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Preventive Veterinary Medicine 110 (2013) 429–434

Contents lists available at SciVerse ScienceDirect

Preventive Veterinary Medicine

journal homepage: www.elsevier.com/locate/prevetmed

Influenza A(H1N1)pdm09 virus infection in Norwegian swine herds 2009/10: The risk of human to swine transmission

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ARTICLE INFO

Article history:
Received 19 September 2012
Received in revised form 4 February 2013
Accepted 11 February 2013

Keywords:
Influenza A(H1N1)pdm09 virus
Risk factors
Biosecurity
Pandemic influenza
Pigs

ABSTRACT

Influenza A viruses cause respiratory infection in humans and pigs, and some serotypes can be transmitted between these species. The emergence of influenza A(H1N1)pdm09 virus infections in the spring of 2009 quickly led to a worldwide pandemic in humans, with subsequent introduction of the virus to pig populations. Following a widespread infection in the human population in Norway, influenza A(H1N1)pdm09 virus was introduced to the influenza A naïve Norwegian pig population, and within a few months pigs in more than one third of Norwegian swine herds had antibodies against the virus. A cross-sectional study was performed on all swine nucleus and multiplier herds in Norway to analyze risk factors for introduction of infection, and the preventive effects of recommended biosecurity practices. A surveillance program provided information on infection status of the study herds, and a questionnaire was administered to all 118 nucleus and multiplier herds to collect information on herd variables. The surveillance program revealed that pigs in 42% of the herds had antibodies against influenza A(H1N1)pdm09 virus. The incidence of serologically positive pigs was similar in both multiplier herds (41%) and closed nucleus herds (43%). Multivariable logistic regression showed that presence of farm staff with influenza-like illness (ILI) (OR = 4.15, CI 1.5–11.4, $p = 0.005$) and herd size (OR = 1.01, CI 1–1.02, $p = 0.009$) were risk factors for infection. The rapid and widespread seroconversion for antibodies against influenza A(H1N1)pdm09 virus in the Norwegian pig population can be explained by the emergence of a novel virus that is readily transmitted between people and swine in a largely susceptible population of humans, and an entirely naïve population of pigs.

1. Introduction

In April 2009, a novel subtype of influenza A(H1N1) virus was detected in people in Mexico and the United States (Dawood et al., 2009). The new virus contained gene segments from both American and Eurasian swine lineages of influenza virus (Garten et al., 2009; Smith et al., 2009). The virus spread rapidly in the human population within the following months, and on 11 June 2009 the World Health Organization (WHO) declared the first pandemic of the 21st century (Chan, 2009).

The initial evidence on human-to-pig transmission of the novel influenza A subtype (H1N1)pdm09 virus was reported from Canada as early as April 2009 (Howden et al., 2009; Weingartl et al., 2010). During the next few months, spread of the new virus to pigs was described from countries all over the world, and several studies have shown the reverse zoonotic potential, i.e. transmission

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http://dx.doi.org/10.1016/j.prevetmed.2013.02.016

from infected humans to pigs, of influenza A(H1N1)pdm09 virus (Hofshagen et al., 2009; Lange et al., 2009; Brookes et al., 2010; Forgie et al., 2011). In a recent study, 49 different introductions of H1N1pdm09 virus from humans into swine were identified globally during 2009–2011 (Nelson et al., 2012). Furthermore, experimental studies have shown that pigs are highly susceptible to infection with influenza A(H1N1)pdm09 virus, and that the virus is transmitted readily between immune-naïve pigs (Lange et al., 2009; Brookes et al., 2010).

Influenza virus infection of pigs is associated with high morbidity within infected herds (up to 100%), but mortality is typically low (less than 1%) (Van Reeth et al., 2012). Experimental studies with influenza A(H1N1)pdm09 virus have shown the clinical signs of infection to include a sudden onset and short course of fever, inappetence, lethargy, coughing, dyspnea, and nasal discharge (Lange et al., 2009; Brookes et al., 2010). Recent reports of pigs naturally infected with influenza A(H1N1)pdm09 virus have shown more variation in morbidity and signs of disease (Howden et al., 2009; Forgie et al., 2011; Holyoake et al., 2011). In a Norwegian field study clinical signs of disease were generally mild, and in more than half of the infected herds no clinical signs were observed by the farmers (Grøntvedt et al., 2011). Influenza viruses can act synergistically with other viral and bacterial pathogens to cause porcine respiratory disease complex (PRDC) (Thacker, 2001; Kim et al., 2003; Hansen et al., 2010). The observed inter-herd variation of clinical signs of influenza-like illness (ILI) reported from Norway may have been influenced by synergistic co-infections, although the Norwegian pig population has documented freedom from important respiratory pathogens like Porcine Reproductive and Respiratory Syndrome Virus, Porcine Respiratory Coronavirus and *Mycoplasma hyopneumoniae* (Lium et al., 2012).

