Working document

The novel A/H1N1 influenza virus
at the human-animal interface

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1. Purpose of this document

The purpose of this document is to provide "food for thought" to reply to the question: What needs to be done in Europe? in relation to the potential risks posed by the novel Influenza A/H1N1 virus at the interface between humans and animals. It focuses on the potential risks at the human-pig interface, although there is at this stage no evidence of the novel virus circulating in domestic pigs or wild boar and of virus transmission from pig to humans.

2. Introduction / facts

2.1. Transmission from swine to human

Swine influenza (SI) is caused by infection with influenza A viruses and is endemic in many pig populations around the world. Transmission of SI virus to humans has been reported in the scientific literature as a rather rare event, following direct contact between infected pigs and humans. It has also been reported that some of the virus strains circulating amongst pigs have a human origin.

Swine influenza is a respiratory disease. Transmission of influenza virus in pigs is via inhalation of aerosols. Whilst it is true that some influenza viruses have the capacity to enter the bloodstream and therefore be detected in muscles and other tissues, this has not been seen following natural infection in swine even with influenza A viruses adapted to pigs. Infection in swine does not produce viraemia and the virus is not found outside the respiratory tract and associated lymph nodes (AQIS, 1991). Therefore, it would be highly unlikely that influenza A viruses circulating in pig populations could be transmitted to humans by pork or pork products or even pig semen.

The EU hygiene requirements for the slaughter of pigs do not allow that sick animals are transported to the slaughterhouse. The obligation to have veterinary inspection in slaughterhouses for the assessment of the clinical conditions of the animals so that only healthy animals are slaughtered (ante-mortem inspection) and the controls made on the carcasses for the assessment of any pathological lesion along the slaughter line (post-mortem inspection carried out in accordance with EU rules give additional guarantees that pigs displaying clinical/pathological signs are excluded from entering the food chain.

The statements made by the OIE/WHO/FAO/WTO/ECDC/EFSA adequately address the issue of safety of pork and pork products for human consumption in relation to influenza.

Pigs might act as a mixing vessel for the reassortment of avian, swine, and human influenza viruses and may play a role in the emergence of novel influenza viruses potentially capable to cause a human pandemic.

2.2. Transmission from human to swine

Pigs have shown to be naturally and experimentally susceptible to infection with the novel A/H1N1 Influenza virus, that has been circulating in the human population in many countries in the word in recent months. No other farmed or domesticated animal species has been found naturally susceptible to this virus. This does not include animals that have been experimentally inoculated, like ferrets.

- **Canada:** On 4 May 2009 the Canadian authorities reported to the Commission the detection of the novel influenza A/H1N1 virus in a pig farm in central Alberta (Annex II) which has most likely been introduced by a carpenter returning from Mexico on 12 April and developed subsequently influenza like illness. On 14 April this worker has been on the farm, he was sampled on 24 April with negative results. As of 25 April the pigs showed loss of appetite and some had fever. No mortality was recorded and all pigs recovered. However, there was some history of chronic infection in the pigs with Mycoplasma. There has been no evidence for pig to human transmission. On May 9, the Government of Alberta announced a limited cull of pigs at the quarantined pig farm where novel influenza A/H1N1 virus had been detected. This decision was not a disease-ordered cull, but was made to find a solution to overcrowding and related negative impact on animal welfare.

2.3. Situation in pigs

Between the 1930s and the 1990s, the most commonly circulating swine influenza viruses among pigs - classic swine influenza A (H1N1) - underwent little change. However, by the late 1990s, multiple strains and subtypes (H1N1, H3N2, and H1N2) of triple-reassortant swine influenza A (H1) viruses - of which genomes included combinations of avian, human, and swine influenza virus gene segments - had emerged and became predominant among North American pig herds.

Within the European pig population the influenza A viruses subtypes H1N1, H3N2 and H1N2 co-circulate widely.

