Transboundary and Emerging Diseases

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ORIGINAL ARTICLE

One-Health Simulation Modelling: A Case Study of Influenza Spread between Human and Swine Populations using *NAADSM*

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Summary

The circulation of zoonotic influenza A viruses including pH1N1 2009 and H5N1 continue to present a constant threat to animal and human populations. Recently, an H3N2 variant spread from pigs to humans and between humans in limited numbers. Accordingly, this research investigated a range of scenarios of the transmission dynamics of pH1N1 2009 virus at the swine–human interface while accounting for different percentages of swine workers initially immune. Furthermore, the feasibility of using *NAADSM* (North American Animal Disease Spread Model) applied as a one-health simulation model was assessed. The study population included 488 swine herds and 29, 707 households of people within a county in Ontario, Canada. Households were categorized as follows: (i) rural households with swine workers, (ii) rural households without swine workers, and (iii) urban households without swine workers. Forty-eight scenarios were investigated, based on the combination of six scenarios around the transmissibility of the virus at the interface and four vaccination coverage levels of swine workers (0–60%), all under two settings of either swine or human origin of the virus. Outcomes were assessed in terms of stochastic 'die-out' fraction, size and time to peak epidemic day, overall size and duration of the outbreaks. The modelled outcomes indicated that minimizing influenza transmissibility at the interface and targeted vaccination of swine workers had significant beneficial effects. Our results indicate that *NAADSM* can be used as a framework to model the spread and control of contagious zoonotic diseases among animal and human populations, under certain simplifying assumptions. Further evaluation of the model is required. In addition to these specific findings, this study serves as a benchmark that can provide useful input to a future one-health influenza modelling studies. Some pertinent information gaps were also identified. Enhanced surveillance and the collection of high-quality information for more accurate parameterization of such models are encouraged.

Introduction

The on-going threat of an influenza pandemic emerging in people was highlighted with the novel pandemic H1N1 influenza virus (pH1N1) in 2009. The pH1N1 was first reported in March to April of 2009 in Mexico, and spread rapidly across the world (Centers for Disease Control and Prevention (CDC), 2009; Fraser et al., 2009; WHO, 2009). By 11 June 2009, a full-scale pandemic was declared by the World Health Organization (WHO, 2009). Molecular analyses showed that the virus was genetically similar to contemporary viruses circulating in swine, based on livestock surveillance data in different continents (Garten et al., 2009; Smith et al., 2009). However, the origin of the

virus and the exact host species involved in the reassortment remains unknown.

The first detection of pH1N1 in swine was reported from the province of Alberta, Canada in May of 2009 (OIE, 2009). It was introduced into the herd by an employee (i.e. human to animal spread of pH1N1), who had recently returned from a vacation in Mexico (Howden et al., 2009). Swine-to-swine transmission of pH1N1 was subsequently demonstrated in several experimental (Itoh et al., 2009; Lange et al., 2009; Vincent et al., 2010; Brookes et al., 2010) and observational studies (Howden et al., 2009; Lange et al., 2009; Pasma and Joseph, 2010). By April of 2010, 20 different countries had reported outbreaks of pH1N1 in swine (Hofshagen et al., 2009; OIE, 2009–2010; Moreno et al., 2010; Pasma and Joseph, 2010; Pereda et al., 2010; Song et al., 2010; Sreta et al., 2010; Welsh et al., 2010; Forgie et al., 2011). Although the respective sources of many of these outbreaks remain unknown, some were confirmed (Norway, in addition to Canada), or were suspected (Finland, Iceland and Russia) of having involved human-to-swine transmission (Hofshagen et al., 2009; Howden et al., 2009; Forgie et al., 2011). In the light of these reports of pH1N1 outbreaks in swine in several countries, it is surprising that no studies have reported either temporal or temporo-spatial spread of the virus between swine farms (Dorjee et al., 2013a; Torremorell et al., 2012). Immediately after the reported outbreaks of pH1N1 in swine in Canada, restrictions on the export of live pigs and pork were imposed by several countries (Lynn, 2009; Reuters, 2009). Even without significant documented spread of pH1N1 from swine to humans, the social and economic consequences arising from the subsequent trade restrictions were devastating. Accordingly, zoonotic influenza A viruses are of interest to animal and public health authorities, given their significant implications for public health, animal health and trade.

Influenza pandemics remain a major zoonotic threat to mankind, occurring over intervals of one to four decades since 1918 (Brown, 2000; Ma et al., 2009; Zimmer and Burke, 2009). Since the first report of transmission of the H1N1 1918 virus from humans to pigs (Shope, 1931), the transmission of influenza A viruses back and forth between people and swine has been well documented (Hinshaw et al., 1978; Easterday, 1980; Dacso et al., 1984; Myers et al., 2007). There is much evidence of reassortments of swine, human and avian influenza viruses occurring in pigs in Europe (Brown et al., 1998) and in North America (Zhou et al., 1999; Karasin et al., 2000; Lekcharoensuk et al., 2006; Olsen et al., 2006). The transmission of influenza viruses from pigs to people has been reported in a number of studies (Brown, 2000; Myers et al., 2007; Robinson et al., 2007; Ma et al., 2009; Zimmer and Burke, 2009). Recently, the transmission of the H3N2 variant from pigs-to-humans, and a subsequent limited spread between humans, was reported in the US (Lindstrom et al., 2012). Based on the findings of this study, swine should be considered potential hosts for the emergence of novel pandemic influenza strains. Cross-sectional serological studies found that those employed in occupations involving direct contact with pigs (e.g. swine farmers, veterinarians, abattoir workers) are at higher risk of zoonotic influenza infection. Swine farmers are relatively at higher risk than veterinarians and abattoir workers (Olsen et al., 2002; Myers et al., 2006). The shift to large-scale swine operations involving frequent restocking of young susceptible pigs has facilitated the persistence of influenza viruses in herds (Vincent et al., 2008; Gray and Baker, 2011). The persistent transmission pressure between swine and those working with pigs in commercial enterprises increases the opportunity for zoonotic spread of novel influenza viruses (Myers et al., 2006). This being the case, it is important to understand the transmission dynamics of influenza at the swine–human interface, to devise intervention strategies.

Recently, mathematical models and simulation tools have been developed to study the spread and control of influenza among human (Longini et al., 2004, 2005; Flahault et al., 2009; Gojovic et al., 2009) and avian (Le Menach et al., 2006; Guberti et al., 2007; Tiensin et al., 2007) populations. A small number of studies have investigated the spread of influenza from birds to birds and from birds to humans (Arino et al., 2007; Iwami et al., 2007; Kim et al., 2010), whereas to the best of our knowledge, only one study investigated the spread of influenza within and between swine and human populations simultaneously (Saenz et al., 2006).

Given, (i) the impact of influenza on human health and the economy, (ii) the importance of swine in the generation of novel influenza viruses, and (iii) the utility of models in providing a better understanding of disease transmission and control dynamics; it is imperative to investigate key parameters influencing the spread and the effectiveness of mitigation strategies against influenza at the swine–human interface through simulating a range of possible scenarios. Such information can be used to guide the development of contingency measures to prevent and control the emergence of future influenza pandemics.