The first human cases of infection with influenza A(H1N1)pdm09 virus in Norway were recorded in early May 2009 among travelers returning from countries where the virus was circulating. A minor epidemic of infection in the human population occurred between July and August, and the peak of infection was reached during October and November the same year. From December onwards, the number of cases steadily decreased (Herrador et al., 2012). The first occurrence of influenza A(H1N1)pdm09 virus in a Norwegian swine herd was recorded on 10 October 2009 (Hofshagen et al., 2009). Prior to this the Norwegian pig population was documented free from swine influenza subtypes H1N1 and H3N2 (Lium et al., 2010). Within a few months the influenza A(H1N1)pdm09 virus had spread to more than one third of swine herds in the country, including closed nucleus herds with high levels of biosecurity (Gjerset et al., 2011). This indicated risk factors for infection other than the import of live pigs into the closed nucleus herds. The national surveillance programme for specific virus infections in swine for 2010 showed that 41% of herds tested had antibodies against influenza A(H1N1)pdm09 virus, while 48% were seropositive in 2011 (Lium et al., 2012). This strongly indicates that influenza A(H1N1)pdm09 virus is established as an endemic infection in the Norwegian swine population.

The aim of this study was to identify risk factors associated with the introduction of influenza A(H1N1)pdm09 virus into naïve Norwegian nucleus and multiplier pig herds during the outbreak in 2009/2010, and to evaluate the preventive effects of commonly practiced biosecurity measures in the initial phase of the outbreak.

2. Materials and methods

2.1. Study population

The study population included all 118 Norwegian nucleus and multiplier herds and was identified using a computerized data base from the Norwegian Pig Health Service. They were all farrow-to-finish herds.

2.2. Laboratory methods

All herds in the study population were tested serologically for influenza A specific NP antibodies by ELISA (ID Screen® Influenza A Antibody Competition test, IDVET, Montpellier, France, according to manufacturer's instructions) and samples tested positive in the ELISA were retested for hemagglutinating antibodies using hemagglutination-inhibition (HI) assays according to the method described in the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Office International des Epizooties, 2008). In addition, where there was suspicion of an active infection due to reported clinical signs in pigs or humans with pig contact, herds were tested for presence of viral RNA by real-time reverse transcription polymerase chain reaction (rRT-PCR) (World Health Organization. The WHO Collaborating Centre for influenza at CDC Atlanta, 2009; Robert Koch-Institut, 2011).

2.2.1. Study design and case definitions

The study was designed as a cross-sectional study, and the observation period (30 September 2009 until 31 October 2010) lasted from before the detection of the first case to the distribution of the questionnaires. The national surveillance program provided documentation on the historic freedom from swine influenza viruses (Lium et al., 2010). The outbreak of influenza A(H1N1)pdm09 virus prompted an extraordinary surveillance program, where a larger screening of the population was initiated using serological laboratory methods to monitor the virus exposure in the herds. All the nucleus and multiplier herds were included in this serological screening. In additions, herds with suspicion of an active infection were tested for the presence of viral antigens. The main diagnostic criterion for a positive herd was having at least one virus positive sample or three or more blood samples (out of 20 or more) positive for antibodies against influenza A virus. If only one or two of the first 20 samples from a herd were seropositive, the herd was retested with blood samples from 20 previously untested pigs, and concluded positive if at least one of these samples were positive. The number of samples collected from each herd was based on an expected within-herd prevalence of 20%. Data from the initial phase of the Norwegian outbreak showed within-herd prevalence ranging from 5 to 100% (mean 59%) (Gjerset et al., 2011). The

Table 1
Classification and description of variables in the questionnaire collected by telephone interview in a cross-sectional study from118 Norwegian nucleus and multiplier farms.

