icrad
International coordination of research on infectious animal diseases

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 862605

Newsletter

2nd Issue July 2021

EDITORIAL

Welcome to the second issue of the ICRAD Newsletter!

ICRAD is well on its way!!!

On 27th of May 2021, the projects funded in the first co-financed call were presented to grant holders at a webinar. The event had attracted a considerable number of participants who could listen to the project coordinators' enthusiastic and inspiring presentations.

This issue of the newsletter will include the various contributions presented at the webinar.

The outcome of the day was very positive. In particular, the presentations strongly illustrated that the projects represent a broad spectrum of research initiatives of high relevance within the field of infectious animal diseases, convincingly reflecting the scope of ICRAD.

The presentations leave the clear impression that ICRAD is definitely on the right track and as such provides high expectations for the next ICRAD call.

This second trans-national call, "One health Approach to Zoonoses Research and Innovation", will be launched 1st of October 2021, and we look forward to turning attention to another exciting period of ICRAD.
Finally, we wish everyone a happy, sunny and joyful summer.

Per Mogensen
ICRAD project manager

Jens Nielsen
ICRAD coordinator

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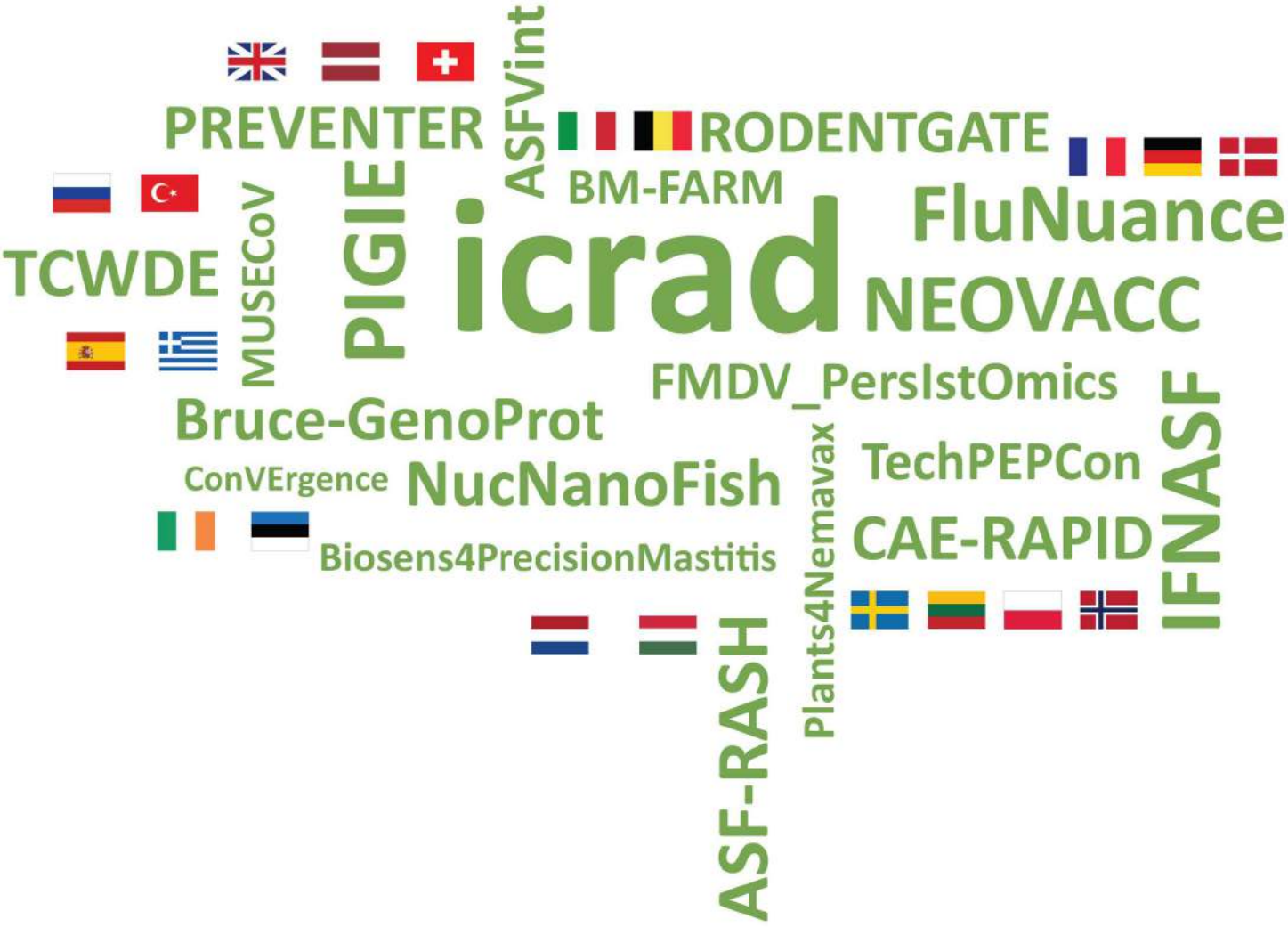
iCRAD Projects



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Special focus on-

IMPROVED UNDERSTANDING OF EPIDEMIC AND EMERGING INFECTIOUS ANIMAL DISEASES-Research Area 1

PREVENTER

Deciphering the role of influenza D virus in bovine and human respiratory diseases in Europe

Recent studies in the USA, Asia, and our preliminary work in Europe have identified a new genus of the Orthomyxoviridae family, named Influenza D virus (IDV). This novel virus was shown to infect farm animals including swine and cattle, and to efficiently replicate and transmit in ferrets, the animal model of choice for transmission of many zoonotic pathogens including influenza A virus (IAV) to humans.