Some more recent facts are reported from countries experiencing infections with novel A/H1N1 influenza in humans:

- **USA:** New scientific data from the USA (Shinde et al. 2009, NEJM in Annex I) are showing that triple-reassortant swine influenza A (H1) viruses had emerged and became predominant among North American pig herds during the last 10 years. It appears that this American triple-reassortant swine influenza is the "progenitor" of the novel influenza A/H1N1 virus currently affecting humans.

- **EU:** Surveillance of pig populations for swine influenza has been carried out in several Member States in the last years. A European Swine Network for Influenza in Pigs (ESNIP2) has demonstrated that subtypes H1N1, H3N2 and H1N2 co-circulate (genotypic diversity) in the EU. The new triple-reassortant H1N1 virus identified in

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N. America has never been reported. In general, the strains that are endemic in the EU are quite stable in contrast to the situation in North America, where multiple genotypes of several different subtypes have emerged and evolved in the past 10 years. The novel influenza A/H1N1 virus recently reported in humans has never been reported in pigs in Europe, and therefore does not appear to be present in the European pig population.

2.4. Experimental studies

The preliminary results of the animal experiment on infection studies with novel A/H1N1 in pigs carried out by the Community Reference Laboratory for avian influenza, Weybridge, UK in collaboration with other EU laboratories show that infection of pigs with this virus behaves like other SI infections. The preliminary conclusions of the study (Annex III) indicate that pigs are susceptible to infection with influenza A (H1N1) virus that results in the induction of detectable levels of clinical disease, virus shedding and pathology in an experimental setting. Importantly, mortality was not a feature and infected animals were able to transmit the virus to naïve contact pigs successively for at least three cycles of transmission, suggesting the virus could become established in susceptible pig populations if introduced.

These results seem to be in line with the preliminary data currently known on other similar experiments carried out in other laboratories.

As regards the vaccines for pigs, USA researchers have tested serum samples from pigs previously infected with U.S swine influenza viruses or vaccinated with commercial vaccines to determine if U.S commercial swine herds are susceptible to the new H1N1 influenza virus. They found that there was limited cross reactivity against the new H1N1 influenza virus. This suggests that pre-existing immunity induced by swine influenza viruses previously circulating in the U.S may not protect pigs against the new H1N1 influenza virus presently circulating in people and vaccines currently used to protect pigs on U.S swine farms operations against swine influenza viruses may not be effective against the new S/O H1N1 influenza virus. Further investigations are ongoing.


3. General principles on the actions that need to be done in Europe in relation to the potential risks caused by the novel Influenza A/H1N1 at the human-pig interface

It is foreseeable that in the next months the virus will continue to circulate and spread in the human population and affect further countries all around the world.

The disease caused in humans is rather mild and this is one of the reasons why the WHO has not declared pandemic level 6.

Human-to-pig transmission has been described outside the EU and may occur in the future, also in Europe. From an animal health perspective, this virus is unlikely to cause more
significant health problems in pigs than the other SI viruses that are endemic all around the world and for which neither OIE nor specific EU control measures have ever been deemed necessary.

From a human health perspective, circulation of virus in pigs is a factor likely to determine the risk of pig-to-human transmission.

The measures to be taken in pig farms to prevent possible human-to-pig transmission, pig-to-pig transmission and pig-to-human transmission should be proportionate to: i) the risk posed by pigs in the transmission of the novel A/H1N1 to humans, if any, compared to the role played by human-to-human transmission, and ii) the degree of seriousness of disease in humans.

There is no evidence or data suggesting that routes of transmission other than direct contact may play a significant role in the human-to-pig or pig-to-human transmission of the novel Influenza A/H1N1 virus.

The most important measure to reduce the risk of human-to-pig transmission and of pig-to-human transmission is to strengthen those bio-security measures on pig farms that should already be in place in any farm and so further reducing the risk that sick people with respiratory signs get in contact with pigs or sick pigs with respiratory signs get in contact with humans.