Different types of models, ranging from simple deterministic differential equation model (also referred to as system dynamic/compartmental or mathematical model) (Mills et al., 2004; Arino et al., 2008; Brauer, 2008) to complex stochastic agent/individual-based models (microsimulation models) (Germann et al., 2006; Carpenter and Sattenspiel, 2009; Lee et al., 2010a; Yang et al., 2009; Tsai et al., 2010) are used for different diseases in human and animal populations. Some individual-based models also incorporate contact network (Ajelli and Merler, 2008;

Davey et al., 2008; Chao et al., 2010) and spatial locations explicitly (Sanson, 1993; Morris et al., 2002; Garner and Beckett, 2005; Harvey et al., 2007; Patyk et al., 2013; Stevenson et al., 2013). For detail review of modelling approaches in animals and humans, readers can refer to the following references (Kao, 2002; Keeling, 2005; Dorjee et al., 2013a). A number of computer software have been developed to implement microsimulation models to assess the spread and control of highly contagious animal diseases, such as *AusSpread* (Garner and Beckett, 2005), *InterSpread Plus* (Stevenson et al., 2013) and *NAADSM* (Harvey et al., 2007; *NAADSM Development Team,* 2008). To date, these tools have been used to model single or multiple livestock species but have not attempted to incorporate spread between domestic animal and human populations. Most published models used to study spread of diseases among domestic livestock populations use the herd, rather than the individual animal, as the unit of interest. In contrast, most models used to study influenza spread among people use the individual, rather than the household or group of people as the unit of interest. However, a few studies in humans have investigated the spread and control of influenza at the individual household level (Wu et al., 2006; Fraser, 2007; Shaban et al., 2009). The *NAADSM* disease modelling framework was originally developed to accommodate different parameters of disease spread between different types of livestock herds or flocks (e.g. dairy cattle, versus beef cattle, versus swine, versus sheep versus goats in the spread of foot and mouth disease) (Harvey et al., 2007). While the concept of using *NAADSM* to model households of people as a type of 'herd' was not originally envisioned in development, it was subsequently proposed by McNab (McNab 2009, personal communication). This approach provided the opportunity to model the interface of the spread and control of zoonotic diseases within and between groups of animals and people under certain simplifying assumptions.

The overall objective of this study was to identify the relative importance of disease transmission parameters affecting the spread and control of contagious pathogens shared between people and swine, using influenza as an example. Specific objectives included: (i) investigation of the feasibility of using *NAADSM* as a tool to model the spread and control of zoonotic diseases; (ii) a study of the transmission dynamics of influenza at the swine–human interface using characteristics of pH1N1 as an example; and (iii) an investigation of the utility of applying targeted vaccination against influenza at the animal–human interface. We chose to use pH1N1 as our example of zoonotic pathogen due to the fact that: (i) it is readily transmissible between humans, swine, and human and swine populations, (ii) information about the biology of this virus is relatively abundant, and (iii) there were several questions arising from pH1N1 concerning its dynamics at the human–swine interface.

Materials and Methods

Study area and populations

A county within the province of Ontario, Canada with a relatively high density of swine farms along with the existence of a range of rural and urban areas (one small city and four towns) was selected for this study. The following spatially explicit units were included as 'production types' in the models: (i) swine herds (SH), (ii) rural households with at least one swine worker (SWH), (iii) rural households with no swine workers (RH), and (iv) urban households without swine workers (UH). Swine workers (owners/managers/labourers of swine farms) served as the bridging population for pH1N1 transmission between swine and human populations. Population data to ensure a representative mixture of each type of unit within the model were extracted from the 2006 official census of Statistics Canada (Statistics Canada, 2007c,f). A total of 488 SH with 664 508 pigs were recorded in the census year of 2006 for the county. As only the aggregate number of SH and pigs were available at the census consolidated subdivision level, the number of animals per farm in the model was generated using a uniform distribution with minimum and maximum values of 500 and 2500 animals, respectively, ($\pm$ 4 standard deviation from a mean of approximately 1500 animals). The number of SWH was approximately 1.5 times the number of SH, based on the data for swine operators and agricultural labourers (general figure not reported by enterprise type) recorded in the 2006 official census. A total of 25 297 people in 8612 rural households were reported in this county. Therefore, an appropriate number of RH (7879) was generated by subtracting the number of SWH (733) from the total rural households. The numbers of UH and people recorded in the five urban areas were as follows: City A – 13 316 households with 30 461 people; Town B – 2733 households with 6617 people; Town C – 2731 households with 6303 people; Town D – 1714 households with 4220 people; and Town E – 601 households with 1446 people. A Poisson distribution with a mean of three and truncated at two and seven for SWH (Statistics Canada, 2007b), and one and six for RH and UH were assumed for the number of people living in each household as per the census record (Statistics Canada, 2007e). The final study population units and respective unit sizes are presented in Table 1.

Swine farm and household locations

Digital vector maps delineating the boundaries of rural and urban areas of this county were obtained from Statistics

Table 1. Description of study populations and probability density functions of the size of units used for the simulation of influenza spread between swine and human populations in a country of Ontario, Canada

Population units	Total no. of units	Distribution of size of units	Total no. of individuals
Swine herds (SH)	488	Uniform (min = 500; max = 2500)	733 107
Swine-worker households (SWH)	733	Truncated Poisson (mean = 3, min = 2; max = 7)	2325
Rural non-swine-worker-households (RH)	7879	Truncated Poisson (mean = 3, min = 1; max = 6)	25 521
Urban households(UH)	21 095	Truncated Poisson (mean = 3, min = 1; max = 6)	54 038
Total	30 195		814 991

Canada (Statistics Canada, 2007a,d). As the specific geographic coordinates of SH, SWH and RH were not available in the official census data, their locations were randomly distributed spatially within the agricultural areas of the county using a Geographic Information System. A minimum distance of one kilometre was specified between swine herds. Swine-worker household locations of owners/managers and labourers were generated within the radii of 100–300 and 300–500 metres of SH, respectively. Although some swine workers stay in towns, it was done to restrict the contact of a SWH to a specific farm for all iterations. This was achieved by also specifying the maximum contact distance between SWH and SH to 0.5 km. RH locations were generated randomly in agricultural polygons with the additional constraint that they must be outside a 500 m radius of any SH and at least a distance of 10 m away from any other household. Similarly, locations of UH were randomly distributed within the five urban boundaries, specifying a minimum distance of 10 m between any two households. All spatial data manipulation and random spatial locations were generated using Quantum GIS (QGIS) version 6.1.0 (Open Source Geospatial Foundation Project. http://qgis.osgeo.org).

