Efficacy and safety of simultaneous vaccination with two modified live virus vaccines against porcine reproductive and respiratory syndrome virus types 1 and 2 in pigs

The objective of the study was to compare responses of pigs vaccinated with a PRRS MLV vaccine against PRRSV-1 or PRRSV-2 with the responses of pigs vaccinated simultaneously with both vaccines. Furthermore, the efficacy of the two PRRSV MLV vaccination strategies was assessed following challenge. The experimental design included four groups of 4-week old SPF-pigs. On day 0 (DPV0), groups 1–3 (N = 18 per group) were vaccinated with modified live virus vaccines (MLV) containing PRRSV-1 virus (VAC-T1), PRRSV-2 virus (VAC-T2) or both (VAC-T1T2). One group was left unvaccinated (N = 12). On DPV 62, the pigs from groups 1–4 were mingled in new groups and challenged (DPC 0) with PRRSV-1, subtype 1, PRRSV-1, subtype 2 or PRRSV-2. On DPC 13/14 all pigs were necropsied. Samples were collected after vaccination and challenge. PRRSV was detected in all vaccinated pigs and the majority of the pigs were positive until DPV 28, but few of the pigs were still viremic 62 days after vaccination. Virus was detected in nasal swabs until DPV 7–14. No overt clinical signs were observed after challenge. PRRSV-2 vaccination resulted in a clear reduction in viral load in serum after PRRSV-2 challenge, whereas there was limited effect on the viral load in serum following challenge with the PRRSV-1 strains. Vaccination against PRRSV-1 had less impact on viremia following challenge. The protective effects of simultaneous vaccination with PRRSV Type 1 and 2 MLV vaccines and single PRRS MLV vaccination were comparable. None of the vaccines decreased the viral load in the lungs at necropsy. In conclusion, simultaneous vaccination with MLV vaccines containing PRRSV-1 and PRRSV-2 elicited responses comparable to single vaccination and the commercial PRRSV vaccines protected only partially against challenge with heterologous strains. Thus, simultaneous administration of the two vaccines is an option in herds with both PRRSV types.
Genetic and biological characterization of a Porcine Reproductive and Respiratory Syndrome Virus 2 (PRRSV-2) causing significant clinical disease in the field

Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) is the cause of severe reproductive and respiratory disease in swine worldwide. In Denmark, both PRRSV-1 and PRRSV-2 are circulating and approximately 35% of pig herds are seropositive for PRRSV. In November 2010, a pig herd in the Northern part of Denmark experienced an infection with PRRSV-2 with clinical signs that were much more severe than normally reported from current Danish PRRSV-2 affected herds. Due to the clinical observations of reproductive failure in sows and high mortality in piglets, it was speculated that a new, more pathogenic or vaccine evading PRRSV strain had emerged in Denmark. The overall aim of the present study was to perform a genetic and biological characterization of the virus isolated from the diseased herd. Complete genome sequencing of isolates from this herd revealed that although the case strain had some unique genetic features including a deduced 3 amino acid deletion, it was in overall very similar to the other PRRS-2 viruses circulating in Denmark. In an experimental trial in growing pigs, no overt clinical signs or pathology were observed following intranasal inoculation with the new virus isolate. Virus shedding, acute phase protein responses and serological responses were comparable to those seen after experimental challenge with a Danish PRRSV-2 reference strain isolated in 1997. Vaccination with a commercial modified live PRRSV-2 vaccine had a clear reducing effect on virus shedding, magnitude, and duration of viremia and viral load in the lungs. Overall, the results indicate that the severe disease observed in the field was contributed by additional factors in combination with the PRRS virus infection.

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Organisations: National Veterinary Institute, Virology, Innate Immunology, Pathology, Boehringer Ingelheim Danmark A/S, Danvet K/S, Technical University of Denmark
Authors: Kvisgaard, L. K. (Intern), Larsen, L. E. (Intern), Hjulsager, C. K. (Intern), Bøtner, A. (Intern), Rathkjen, P. H. (Ekstern), Heegaard, P. M. H. (Intern), Bisgaard, N. P. (Ekstern), Nielsen, J. (Ekstern), Hansen, M. S. (Intern)
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Pathogenicity of three genetically diverse strains of PRRSV Type 1 in specific pathogen free pigs