The recommendation already made by the Commission that as a normal precaution pig farmers should rigorously apply the general biosecurity and hygiene measures in order to reduce the risk that any virus enters a pig farm maintains its validity.

However, additional measures such as systematic vaccination of staff working in contact with pigs should also be assessed.

There is no information suggesting that this virus behaves in humans or pigs differently from any other influenza virus causing infection in the respiratory tract, only. In addition, the oral route is not known to be a normal route of transmission of influenza virus to humans or pigs. For these reasons, at this stage there is no indication that infection of pigs with the novel virus may have any significant food safety implication.

Vigilance on pig farms in Europe will also need to be enhanced, in particular in the next autumn and winter. Surveillance for the novel Influenza A/H1N1 virus in pig farms must have a clear aim. At this stage, surveillance actions should: 1) in the context of risk management, focus on early detect virus in farms with an identified risk of human-to-pig transmission; and 2) in the context of risk assessment and research, be aimed at better understanding the risk of possible undetected circulation of virus in pig farms.

As regards point 1) above, thorough investigations, sampling and testing should be carried out in farms identified as at high risk on epidemiological grounds, so that if the pigs are found positive adequate quarantine and bio-security measures can be adopted to prevent any further virus spread from the pigs in question. To this aim good and timely communication should be ensured between public health and animal health authorities to enable rapid investigation of pig farms when an epidemiological link to human cases has been established.

As regards point 2) above, the surveillance/monitoring activities of the ESNIP project have shown be very informative and useful and should be continued and intensified.
When investigations and sampling are carried out in pig farms in order to detect the A/H1N1 virus, they should be first focused on those pigs showing respiratory signs and those that have been potentially exposed to infected humans.

In order to ensure the surveillance above the veterinary and public health authorities in the Member States should ensure that adequate information is provided to pigfarmers, private veterinarians, general practitioners, and that the veterinary laboratories have the necessary diagnostic capability on pig samples.

It is too early at this stage to envisage a role of animal vaccines in the prevention and control of the novel A/H1N1 virus in pigs, although the first data available do not suggest that currently available vaccines can be effective against it.

Activities to be planned on pig farms in the next months should however be flexible allowing an adaptation to a possible further evolution of the virus and of its transmission patterns.

It is highly desirable that the initiatives of all players on risk assessment (EFSA, ECDC) and risk management (Commission services, MSs and international organization) and research levels are coordinated so that joint efforts result in a better capability to react in a proportionate and effective way to the risks that this virus may pose at the human-animal interface.
Annex I

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Annex II

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Annex III

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Annex IV

EU legislation and international standards and statements

**EU:** Council Directive 82/894/EEC on the notification of animal diseases\(^3\) lists the diseases of terrestrial animals which are subject to notification. Swine Influenza is not listed there and therefore no legal obligations exist to notify and control the disease.

The Standing Committee on the Food Chain and Animal Health has on 5 May endorsed a statement with regard to the novel A/H1N1 influenza.\(^4\)

**OIE:** Although there is no obligation for notification\(^5\), Canada has notified on 5 May 2009 the incident to the OIE, due to the emerging nature of the disease. The OIE has issued several statements on its website:

OIE statement: A/H1N1 influenza like human illness in Mexico and the USA:

OIE position on safety of international trade of pigs and products of pig origin:
http://www.oie.int/eng/press/en_090428.htm

Joint WTO/OIE/WHO/FAO statement on A/H1N1 influenza

The OIE strongly counsels against the culling of pigs:

OIE comments on the findings of “A/H1N1” in pigs in Canada:

OIE reaction to trade restrictions imposed following transmission of virus “A/H1N1” from human to pigs: http://www.oie.int/eng/press/en_090507.htm

Joint statement by FAO/WHO/OIE on H1N1 and safety of pork:
http://www.oie.int/eng/press/en_090507_bis.htm


Annex V

EU funded research

The EU (DG RTD) has funded research projects in FP5 and FP6 addressing a wide range of aspects of influenza of humans and animals. A detailed information of the projects can be found at the website: http://ec.europa.eu/research/health/infectious-diseases/emerging-epidemics/projects_en.html.