Our objective is to develop an integrated approach to not only assess the emergence threat associated with influenza D viruses' circulating in Europe, but also the role played by the virus in cattle respiratory disease complex and the risk it may play for human. The first question that will be tackled relates to the role of IDV among respiratory pathogens of cattle and humans. We will therefore survey IDV occurrence and prevalence in the 2 species in Europe and collect field data (samples but also questionnaires on biosecurity and mitigation measures) to understand IDV's place within its pathogens counterparts. In field samples collected at a given time it will however not be possible to understand the sequence of infection (which pathogen is more likely to infect first/second), nor whether the co-circulating pathogens act in synergy or antagonism in the host. In vitro and ex vivo culture methods will then be used to better understand these aspects and come closer to the field situation. All parts of the projects will act as support for the models for risk assessment: to estimate the IDV human risk exposure through aerosols in cattle farms at risk (viral circulation), a quantitative risk assessment modelling will indeed be performed and refined using field and experimental data. Based on prospective scenarios analysis, the effect of medical (vaccination) and/or sanitary (biosecurity) mitigation measures will be evaluated through the previous modelling.

The output of the project will enhance European cooperation and generate a sustainable network necessary for detecting, preventing and responding to an emerging animal disease that could constitute a threat not only to animal health and welfare but also to European food production and directly or indirectly to human health. To carry out the present project, the consortium is composed of 5 partners: Dr. Mariette Ducatez, INRAE, France (coordinator); Dr. Ana Moreno, Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia Romagna, Italy; Prof. Dr. Claude Saegerman, University of Liège, Belgium; Dr. Sara Hagglund, Swedish University of Agricultural Sciences, Sweden; and Prof. Dr. Husseyin Yilmaz, Istanbul University-Cerrahpasa, Veterinary Faculty, Turkey.

Dr. Mariette Ducatez, INRAE

FluNuance

Virulent Non-Notifable Avian Influensa; Determinants of Virulence of emerging viruses

Disease outbreaks are a major threat for the European poultry industry. Avian Influenza A virus (AIV) is a global problem, causing widespread harm to animal and public health, animal welfare and food production. In poultry, pathogenicity of AIV strains is binary classified into Highly Pathogenic (HPAI) and Low Pathogenic (LPAI), using an intravenous pathogenicity index (IVPI) test in 6-week-old chickens and/or the presence of multiple basic amino acids at the cleavage site of the virus hemagglutinin (HA). Many non-notifiable (nn-LPAI; i.e. non H5/H7 subtype) AIV strains usually cause mild or moderate infections, but with highly variable mortality. High virulence nn-LPAIVs are not predicted by IVPI, as shown by recent outbreaks in Belgium, where an H3N1 strain formally classified as LPAI (IVPI = 0.13) nevertheless caused >50% mortality and a 100% drop in egg production.

FluNuance is a multidisciplinary approach to unravel the determinants of increased virulence in LPAI viruses in chicken, mallard, geese and pigeon in order to better predict the severity of emerging AIV strains.

Prof. Dr. Sjaak de Wit, Royal GD

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PIGIE

Understanding the dynamics and evolution of swine influenza viruses in Europe: relevance for improved intervention and sustainable pig production

In recent years, the epidemiological patterns of infections with swine influenza A viruses (swIAV) have changed from epizootic to endemic in many European pig herds. Moreover, the diversity of swIAVs has dramatically increased, possibly driven by the changes in viral dynamics and reverse zoonotic incursions of the H1N1 virus responsible for the 2009 human pandemic, which is now circulating concurrently with other swIAV lineages. Thus, novel reassortants and antigenic variants have emerged regionally, and these may escape current prevention and control strategies based on licensed vaccines.

The self-sustaining forms of swine influenza adversely affect animal health and welfare, resulting in severe economic losses and constitute an increasing risk for public health. The conditions sustaining recurrent swIAV infections may depend on multiple factors including production systems, biosecurity level, housing conditions, co-infections, vaccination protocols, vaccine strain composition and pre-existing herd immunity, but the precise influence of each factor is poorly understood. The objectives of PIGIE are to increase knowledge of within-herd viral dynamics and evolution in order to design intervention and prevention measures to mitigate swIAV persistence in intensive herds. Longitudinal studies will be conducted in six countries that represent 80% of the pork production in Europe and will focus on herds typical of national production systems and farms that experience continuous swIAV infections. Epidemiological, virological and immunological data will be compiled, and swIAV diversity will be studied at the genetic and antigenic levels. Mitigation points will be identified, linking viral characteristics to production systems where possible. Control strategies will be evaluated through consecutive longitudinal studies. Thus, PIGIE will provide improved understanding of the epidemiology and means of control of swIAVs. Moreover, PIGIE data will be important for further development of more accurate diagnostic tools and relevant vaccines, which would take into account swIAV genetic and antigenic diversity.