Model structure

North american animal disease spread model (NAADSM)

The supercomputer version of the *NAADSM* 3.1.24 (*NAADSM Development Team,* 2008) was used for the construction and simulation of models for pH1N1 spread in swine and human populations. The *NAADSM* is an agent-based platform that simulates the spread of diseases in populations using stochastic, spatially explicit, state-transition methods. The epidemiological unit of interest within *NAADSM* is an aggregation of animals managed together as a single unit at a single geographic location, typically as herd or flock. The platform was developed to simulate the spread and control of contagious animal diseases (e.g. foot and mouth disease) between spatially explicit groups of animals, either of the same or different species and production types. It is flexible in the manner in which users can define the spread of a disease between different pairs of units (e.g. dairy cattle to beef cattle; swine farrowing operation to swine grower/finisher operations, etc.). It models disease transmission between farms by direct contact (through movement of live animals between farms), indirect contact (through the movement of people and contaminated fomites) as well as airborne and local area spread. The local area spread feature enables to specify other mechanisms of disease spread locally through insects, pests, spread between animals of two adjacent farms across the fence and lapses in biosecurity measures (Reeves et al., 2012). It has provisions to quantify the predicted number of infected places arising from a number of different disease intervention strategies, such as quarantine and movement control, vaccination, depopulation and zoning. Each unit is initially assigned attribute data, including: a unique unit ID; the type of unit (e.g. dairy, beef, swine, etc.); number of animals in that unit; location of the unit (i.e. point geocoordinates in longitude and latitude); and disease transition state. A detailed description of *NAADSM* has been provided by Harvey et al. (2007) and Hill and Reeves (2006).

Disease states

A susceptible-exposed-infectious-recovered (SEIR) model structure was used for each of the types of epidemiological units of interest described in this study. Susceptible units were herds or households susceptible to infection but not infected; exposed/latent units were those that had been infected but were not shedding organisms; infectious units were units shedding organisms, while recovered units were those that had recovered and were immune to further infection. The unit-level latent period was assumed equal to the time from the first individual within the unit became infected to the time when the first individual transited to the infectious state. The unit remained in the infectious state from the time when the first individual within the unit became infectious to the time until the last individual in that unit transited to the recovered state. Therefore, the unit-level latent period was equal to the duration of individual-level latent state, whereas a unit-level clinical infectious period varied with the size of the infected unit. Following infection, a susceptible unit transited through the subsequent disease states beginning on the day following infection in a cyclic fashion in the absence of any

intervening control measures, such as vaccination or depopulation. The duration of each of these disease states for any particular unit type was either based on a fixed value or was chosen stochastically from the defined probability distribution as described in the model parameters section below. Permanent immunity was simulated by setting a naturally immune duration which exceeded the duration of the simulated period (365 days).

Disease transmission

To investigate the transmission dynamics of pH1N1 between swine and human populations, its spread was simulated between different combinations of pairs of unit types as follows: (i) amongst swine herds (SH to SH), (ii) between SH and SWH, and (iii) among SWH, RH and UH, simultaneously. The influenza transmission among swine herds was simulated by both direct and indirect contacts, while the spread between SH and SWH, and among households occurred only through direct contact. A latently infected SH unit was also assumed infectious to other susceptible SH units by direct contact as shipment of latently infected pigs to susceptible units would most likely result in transmission of infection. In all other cases only the infectious units would transmit the infection to the susceptible units. For the disease spread from SH to SWH and *vice versa*, direct contacts were assumed to have occurred when the swine workers came in contact with pigs on farms (SH) during the course of their daily work. To ensure that each SWH was assigned to a specific farm throughout the simulation, a movement distance restriction zone of uniform distribution between 100 and 500 m was created as per the synthetically generated locations of SWH described above.

For influenza spread among households, a direct contact was assumed to have occurred implicitly when an individual from an infectious household established contact with individuals at any place, such as schools, workplaces or other areas where individuals congregate. Individuals who become infected as a result of contact with an infectious person outside their home could, in turn, infect individuals within their home and outside of their home. Similar assumptions have been made in modelling influenza spread at the household level (Wu et al., 2006; Fraser, 2007; Shaban et al., 2009). The influenza transmissions between infectious and susceptible units through direct and indirect contacts were simulated as a function of contact rate, the probability of infection per contact and movement distance distribution between the units.

Model parameters

Duration of disease states

Parameters for both the individual- and unit-level duration of the different disease states for swine and human populations are presented in Tables 2 and 3 respectively. The individual level parameters for swine and human populations were extracted from the published literature (references are

Table 2. Parameters and their probability density functions for swine farms used in the simulation of influenza spread between swine and human populations in a county of Ontario, Canada

Input parameters	Individual	Herd level	References
Latent period (day)	1[a]	Fixed value of 1[b]	[a](Brookes et al., 2010; Lange et al., 2009; Vincent et al., 2010);
Subclinical infectious (day)	0–6[a]	BetaPERT(0, 3, 6)[b]	[b]Generated from the individual-level parameters using WH 0.9.5 software†;
Clinical infectious (day)	1–15[a]	BetaPERT (5; 25;45)[b]	[c](Blaskovic et al., 1970; Desrosiers et al., 2004);
Immune period (day)	365–840[c]	Fixed value 366[d]	[d]Assumed permanent immunity by using a value greater than the duration of the simulation period (365 days)

†WH 0.9.5 is the software that simulate within-herd disease transmission stochastically and generates herd-level durations of disease states (A. Reeves, M. Talbert, M. D. Salman, and A. E. Hill, submitted). Parameters were extracted from the references with the same superscripts.

Table 3. Parameters and their probability density functions for households used in the simulation of influenza spread between swine and human populations in a county of Ontario, Canada

Input parameters	Individual	Household	References
Latent period (day)	1–3[a]	BetaPERT (1, 2, 3)[b]	[a](Pourbohloul et al., 2009; Boëlle et al., 2009; Tuite et al., 2010);
Subclinical infectious (day)	0–3[a]	BetaPERT (0, 2, 3)[b]	[b]Generated from the individual-level parameters using WH 0.9.5 software†;
Clinical infectious (day)	4–10[a]	BetaPERT (4, 12, 20)[b]	[c]Assumed permanent immunity by using a value greater than the duration of the simulation period (365 days)
Immune period (day)	–	Fixed value of 366[c]	

†WH 0.9.5 is the software that simulate within-herd disease transmission stochastically and generates herd-level durations of disease states (A. Reeves, M. Talbert, M. D. Salman, and A. E. Hill, submitted). Parameters were extracted from the references with the same superscripts.

provided in tables). As no information on clinical infectious period existed at the herd or household levels, they were generated from the individual-level parameters using the *WithinHerd* (*WH*-within-herd disease spread model) software version 0.9.5 (A. Reeves, M. Talbert, M. D. Salman, and A. E. Hill, submitted). This is a stochastic modelling framework that simulates the within-unit disease spread and generates the unit-level durations of disease states. The same swine and household populations were used for the within-unit influenza spread simulations. A BetaPERT distribution (which was the best fitting probability distribution for clinical infectious duration based on the outputs of the within-herd transmission model) based on the minimum, mode and maximum values of 100 iterations of the within-unit spread models of swine herd (except for latent period for which a fixed value of 1 day was assumed) or household populations were then used for *NAADSM* models. The durations of immunity period for SH and households were assumed to be permanent as immunity to specific strain of influenza viruses are long lasting.