Studies from Eastern European countries proved that porcine reproductive and respiratory syndrome virus Type 1 (PRRSV-1) harbours high genetic diversity and that genetically divergent subtypes 2-4 circulate in this area. In the present study, we compared the pathogenicity of two different PRRSV-1 subtype 2 strains and a strain representing PRRSV-1 subtype 1. Four groups of 8-week-old specific pathogen free pigs were either infected with subtype 2 strain ILI6, subtype 2 strain or BOR59, subtype 1 strain 18794, or mock inoculated. The most pronounced clinical signs were observed in pigs infected with BOR59. Pigs from both subtype 2 strain infected groups exhibited significantly elevated mean body temperatures on DPI 2 compared to the other two groups, the difference remaining significant up to DPI 13 for the BOR59 group, only. The pigs in the latter group also displayed significantly highest levels of early viremia together with the most rapid APP response. Overall, the results indicated that BOR59 strain can be considered a highly pathogenic strain, similarly to subtype 3 strains Lena and SU1-bel, while the virulence of the other subtype 2 strain IIL6 was intermediate between BOR59 and subtype 1 strain.
Forbedret diagnostik af mink enteritis virus (MEV)

General information
State: Published
Organisations: National Veterinary Institute, Section for Virology
Authors: Kvisgaard, L. K. (Intern), Holm, E. (Intern), Chriél, M. (Intern), Larsen, L. E. (Intern), Hjulsager, C. K. (Intern)
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Immunity raised by recent European subtype 1 PRRSV strains allows better replication of East European subtype 3 PRRSV strain Lena than that raised by an older strain
Stable spatial distribution of porcine reproductive and respiratory syndrome (PRRSV)-1 subtypes in Europe is accompanied by a strong population immunity induced by local PRRSV strains. In the present study, it was examined if the immunity induced by three West European subtype 1 PRRSV strains (2007 isolate 07V063 and 2013 isolates 13V091 and 13V117) offers protection against the highly virulent East European subtype 3 PRRSV strain Lena. The number of fever days was greater (p < 0.05) in the control group (7.6 ± 1.7 days) compared to the immune groups (07V063-immune: 4.0 ± 1.2 days, 13V091-immune: 4.6 ± 1.1 days, 13V117-immune: 4.0 ± 2.9 days). In all groups, protection was characterized by reduction (p < 0.05) of AUC values of nasal shedding (control: 14.6, 07V063-immune: 3.4, 13V091-immune: 8.9, 13V117-immune: 8.0) and viremia (control: 28.1, 07V063-immune: 5.4, 13V091-immune: 9.0, 13V117-immune: 8.3). Reduction of respiratory disease, nasal shedding (mean AUC and mean peak values) and viremia (mean AUC and mean peak values) was more pronounced in 07V063-immune (p < 0.05) than in 13V091-immune and 13V117-immune animals. Inoculation with subtype 1 PRRSV strains caused priming of the Lena-specific virus neutralization antibody response. Upon challenge with Lena, we observed a very strong serological booster effect for neutralizing antibodies against strains used for the first inoculation. Our results indicate that inoculation with subtype 1 PRRSV strains can partially protect against antigenically divergent subtype 3 strains. The lower protection level elicited by recently isolated subtype 1 PRRSV strains may impair the outcome of the spatial expansion of subtype 3 strains from East Europe to West Europe.

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Organisations: National Veterinary Institute, Section for Virology, Ghent University
Authors: Trus, I. (Ekstern), Frydas, I. S. (Ekstern), Reddy, V. R. A. P. (Ekstern), Bonckaert, C. (Ekstern), Li, Y. (Ekstern), Kvisgaard, L. K. (Intern), Larsen, L. E. (Intern), Nauwynck, H. J. (Ekstern)
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Introduktion af polte i PRRSV-besætninger: Notat nr. 1609

I dette veterinære speciale blev det vist, at polte, der var vaccineret mod PRRS-virus (PRRSV), ikke udskilte virus ved første løbning. Studiet fandt en tendens til en sammenhæng mellem brug af karantæne og det, at poltene var beskyttet af antistoffer mod PRRSV.
Studiet inkluderede 69 besætninger positive for PRRSV. Der blev taget 5 blodprøver fra løbeklare polte i hver besætning, og et spørgeskema vedrørende polterekrutteringsstrategi, vaccinationsstrategi m.m. blev udfyldt.

Blodprøverne blev analyseret for PRRSV ved RT-qPCR, ELISA og IPT.

Studiet viste, at poltene fra de deltagende besætninger ikke havde PRRSV i blodet (var viræmiske) ved første løbning, og at der var en lille del, som ikke havde dannet antistoffer mod PRRSV trods vaccination. Sidstnævnte kunne tyde på et svigt i vaccinationsproceduren i besætningerne. Desuden var det meget få besætninger, der reelt havde en optimal karantæne. En optimal karantæne blev defineret som en stald, der ikke delte luftrom med øvrige staldafsnit, havde separat indgang og kørte alt ind/alt ud. På trods af at poltene ikke var viræmiske ved løbning, fører studiet ikke til ændringer i anbefalingerne vedrørende introduktion af polte i PRRS-positive besætninger.