Dr. Gaëlle SIMON, French Agency for Food, Environmental and Occupational Health & Safety (ANSES)

Bruce-GenoProt

Acomprehensive proteogenomic analysis of Brucella to understand the epidemiology, biology, virulence mechanisms, and hostpathogen interaction

Brucellosis is a highly contagious zoonosis with public health impact and causing substantial economic losses among livestock. However, humans and livestock infection concerning wildlife contact and environmental contamination cannot be assessed and still, several aspects of its biology, host/pathogen interaction and virulence mechanisms are not entirely understood. To explain its epidemiology, virulence mechanisms, and host specificity, a better understanding of the genome, proteome and metabolome of brucellae is required.

Several innovation questions want to be addressed by the project, e.g. what is the status and extend of brucellosis in the environment and wildlife, what are the host and pathogen factors that contribute to virulence mechanisms and infection, what are the unique proteins expressed in B. abortus and B. melitensis cultured from different hosts that might play roles in virulence mechanisms and host/pathogen interaction. Therefore, the project aimed to assess the role of the environment and wildlife in the transmission and dissemination of brucellosis. Moreover, a comprehensive evaluation of the differences in B. abortus and B. melitensis genomes and pan-proteome using Next Generation Sequencing (NGS) and proteomics technologies and cell line infection experiment will be applied. This will clarify the differences between Brucella populations of different animal hosts and provide an overview of the unique genes and virulence factors in each species and help to understand the consequences of regulatory processes on Brucella protein composition. We will use the data obtained from the WGS and proteomes to assess the secret behind host specificity and host/pathogen interaction phenomena in brucellae. This will help to unravel the unknown mechanism of infection and develop strategies to hinder the spillover of infections. We expect to develop a cgMLST scheme for epidemiological investigations and tracing back the sources of brucellosis in domestic ruminants.

Dr. Gamal Wareth, Friedrich-Loeffler-Institute (FLI)

IFNASF

Characterization of virus-and host-specific modulation of type I IFN in African Swine Fever Virus virulence or attenuation

African Swine Fever Virus (ASFV) provokes a serious disease affecting both wild boar and domestic pigs. An outbreak in the Caucasus in 2007 started its spread across Russia and Eastern Europe, and from August 2018 to China and neighboring countries in Asia and Pacific with a total loss of 10.5 million domestic pigs. Importantly, both naturally attenuated strains and genetically modified virulent-and attenuated-derived strains have shown to confer protection. However, safety, absence of negative DIVA tests and cells for industrial scaling up, impair these tools to be securely used as vaccines.

IFNASF combines in vitro and in vivo approaches to identify and characterize the viral and host determinant for type I IFN modulation

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during ASFV infection. Firstly, several candidate genes from virulent ASFV strains will be tested as responsible of type I IFN synthesis modulation by using 293T-IFNB-FFluc cells. Functional genes which will be cloned in modified vaccinia virus Ankara vector (MVA), providing high-level gene expression, and inducing the activation of type I IFN pathway production. This will allow the study of the potential inhibitory properties of the ASFV candidate genes. Secondly, we will implement scRNA-seq in domestic pigs infected with either virulent or attenuated ASFV strains, allowing the identification of cellular subsets involved in type I IFN production and subsequent verification at protein level and the characterization of upregulated viral genes in non-IFN producers infected cells, potential candidates to be further cloned in MVAs. Finally, the identified ASFV genes would be deleted from virulent ASFV strains (by a CRISPR/Cas9 technology previously implemented in our labs), and the recombinant viruses tested in pig trials to check their role in IFN repression and vaccine potential.

Dr. Yolanda Revilla, CBMSO-CSIC-UAM

ASFVint

Decoding a virus Achilles heel: the African swine fever virus interactome

A major gap in the development of strategies to prevent and fight ASFV is the absence of knowledge of the functions of viral proteins and their interactions with host proteins, which is a prerequisite for the rational development of new antiviral strategies, or vaccines. Functional characterization of virus-host protein-protein interactions will be critical to understand how viral proteins target cellular functions to allow viral replication and spread. The ASFVint project is designed to identify cellular signalling pathways, functional modules, and machineries that are manipulated by the virus to its own benefit or even are essential for ASFV replication. To achieve this goal, we will use high-throughput systems biology approaches to map interactions between viral and cellular proteins in a systematic way. In this project, six partners (ANSES, FLI, INIA, INRAe, TPI and UTARTU) will combine their expertise in ASFV and protein-protein interactions to define and validate the first ASFV interactome.

Un-biased proteomic and targeted function of selected ASFV proteins in IFN and autophagy cellular pathways approaches will be performed using multiple approaches. The most relevant interactions will be validated by biochemical approaches, before testing their biological significance in the context of infection. Using these strategies, we will evaluate the potential pro or antiviral functions associated with the interactions identified.