Contact frequencies

Daily direct and indirect contact frequencies among SH were extracted from the published and unpublished sources (Table 4). Data on how frequently pairs of different household population types contact each other were not available. Therefore, assumptions based on the informed judgement of the co-authors were made. These assumptions, along with the average daily individual contact frequency of 13.5, extracted from Mossong et al. (2008) and Lee et al. (2010a), were used to derive the mean daily contact rate between different pairs of the population types (Table 4). As SWH and RH were in rural communities, only half the individual daily contact frequency noted previously was used here. Co-authors also discussed and used their best judgement to specify the movement distance distributions between source and recipient units for all populations.

Disease transmission probabilities

In general, it is difficult to measure the transmission probability per contact, and therefore, it is mostly derived from calibrating models to match either the cumulative number of cases or R_0 (basic reproductive number) of on-going or historical outbreaks (Saenz et al., 2006; Rahmandad and Sterman, 2008; Vynnycky and White, 2010). Given an R_0, a contact rate (C) and an average duration of infectiousness of totally susceptible individuals (D), transmission probability per contact (P), which is the probability that infection will be transferred between an infected and a susceptible units given an adequate contact has been made can be

Table 4. Contact structure and influenza transmission parameters used in the simulation of influenza spread between swine and human populations in a county of Ontario, Canada

Contact type	Mean contacts/day	Distance distribution of recipient units (km)	Probability of infection (Low/medium/high)	References
Swine to swine				[a](Christensen et al., 2008; Bates et al., 2001) and unpublished data from Ontario Veterinary College;
SH-SH (Direct contact)	0.06[a]	BetaPERT(0.8, 20, 100)[b]	1[c]	[b]Assumption based on the informed judgement of co-authors;
SH-SH (Indirect contact)	0.196[a]	BetaPERT (0.8, 20 100)[b]	0.01[b]	[c]Assumed based on based on experimental studies (Brookes et al., 2010; Lange et al., 2009; Vincent et al., 2010);
Swine to human				[d]Bases on the assumptions explained in the main text;
SH-SWH	1[d]	Uniform(0.1, 0.5)[b]	(0.024/0.3/1[d]	[e]Assumed once/week based on the informed judgement of co-authors and multiplied by half the individual contact rate from Lee et al. (2010a) and Mossong et al. (2008);
Human to swine				[f]Derived from R_0 value of pH1N1 2009 as explained the text;
SWH–SH	1[d]	Uniform(0.1, 0.5)[c]	(0.024/0.3/1)[d]	[g]Assumed five times/week based on the informed judgement of co-authors and multiplied by half the individual contact rate from Lee et al. (2010a) and Mossong et al. (2008);
Human to human				[h]Assumed once/year based on the informed judgement of co-authors and multiplied by the individual contact rate from Lee et al. (2010a) and Mossong et al. (2008);
SWH-SWH	0.857[e]	BetaPERT(0.5, 20, 100)[b]	(0.024)[f]	[i]Assumed twice/year based on the informed judgement of co-authors and multiplied by the individual contact rate from Lee et al. (2010a) and Mossong et al. (2008);
SWH-RH	4.286 [g]	BetaPERT(0.1, 10, 30)[b]	(0.024)[f]	[j]Based on the individual contact rate from Lee et al. (2010a) and Mossong et al. (2008)
SWH-UH	0.857[e]	BetaPERT(1, 30, 65)[b]	(0.024)[f]	
RH-SWH	0.857[e]	BetaPERT(0.1, 10, 30)[b]	(0.024)[f]	
RH-RH	4.286 [g]	BetaPERT(0.01, 20, 100)[b]	(0.024)[f]	
RH-UH	0.857[e]	BetaPERT(1, 30, 65)[b]	(0.024)[f]	
UH-SWH	0.036[h]	BetaPERT(1, 30, 65)[b]	(0.024)[f]	
UH-RH	0.071[i]	BetaPERT(1, 30, 65)[b]	(0.024)[f]	
UH-UH	12.893[j]	BetaPERT(0.01, 10, 30)[b]	(0.024)[f]	

SH, Swine herds; SWH, Swine-worker households; RH, Rural non-swine-worker households; UH, Urban households.
Parameters were extracted from the references with the same superscripts.

derived from the following formula (Rahmandad and Sterman, 2008; Vynnycky and White, 2010; Rahmandad et al., 2011):

$$R_0 = C * P * D.$$

However, neither an estimate of R_0 nor historical data on influenza spread between farms are available in the literature. Therefore, for simplicity, transmission probabilities of 100% and 1% were assumed for direct and indirect contacts, respectively. In reality, all other parameters being equal, the transmission probability among units will vary depending on the within-unit prevalence and the number of animals shipped from infected to susceptible farms. These assumptions may not be unreasonable as within-herd spread of influenza in swine is known to be rapid and no immunity is anticipated to exist in naïve recipient herds to a novel strain such as pH1N1.

For spread among households, the transmission probability per contact (P) was estimated from individual-level data using the formula provided above. The mean transmission probability and its 95% probability interval were estimated based on the minimum, most likely and maximum R_0 values of 1.3, 1.5, and 2.2, respectively (Fraser et al., 2009; Pourbohloul et al., 2009; Tuite et al., 2010), and corresponding daily contact frequencies of 6.9, 13.1, and 18.2 (Mossong et al., 2008), and the duration of infectious period of 2, 7, and 10 days, respectively (Pourbohloul et al., 2009; Yang et al., 2009) using a Monte Carlo simulation of 1000 iterations in the *PopTool* version 3.2.5 (Microsoft Excel add-in program available at www.poptools.org). An estimated mean of 0.024 with 95% probability interval 0.012–0.048 of transmission probability per contact were obtained. This estimate was similar to the median value of 0.043 used by Lee et al. (2010a).

Other assumptions made within the model were as follows: all swine and human populations were totally susceptible to the virus, all populations were closed with no addition or losses throughout the simulation period (the mortality of pigs from pH1N1 is negligible [OIE, 2009], and pH1N1 mortality in humans is < 1%); populations were homogeneous with random mixing both within and between groups as defined by the contact structures. In addition, the disease spread through direct or indirect contacts between our study populations and similar populations of other counties in the province were not considered.