Variable group	Variable subgroup	Variable description
Demographics	Farm details	Contact information of farmer, address, contact information of veterinarian.
Herd characteristics	Type of production	Nucleus herd (self-replacement), multiplier herd (self-replacement, purchase replacement).
	Size of production	Number of breeding animals, number of litters per herd and year, number of litters during study period of 18 months.
	Management	Farrowing system, type of batch farrowing, all in–all out practice in different stages of production.
	Trade of live animals	From nucleus herds to multipliers (replacement gilts) and commercial herds (growers or fatteners). From multipliers to commercial herds only (replacement gilts, growers or fatteners).
Health status	Pig health status	Disease status as perceived by the farmer; occurrence, severity, duration and proportion of coughing, sneezing, depression, fever, loss of appetite and/or increase in reproductive disturbances.
	Human health status	Date and occurrence of human influenza-like illness in farmer, close family, staff, veterinarian and/or visitors; confirmation on diagnosis by physician, confirmation on diagnosis by laboratory testing.
	Human vaccination	Date of vaccination against influenza A(H1N1)pdm09 in farmer, close family, staff, veterinarian and/or visitors; vaccination before or after observation of clinical signs in pigs.
Biosecurity	Live animal transport	Farmer owned vehicle, slaughterhouse owned vehicle, co-transport to/from different herds, routines of washing and disinfection of vehicles between transports (every time, occasionally, never), presence of live animals in transport vehicle on arrival at farm. Separate room for animals before loading onto transport. Separation of animals sold as live animals, or sold for slaughter. Ramp for loading animals onto transport vehicle, with at least one door closed to remaining animal housing.
	Prevention of pathogen introduction by farmer, staff, veterinarian and/or visitors	Extent and frequency of animal contact by farmer, staff, veterinarian and visitors. Design and use of physical hygiene barrier in pig house entrance; change of footwear and/or coveralls; handwashing and/or hand disinfection; disposable gloves; disposable facemask; use and duration of human quarantine after travel abroad. Alterations in any of these measures before and after influenza outbreak.
	Prevention of pathogen introduction by animals	Type, duration and extent of quarantine of introduced animals, multisite quarantine, separate ventilation, separate manure handling.

sample size selected provides a 94% confidence of detecting a within-herd prevalence of 0.2 by using a test with 95% sensitivity (Tse et al., 2012).

2.3. Herd data

A questionnaire of 137 questions (123 were closed) was created to record name and contact information for the farmer, husbandry information on the herds, the health status of humans and pigs, and biosecurity measures practiced. All variables collected by questionnaire are shown in Table 1.

The questionnaire was distributed by surface mail in mid-November 2010. Enclosed with the questionnaire was a letter encouraging the farmers to familiarize themselves with the questions, and informing them that they would be invited to answer the questionnaire in a telephone interview within the weeks that followed. The interviews were performed by the first author during a period of 7 weeks between November 2010 and January 2011. A paper copy of the questionnaire was used to register the answers for each interview.

2.4. Data analysis

2.4.1. Software

Unless otherwise specified, all data handling and statistical analysis were conducted using Stata Version 12 (Stata-Corp, College Station, TX, USA).

2.5. Statistical analysis

2.5.1. Definition of the outcome and explanatory variables

The herd was the unit of analysis and status of influenza A(H1N1)pdm09 virus infection was the binary outcome variable for the statistical analyses. A causal diagram was constructed, hypothesizing humans with influenza-like illness in close contact with pigs as the primary predictor, with secondary and potentially interactive predictors grouped under herd characteristics and biosecurity. Univariable analysis was performed for these predictors (Table 1) to measure the association with the outcome variable by calculating odds ratios (OR) and their statistical significance (Fisher exact test). Continuous variables were

tested by univariable logistic regression after their linearity with the logit of the outcome were confirmed using lowess curves, and normality was assessed using graphical methods.

2.5.2. Variables without values

Missing values occurred for some of the variables because they were not applicable to a particular herd. For example, questions on relief workers had no values recorded in herds where relief workers were not employed. Such a variable was combined with other similar variables to form a combined variable for the multivariable model to preserve maximum degrees of freedom and representation. For example, farmers were combined with workers and relief workers to form a new variable called "humans in frequent direct contact with pigs".