Anbefalingerne er derfor stadig at immunisere poltene og så sætte dem i karantæne i minimum 8 uger og allerede 12.

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Organisations: National Veterinary Institute, Section for Virology
Authors: Hoelstad, B. E. (Intern), Sonne Kristensen, C. (Ekstern), Qvist Pawlowski, M. (Ekstern), Hjulsager, C. K. (Intern), Kvisgaard, L. K. (Intern), Lauritsen, K. T. (Intern), Larsen, L. E. (Intern)
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Simultaneous vaccination with PRRS MLV against both PRRSV type 1 and type 2: PRRSV in lungs following challenge

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Organisations: National Veterinary Institute, Section for Virology, SEGES Pig Research Center, Technical University of Denmark, Warsawa University
Authors: Kristensen, C. S. (Ekstern), Kvisgaard, L. K. (Intern), Haugegaard, S. (Ekstern), Pawlowski, M. (Ekstern), Carlsen, S. H. (Ekstern), Stadejek, T. (Ekstern), Larsen, L. E. (Intern)
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The Non-structural Protein 5 and Matrix Protein Are Antigenic Targets of T Cell Immunity to Genotype 1 Porcine Reproductive and Respiratory Syndrome Viruses

The porcine reproductive and respiratory syndrome virus (PRRSV) is the cause of one of the most economically important diseases affecting swine worldwide. Efforts to develop a next-generation vaccine have largely focused on envelope glycoproteins to target virus-neutralizing antibody responses. However, these approaches have failed to demonstrate the necessary efficacy to progress toward market. T cells are crucial to the control of many viruses through cytolysis and cytokine secretion. Since control of PRRSV infection is not dependent on the development of neutralizing antibodies, it has been proposed that T cell-mediated immunity plays a key role. Therefore, we hypothesized that conserved T cell antigens represent prime candidates for the development a novel PRRS vaccine. Antigens were identified by screening a proteome-wide synthetic peptide library with T cells from cohorts of pigs rendered immune by experimental infections with a closely related (subtype 1) or divergent (subtype 3) PRRSV-1 strain. Dominant T cell IFN-gamma responses were directed against the non-structural protein 5 (NSP5), and to a lesser extent, the matrix (M) protein. The majority of NSP5-specific CD8 T cells and M-specific CD4 T cells expressed a putative effector memory phenotype and were polyfunctional as assessed by coexpression of TNF-alpha and mobilization of the cytotoxic degranulation marker CD107a. Both antigens were generally well conserved among strains of both PRRSV genotypes. Thus, M and NSP5 represent attractive vaccine candidate T cell antigens, which should be evaluated further in the context of PRRSV vaccine development.

General information
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Organisations: National Veterinary Institute, Section for Virology, Animal and Plant Health Agency, University of Veterinary Medicine, University of Surrey, University College London
Authors: Mokhtar, H. (Ekstern), Pedrera, M. (Ekstern), Frossard, J. (Ekstern), Biffar, L. (Ekstern), Hammer, S. E. (Ekstern), Kvisgaard, L. K. (Intern), Larsen, L. E. (Intern), Stewart, G. R. (Ekstern), Somavarapu, S. (Ekstern), Steinbach, F. (Ekstern), Graham, S. P. (Ekstern)
Application of qPCR assays for diagnosing causes of viral mink diarrhea. Preliminary results

Gastrointestinal (GI) disorders is the main cause for submitting mink (Neovison vison) carcasses for post-mortem examination at the National Veterinary Institute in Denmark and has been described as the predominant cause of disease and mortality in the Danish mink production (Rattenborg et al. 1999). Diarrhea in mink can be caused by infectious agents (virus, bacteria and parasites) and food-related/multifactorial conditions. Known enteric viral infections are mink enteritis virus (MEV) and mink astrovirus. Coronavirus and caliciviruses have also been implicated as potential causes or contributors to diarrhea in mink. Rotavirus is poorly described in mink, but has previously been demonstrated in feces from mink pups with and without clinical signs (Jorgensen et al. 1996). The pathogenicity of these viruses could be related to viral load, virulence and the age of the mink. Therefore, there is a need for a quantitative diagnostic approach. We have developed new or adapted previously published real-time PCR/RT-PCR assays for MEV, astrovirus, rotavirus and coronavirus diagnostics.