Close collaboration between human and animal health researchers is essential in order to tackle influenza and other zoonotic infections. In this regard, in response to the H5N1 crisis in 2005, a special joint call covering animal and human health topics was launched and 17 project subsequently selected for funding.

Some of the projects specifically address issues related to the molecular basis of species specificity and interspecies transmission, control strategies and an EU swine influenza network.

A selection of projects addressing totally or partially swine influenza is found as addendum.

Further research activities

In response to the new influenza A H1N1 further research activities have been jointly planned between the Health Theme and the Food, Agriculture and Fisheries, Biotechnology Theme of FP7. The topics are proposed in the 2010 Workprogrammes which is currently in consultation and relate to issues such as novel therapeutics against influenza, swine influenza surveillance network and pathogenesis and transmission of influenza in pigs.

The EC supports international collaborations in research and the sharing of research results and data.
Addendum: EU supported research related to swine influenza in the 5th and 6th FPs

5th Framework Programme (1998-2002) A concerted action was supported in Key Action 2 "Control of infectious diseases" of the Quality of Life Programme of the 5th FP.


It involved 14 partners from 10 countries in Europe.

- CIDC-Lelystad, The Netherlands
- Gent University, Belgium
- Veterinary Laboratories Agency, UK
- Instituto Zooprofilattico Sperimentale della Lombardia e dell’Emilia Romagna “B. Umbertini, Italy
- Central Veterinary Research Laboratory, Ireland
- Institute Infectious Disease and Veterinary Epidemiology, Czech Republic
- National Veterinary Research Institute, Poland
- BioScreen European Veterinary Disease Management Center GmbH, Germany
- Merial SAS Research & Development, France
- Agence Française de Sécurité Sanitaire des Aliments, France
- Institut Pasteur Dépt. de Virologie, France
- National Institute Medical Research, UK
- Intervet International BV, The Netherlands

The objective of this co-operative surveillance network, was to standardise and harmonise techniques and protocols for virus isolation and typing and to exchange reference material and information about recent swine influenza virus (SI) strains. The available information about recent SI field isolates has been stored in a database and the field isolates have been stored in a central virus bank to assure free access by all partners. The database provides a first epidemiological picture about SI in Europe that has been used to define recommendations for SI control.


SSPE-CT2005-022749 « European Surveillance network for Influenza in pigs » ESNIP2 (Coordination Action) EU contribution 300,000 €. Duration 01.01.2006 to 30.03.2009

Participants:
- Gent University, Belgium
- Veterinary Laboratories Agency, Weybridge, UK
- CIDC Lelystad, NL
- Istituto Zooprofilattico Sperimentale della Lombardia e dell’Emilia Romagna, Italy
- AFSSA, LERAP, France
- Philipps-Universität Marburg, Germany
- Merial SAS, France
- Laboratorios HIPRA S.A., Spain
- National Diagnostic Research Veterinary Institute, Sofia, Bulgaria
- The University of Hong Kong, Hong Kong SAR
- University of Wisconsin-Madison, USA (did not signed the contract but collaboration was maintained)

The aims of ESNIP2 were to further expand the epidemiology and evolution of swine influenza viruses in Europe and to apply this knowledge to optimize diagnostic techniques for swine influenza. In addition, it aimed at providing insights into public health risk of influenza in swine by monitoring pigs for avian influenza viruses and by comparison of these in swine and in human populations.

The areas specifically focused on the following objectives: Major changes in the influenza viruses circulating in European swine population. Antigenic and genetic SIVs evolution. Improving conventional diagnostic methods for SIV. Developing and validation of a novel and rapid assay for the detection of influenza A nucleic acid in swine tissue samples. Expanding the current Influenza virus Bank and the electronic data regarding epidemiology and diagnosis of SIV. An screening of the European swine population for avian influenza viruses and a comparison of the influenza situation in swine with that in humans and birds is also included in this
proposal. An ESNIP Mini symposium was held on 4-5 June 2008 in Gent. The final report will be available shortly.

