Research outputs:

**Effects of control measures on the spread of LA-MRSA among Danish pig herds between 2006 and 2015 – a simulation study**

There has been a rapid increase in Danish pig herds testing positive for livestock-associated Methicillin-resistant Staphylococcus aureus (LA-MRSA) since the first screening in 2008. Despite a national action plan to control LA-MRSA in the Danish pig population, 88% of pig herds tested positive in a 2016 cross-sectional study of 57 herds. The national action plan was initiated in April 2015 and aimed to reduce the spread of LA-MRSA among pig herds. However, its success is uncertain. We used a simulation model mimicking the spread of LA-MRSA among pig herds between 2006 and 2015 to evaluate the impact of control strategies if these had these been implemented in 2007 or 2010. The strategies were combinations of the following control measures: (1) a reduced number of herds using high-risk antibiotics, (2) a reduced probability of indirect transmission among herds via humans, (3) movement restrictions, and (4) voluntary eradication in 5–7.5% of the herds. Almost all tested control strategies simulated a reduction in the spread of LA-MRSA. The combination of two, three or four intervention strategies showed additive effects and led to larger reductions in the predicted herd prevalence. In addition, the prevalence of LA-MRSA-positive herds at the time when control measures were initiated influenced the effects of the control strategies. Combining the simulated control measures can be considered in future action plans to control LA-MRSA.
Detection of Francisella tularensis in three vole species in Central Europe

Francisella tularensis is a zoonotic, gram-negative bacterium that causes tularemia in humans. Depending on its subspecies and the route of transmission, mild to lethal courses have been reported. F. tularensis subsp. holarctica is the only subspecies found in Europe and affects a plenitude of vertebrates including lagomorphs and rodents. Population outbreaks of certain rodent species are likely to be involved in the transmission of this pathogen. This molecular survey aims to evaluate the presence of F. tularensis in small mammals from three Central European countries. Using a real-time polymerase chain reaction, F. tularensis DNA was detected in common voles (Microtus arvalis) from Switzerland and in field voles (Microtus agrestis) and a bank vole (Myodes glareolus) from Germany, but not in any other small mammal species. All common voles from the Czech Republic were negative for F. tularensis DNA. The prevalence in the three vole species varied between 1.3% and 3.0%. In conclusion, Francisella tularensis DNA was detected in three vole species in two of three countries investigated. The observed low prevalence raises questions on the role of voles for the transmission of Francisella tularensis in Central Europe.

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Simulation modelling of LA-MRSA dispersal and control between swine herds

Staphylococcus aureus (SA) is a ubiquitous bacterium in humans and animals. It can cause minor skin infections that do not usually require treatment. SA, as well as Methicillin-resistant SA (MRSA), which is resistant to a wide range of antimicrobials, can lead to severe infections in humans, especially in individuals with a suppressed immune status. MRSA can originate from livestock and is referred to as livestock-associated MRSA (LA-MRSA) with pigs as the main reservoir. In Denmark, the number of pig herds tested positive for LA-MRSA has increased rapidly since 2008, when a Europe-wide study found only 3.5% of production herds positive for LA-MRSA. However, in 2016, the prevalence found in a national LA-MRSA screening had reached 88%. At the same time, the number of human cases increased in people working at pig farms but also in people with no livestock contact.

In 2014, Denmark initialised a national action plan to limit the spread of LA-MRSA. However, the effects were not sufficient to reduce the number of LA-MRSA-positive herds, nor to limit the number of newly infected humans. To be able to increase the efficacy of control programmes in the pig industry, it is necessary to understand the transmission routes of LA-MRSA among pig herds. This includes the trade of pigs as a potential mechanism for spread, as well as other contact among herds that might lead to the transmission of LA-MRSA. Such knowledge would help to evaluate control options that might reduce the number of LA-MRSA-positive herds in the future.

A network analysis using information on Danish pig holdings and their trade connections between 2006 and 2015 was performed to gain a general knowledge of temporal trends in the number of registered pig herds and pig movements. In addition, we investigated loyalty patterns and contact chains for the 24 registered holding types to identify holding types with a potentially higher risk of disease spread via pig movements (Manuscript I).
The total number of active holdings and the number of pig movements both decreased during the study period, while the holding size increased. We observed a large out-going contact chain for breeding and multiplier herds, which reflects the pyramidal structure of the underlying network and highlights the risk of spreading a disease via pig movements to a wide range of other herds if a pathogen were to affect breeding and multiplier herds. However, horizontal connections among pig herds also exist, which could lead to additional spread among herds of the same holding type.

An agent-based Monte Carlo simulation model mimicking the spread of LA-MRSA among pig herds was developed to study the epidemic behaviour and to identify the driving factors for LA-MRSA spread among pig herds (Manuscript II). As well as transmission based on pig movements registered in the study period from 2006 to 2015, indirect transmissions between holdings were modelled based on distance-dependent probability distributions. Three types of indirect contact were modelled: (1) abattoir trucks collecting pigs from several holdings, (2) humans such as veterinarians, farm workers or guests visiting several holdings on the same day and (3) contact between herds with the same owner. Within-herd dynamics were modelled as a three-compartment SIS model with different transmission rates within the three compartments of sows, weaners and finishers, and with high- and low-risk transmission routes between these compartments. Several scenarios were evaluated to simulate the spread after introduction of LA-MRSA in varying proportions of breeding and multiplier and production herds in 2006 and/or 2009. We compared the model outcomes to the results of LA-MRSA surveys conducted in Denmark during the study period. An extensive sensitivity analysis was performed to study the effect of uncertainty of model parameters (Manuscript II).