The technical test validation was initially carried out on archived diarrhea samples from diagnosed positive animals and on normal and diarrhea samples from a case-control study. In order to further validate the applicability of the assays, a testing scheme for normal and affected farms was set up and initiated in June 2015. This protocol will allow optimization of test characteristics (sensitivity, specificity and predictive value) and assessment of the validity of using pooled samples in order to reduce test costs.

General information

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Organisations: National Veterinary Institute, Section for Virology
Authors: Hattby, C. M. (Intern), Kwisgaard, L. K. (Intern), Larsen, L. E. (Intern), Chriél, M. (Intern), Hjulsager, C. K. (Intern)
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Characterization of the PRRSV strain circulating in a PRRSV type 1 positive herd before, during and after vaccination with a PRRSV type 1 vaccine

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Organisations: National Veterinary Institute, Section for Virology, Danish Pig Production
Authors: Kvisgaard, L. K. (Intern), Kristensen, C. S. (Ekstern), Hjulsager, C. K. (Intern), Larsen, L. E. (Intern)
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Main Research Area: Technical/natural sciences
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Detection of PRRSV in air sampled inside and outside PRRSV-positive herds in Denmark

General information
State: Published
Organisations: National Veterinary Institute, Section for Virology, Technical University of Denmark, Svinevet Pig Practise, Boehringer Ingelheim Danmark A/S
Authors: Priebe, A. (Ekstern), Kvisgaard, L. K. (Intern), Rathkjen, P. H. (Ekstern), Hjulsager, C. K. (Intern), Havn, K. (Ekstern), Larsen, L. E. (Intern)
Number of pages: 1
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Development of a real-time RT-PCR assay that detects a broad range of Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) Type 1 subtypes

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Organisations: National Veterinary Institute, Section for Virology, Parco Technologico Padano
Authors: Kvisgaard, L. K. (Intern), Hjulsager, C. K. (Intern), Botti, S. (Ekstern), Larsen, L. E. (Intern)
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Different clinical, virological, serological and tissue tropism outcomes of two new and one old Belgian type 1 subtype 1 porcine reproductive and respiratory virus (PRRSV) isolates

In this study, the pathogenic behavior of PRRSV 13V091 and 13V117, isolated in 2013 from two different Belgian farms with enzootic respiratory problems shortly after weaning in the nursery, were compared with the Belgian strain 07V063 isolated in 2007. Full-length genome sequencing was performed to identify their origin. Twelve weeks-old pigs were inoculated intranasally (IN) with 13V091, 13V117 or 07V063 (9 pigs/group). At 10 days post inoculation (dpi), 4 animals from each group were euthanized and tissues were collected for pathology, virological and serological analysis. 13V091
infection resulted in the highest respiratory disease scores and longest period of fever. Gross lung lesions were more pronounced for 13V091 (13%), than for 13V117 (7%) and 07V063 (11%). The nasal shedding and viremia was also most extensive with 13V091. The 13V091 group showed the highest virus replication in conchae, tonsils and retropharyngeal lymph nodes. 13V117 infection resulted in the lowest virus replication in lymphoid tissues. 13V091 showed higher numbers of sialoadhesin-infected cells/mm(2) in conchae, tonsils and spleen than 13V117 and 07V063. Neutralizing antibody response with 07V063 was stronger than with 13V091 and 13V117. It can be concluded that (i) 13V091 is a highly pathogenic type 1 subtype 1 PRRSV strain that replicates better than 07V063 and 13V117 and has a strong tropism for sialoadhesin-cells and (ii) despite the close genetic relationship between 13V117 and 07V063, 13V117 has an increased nasal replication and shedding, but a decreased replication in lymphoid tissues compared to 07V063.
PRRS-virus meget stabilt over tid

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Authors: Kristensen, C. S. (Ekstern), Kvisgaard, L. K. (Intern)
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PRRSV type 1 detection in aerosols from three swine herds in Denmark

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Authors: Priebe, A. (Ekstern), Rathikjen, P. H. (Ekstern), Larsen, L. E. (Intern), Kvisgaard, L. K. (Intern), Hjulsager, C. K. (Intern), Angulo, J. (Ekstern), Havn, K. (Ekstern)
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**PRRSV type 1 detection in aerosols inside a PRRSV-positive swine herd in Denmark**

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Authors: Priebe, A. (Ekstern), Rathkjen, P. H. (Ekstern), Larsen, L. E. (Intern), Kvisgaard, L. K. (Intern), Hjulsager, C. K. (Intern), Angulo, J. (Ekstern), Havn, K. (Ekstern)
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**Simultaneous vaccination with PRRS mlv against both PRRSV type 1 and type 2: duration of viraemia and level of clinical protection**