Collectively, deciphering virus-host molecular interactions opens new perspectives to predict/simulate future emergences and develop effective countermeasures for disease control, such as novel spectrum anti-infectious compounds and rationally designed ASFV vaccines.

Dr. Marie-Frédérique LE POTIER, French Agency for Food, Environmental and Occupational Health & Safety

ASF-RASH

African Swine Fever pathogenesis and immune responses in Resistant And Susceptible Hosts

African swine fever (ASF) is one of the most dangerous viral diseases that threaten global pig industry and free-living swine populations. The causative agent, African swine fever virus (ASFV), is a large and complex virus with a double stranded DNA genome. ASFV is endemic to sub-Saharan Africa, where it is transmitted in a sylvatic cycle between its perfectly adapted natural hosts, Ornithodoros soft ticks and warthogs. In 2007, ASFV was introduced into eastern Europe from where it spread pandemically now affecting Europe and large parts of Asia leading to socio-economic consequences of global proportion. Although known for over 100 years, very few is known about this multi-systemic disease including immunological factors and correlates of protection. For example, it still remains unclear why, when introduced into the domestic pig sector or into Eurasian wild boar populations, the disease can resemble a viral hemorrhagic fever with exceptionally high lethality (over 90% of the infected animals die) while warthogs and other indigenous African suids show almost no clinical signs. The same is true for local resistance phenomena with higher proportions of surviving or seropositive pigs.

Within the ASF-RASH project, that started in March 2021, the pathogenesis of the disease will be comparatively investigated in susceptible and resistant host species, and correlates of immune responses associated with the favorable or lethal outcome of the disease will be defined. This will include the issues of long-term protection, protection via maternal antibodies, alternative routes of transmission, evolution on the part of the pathogen, and dose dependencies. The project brings together six partners with high international reputations in ASFV research and pig immunology from Germany (FLI), Belgium (Sciensano, UGhent), Denmark (SSI), The Netherlands (WBVR), and Switzerland (IVI) working towards the generation of valuable and novel data to help the global fight against ASF.

Dr. Sandra Blome, Friedrich-Loeffler-Institut

ConVErgence

Assessing swine as potential hosts for emerging Coronaviruses

Emerging CoVs are a major threat for swine production worldwide. Among swine emerging CoVs, at least two, namely the Swine Acute Diarrhoea Coronavirus (SADS-CoV) and the Porcine Epidemic Diarrhoea virus (PEDV), show phylogenetic relatedness with bat viruses, thus suggesting their possible role as potential reservoir hosts of emerging CoVs. We have recently confirmed that Italian swine are in contact with several bat species and this provides opportunities for pathogen spillover. Similarly, swine are exposed to SARS-CoV-2, increasing odds for infection even if pigs are scarcely susceptible. Spillover of SARS-CoV-2 in swine might result in serious consequences for human and animal health. Critically, most CoVs cause similar symp-

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toms in pigs so that spillover of novel viruses might be misdiagnosed with one of the known swine CoVs. In addition, the presence of endemic CoVs in swine may provide a backbone for recombination events, generating variants with unknown zoonotic and epizootic potential. ConVErgence aims to (i) address knowledge gaps regarding the emergence of novel CoVs in swine through spillover from humans and bats, and (ii) to provide a genetic and biological characterization of emerging CoVs.

In ConVErgence, fieldwork has been planned to detect rare transmission events in swine farms. We will quantify bat/pigs interactions related to different farming and structural characteristics using advanced techniques. We will investigate human/pig relationships using biosafety checklists. We will virologically screen samples from swine and bats and use specific serological assays to test for swine exposure to selected CoVs of either human or bat origin. We will characterise all CoVs detected in the study, first genetically and then phenotypically, through 3D in vitro systems of different origin. Finally, all data will be used to build mathematical models to investigate dynamics of CoVs in the bat reservoir and to model the spillover (and circulation) of emerging CoVs in swine.

Dr. Paola De Benedictis, Istituto Zooprofilattico Sperimentale delle Venezie

MUSECoV

MUlti-Scale Eco-evolution of Coronaviruses: from surveillance toward emergence prediction

Coronaviruses can infect a huge variety of animal species, mammals and birds. They can evolve through different mechanisms of mutations and homologous recombinaisons. This genetic evolution of their genome allows them to acquire sometimes, new biological properties such as a change in virulence or the ability to infect a new host. The emergence of SARS-CoV-2 is a paradigm of the ability of coronaviruses to transgress species barriers. This virus emerged from a bat reservoir and adapted to humans but can also infect some animal species in natural settings (minks, ferrets, cats, dogs, captive felidae and monkeys). MuseCov is a global project dedicated to explore the genetic evolution of animal coronaviruses in different contexts. We aim to:

- monitor the coronavirus circulation and genetic diversity in wildlife (bats, some bird species, and hedgehogs) and domestic animals (pets, poultry). We will also investigate the possible circulation of SARS-CoV-2 in animals, especially in pets. To full-fill these objectives, we will develop new coronaviruses detection tools based on biosensor technologies
- explore and characterize the ecological drivers and coronavirus evolution through in-host genetics and whole genome / deep sequencing of animal coronaviruses in natural, farm or in vitro settings
- decipher molecular events leading to cross-species transmission by exploring the ability of wildlife coronaviruses to use human proteins as viral receptors, and by studying aspects of intracellular host determinants

The MuseCov program will deliver data concerning the dynamics of interactions between coronaviruses, and different animal hosts, providing novel insights concerning the mechanisms and pathways of coronavirus adaptations in various animal compartments.