2.5.3. Building the multivariable logistic regression model

A multivariable logistic regression model was constructed to predict the likelihood that a herd would be infected (Dohoo et al., 2009). The parsimonious model was built by forward selection. Inclusion criteria for building the multivariable model were predictors that showed significant association (Wald statistics) with the binary outcome in the univariable analysis. Due to the large number of risk factors evaluated, in order to decrease the Type 1 error rate, the alpha level for significance was lowered to 0.01. Confounding was checked by observing whether there was a change of at least 30% to the ORs or coefficients of existing predictors when a new predictor was added. To assess the quality of the final model's fit with the data, the Hosmer–Lemeshow goodness of fit diagnostics and LROC curves were used.

3. Results

Farm personnel (mainly farm owners) from all 118 herds answered the questionnaire, giving a response rate of 100%. Three herds were excluded from the statistical analyses because of uncertain infection status at the time of the study, leaving the study with 115 herds comprising 47 nucleus herds and 68 multiplier herds. A total of 20 (43%) nucleus herds and 28 (41%) multiplier herds were classified as positive for influenza A(H1N1)pdm09 by the diagnostic criteria previously described. This gave 48 positive herds and 67 negative herds for the study. Chronological data on presence of clinical signs of ILI from both humans and pigs were reported from 14 of the 48 positive herds. Twelve (85.7%) of these 14 herds had ILI in humans occurring before the pigs began to show typical signs of influenza infection. The median time between occurrences of clinical signs in humans and in pigs was 21 days.

3.1. Multivariable analysis

In the final logistic regression model, the primary predictor of human ILI in farm staff (farmer, farm worker or relief farm worker) (OR = 4.15, CI 1.5–11.4, $p = 0.005$) was associated with positive herd status. In addition, risk of infection increased with herd size (OR = 1.01, CI 1–1.02, $p = 0.009$) represented by number of sows per year.

The area under the ROC curve was 0.71 and goodness of fit statistics such as Pearson (Chi-square = 49, $p = 0.52$) and Hosmer–Lemeshow (Chi-square = 6.72, $p = 0.56$) suggest an acceptable fit of the model. At the predicted probability of 0.5 as cut point, about 65% of the farms were correctly classified, which indicated that the model had limited predictive ability.

4. Discussion

Before the introduction of influenza A(H1N1)pdm09 virus the Norwegian pig population was documented naïve to influenza A viruses and pigs were not vaccinated against influenza infection (Lium et al., 2010). Thus no protective or cross-protective immunity was present at the time of introduction of the novel virus, and the pigs were assumed to be highly susceptible to the infection. The following routes of introduction of influenza A virus into pig herds have to be considered when identifying and assessing possible risk factors: direct or indirect contact with infected host (animal or human), animate or inanimate vector or potentially airborne spread of virus by aerosols (Tellier, 2006, 2009; Torremorell et al., 2012). There is no evidence that influenza virus in pigs is transmitted through semen (Torremorell et al., 2012).

The results of this study show that ILI among farm staff was identified as the most important risk factor associated with introduction of influenza A(H1N1)pdm09 virus to the swine herds in the initial phase of the outbreak. The hypothesis of people as the primary source of infection to the Norwegian nucleus and multiplier herds was strengthened by chronological information. In 14 herds with dates on occurrence of ILI in both humans and pigs, 12 herds reported human ILI preceding signs of infection in the pigs.

Size of production (as indicated by the number of sows) was the only other risk factor (OR 1.01, $p < 0.01$) remaining after multivariable analysis, indicating an increased risk of infection by increasing herd size. Typically, the number of contacts (people, vehicles, and animals) increases with herd size. In the reverse zoonotic situation, an increase in human to pig contacts might be one of the possible explanations on the effect of herd size.

The relative importance of humans as the main source of introduction is likely reduced as the circulation of influenza A(H1N1)pdm09 virus in the human population in Norway has been low in the two influenza seasons that have passed since 2009/10 (Folkehelseinstituttet, 2011, 2012). In addition, human immunity rapidly increased due to vaccination and natural infections. In herds where a positive diagnosis of infection with H1N1pdm09 was established by detection of virus or suspected by the presence of clinical signs of pig ILI, restrictions on animal movement were implemented by the Norwegian Food Safety Authority. This might also have contributed to reducing spread of disease between individual herds. However, the preventive effects of restrictions on animal movement was likely to be limited at the population level because in 60% of positive herds, farm personnel did not detect or report any signs of influenza in pigs, and thus were not subject to restrictions (Grøntvedt et al., 2011).