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Organisations: National Veterinary Institute, Section for Virology, Technical University of Denmark, Danish Pig Production
Authors: Kristensen, C. S. (Ekstern), Kvisgaard, L. K. (Intern), Pawlowski, M. (Ekstern), Holmgaard Carlsen, S. (Ekstern), Hjulsager, C. K. (Intern), Larsen, L. E. (Intern)
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Publication date: 2015
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**Strain-specific serological response after simultaneous vaccination with PRRS MLV against**

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The immunity raised by recent European subtype 1 PRRSV strains allows a better replication of East European subtype 3 PRRSV strain Lena than the immunity raised by an older strain -increased risk for spatial expansion of PRRSV Lena-like strains

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Analysis of ORF5 and Full-Length Genome Sequences of Porcine Reproductive and Respiratory Syndrome Virus Isolates of Genotypes 1 and 2 Retrieved Worldwide Provides Evidence that Recombination Is a Common Phenomenon and May Produce Mosaic Isolates

Recombination is currently recognized as a factor for high genetic diversity, but the frequency of such recombination events and the genome segments involved are not well known. In the present study, we initially focused on the detection of recombinant porcine reproductive and respiratory syndrome virus (PRRSV) isolates by examining previously published data sets of ORF5 sequences (genotypes 1 and 2) obtained worldwide. We then examined full-length genome sequences in order to determine potential recombination breakpoints along the viral genome. For ORF5, 11 sets of genotype 1 sequences from different geographical areas, including 2 Asian, 1 American, and 7 European regions, and three sets of genotype 2, including sets from China, Mexico, and the United States, were analyzed separately. Potential recombination breakpoints were detected in 10/11 genotype 1 sets, including 9 cases in which the clustering of at least one isolate was different before and after the breakpoints. In genotype 2, potential breakpoints and different tree clustering of at least one strain before and after the breakpoint were observed in 2 out of 3 sets. The results indicated that most of the ORF5 data sets contained at least one recombinant sequence. When the full-length genome sequences were examined, both genotype 1 and 2 sets presented breakpoints (10 and 9, respectively), resulting in significantly different topologies before and after the breakpoints. Mosaic genomes were detected in genotype 1 sequences. These results may have significant implications for the understanding of the molecular epidemiology of PRRSV. IMPORTANCE PRRSV is one of the most important viruses affecting swine production worldwide, causing big economic losses and sanitary problems. One of the key questions on PRRSV arises from its genetic diversity, which is thought to have a direct impact on immunobiology, epidemiology, diagnosis, and vaccine efficacy. One of the causes of this genetic diversity is recombination among strains. This study provides evidence that recombinant PRRSV isolates are common in most of the countries with significant swine production, especially PRRSV genotype 1. This observation has implications in the proper characterization of PRRSV strains, in the future development of phylogenetic studies, and in the development of new PRRSV control strategies. Moreover, the present paper emphasizes the need for a deeper understanding of the mechanisms and circumstances involved in the generation of genetic diversity of PRRSV.

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Organisations: National Veterinary Institute, Section for Virology, Universidad Autonoma de Barcelona, The Pirbright Institute, Centro de Investigacion en Alimentacion y Desarrollo
Authors: Martín-Valls, G. E. (Ekstern), Kvisgaard, L. K. (Intern), Tello, M. (Forskerdatabase), Darwich, L. (Ekstern), Cortey, M. (Ekstern), Burgara-Estrella, A. J. (Ekstern), Hernández, J. (Forskerdatabase), Larsen, L. E. (Intern), Mateu, E. (Ekstern)
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Authors: Larsen, L. E. (Intern), Kvisgaard, L. K. (Intern), Hjulsager, C. K. (Intern), Bøtner, A. (Intern), Rathkjen, P. H. (Ekstern), Heegaard, P. M. H. (Intern), Bisgaard, N. (Ekstern), Hansen, M. S. (Intern), Nielsen, J. (Ekstern)
Publication date: 2014

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Source: PublicationPreSubmission
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Genetic and antigenic drift of Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) in a closed population evaluated by full genome sequencing