Pig movements alone were not sufficient to mimic the observed increase in LA-MRSA-positive herds in Denmark in any of the modelled scenarios. However, the model identified three factors that played important roles in the between-herd spread of LA-MRSA: (1) the within-herd dynamics, (2) the frequency and effectiveness of indirect transmission via humans and (3) unexplained introduction of LA-MRSA to swine herds. We enhanced this simulation model to retrospectively evaluate how different control strategies would have influenced the spread of LA-MRSA (Manuscript III). These strategies were combinations of the following control measures: (1) reduced numbers of herds using high-risk antibiotics, (2) reduced probability for indirect transmission between herds via humans, (3) movement restrictions and (4) voluntary eradication in 5-7.5% of the herds. The effects of implementing control in 2007 were compared to implementation in 2010.

Almost all tested control strategies simulated a reduction in the spread of LA-MRSA. The combination of two, three or four intervention strategies showed additive effects and led to larger reductions in the predicted herd prevalence. An extreme scenario (impeding the use of high-risk antibiotics, reducing risk of spread via indirect contact by 75%, implementing movement restriction and culling a percentage of positive herds) was able to reduce the predicted prevalence by 86% compared to the predicted prevalence without control. Control measures initialised in 2007 had a greater effect compared to initialisation in 2010 due to the lower initial prevalence in 2007. In conclusion, pig movements alone were not sufficient to mimic the development of LA-MRSA herd prevalence observed in Denmark in 2008 and 2014. However, they were responsible for around 75% of transmissions. Within-herd dynamics and the frequency and effectiveness of indirect contact between pig herds via humans showed the highest impact on the predicted herd prevalence. Control measures showed the highest relative reduction when implemented in 2007 and when all four potential control measures were combined. Categorising herds according to the size of their out-going contact chain increased the effect of eradication as a control measure, as herds with higher risk of spreading LA-MRSA via pig movements were prioritised in the eradication process. However, eradication should be combined with movement restrictions to minimise the risk of re-introduction.
addition, whole-genome sequence data from 82 isolates representing an international reference collection and 83 isolates from Danish patients were included in the analysis. The results demonstrated that the increasing prevalence of LA-MRSA CC398 in Danish pigs and patients was caused by clonal expansion of three dominant lineages. The results also showed that these lineages were enriched for the tetracycline resistance gene tet(K) and other determinants conferring resistance to some of the most frequently used antimicrobials in Danish pigs. The association between pig movements and the spread of LA-MRSA CC398 was assessed in a Poisson regression analysis of 17,009 pig movements into 273 farms with known LA-MRSA CC398 status. The results demonstrated that animal movements have played a critical role in the dissemination of LA-MRSA CC398 within the Danish pig production system, although other transmission routes may also have contributed. Consistent with this scenario, the genetic relatedness of isolates from different farms was positively correlated with the number of animal movements between the farms.IMPORTANCE Livestock-associated methicillin-resistant Staphylococcus aureus clonal complex CC398 (LA-MRSA CC398) is resistant to nearly all β-lactams and several non-β-lactam antimicrobials. Over the last decade, it has become widespread in pig farms across Europe and is now an important cause of human infections in countries with previously low levels of MRSA, such as the Netherlands and Denmark. The hitherto uncontrolled spread of LA-MRSA CC398 underscores an urgent need to understand its epidemiology in order to develop evidence-based interventions. This study demonstrates that pig movements between farms in combination with increased bacterial resistance to specific antibiotics and heavy metals were important drivers of the rapid spread of LA-MRSA CC398 in the Danish pig production system. These findings should be taken into consideration when researchers and policy makers evaluate and decide on actions and policies to limit the spread of LA-MRSA CC398 and other pathogens in food animals.
Harmonizing methods for wildlife abundance estimation and pathogen detection in Europe-a questionnaire survey on three selected host-pathogen combinations

Background: The need for wildlife health surveillance as part of disease control in wildlife, domestic animals and humans on the global level is widely recognized. However, the objectives, methods and intensity of existing wildlife health surveillance programs vary greatly among European countries, resulting in a patchwork of data that are difficult to merge and compare. This survey aimed at evaluating the need and potential for data harmonization in wildlife health in Europe. The specific objective was to collect information on methods currently used to estimate host abundance and pathogen prevalence. Questionnaires were designed to gather detailed information for three host-pathogen combinations: (1) wild boar and Aujeszky's disease virus, (2) red fox and Echinococcus multilocularis, and (3) common vole and Francisella tularensis.