Scenarios

The transmission dynamics and the extent of spread of pH1N1 both within and between swine and human populations were assessed under the two broad scenarios of the virus origin, from a swine herd or from urban households. Within each of these broad scenarios, the speed, duration and magnitude of the disease spread were investigated at three different levels of the transmissibility (low, medium and high) at the swine–human interface. Six possible combinations of transmissibility of the virus at the swine–human interface were investigated; (i) low animal to human – low human to animal (LL), (ii) medium animal to human – low human to animal (ML), and so forth, as summarized in Fig. 1. The values used for low (low animal to human or low human to animal) and high (high animal to human or high human to animal) transmissibility were equal to those estimated for human to human

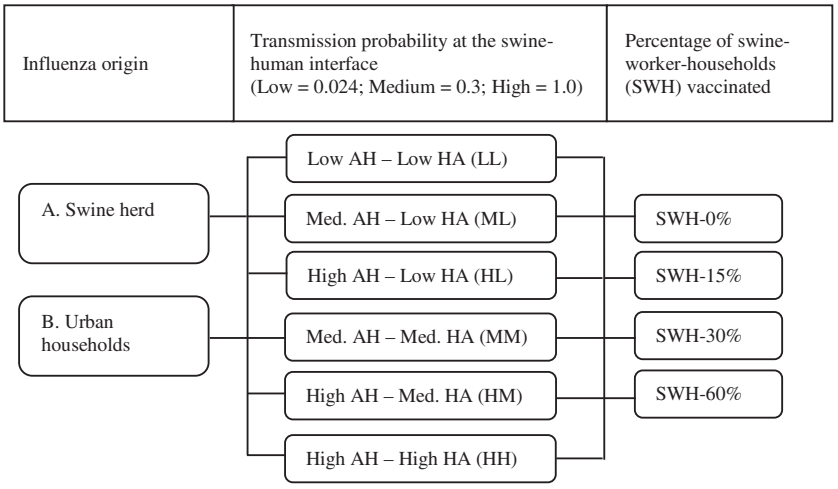

Fig. 1. Graphical description of scenarios used for the simulation of the simultaneous spread of pandemic influenza H1N1 2009 virus between swine and human populations in a county of Ontario, Canada. AH, animal to human, HA, human to animal, SWH- 0% to 60% refers to the percentage of swine-worker households vaccinated prior to the disease outbreak with the assumption of a 100% protective effect.

spread ($P = 0.024$) and swine to swine spread ($P = 1.0$), respectively. A medium transmissibility (medium animal to human or medium human to animal) of $P = 0.3$ was used based on the higher value suggested by Lee et al. (2010a).

Furthermore, each of these scenarios was investigated at four levels of initially immune SHW population (0%, 15%, 30%, and 60%). It was assumed that all members of the SHW family have been vaccinated and was 100% immune to the infection throughout each simulated outbreak. It was based on the assumption that a limited stockpile of effective vaccine was available at the very early phase of an outbreak and assessing the benefit of targeted vaccination of SWH population. A total of 48 scenarios (6 scenarios of the transmissibility of the virus multiplied by four levels of the vaccination coverage, all under the two settings of virus seeding, SH or UH (index case) were investigated(Fig. 1). In the case where the virus originated in swine herd the infection was seeded into a single randomly selected SH for all iterations. For the scenario of virus originating in human population, it was seeded in five randomly selected UH for all iterations. Each scenario was simulated over 1000 iterations in time-steps of one day for 365 days.

Statistical analyses

The models' outcomes were assessed in terms of the parameters that were relevant from epidemiological and regulatory perspectives. They included: (i) stochastic 'die-out' fraction–proportion of iterations that did not result in an epidemic outbreak; defined as <1% of units (total populations combined) becoming infected, (ii) time to peak epidemic day – day on which a highest number of infectious units was observed, (iii) epidemic size of a peak day – number of infectious units observed on the peak epidemic day, (iv) outbreak duration – time to end of an outbreak defined as the time until no latent or infectious unit was present, or a cut-off value of 365 days if the outbreak persisted beyond the simulated time period, and (v) outbreak size – total number of infected units. Summary statistics associated with these outcomes (5th, 50th and 95th percentiles of 1000 iterations) were generated for all scenarios. The cut-point of <1% of units infected was chosen to define the 'stochastic die-out' fraction as the percentage of units infected was >30% in all other iterations. The effects of the three parameters; (i) origin of the virus, (ii) transmissibility of the virus at the swine–human interface, and (iii) vaccination of SWH population on the outbreak duration and proportion of units infected were evaluated by fitting the survival and binomial logistic regression models, respectively. Fitting the multivariable models allowed for an assessment of interaction effects between these parameters on the outcomes.

An accelerated failure-time (AFT) survival model (using the generalized linear model (glm) function with a gamma distribution) was fitted to the epidemic duration as the outcome variable, and the three input parameters as predictor variables. All iterations were considered failed event at the end of the outbreak duration. All input parameters were coded as categorical variables. The origin of the virus was coded as 1 = swine origin (reference category) and 2 = human origin. The transmissibility of the virus at the interface was coded as 1 = LL (reference category), 2 = ML, 3 = HL, 4 = MM, 5 = HM, and 6 = HH. The vaccination coverage of SWH was coded as 1 = 0% (reference category), 2 = 15%, 3 = 30%, and 4 = 60%. All two-way interactions among the predictors were evaluated and retained if significant at $P < 0.05$ and if the relative difference in the predicted duration of epidemic at any levels of the interaction terms was greater than one-week duration. This criterion was used because even a small difference between two interaction terms tended to exhibit statistical significance due to large sample size (each scenario being simulated 1000 times). Akaike Information Criterion (AIC) and Cox–Snell residual plots were used to select the best fitting AFT parametric survival model as well as to evaluate the overall fit of the model to the data (Dohoo et al., 2009). Residuals were evaluated using deviance residual and plotting the residuals against the fitted values or individual predictors.

The effect of the predictors on the size of epidemic was assessed using logistic regression for binomial data (glm function with binomial family distribution and logit link). All predictors were entered into the model as described in the survival model above. The number of each population type infected in each scenario was combined together into single outcome variable, and a variable of the population type was generated. This variable was coded as 1 = SH, 2 = SWH, 3 = RH, and 4 = UH. This allowed assessing the effects of the predictors on epidemic size for each of the population type using a single model. All two-way interactions among the predictors were examined and retained if they were significant at $P < 0.05$ and, if the relative difference in the predicted proportion of units infected at any levels of the interaction terms was ≥5%. Model diagnostics and residuals were evaluated based on the deviance chi-squared test and deviance residuals. Results of the survival and the binomial logistic regression models are presented in terms of predicted margins of median epidemic duration and proportion of units infected at the representative values of the covariates. All analyses were implemented in Stata version 12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX, USA: StataCorp LP).

Results

Stochastic 'die-out' fraction

The stochastic nature of the modelling approach used in this study was reflected not only in the variability of the

predicted measures, but also by the probability of an infection dying out without leading to an outbreak, by chance alone. We observed that 1188 of the 24 000 iterations, equivalent to 5% of the number of simulated influenza outbreaks underwent stochastic 'die-out' when the virus originated in swine. Furthermore, the majority of the 'die-out' iterations (59%) were observed in the LL scenario amongst the scenarios of the transmissibility of the virus at the swine–human interface (Fig. 2). Similarly, among the categories of the vaccination coverage, the maximum number of 'die-out' iterations (42%) occurred in the 60% vaccination coverage category (Fig. 2). No such 'die-out' was observed when the infection was seeded into five randomly selected UH (human origin of the virus).