Prof. Sophie Le Poder, ANSES

TCWDE

Tackling chronic wasting disease in Europe

Chronic wasting disease (CWD) is a prion disease, similar to scrapie and bovine spongiform encephalopathy (BSE, or "mad cow disease"), which is widespread among wild and captive cervids in North America, with devastating consequences for certain populations. Recent reports of experimental oral transmission of CWD to non-human primates also raise concerns about its zoonotic potential. CWD was first identified in Europe as a novel prion disease in wild reindeer in Norway in 2016, and subsequently found in small numbers of moose and red deer in Norway, Finland and Sweden. Analysis of these cases suggest the presence of a number of distinct prion strains, which differ markedly from those predominant in North America. Differences in European CWD strains and deer species/populations from those in North America mean that further research is urgently needed to develop risk assessments and control strategies specific to the European context. This project will integrate research on the epidemiology and population dynamics of the disease in affected countries, with experimental approaches to study host/pathogen interactions relevant to disease transmission in wildlife, livestock and people. Information on CWD cases and cervid population data in Norway and Sweden will be used to develop models to evaluate surveillance strategies, predict CWD spread in affected populations, and indicate potential for transmission through contacts with semidomesticated reindeer and livestock. PRNP gene sequencing of European cervids will allow identification of novel variants that may be associated with resistance to CWD and could be used in selective breeding for disease control.

The potential for transmission of European CWD isolates to sheep, cattle, pigs and humans will be assessed using in vitro and in vivo models. Project outcomes will support risk assessments of potential impacts of CWD on animal/human health, and lead to improved and cost-effective surveillance and control strategies.

Dr. Fiona Houston, University of Edinburgh

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RODENTGATE

Future Rodent Management For Pig And Poultry Health

Apart from consuming and spoiling animal feed, and damaging infrastructure in and around farm buildings, rodents are a considerable threat to animal health and One Health. They can cause direct stress on pigs and poultry but are mainly important as carriers of pathogens. These include economically very significant diseases like Swine dysentery, Aujeszky's Disease, PCV2 and Encephalomyocarditis. Wild brown rats can carry Influenza A and might act as an intermediate for the transmission of avian influenza between wild birds and poultry. For some other diseases like African Swine Fever, rodents may act as mechanical reservoirs or they may support ticks that can carry ASF. Rodents also play a role in the epidemiology of leptospirosis and salmonellosis or in spreading antibiotic resistant bacterial strains such as livestock associated MRSA. They can pick up the infection from infected pigs or poultry and spread it within and between farms, they can act as a bridge between wild fauna and livestock, and they can maintain the infection locally when a farm is emptied and decontaminated after a disease outbreak or livestock turnover. Thus, there are very good reasons for rodent management on pig and poultry farms. An important approach has always been the use of rodenticides. However, concerns about the environmental safety of the most common rodenticides has led to changes in the European and national regulations that restrict their use and pose new challenges for efficient rodent management on farms. There is also the problem of resistance against these poisons. This project RODENTGATE will investigate the rodent-related risks for animal health in the pig and poultry industry and how this might change with altered rodent control.

Ecologically-based rodent management is a strategy that combines an Integrated Pest Management approach with a thorough knowledge of the rodent ecology, enabling interventions to be precisely targeted in time and space, whilst being ecologically and economically sustainable. This requires a very good understanding of the rodent demography, life history, space use, dispersal capacities as well appropriate documentation of pathogen presence and transmission patterns in the rodent population. Proper understanding of transmission mechanisms is crucial since killing hosts may have unexpected effects on the spreading of an infection.

RODENTGATE's specific objectives are
1) to document changes in disease risk for pigs and poultry when classical rodent management around farms is prevented and rodent populations around farms change in abundance or composition and
2) to propose appropriate evidence-based and economically sustainable strategies for the ecologically-based management of rodents and rodent-borne infections around farms.

Working towards these objectives raises a number of questions:
- What is the current status of rodent-borne pathogens in pigs and poultry, kept under different husbandry styles in different parts of the EU?
- What is the presence and diversity of relevant pathogens in wild rodents in and around pig and poultry farms?
- What is the role of rodents in spreading pathogens between farms, especially after disease outbreaks and subsequent culling or seasonal emptying of a farm?
- How will pig and poultry health be affected if rodent population composition and/or abundance around farms changes following a ban on rodenticides?
- How can the efficiency of rodent management practices on farms be maintained under restricted or no-rodenticide situations?