Results: We received a total of 70 responses from 19 European countries. Regarding host abundance, hunting bags are currently the most widely accessible data source for widely distributed mid-sized and larger mammals such as red fox and wild boar, but we observed large differences in hunting strategies among countries as well as among different regions within countries. For small rodents, trapping is the method of choice, but practical applications vary among study sites. Laboratory procedures are already largely harmonized but information on the sampled animals is not systematically collected. Conclusions: The answers revealed that a large amount of information is available for the selected host-pathogen pairs and that in theory methods are already largely harmonized. However, the comparability of the data remains strongly compromised by local differences in the way, the methods are applied in practice. While these issues may easily be overcome for prevalence estimation, there is an urgent need to develop tools for the routine collection of host abundance data in a harmonized way. Wildlife health experts are encouraged to apply the harmonized APHAEA protocols in epidemiological studies in wildlife and to increase cooperation.
Network analysis of pig movements: Loyalty patterns and contact chains of different holding types in Denmark

Understanding animal movements is an important factor for the development of meaningful surveillance and control programs, but also for the development of disease spread models. We analysed the Danish pig movement network using static and temporal network analysis tools to provide deeper insight in the connection between holdings dealing with pigs, such as breeding and multiplier herds, production herds, slaughterhouses or traders. Pig movements, which occurred between 1st January 2006 and 31st December 2015 in Denmark, were summarized to investigate temporal trends such as the number of active holdings, the number of registered movements and the number of pigs moved. To identify holdings and holding types with potentially higher risk for introduction or spread of diseases via pig movements, we determined loyalty patterns, annual network components and contact chains for the 24 registered holding types. The total number of active holdings as well as the number of pig movements decreased during the study period while the holding sizes increased. Around 60-90% of connections between two pig holdings were present in two consecutive years and around one third of the connections persisted within the considered time period. Weaner herds showed the highest level of in-loyalty, whereas we observed an intermediate level of in-loyalty for all breeding sites and for production herds. Boar stations, production herds and trade herds showed a high level of out-loyalty. Production herds constituted the highest proportion of holdings in the largest strongly connected component. All production sites showed low levels of in-going contact chains and we observed a high level of out-going contact chain for breeding and multiplier herds. Except for livestock auctions, all transit sites also showed low levels of out-going contact chains. Our results reflect the pyramidal structure of the underlying network. Based on the considered disease, the time frame for the calculation of network measurements needs to be adapted. Using these adapted values for loyalty and contact chains might help to identify holdings with high potential of spreading diseases and thus limit the outbreak size or support control or eradication of the considered pathogen.

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A Simulation Model to Determine Sensitivity and Timeliness of Surveillance Strategies
Animal surveillance systems need regular evaluation. We developed an easily applicable simulation model of the German wild boar population to investigate two evaluation attributes: the sensitivity and timeliness (i.e. the ability to detect a
disease outbreak rapidly) of a surveillance system. Classical swine fever (CSF) was used as an example for the model. CSF is an infectious disease that may lead to massive economic losses. It can affect wild boar as well as domestic pigs, and CSF outbreaks in domestic pigs have been linked to infections in wild boar. Awareness of the CSF status in wild boar is therefore vital. Our non-epidemic simulation model is based on real data and evaluates the currently implemented German surveillance system for CSF in wild boar. The results show that active surveillance for CSF fulfills the requirements of detecting an outbreak with 95% confidence within one year after the introduction of CSF into the wild boar population. Nevertheless, there is room for improved performance and efficiency by more homogeneous (active and passive) sampling of wild boar over the year. Passive surveillance alone is not sufficient to meet the requirements for detecting the infection. Although CSF was used as example to develop the model, it may also be applied to the evaluation of other surveillance systems for viral diseases in wild boar. It is also possible to compare sensitivity and timeliness across hypothetical alternative or risk-based surveillance strategies.

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The challenge of detecting classical swine fever virus circulation in wild boar (Sus scrofa): Simulation of sampling options
Classical swine fever (CSF) is one of the most important viral diseases of domestic pigs (Sus scrofa domesticus) and wild boar (Sus scrofa). For at least 4 decades, several European Union member states were confronted with outbreaks among wild boar and, as it had been shown that infected wild boar populations can be a major cause of primary outbreaks in domestic pigs, strict control measures for both species were implemented. To guarantee early detection and to demonstrate freedom from disease, intensive surveillance is carried out based on a hunting bag sample. In this context, virologic investigations play a major role in the early detection of new introductions and in regions immunized with a conventional vaccine. The required financial resources and personnel for reliable testing are often large, and sufficient sample sizes to detect low virus prevalences are difficult to obtain. We conducted a simulation to model the possible impact of changes in sample size and sampling intervals on the probability of CSF virus detection based on a study area of 65 German hunting grounds. A 5-yr period with 4,652 virologic investigations was considered. Results suggest that low prevalences could not be detected with a justifiable effort. The simulation of increased sample sizes per sampling interval showed only a slightly better performance but would be unrealistic in practice, especially outside the main hunting season. Further studies on other approaches such as targeted or risk-based sampling for virus detection in connection with (marker) antibody surveillance are needed.

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