Peak epidemic day and size

It took approximately 25 days to infect the first UH in the case of the virus originating in swine population, whereas it took approximately 45 days to infect the first SH when the virus originated in the human population. The time to reach the peak epidemic day and the epidemic size of the peak day were estimated as the median of 1000 iterations for each scenario. In general, the delay to peak epidemic day was shorter, and the epidemic sizes of the peak days were higher as the transmissibility of the virus at the swine–human interface increased. In contrast, as the vaccination coverage of SWH increased the delay to peak epidemic day was longer, and the epidemic sizes of the peak days were smaller in both swine herd and household populations.

As the origin of the virus was directly correlated with delay to the peak epidemic day and the epidemic size of the peak day in the corresponding swine herd or household populations, respectively, we focused our attention on the effects of the transmissibility of the virus and vaccination parameters on these outcome measures to the UH origin for SH population, and SH origin for the household populations. In the case of SH, the higher transmissibility of the virus (MM to HH) shortened the delay to peak epidemic day by 3–5 weeks (15–26% reduction) compared with low transmissibility (LL to HL) across all levels of vaccination coverage (Fig. 3). The delay to the peak epidemic days among LL to HL or MM to HH were practically small (difference of approximately <1 week i.e. <8% reduction). The differences in the epidemic sizes of the peak days among different scenarios of the transmissibility were small (difference of ≤4 infected units) across all levels of the vaccination coverage.

Vaccinating 60% of SWH delayed the peak epidemic day by 2–3 weeks (14–20% longer) when compared to the scenario with no vaccination, in the SH population across all levels of the transmissibility (Fig. 3). However, the vaccination coverage up to 30% had only a small effect (<7% increase in the time to peak epidemic day). The differences in the epidemic sizes of peak days among various vaccination coverage levels were small (≤4 units infected).

In the household populations, the delay to peak epidemic day was longer by approximately 3–6 weeks (15–31%

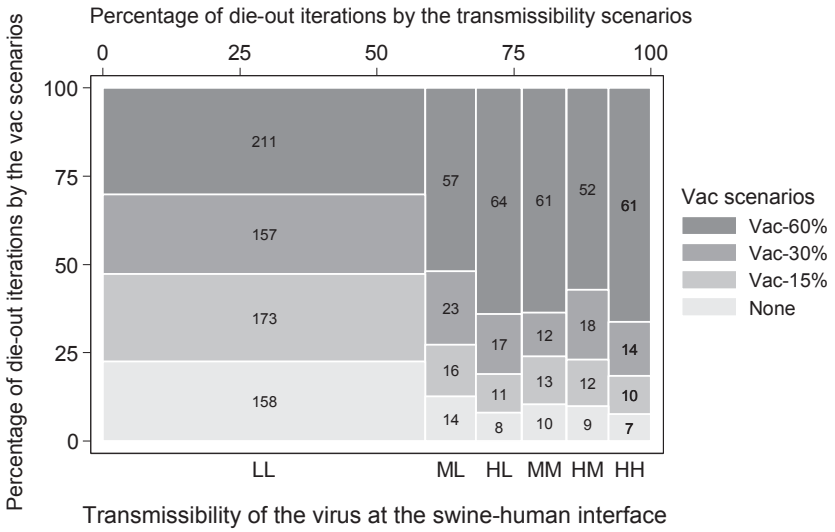

Fig. 2. Percentage of iterations with stochastic 'die-outs' (<1% of units infected) of 24 scenarios of the simultaneous spread of the influenza (swine origin) between swine and human populations. These scenarios consisted of combinations of the six levels of transmissibility of the virus at the swine-human interface and four levels of the vaccination coverage of swine-worker-household population. Each scenario was simulated for 1000 iterations. Transmissibility abbreviations are outlined in Figure 1.

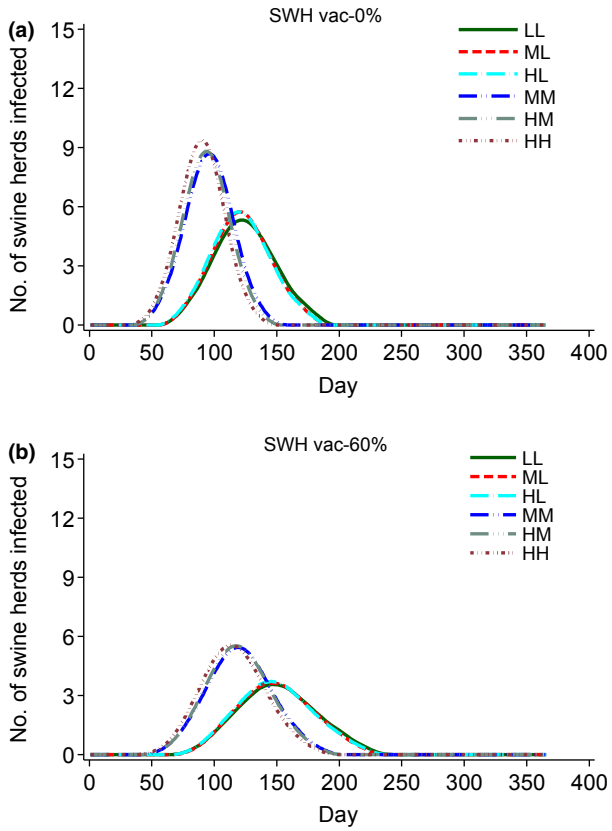

Fig. 3. Epidemic curves illustrating the spread of the influenza in the swine herds (SH) in the case of virus originating in the urban households under the different levels of transmissibility of the virus at the interface, and at the two levels of the vaccination coverage of the swine-worker households (SWH). As the effects of transmissibility at the 15% to 30% vaccination coverage levels were similar to the scenario when none was vaccinated, only the epidemic curves at 0% and 60% vaccination coverage levels are shown. Transmissibility abbreviations are outlined in Figure 1.

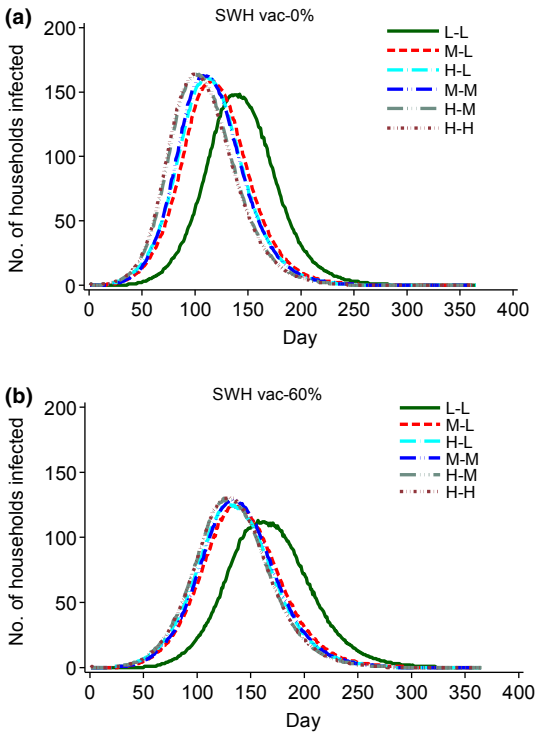

Fig. 4. Epidemic curves illustrating the spread of the influenza in the household population in the case of virus originating in a swine herd under the different levels of transmissibility of the virus at the interface, and at two levels of the vaccination coverage of the swine-worker households (SWH). As the effects of the transmissibility of the virus of the 15% to 30% vaccination coverage were similar to that of a scenario when none was vaccinated, only the epidemic curves at 0% and 60% vaccination coverage are shown. Transmissibility abbreviations are outlined in Figure 1.