These questions will be addressed by a multidisciplinary consortium of scientists from Belgium, UK, Germany, The Netherlands, and Poland, using a combination of analysis of existing data, sampling rodents, environment and livestock on farms, molecular diagnosis of pathogens, field work on rodent population biology and movements, ecological modelling, control strategy development and communication with the pig and poultry industry and pest control industry.

Prof. Dr. Herwig Leirs, Universiteit Antwerpen

FMDV_PersIstOmics

From proteogenomic host response signatures of persistent foot-and-mouth disease virus (FMDV) infection to diagnostic markers and therapeutic control

Foot-and-mouth disease (FMD) is one of the most devastating contagious viral diseases of cloven-hoofed livestock. More than 50% of ruminants that had been exposed to foot-and-mouth disease virus (FMDV), even vaccinated, will carry the virus in the nasopharynx for a prolonged period called persistent infection or "carrier state". Carriers are often considered a potential source of infectious virus and an impediment for international trade. Fear of contagion from carriers is a major obstacle for the implementation of vaccinate-to-live policies for FMD control in free countries. Despite decades of research, the mechanisms underlying FMDV persistence remain largely unknown. Investigations performed so far suggest that the maintenance of persistent infection is mainly related to the host's immune responses. Filling the gap of knowledge regarding the carrier state is critical to be able to predict, prevent, detect or cure FMDV persistence. In a previous EU funded project, we have established a new in vitro model of FMDV persistence in primary bovine dorsal soft palate (DSP) cells cultured as multilayers to mimic in vivo conditions. In this model, we identified time-dependent gene signatures during FMDV infection and found that a long-lasting stimulation of interferon indeed stimulated antiviral genes (ISG) along with persistence but is ultimately ineffective to clear the virus.

Some highly regulated genes, which have potential use as diagnostic markers were also identified. The FMDV_PersIstOmics project aims to determine mechanisms and factors that may help to prevent/control persistent infection and to improve diagnostics :
(i) uncover alterations of the host response during persistent FMDV infection of cattle (ii) evaluate genes highly regulated during FMDV persistence as candidate host markers of persistent infection and (iii) identify pathways that could be targeted to prevent the establishment of FMDV persistence or terminate the infection. It will have broad applicability for the design of new FMD control measures.

Dr. Sandra Blaise-Boisseau, ANSES

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BM-FARM

Biomarkers and Microbiome in Farms for Antimicrobial Resistance Management

Excessive antimicrobial use (AMU) in humans and animals has resulted in the proliferation of multi-resistant bacteria that have also spread to the environment. When these bacteria infect humans, there is no treatment to stop them, and more deaths due to multi-resistant bacteria than due to cancer are expected by 2050.
Pigs are responsible for the highest volume of AMU of any species, mainly to prevent post-weaning diarrhea, respiratory outbreaks, and systemic infections often related to Streptococcus. These infections affect only some groups of animals, but it is difficult to predict which groups will be affected. Regular in-feed preventive AMU has been the main approach until now, however this approach will not be allowed in the EU from January 2022.

Being able to anticipate the groups of animals with higher risk of disease would be of great help to avoid AMU. There is no single indicator to detect sensitive groups of animals. It is often a combination of environmental and host factors. Project BM-FARM will combine data on productive performance, salivary biomarkers, and microbial ecosystems in farms to predict those groups of animals that will be at high risk of disease and modify their management accordingly to minimize AMU.

This project will be developed 100% in real environments and will use data that can be easily obtained by farmers to achieve impact rapidly. All the information will be integrated in a final indicator of risk of disease for rapid decision making at farm level. The information obtained while preparing the risk indicator will also help understand the complex relationships between the host, the pathogen, and the environment.

Dr. Edgar Garcia Manzanilla, Teagasc, Irish Agriculture and Food Development Authority

end of presentations of IMPROVED UNDERSTANDING OF EPIDEMIC AND EMERGING INFECTIOUS ANIMAL DISEASES-Research Area 1

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Special focus on-

GENERIC TECHNOLOGY PLATFORMS FOR PRODUCING NOVEL AND/OR IMPROVED VACCINES-Research Area 2

NucNanoFish

Nucleic NanoVaccines for Fish

Aquaculture is the fastest food production sector, but the impact of viral infections on fish health and welfare is particularly strong, involving important economic losses, and only few vaccines are available. A number of experimental DNA vaccines against fish viral infections have been developed, some providing high protection but they are injected and cannot be easily administered to young fish. Several DNA vaccines have been recently made commercially available. mRNA vaccines hold much hope, seem to be fast to produce and should be safer than DNA vaccines. The NucNanoFish project proposes to establish a nucleic acid platform using biodegradable nanoparticles for efficient delivery of vaccines, through intra-muscular or oral/immersion routes, according to well-known viral diseases of several European farmed fish species. NucNanoFish will design, produce and test DNA/mRNA nucleic acid vaccines loaded or not onto safe-by-design LipoNanoParticles (LNP). LNP are based on a PLA/PLGA (Poly-Lactic/Glycolic Acid) core surrounded with a lipid corona. We hypothesize that their efficient uptake by mucosa or the recruitment of Antigen Presenting Cells at site of injection will favour a protective immune response at the portal of virus entry of each relevant pathogen. The biodistribution of LNP-DNA / mRNA vaccines after administration by intramuscular (im), oral or bath route will be characterized and their nanotoxicity evaluated.

