemented and consisted of a complete emptying of the pig herds, followed by extensive washing and disinfection. Through mapping and detection of the outbreak, LA-MRSA was discovered in a total of 26 herds. However, the greatest likelihood is that there were only 3-4 index herds and the remaining herds were secondary herds who were introduced to LA-MRSA through procurement of animals from an index herd.

Sampling in the monitoring/mapping program has been based on tests from both hides and environment. Sterile cloths soaked in sterile water have been used. On the hide, there is a 5x5 cm large area behind the ears of up to 60 individuals (20 sows, 20 finisher/recruit sows, 20 piglets) that has been tested by rubbing with two fingers. 30 samples from the environment have also been taken. Each cloth has been used on 20 animals (the pool) or on 15 environmental points (the pool). Sampling in contact herds has been individual samples from up to 200 animals (from all sections), as well as 30-60 samples from the environment.

In reorganised herds, negative environmental tests are required (75 environmental tests per room from all animal rooms and adjacent rooms) before addition of new pigs. Sampling after addition of animals in piglet production herds has been all sows, up to 100 finisher/recruit sows, up to 100 piglets, as well as 30-60 environment samples. In finisher herds, samples have been taken from 400 finishers, as well as 30-60 environment samples. In combined herds (farrow-to-finish) samples have been taken from all sows, up to 100 finishers/recruit sows, up to 100 piglets, as well as 30-60 environment samples. In positive herds, employees in direct contact with animals have also been sampled and those with the carrier state were given treatment.

Monitoring of reorganised herds has shown very promising results and as of today most of these have tested negative three times after newly-added pigs. In total, 26 herds which showed LA-MRSA have been reorganised in Norway during the period of 2013-14, of which 3 herds have had unsuccessful reorganisation (one herd has had unsuccessful reorganisation twice with unknown cause). For one of the herds with unsuccessful reorganisation, the infection was reintroduced through the purchase of LA-MRSA positive pigs. For the others, the cause of the unsuccessful reorganisation was uncertain. These have all been recently reorganised and as of November 2014, only the herd that had two unsuccessful reorganisations has continued to be positive. Additionally, 3 herds were reorganised relatively recently and are therefore temporarily not being tested after reorganisation.

All of the LA-MRSA positive herds from 2013 and 2014 were further followed up on. For finisher herds, which is to say those which have tested negative twice after having taken in new pigs, and as monitoring in sow herds, new animals will be tested after 3, 6 and 9 months. In the upcoming years, it is proposed that the entire pig population be studied under the auspices of an annual monitoring program with breeder and multiplier herds being studied each year, but the others should alternate between studying sow herds and finisher herds.

APPENDIX 3. MRSA EXPERT GROUP

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APPENDIX 4. MANDATE FOR MRSA EXPERT GROUP

Mandate for MRSA expert group	
New risk assessment of MRSA	
1. Background	The Ministry of Food, Agriculture and Fisheries of Denmark also decided in August 2014 that in addition to the ongoing screening studies of the prevalence of MRSA in 200 randomly selected finisher herds and the ongoing research which will shed light on many of the unknown conditions regarding the spread of MRSA in herds and the surrounding environment, there should be an ongoing screening of all pig herds at the breeding level. It was also decided, in collaboration with the Minister of Health, to form an interdisciplinary group of experts consisting of experts from the human and veterinary sides to make a renewed risk assessment of the MRSA situation in light of the increasing incidence of human cases.
2. Objectives and tasks	The purpose of the expert group is, based on the results of the two veterinary screening studies, amongst others, to conduct a new risk assessment and use it to prepare proposals for a veterinary control strategy and to suggest possible measures that can be introduced here and now, pending the results of the research initiated by DTU in collaboration with Statens Serum Institut. These research projects will illustrate the spread of infection within the herds and to the population and examine possible measures that can reduce the disease burden. The risk of infection from meat should be included in the expert group's considerations.

3. The project group's organisation	The MRSA expert group is composed of representatives from the Danish Health and Medicines Authority, Statens Serum Institut (SSI), the Organisation of Danish Medical Societies, the Danish Veterinary and Food Administration, the Danish National Veterinary Institute, the Danish Veterinary Association and Norwegian experts who have been involved in the Norwegian MRSA efforts. The Danish Veterinary and Food Administration handles the Chair and Secretariat functions. There will be a series of meetings and by the end of November 2014, there will be a report to the Ministers containing a risk assessment based on the prevalence of MRSA in the studied pig herds and with suggestions for new measures which can be introduced here and now.