Biosecurity practices and pig vaccination are considered the primary means of preventing or minimizing transmission of influenza A virus in pigs and from pigs to other species (Torremorell et al., 2012). In the Norwegian pig population the documented freedom from influenza infection and the presence of an active serological surveillance program has led to a strict no-vaccination policy determined by the Norwegian Food Safety Authority. The multivariable analysis in this study failed to find any statistically significant protective effect of the recommended biosecurity measures. This apparent lack of protective effects may have several explanations in addition to the possibility of actual failure in protectiveness. The degree of compliance and implementation of recommended biosecurity measures varied, especially recommendations given in context with the disease outbreak like the use of disposable gloves and disposable facemasks. In addition, reliable information on the time of implementation of such biosecurity measures relative to the time of herd infection was difficult to ascertain (Grøntvedt et al., 2011).

The herd sizes in Norway are generally small and they have few farm personnel. This may in turn lead to difficulties having substitute farm workers available in cases of illness in the regular staff and thus forcing staff with ILI to work in close contact with susceptible animals despite their illness, challenging the biosecurity routines. This impression was verified by respondents' remarks during the telephone interviews in this study. Human vaccination in Norway started on 19 October 2009 with an AS03 adjuvanted monovalent vaccine against influenza A(H1N1)pdm09 (Pandemrix®, GlaxoSmithKline Biologicals s.a., Rixensart, Belgium). Vaccination of personnel in close contact with swine production was recommended by the Norwegian Institute of Public Health on 23 October (Folkehelseinstituttet, 2009; Herrador et al., 2012). By 26 October, a positive diagnosis for influenza A(H1N1)pdm09 had been verified for 23 out of 51 (45.1%) tested herds (Hofshagen et al., 2009). By the end of 2009, 35.8 per cent (91/254) of all herds tested in Norway were positive for A(H1N1)pdm09 virus (Gjerset et al., 2011). Although there was a high compliance of vaccination among farm personnel in the present study (range 70.4–91.2%), the possible protective effects on human-to-pig transmission was likely reduced due to late implementation. For preventive practices to have effect, they need to be established in advance of exposure.

The questionnaires were conducted by a single interviewer with personnel working directly on the farm to reduce information bias. Information bias was also reduced in the interview by the opportunity to clarify misunderstanding of questions. Confidentiality of results was guaranteed to reduce information bias, as information on relevant variables was reported by the respondents and not by direct observation. The respondents were given a pre-defined case definition of influenza-like illness (fever, malaise, coughing and sore throat) at the appropriate time during the telephone interview to reduce misclassification of human ILI. The outcome criteria as positive and negative were based mainly on serological data, where positive ELISA tests for influenza A virus antibodies were confirmed with a HI test for influenza A(H1N1)pdm09 virus specific antibodies to optimize specificity. In addition, detection of viral antigens was used to strengthen the diagnosis in herd with clinical signs of ILI in pigs or humans with pig contact.

Recall bias is a potential challenge in retrospective studies, and the interviews in this study were performed approximately 1 year after the disease outbreak. However, the incursion of a previously undiagnosed infectious disease in the Norwegian pig population, combined with a concurrent pandemic outbreak in humans and the continued attention by public and veterinary health authorities and media would likely lead to a heightened awareness and recollection among farmers. In addition, the nucleus and multiplier herds are obliged to keep written records on all medical treatments of pigs.

5. Conclusion

The introduction of influenza A(H1N1)pdm09 virus to Norway led to a unique situation where highly susceptible human and naïve pig populations were exposed to a virus that readily transmits between humans and pigs. In conclusion, this study shows that the most important risk factor in the initial phase of the epidemic was farm personnel with ILI, with herd size as a secondary risk factor. Therefore, the critical preventive measure to avoid introduction of influenza A(H1N1)pdm09 virus was to enforce strict prohibition of access for people with ILI. The results of this study could indicate that transmission from infected humans in direct contact with susceptible pigs was likely to occur irrespective of the implementation of recommended biosecurity measures in the initial phases of the influenza A(H1N1)pdm09 outbreak.

Conflict of interest

None.

Acknowledgements

The authors sincerely thank all the farm personnel of the Norwegian nucleus and multiplier herds who responded to the questionnaire. The authors are grateful to Mrs. Cathrine Hexeberg of the Norwegian Pig Health Service who contributed to the development of the questionnaire. The authors would like to acknowledge the input on the data analysis from Prof. Ane Nødtvedt.

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