The induction of immune responses (both systemic and mucosal) after administration of LNP-DNA and mRNA vaccines by im injection or following oral vaccination or bath will be investigated, both at systemic/mucosal level. In particular, the effects of diet-associated gut conditioning on LNP uptake by gut, and induction of adaptive immunity will be studied. The protection afforded by vaccination using relevant LNP formulations will be checked. Combining all data, we could identify correlates of protection, which will constitute a cornerstone to develop the further generation of nucleic acids fish vaccines.

Dr. Bernard Verrier, CNRS

Plants4Nemavax

Plant-based production of glyco-engineered nematode vaccines

Parasitic nematodes are amongst the most common pathogens in grazing ruminants worldwide. The continuous exposure to these worms has a significant impact on the health status and productivity of the animals.

Control of these infections currently relies almost completely on periodic mass administration of anthelmintic drugs. However, with the increasing incidence of anthelmintic resistance around the world, there is an urgent need for alternative control measures. Vaccination is often put forward as the most rational and cost-effective alternative to control infections with parasitic worms. However, the ability to produce immune protective recombinant worm vaccine antigens have shown to be a major bottleneck. In particular the inability of the expression systems to reconstitute the vaccine antigens with their native post-translational modifications, such as glycans. By adapting the post-translational machinery of tobacco plants, it has now become technically possible to synthesize proteins with a well defined and tailored glycan composition. The aim of this project is to use this versatile plant-based production platform to express a set of well-defined nematode vaccine antigens from the bovine parasites Ostertagia ostertagi and Cooperia oncophora and the ovine parasite Teladorsagia circumcincta and subsequently evaluate for their immunostimulatory and protective capacities in vivo in comparison to the native versions of the vaccines. The outcome of this project should deliver proof-of-concept whether efficacious nematode vaccines can be produced if glycans are taken into account properly. This would provide a major breakthrough in parasite vaccine development.

Prof. Dr. Peter Geldhof, Ghent University

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 862605

NEOVACC

Novel strategies to enhance vaccine immunity in neonatal livestock

The NEOVACC project addresses the significant challenge of effective vaccination of neonatal animals in the presence of maternally derived antibodies (MDA). This is critically important since MDA inhibits immune responses of neonates to vaccination and as MDA wanes immunised animals remain vulnerable to pathogen challenge. NEOVACC will therefore evaluate novel vaccine strategies designed to enhance immune responses in neonatal animals with MDA. We will focus on bovine respiratory syncytial virus (BRSV) and porcine reproductive and respiratory syndrome virus (PRRSV), as prime examples of endemic livestock diseases that require next-generation vaccines to improve control. We will explore a state-of-the-art structural vaccinology approach to design novel immunogens based on the BRSV pre-fusion (preF) protein for neonatal calves. We will determine whether discrete differences exist between maternal and calf antibody binding to epitopes on BSRV preF. We will then design and select BRSV preF epitope scaffolds which would not be recognised by MDA and evaluate their vaccine potential using our established BSRV challenge model.

The second approach aims to exploit DNA vaccination to overcome MDA interference. We will evaluate novel DNA-based vaccines encoding well-defined PRRSV antigens fused to moieties that target antigen to professional antigen- presenting cells and assess their ability to prime immune responses in MDA+ piglets and augment a subsequent modified live vaccine (MLV) boost. We will conduct a parallel in vitro investigation to better understand the ability of these novel constructs to circumvent MDA interference. Finally, we will evaluate the potential of peptide-based immune checkpoint inhibitors (ICIs) to adjuvant responses to PRRSV MLV. By transiently blocking negative immunoregulation, we hypothesise that PRRSV MLV genetically engineered to express ICIs would allow neonatal animals to mount more robust immune responses. In addition to developing novel BSRV and PRRSV vaccine candidates, the approaches employed to design vaccine antigens, to deliver DNA encoded antigens in a targeted manner to augment B cell responses, and to potentiate responses through immune checkpoint inhibition may be more broadly applied, including to human clinical settings.

Prof. Simon Graham, The Pirbright Institute

end of presentations of GENERIC TECHNOLOGY PLATFORMS FOR PRODUCING NOVEL AND/OR IMPROVED VACCINES-Research Area 2

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Special focus on-

HIGH-THROUGHPUT, RAPID, ACCURATE AND EASY TO USE IN-FIELD DETECTION TECHNOLOGIES-Research Area 3

CAE-RAPID

Development of a rapid screening test for on-site serological diagnostics of caprine arthritis-encephalitis using individual milk samples

Caprine arthritis-encephalitis (CAE) is a globally widespread disease of goats caused by small ruminant lentivirus (SRLV) from the Retroviridae family. At present it is considered one of the main threats to goat production in European countries with a considerable negative influence on mobility, welfare and productivity. The main route via which SRLV enters and spreads in a herd is the introduction of an asymptomatically infected goat. Therefore prevention is crucial for an effective CAE control. The major challenge of CAE diagnostics results from the long time which elapses between infection and emergence of the first apparent signs. During this time the disease insidiously spreads between goats and when the farmer realizes that something wrong is going on usually a high proportion of goats in the herd are already infected. Currently, the mainstay of CAE diagnostics are serological tests. Even though they are highly accurate, their price including the veterinary service necessary for blood sample collection and its transportation to the laboratory, and the time which it takes to obtain results from the laboratory hinder their routine use when a single animal needs to be tested.