longer) when the transmissibility of the virus at the interface was low (LL) compared with the higher transmissibility (ML to HH) across all levels of the vaccination (Fig. 4). This effect was more apparent in the scenario with no vaccination. The epidemic size of peak day was lower by 11–22 infected households (a moderate reduction of 7–15%) when the transmissibility of the virus was low (LL) than at the higher transmissibility levels (ML to HH).

Vaccinating 60% of the SWH delayed the peak epidemic day by 2–5 weeks (13–33% longer) and reduced the epidemic size on the peak day by 33–37 infected households (a moderate reduction of 20–22%) when compared with none were vaccinated. However, the effects of 15% to 30% vaccination coverage on these two outcomes measures were small (<12% change on the delay time and the epidemic sizes of the peak days).

Epidemic duration

The overall median (5th and 95th percentiles) epidemic duration was 308 (261–365) days. The result of the survival model on the epidemic duration indicated that an AFT model with gamma distribution fitted the data best. All the predictors (that is input parameters from the scenarios) had a significant effect on the epidemic duration. The only significant interaction observed was between the transmissibility of the virus and the proportion of SWH vaccinated. The predicted median epidemic duration was 6 days longer in the case where the virus originated in swine than in human, at all levels of the transmissibility and the vaccination coverage. Though statistically significant, this difference was too small to be considered practically meaningful. The interaction effect between the transmissibility and vaccination was mainly due to the significant change in the slope (shortening of the epidemic duration) between low (LL) versus the higher transmissibility (ML to

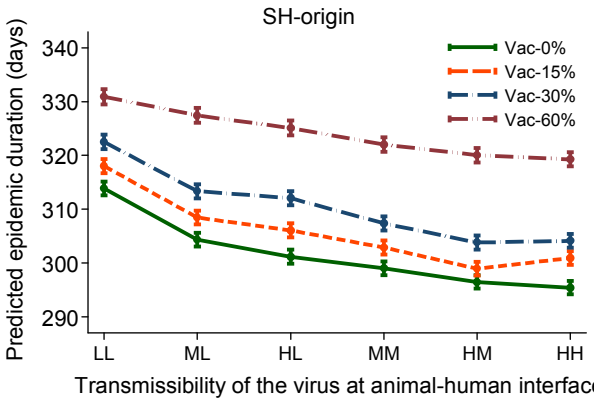

Fig. 5. The interaction plot for the transmissibility of the virus at the interface and the vaccination of the SWH population on the predicted median epidemic duration for the influenza outbreaks in the case of the virus originating in a swine herd. The effects were similar in the case of virus originating in the urban households. SH, swine herds; SWH, swine-worker households; RH, rural non-swine-worker households, UH, urban households. Transmissibility abbreviations are outlined in Figure 1.

HH) at the low vaccination coverage (0% to 30%) (Fig. 5). This means under low vaccination coverage the increase in the transmissibility of the virus (LL versus ML to HH) will shorten the epidemic duration relatively more (3–6% reduction) compared with the vaccination coverage of 60% (1–3% reduction).

The deviance residuals did not indicate any particular outlying observation, except for the stochastic 'die-out' fraction (1188 iterations). Excluding these iterations increased the predicted median epidemic duration up to 7% for the origin of the virus and for the interaction term between the transmissibility and vaccination coverage.

Epidemic size

The overall median (5th–95th percentiles) of infected units were 83% (67–98%) of SH, 69% (34–99%) of SWH, 54% (47–58%) of RH, and 35% (34–36%) of UH. The logistic regression results showed that the effect of the transmissibility and the targeted vaccination of SWH on the epidemic size depended (significant interaction) on the population types (Fig. 6). Furthermore, the interaction effect between the transmissibility and the vaccination on the epidemic size was significant. The proportion of SH infected was significantly higher when the transmissibility of the virus from human to animal was higher (MM to HH) compared with when it was low (LL to ML) (Fig. 6a). However, the magnitude of the difference was relatively larger (by 9–13%) at vaccination coverage of 60% compared with coverage of 0–30%. While the vaccination coverage up to 30% caused a small reduction (1–8%) in the proportion of SH infected, 60% coverage had significant reduction (8–21%), particularly at the low transmissibility of the virus from human to animal spread (LL to ML) (19–21% reduction).

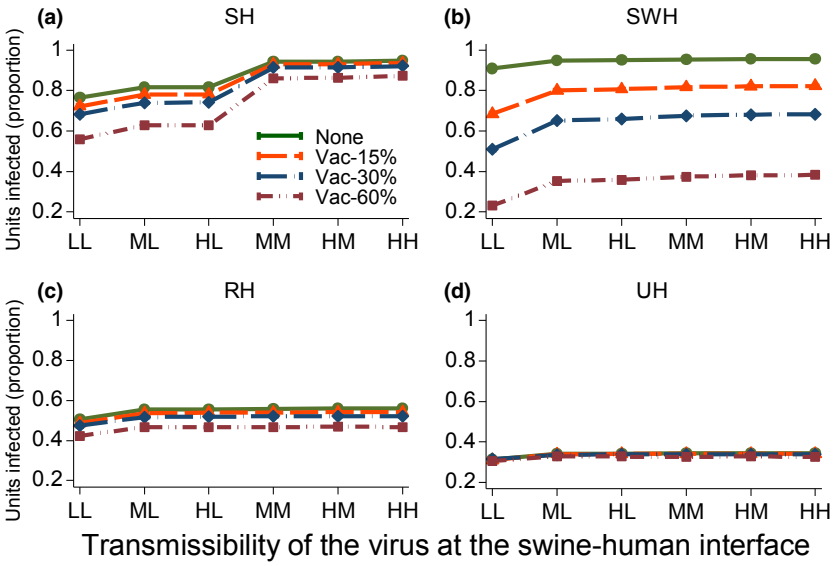

Fig. 6. The interaction plots for the transmissibility of the virus at the interface and the vaccination of the SWH population on the proportion of units infected for the influenza outbreaks in the case of the virus originating in swine herd. The effects were similar in the case of virus originating in the urban households. SH, swine herds; SWH, swine-worker households; RH, rural non-swine-worker households, UH, urban households. Transmissibility abbreviations are outlined in Figure 1.