Porcine Reproductive and Respiratory Syndrome (PRRS) viruses are divided into two major genotypes (Type 1 and Type 2) based on their genetic diversity. Type 1 PRRSV is further divided into at least 3 subtypes, but until now only subtype 1 has been detected in Western Europe and North America. Both genotypes are circulating in Denmark and since gilt vaccinations are widely used it is essential to monitor the diversity of circulating PRRS viruses. Prior to the present study, however, the diversity of circulating viruses in Denmark was virtually unknown. The main objective was to assess the diversity of circulating PRRS viruses in Danish pigs and to investigate the genetic drift of the virus in a closed population with very limited introductions of new animals. The study included phylogenetic analysis of full genome sequences of eight Type 1 and nine Type 2 PRRS viruses, including the very first Danish isolated Type 1 virus and the very first Danish Type 2 PRRS virus isolated from a non-vaccinated pig herd. Furthermore, by sequencing ORF5 and ORF7 of 43 Type 1 and 57 Type 2 viruses isolated between 2003 and 2013, the level of genetic diversity was assessed. The results showed a very high genetic diversity among the Danish viruses throughout the genome within the same genotype. A global phylogenetic analysis showed that the Danish Type 1 PRRSV formed two major clusters, one vaccine (Porcilis)-like clade exclusively containing viruses isolated after the Porcilis vaccine was introduced and another distinct clade consisting mainly of viruses isolated in Denmark. Phylogenetic analysis in a global Type 2 PRRSV framework classified all Danish Type 2 viruses to a single cluster (sub-lineage 5.1) which comprised viruses closely related to the Type 2 prototype isolate VR2332. Both Type 1 and Type 2 harbored deletions in the region encoding nsp2 and some significant amino acid changes were also seen in antigenic sites. Acknowledgement: The study was supported by EU Grant n° 245141 (New tools and approaches to control Porcine Reproductive and Respiratory Syndrome in the EU and Asia (PoRRSCon) coordinated by Prof. H. Nauwynck.

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Organisations: National Veterinary Institute, Section for Virology
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A fast and robust method for full genome sequencing of Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) Type 1 and Type 2

PRRSV is a positive-sense RNA virus with a high degree of genetic variability among isolates. For diagnostic sensitivity and vaccine design it is essential to monitor PRRSV genetic diversity. However, to date only a few full genome sequences of PRRSV isolates have been made publicly available. In the present study, fast and robust methods for long range RT-PCR amplification and subsequent next generation sequencing (NGS) were developed and validated on nine Type 1 and nine Type 2 PRRSV viruses. The methods generated robust and reliable sequences both on primary material and cell culture adapted viruses and the protocols performed well on all three NGS platforms tested (Roche 454 FLX, Illumina HiSeq2000, and Ion Torrent PGM™ Sequencer). These methods will greatly facilitate the generation of more full genome PRRSV sequences globally.

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State: Published
Organisations: National Veterinary Institute, Section for Virology, Section for Public sector service and commercial diagnostics, Molecular Evolution, University of Edinburgh
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BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.892 SNIP 0.998
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Fast and robust methods for full genome sequencing of Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) Type 1 and Type 2

The high level of diversity among PRRS viruses makes it very important to monitor the overall genetic variations in relation to the sensitivity of diagnostic tests and vaccination efficacy, but only few full genome sequences of PRRSV strains isolated in Europe have been made public available. In the present study, fast and robust methods for long range RT-PCR amplification and subsequent next generation sequencing (NGS) of PRRSV Type 1 and Type 2 viruses were developed and validated on nine Type 1 and nine Type 2 PRRSV viruses. The methods were shown to generate robust and reliable sequences both on primary material and cell culture adapted viruses and the protocols were shown to perform well on all three NGS platforms tested (Roche 454 FLX, Illumina HiSeq 2000, and Ion Torrent PGM™ Sequencer). To complete the sequences at the 5' end, 5' Rapid Amplification of cDNA Ends (5' RACE) was conducted followed by cycle sequencing of clones. The genome lengths were determined to be 14,876-15,098 and 15,342-15,408 nucleotides long for the Type 1 and Type 2 strains, respectively. These methods will greatly facilitate the generation of more complete genome PRRSV sequences globally which in turn may lead to identification of markers of virulence and improve our understanding of PRRSV evolution and pathogenesis.