CAE-RAPID aims to improve individual diagnostics of CAE by providing an easily available and convenient tool for reliable exclusion and early detection of the infection. The rapid test for detection of antibodies to SRLV in a drop of milk, serum or whole blood will be intended for use in two basic situations. First, for on-site screening of asymptomatic goats which are intended to be purchased or introduced into the herd. Second, for on-site screening of goats in which first clinical signs have emerged. The test will be a screening diagnostic method. It will be expected to maximize diagnostic sensitivity and the negative predictive value, so that a goat testing negative could be safely introduced into or retained in the herd. Positive results will need to be verified in the laboratory.

Dr. Michał Czopowicz, Warsaw University of Life Sciences-SGGW

TechPEPCon

Use of frontline technologies to screen pathogens, environment and pigs for a better disease control in swine herds

Pig industry has evolved extremely fast during the last decades. The exponential increase in the number of animals combined with their worldwide transport and the globalization of feed components favors a continuous fast spread of infectious agents throughout the world. Major gaps in their control are difficulties to (1) recognize diseases at an early stage, (2) swiftly identify pathogens and pathogen complexes, and (3) convince farmers on the importance of an efficient biosecurity. Novel technologies will now be used to address these issues. (1) Real-time detection of clinical signs using sensors recording animal physiological and environmental conditions (Healthy Climate Monitor). (2) Use of a new sampler developed by Ghent University allowing on-site purification of material from live and deceased animal. Direct nanopore sequencing and data analysis through a novel diagnostic software platform allow rapid virus and bacteria identification, without the need of any prior pathogen knowledge. (3) A risk-based biosecurity scoring system (Biocheck.UGent) to evaluate the quality of the on-farm biosecurity.

These technologies will be first applied to farms without overt clinical signs but with low productivity. Subclinical bacteria and virus circulation will come to light. This will allow recommendations to improve the biosecurity level. Secondly, the same technologies will be used on farms with clinical outbreaks. The pathogens will be identified together with negative environmental and biosecurity factors. This will allow to develop pathogen-specific treatments and prevention together with adaptation of the environment and biosecurity. Newly identified viral isolates will be used in experimental infections to determine their clinical and pathological outcome. Finally, a spatio-temporal pathogen tracking system for veterinary medicine will be developed for farmers, veterinarians, decision makers and pharmaceutical companies as a tool for surveilling and combating emerging endemic and epidemic viral diseases.

Prof. Hans Nauwynck, Ghent University (UGent)

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International coordination of research on infectious animal diseases

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Biosens4PrecisionMastitis

Channel-based biosensors to support a precision agriculture approach for improved bovine mastitis management

Bovine mastitis affects animal health and welfare, reducing milk yields and quality. When high rates of infection are detected within the herd, culling is recommended. If signs indicate infection can be controlled, antimicrobials are administered, and isolation of infected cows is enforced. Indeed, antibiotics are often given without mastitis confirmation, even to entire herds during drying off periods. Antibiotic residues can end up in milk, and be released into water and soil, underpinning antibiotic resistance.

Late and poor intervention is mostly due to significant limitations in the diagnosis of mastitis. On-farm, somatic cell count indicates the likeliness of milk to contain harmful bacteria. In the lab, cell culture and PCR identify bacterial pathogens, but they are time-consuming and costly. Moreover, none of these methods reports infection at the early stages of disease when animals are highly infective, and therapies are most effective.

Biosens4PrecisionMastitis aims to deliver new diagnostic tools to detect mastitis at the early stages of the disease, by targeting biomarkers of the early immune response of cows: miRNAs, cytokines and antimicrobial peptides. This new concept is expected to confirm infection, rather than just exposure, and report disease status and aetiology. To underpin the reliability of the method, the project will identify distinct biomarker signatures in milk collected from a herd in a natural setting, instead of using animal models, to avoid underestimating potential effects acquired through natural patterns of pathogen exposure. Our solution will combine the identified biomarker signatures with biosensing technology based on advanced materials to perform non-invasive and stress-free "milk biopsies" on-site, in near-to-real time, at a low cost and by harnessing readily available equipment. These tools will support constant animal surveillance to identify actionable cases and guide farmer's intervention, providing valuable advantage to the European dairy industry.

Prof. Beatriz Prieto Simón, University Rovira i Virgili

end of presentations of HIGH-THROUGHPUT, RAPID, ACCURATE AND EASY TO USE IN-FIELD DETECTION TECHNOLOGIES-Research Area 3

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Improved Understanding of
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