SSPE-CT2004-513645 New and emerging technologies: improved laboratory and on-site detection of OIE List A viruses in animals and animal products LAB-ON-SITE. STREP with an EU contribution of 1 500 000 euro. Duration 01.11.2004 to 31.08.2008 (finished). Website www.labonsite.com

Participants:
- The National Veterinary Institute, Sweden
- The Queen’s University of Belfast, UK
- Danish Institute for Food and Veterinary Research, Denmark
- Universidad Complutense de Madrid, Spain
- Veterinary Institute of Debrecen, Hungary
- SVANOVA Biotech AB, Sweden
- Istituto Zooprofilattico Sperimentale della Lombardia e dell”Emilia Romagna, Italy
- Gent University, Belgium
- Institute for Animal Health, UK

The is a very comprehensive effort in diagnosis covering 9 list A diseases including FMD, CSF and highly pathogenic avian influenza and also including swine influenza. It aimed to develop, standardise and disseminate novel pen side procedures for OIE List A diseases that can be used by “first line” diagnosticians and to apply recent advances in technologies to the development, standardisation and dissemination of new rapid, sensitive and specific laboratory-based methods for these diseases.


Participants:
- Central Institute for Animal Disease Control, NL
- Agence Francaise de Securité Sanitaire des Aliments, France
- Australian Animal Health Laboratory, Australia
- Istituto Zooprofilattico Sperimentale delle Venezie, Italy
- Gent University, Faculty of Veterinary Medicine, Belgium
- Veterinary Laboratories Agency, DEFRA, UK
- Phillips Universität Marburg, DE
- Tierärztliche Hochschule Hannover, DE
- Institute of Virology and Immunoprophylaxis, CH
- Utrecht University, Faculty of Veterinary Medicine, NL
- Roslin Institute, UK
- The Hebrew University of Jerusalem, IL

The primary objective of FLUPATH is to increase understanding of the ecology and pathogenesis of avian influenza infections, and to use this knowledge for the prevention of avian influenza outbreaks and for outbreak management. Four distinct research areas are defined. The first addresses the issue of pathogen-host interactions and virulence determinants at the molecular level. The second is mainly concerned with studying the ecology and pathology of avian influenza strains in different host species. The third focuses on virus-receptor interactions with the goal to determine the role of receptor specificity and neuraminidase activity in interspecies transmission, pathogenicity and emergence of potentially new pandemic strains. The fourth workpackage focuses on the interaction of high- and low pathogenic viruses with the innate immune system and is primarily concerned with the identification of virulence factors that determine avian influenza virus pathogenesis and transmissibility.

SP5B-CCT-2006-044161 Innate immunity in influenza virus infection of mammalian airways FLUINNATE (STREP) EU contribution 1 436 130 €. Duration 01.01.2007 to 31.12.2009. Dedicated call on influenza. Website: www.fluinnate.org

Participants:
- Albert-Ludwigs-Universität Freiburg, DE
- Novartis Vaccines and Diagnostics, IT
The FLUINNATE objectives focus on the identification of influenza A virus genes and gene products which contribute to virulence/pathogenicity in experimental animal and tissue culture models. The required animals are available and will consist of mice with the wild-type Mx1 gene as part of the full innate immune response, various strains with targeted mutations in specific genes and pigs as natural hosts and 'mixing vessels' for influenza A viruses. In addition, human airway and porcine epithelial cell cultures will be established and characterised. Human airway epithelial cell cultures are a rare but most precious substrate to study the biology of influenza virus infection.