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Authors: Kvisgaard, L. K. (Intern), Hjulsager, C. K. (Intern), Fahnæ, U. (Intern), Breum, S. Ø. (Intern), Ait-Ali, T. (Ekstern), Larsen, L. E. (Intern)
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Genetic and antigenic characterization of complete genomes of Type 1 Porcine Reproductive and Respiratory Syndrome viruses (PRRSV) isolated in Denmark over a period of 10 years

Porcine Reproductive and Respiratory Syndrome (PRRS) caused by the PRRS virus (PRRSV) is considered one of the most devastating swine diseases worldwide. PRRS viruses are divided into two major genotypes, Type 1 and Type 2, with pronounced diversity between and within the genotypes. In Denmark more than 50% of the herds are infected with Type 1 and/or Type 2 PRRSV. The main objective of this study was to examine the genetic diversity and drift of Type 1 viruses in a population with limited introduction of new animals and semen. A total of 43 ORF5 and 42 ORF7 nucleotide sequences were obtained from viruses collected from 2003 to February 2013. Phylogenetic analysis of ORF5 nucleotide sequences showed that the Danish isolates formed two major clusters within the subtype 1. The nucleotide identity to the subtype 1 protogenotype Leilystad virus (LV) spanned 84.9–98.8% for ORF5 and 90.7–100% for ORF7. Among the Danish viruses the pairwise nucleotide identities in ORF5 and ORF7 were 81.2–100% and 88.9–100%, respectively. Sequencing of the complete genomes, including the 5′- and 3′-end nucleotides, of 8 Danish PRRSV Type 1 showed that the genome lengths differed from 14,876 to 15,098 nucleotides and the pairwise nucleotide identity among the Danish viruses was 86.5–97.3% and the identity to LV was 88.7–97.9%. The study strongly indicated that there have been at least two independent introductions of Type 1 PRRSV in Denmark and analysis of the full genomes revealed a significant drift in several regions of the virus.

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Type 2 Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) was first detected in Europe in 1996 coincident with the introduction of a live attenuated vaccine. Since then, only limited ORF5 and ORF7 sequences of Type 2 PRRS viruses have been reported throughout Europe. In the present study, the genetic and antigenic diversity of 11 complete genomes and 49 ORF5 and 55 ORF7 nucleotide sequences obtained from 57 viruses in Denmark from 2003 to 2012 were examined. The genetic identity of the 11 complete genomes to the vaccine strain (Ingelvac PRRS MLV) ranged between 93.6 and 99.6% while the 49 ORF5 sequences examined were 94.0–99.8% identical to the vaccine strain. Among the Danish sequences, the pairwise nucleotide identity was 90.9–100% and 93.0–100.0% for ORF5 and ORF7, respectively. Analysis of the genetic region encoding NSP2 revealed high diversity among the Danish viruses with an 86.6–98.9% range in similarity. Furthermore, several of the sequenced viruses harbored deletions in the NSP2 coding region. Phylogenetic analysis in a global Type 2 PRRSV framework classified all Danish isolates to a single cluster (sub-lineage 5.1) which comprised strains closely-related to the Type 2 prototype isolate VR2332.
Porcine Reproductive and Respiratory Syndrome Virus (PRRSV)

This PhD thesis presents the diversity of Porcine Reproductive and Respiratory Syndrome viruses (PRRSV) circulating in the Danish pig population. PRRS is a disease in pigs caused by the PRRS virus resulting in reproductive failures in sows and gilts and respiratory diseases in pigs. Due to genetic heterogeneity, PRRSV is divided into two genotypes, Type 1 and Type 2. Type 1 PRRS viruses are further divided into at least 3 subtypes. The virus evolves rapidly and reports of high pathogenic variants of both Type 1 and Type 2 appearing in Europe, North America, and Asia have been reported within
The diversity of Porcine Reproductive and Respiratory Syndrome Virus Type 1 and 2 in Denmark

Both Type 1 and Type 2 PRRS viruses are circulating among Danish pigs. The first appearance of Type 1 PRRSV in Denmark was in 1992 whereas the Type 2 PRRSV was introduced in 1996 after the use of a live attenuated vaccine that reverted to virulence. Since then, vaccination to control the disease for both PRRSV genotypes has been widely used in Denmark and it is therefore highly relevant to monitor the diversity of currently circulating PRRSV strains. Only subtype 1 of the Type 1 PRRSV strains and vaccine-like Type 2 PRRSV strains were previously detected in Denmark, however, only few Danish PRRSV strains were sequenced. Denmark exports more than 50,000 living pigs each month. A portion of these pigs inevitably harbor PRRSV. Thus, the diversity of PRRSV in Denmark is of interest to other countries besides Denmark. The main objective of the present study was to close the gap in knowledge on the genetic diversity of currently circulating PRRSV strains in Danish pigs by sequencing ORF5 and ORF7 of approximately 41 Type 1 and 50 Type 2 strains collected in the years 2003-2012 were examined. The diversity study confirmed that only Type 1 subtype 1 PRRSV is circulating in the Danish pig population. The examination of the Danish PRRS field viruses confirmed that there is a high overall diversity among Type 1 viruses in Europe. The phylogenetic study also indicated the presence of two Danish virus clusters, one dominating vaccine/LV like and one resembling an early introduced strain.