APPENDIX 5. THE EXPERT GROUP'S ANSWERS TO CLARIFYING QUESTIONS FROM THE MINISTRY OF FOOD, AGRICULTURE AND FISHERIES OF DENMARK

1. Weaning of pigs: The expert group specifically recommends that 'weaning should be a minimum of 28 days in all herds.' The recommendation does not seem to be directly supported in the group's considerations of weaning age on p. 29- 30 in the report. Does the expert group believe that the weaning age should be raised?

"The expert group believes that the average age of weaning in the individual herd should be a minimum of 28 days. The expert group assesses that the best effect is achieved through positive communication and not through regulation. This means action through advise from consultants and practicing veterinarians and not through legislation."

2. Flock medication: The connection between the recommendation that flock medication should be further reduced and the argument on report page 28 seems unclear. The expert group recommends immediate new initiatives against flock medication or an evaluation of the already adopted pending initiatives, cf. the report p. 28

"The expert group believes that flock medication should be limited."

In June 2014, the Danish Veterinary and Food Administration introduced some restrictions in the area, which will be fully implemented by the end of November 2014. Therefore, it would be appropriate to wait for an evaluation of the effect of these adopted measures before further restrictions are considered."

3. Zinc: The recommendation of more restrictive use of zinc is clarified in light of the section on zinc on p. 29 of the report. Does the expert group recommend, based on the current decision to create control campaigns, that zinc is to be used only in authorised medicines and feed under the approved maximum amount?

"Yes, the expert group recommends a campaign aimed at reducing the use of medical zinc. The campaign will be implemented in combination with a dialogue with practicing veterinarians. "

4. The breeding level: What is meant by 'focus on breeding companies that have both positive and negative farms and further out into the production herds'? Does the expert group hereby recommend that a report be included in the upcoming research into modes of transmission or is there a special effort with regards to breeding herds?

"The expert group recommends that breeding herds with both positive and negative properties be included in the initiated research and that in this context there is also focus on the MRSA-negative herds in the screening study in order to get clarification on infection protection measures which explain why these herds can keep themselves MRSA-free."

5. Separation measures in stables: is it recommended to implement such measures now or it is recommended to wait for research?

"The expert group recommends that increased sectioning should be used in the herds, because this situation will improve hygiene and reduce infection pressure for bacteria and other infectious agents. Here, the instrument should be increased advisement based on future research results."

6. Low-prevalence areas: it is recommended in the report that it be studied whether there are grounds to establish protected zones in low-prevalence areas. However, it seems that screening results do not indicate that there are such areas. Can this recommendation be explained?

"The expert group assesses that the possibility of establishing low-prevalence areas should be covered, because this can provide direction in the future reduction of animal MRSA as well as important research on the spread of infection."

7. The expert group recommends increased advisement and information to citizens and professionals. What is the reason that the current MRSA advisory service should be strengthened?

"The grant for the advisory service is 1 FTE (hygiene nurse) for 3 years. Since starting up, there has been a lot of pressure on the advisory service with a high demand for expert knowledge as well as lectures and teaching, this demand has significantly exceeded what was expected. It is expected that there will continue to be a greater need than what one person can do in the form of answering questions, teaching and instruction on hygienic conditions."

8. Does the expert group recommend implementation of socio-economic analysis? What is the reason for the recommendation and the purpose of a socio-economic analysis of the economic health costs? Are aspects of the socio-economic analysis included in ongoing or future research projects? Will it be possible to implement a fair socio-economic analysis with regards to the economic health costs of animal MRSA for healthcare (hospitals, municipalities, general practice)?

"The expert group believes that a socio-economic analysis of the economic health situation is highly significant, since one of the major challenges for health care is the care of patients who may be infected with MRSA (in addition to the diseases that MRSA causes). The benefits of improved control of MRSA in production will naturally be viewed in relation to these challenges. Therefore, we need to look at the social and health economics in various scenarios.

An economic analysis of the planned research project is included.

However, the expert group stated that detailed analysis of the specific health care costs associated with LA-MRSA should be specifically addressed.

The planned research project's implemented socio-economic analysis is a more general analysis. A detailed economic health analysis should be part of the overall socio-economic analysis and it should be ensured that this is implemented as part of the project. If this cannot be accomplished within the research project's economic framework, it should be done as an independent analysis."