The influenza viruses used will be human, avian and swine strains, some of which will be generated by reverse genetics entirely from plasmids. Stock viruses and single and multi-segment reassortants will be produced and fully characterised together with the parental strains with respect to growth kinetics in tissue culture and in vivo, the capacity to induce or respond to interferon, and the capacity to induce disease or death in experimental animals. The technology for expressing, purifying and analysing the viral RNA polymerase complex will be established and further refined, as well as biochemical and biophysical approaches to identify co-purifying host cellular factors. Advanced tests for protein-protein interactions such as the yeast three-hybrid system will be set up and candidate interactors evaluated in functional tests, based on transfection experiments. The real-time RT-PCR methodology will be optimised for the analysis of interferon and cytokine responses and gene array data will be generated.

SSPE-CT-CT 2006-044212 Training and technology transfer of avian influenza and disease management skills FLUTRAIN (Coordination action) EU contribution 1 809 133€. Duration 01.03.2007 to 28.02.2010 – Dedicated call on influenza.
Website http://flutrain.captureclients.net/general.php

It foresees a comprehensive training and the transfer of technology to accession and INCO countries with the clear goal of aiding these countries in combating AI with the most up-to-date diagnostic and disease management procedures. The first goal is to organise several workshops over the duration of the project (3 years) that will call on experts in the influenza field to pass on their expertise in the diagnosis and management of influenza to participants from accession and INCO countries. Training opportunities are also provided in partner labs in order to consolidate the information and practical experience gained during the workshops. A website has been developed which will enable participants and the general public to access the training programs and will provide them with e-learning opportunities. The second goal of FLUTRAIN will be the transfer of technology to accession and INCO countries. This will include the provision of new, simplified and cost effective diagnostic approaches. It will also involve the transfer of deliverables, both for serological and virological diagnosis that have been or are being developed in other EU supported projects. Although the major thrust is on avian influenza, swine influenza is also included and discussions are being held with the coordinator in order to reinforce this area.

Participants
- Istituto Zooprofilattico Sperimentale delle Venezie, Italy
- Veterinary Laboratories Agency, DEFRA, UK
- Central Institute for Animal Disease Control, NL
- Veterinary and Agrochemical Research Centre, BE
- University of Ghent, BE
- Swedish University of Agricultural Science, SE
- Istituto Zooprofilattico di Brescia, Italy
- Danish Technical University, DK
- Università degli Studi di Padova, Italy
- Capture Productions Limited, IE
- Svanova Biotech AB, SE

FLU-LAB-NET aims at enhancing and reinforcing of the Community Reference Laboratory and National Reference Laboratory network for avian influenza (AI) within the EU.

The FLU-LAB-NET programme will strengthen harmonisation and development of laboratory and diagnostic methods, coordination of research efforts and sharing of expertise. Rapid responses to national and global emergencies with data sharing will be key areas of exploitation, contributing to a European laboratory task force capability for AI in animal species.

Rapid, formal interactive communications will be addressed through web-based forums. Laboratories involved in influenza research in domestic mammals will also participate. FLU-LAB-NET will also foster formal links and coordinate with corresponding human, swine and equine influenza networks. FLU-LAB-NET provides opportunities for identification and development of the complementarities of global, multi-disciplinary influenza research programmes. Strategically important third country and INCO partners are also included in this network, in order to raise laboratory standards and benefit from knowledge sharing. This will promote greater trust, understanding and early access to information that may be of importance to both veterinary and public health in the EU.

As well as public pages, FLU-LAB-NET communities provide private discussion forums for participating laboratories. Requests for registration should be channelled through member state FLU-LAB-NET representatives.

Participants: a total of 43 partners are involved among others GentUniversity

Other activities
A workshop on "Research in Swine Viral Diseases- Building Bridges" Shanghai, P.R. China 7-9 July 2008 included swine influenza among other viral diseases jointly organised by DG RTD, the Chinese Academy of Agricultural Sciences and the EU projects EPIZONE, PCVD, ASEMDIALOG and CONFLUTEC. http://www.epizone-eu.net/Lists/PublishedNewsItems/DispForm.aspx?ID=141