Manuscript III is focusing on the diversity of Type 2 PRRSV in Denmark. For the first time examinations of complete genomes of European isolated Type 2 PRRSV were performed. Furthermore, ORF5 and ORF7 sequences obtained from 57 viruses collected in the years 2003-2012 were examined. The diversity study confirmed that Danish Type 2 PRRSV viruses share high genetic similarity to the vaccine strain and there was no obviously reason to believe that new Type 2 PRRSV strains have been introduced. However, a few viruses showed both a higher diversity to the other Danish viruses and to the vaccine strain and one virus harbored the largest deletion in NSP2 reported in Danish Type 2 PRRSV.

Manuscript IV is focusing on an experimental infection study in pigs with Type 2 PRRS virus causing significant clinical disease in the field. Genetic and antigenic examination of ORF5 and partial NSP2 sequences obtained from the case virus revealed several variations compared to the vaccine strain. However, complete genome comparison of the case virus to the vaccine strain showed high genetic similarity and no obvious virulence maker was found. The results of the experimental infection study revealed that the strain induced only sparse clinical symptoms and the magnitude and duration of viraemia was comparable to an older Danish Type 2 strain. The results emphasized that infections in the field is often more severe than in experimental studies due to the multifactorial nature of PRRSV. Furthermore, the study underlined the need for more research on virulence markers of PRRSV.
significant higher level of identity in that the ORF5 sequences were 94 - >99 % identical at the nucleotide level. Most of the Type 2 viruses, shared high level of identity to the VR2332 vaccine strain (Ingelvac MLV), but a few more diverse isolates were also identified, including strains with interesting deletions in NSP2 and other genes. The full genome sequences of Danish strains showed an overall nucleotide identity of 88-98% (Type 1) and 94 % to >99 % (Type 2). The impact of these results will be discussed.

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**Diversity of type i porcine reproductive and respiratory syndrome virus (PRRSV) in europe: A PORRSCON study**

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**PRRSV outbreak with high mortality in northern part of Denmark**
Porcine reproductive and respiratory syndrome virus (PRRSV) belongs to the Arteriviridae family and is the cause of significant respiratory and reproductive disease in swine worldwide. Strains of PRRSV are divided into two genotypes: type 1 and type 2, also referred to as EU and US type, respectively, due to their geographical origin. In Denmark the type 1 virus was first recognized in 1992, and since 1996 both types of PRRSV are widely spread. Approximately 50 % of the herds are seropositive for PRRSV antibodies against either or both types of PRRSV.

In November 2010, a severe case of PRRSV with high mortality rate in piglets occurred in Northern Jutland. PRRSV type 2 was detected by real-time RT-PCR in lung tissue from 10 days old piglets. The outbreak was treated by extensive vaccination with Ingelvac® PRRS MLV and strict management procedures. 6 weeks later, the mortality of liveborn piglets had dropped to normal levels. From week 6 until week 14 after the initial outbreak, up to 75 % of fetuses were born as mummified. PCV2 and PPV have not been detected in the fetuses. 15 weeks after the initial outbreak, the number of liveborn piglets and the mortality until weaning was back to normal. Total losses of piglets until weaning for the 15 week period were about 50 %. Losses in the nursery and finisher barn are still substantial 15 weeks after the initial outbreak. Sequencing of ORF5 and ORF7 confirmed the type of PRRSV to be type 2, and revealed distinct nucleotide differences compared to other Danish PRRSV type 2 sequences in the ORF5 region. We speculate that the virus causing this outbreak is more pathogenic than previously recognized Danish PRRSV type 2 strains.
Projects:

**Host range selection, virulence determinants and pathogenesis of influenza A viruses: Towards the identification of new antiviral drugs and vaccines**

National Veterinary Institute
Period: 01/08/2015 → 31/07/2018
Number of participants: 3
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Supervisor:
Kvisgaard, Lise Kirstine (Intern)
Main Supervisor:
Larsen, Lars Erik (Intern)

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**Porcine Reproductive and respiratory Syndrome Virus (PRRSV)**

National Veterinary Institute
Period: 01/07/2010 → 30/09/2013
Number of participants: 6
Phd Student:
Kvisgaard, Lise Kirstine (Intern)
Supervisor:
Hjulsager, Charlotte Kristiane (Intern)
Main Supervisor:
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Examiner:
Rasmussen, Thomas Bruun (Intern)
Bækbo, Poul (Ekstern)
Stadejek, Tomasz (Ekstern)

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