For the SWH units, a significant difference in the proportion of SWH infected was observed between the low (LL) versus higher transmissibility (ML to HH) of the virus (Fig. 6b). Furthermore, this difference was relatively larger when SWH were vaccinated (15–60%) compared to no vaccination, a difference of 12–17% versus 4–5%, respectively. Similarly, vaccination reduced the proportion of SWH infected by 13–68%, with relatively larger reduction at the low transmissibility of the virus (LL). While the vaccination caused a small reduction in the percentage of RH infected (up to 9% reduction), the transmissibility of the virus had negligible effect on the proportion of RH and UH infected (Fig. 6c and d).

The overall goodness-of-fit test of the final model using deviance chi-squared test showed a significant lack of fit ($P < 0.001$) with a deviance over-dispersion parameter of 197.9. Most observations with extreme deviance residuals were the stochastic 'die-out' fraction. Excluding these observations improved the fit of the model substantially (a deviance over-dispersion parameter of 4.87). However, 18% of the iterations still had deviance residuals greater than or $> \pm 3$. These residuals were spread over all covariate patterns and were related to the stochastic variability in the outcome within the same covariate pattern. In contrast to statistical modelling of risk factors, the proportion of ill-fitting residuals from the predicted outputs actually provides insight into stochastic variability in the predicted outcome by chance alone. As there was no reason to exclude these observations associated with the stochastic 'die-out' fraction, the results using the full data set were reported.

Discussion

Several questions related to the transmission dynamics of zoonotic influenza viruses at the swine–human interface have recently been raised by infectious disease control authorities around the world, including the potential benefit of targeted vaccination of swine workers. Therefore, in this study, we investigated the transmission dynamics of pH1N1 2009 virus between swine and human populations by modelling its spread among and between swine and human populations simultaneously. Furthermore, the benefit of vaccinating varying proportions of SWH was assessed. To our knowledge (Dorjee et al., 2013a), only a single study has modelled the spread of zoonotic influenza between swine and human populations simultaneously (Saenz et al., 2006). Our approach differs from that of Saenz et al. (2006) in a number of ways. Most importantly: (i) this is a stochastic, spatially explicit agent-based model with the unit of simulation being the farm or household, while the previous study used an aggregate deterministic model with homogeneous mixing, (ii) we categorized the non-swine worker human population into a mix of rural and urban households, and (iii) we assessed the effect of different levels of transmissibility of the virus at the swine–human interface, while the previous model investigated the amplifying effect of the influenza spread in rural population by swine and swine worker populations.

The 5% stochastic 'die-out' fraction observed in cases of a single infection seeded into the SH population indicates a fraction of outbreaks that can be expected to undergo random extinction without causing an outbreak of epidemic proportion, given the assumptions inherent in this model. The fact that the majority of this fraction was observed in cases that assumed low transmissibility of the virus at the interface (LL) and/or where 60% of the SWH were vaccinated indicates the beneficial effect of lowering the transmissibility of the virus or of achieving high coverage of targeted vaccination as a means of preventing a proportion of outbreaks. Although the magnitude of this effect will be affected by the location of the index premise and the density of the populations surrounding it, we would expect to observe such phenomena in real-world situations. The extent to which such location-specific effects might be a factor could not be ascertained due to the fact that the current version of the *NAADSM* lacks the ability to randomly seed infections at different locations for each iteration.

The significant difference between the scenarios of low (LL to ML) versus medium to high (MM to HH) transmissibility of the virus from humans to animals in terms of all outcome measures in SH population indicated that the spread from humans to animals had a larger impact than the animal to human spread. To a large extent, this was due to higher contact rate between SH and SWH than between SH units. This result suggested that if we are to obtain a significant positive beneficial effect on the outcome measures we should reduce the transmissibility of the virus from humans to animals to this low level. Reducing it to the low level would significantly prolong the time to peak epidemic, lower the epidemic size of the peak day, as well as the overall outbreak size in the SH population. Similar significant beneficial effects of lowering the transmissibility of the virus at the interface would be obtained even in the household population. However, the transmissibility of the virus both from animals to humans and *vice versa* had to be reduced to the low level (LL). The lowering of the transmissibility of the virus to the LL level also had the beneficial effect of reducing the overall size of the epidemic in SWH population. The positive implication of delaying the time to peak epidemic day is that veterinary and public health authorities would be provided with more time to mobilize resources and implement appropriate disease response measures, such as the delivery of antivirals, vaccination, or other social distancing measures. Furthermore, reducing the epidemic size on the peak day should reduce the burden of disease control activities (such as movement control and

vaccination in animals) including the burden on health care facilities.

An important finding of this study is that it highlights the crucial role the transmission dynamics of influenza at the swine–human interface can play in influenza spread between swine and human populations. It indicated that opportunities exist to prevent or minimize the outbreak of zoonotic influenza by lowering the transmissibility of the virus at this interface. Transmissibility of the virus at the swine–human interface can be minimized through various mechanisms, including the following: good personal hygiene, avoiding direct contacts with sick pigs, using gloves and not smoking while working with pigs (Ramirez et al., 2006), instructing swine workers to stay away from work when suffering from influenza like illnesses, and following strict farm biosecurity measures. As significant differences in the outcome measures were observed between low and medium to high levels of the transmissibility, further sensitivity analysis needs to be carried out between low and medium range of values to determine the threshold level at which a significant beneficial impact can be achieved. It is recommended that studies are carried out to quantify the percentage reduction in infection achieved through these important preventive measures at the swine–human interface to improve the parameterization of future modelling studies.

The transmissibility of the virus at the swine–human interface had little or negligible impact on the epidemic size in the RH and UH populations. This might suggest that once the infection has been introduced in the rural or urban populations it would spread in these populations independent of its spread at the swine–human interface, given the relatively larger population sizes and higher contact rates.

It is notable that despite reports of several outbreaks of pH1N1 across the globe in both human and swine populations, and the heightened interest in gaining a better understanding of the transmission dynamics involved at the swine–human interface, only one study was found that reported transmission back from pigs to humans (Howden et al., 2009). Furthermore, no study could be found that reported the transmission of pH1N1 from one farm to another, either through direct shipment of animals or indirect contact (through movement of swine workers, veterinarians and other fomites). More representative studies to estimate different stages of pH1N1 or other influenza viral infection at the farm level may provide useful information to parameterize models in the future.

Significant beneficial effects on all the outcome measures were observed as the level of targeted vaccination of SWH increased, though the most significant changes were observed when 60% coverage was reached. These effects were most evident in the SH and SWH populations and to a lesser extent in the RH population. Its effect was negligible on the proportion of UHs infected, likely for similar reasons to those mentioned for the transmissibility above. Within the model, we assumed that an effective vaccine was available prior to the influenza outbreak. Questions still remain as to whether such a vaccine would be readily available during the emergent phase of a novel virus. However, if a limited amount of such vaccine were to be available early on in an outbreak, targeting swine workers in cases where the virus was of swine origin should prove beneficial. Future work could investigate effect of using vaccine of lower efficacy developed from related strain of the virus (offering cross-immunity), and the effects of vaccinating similar proportions of the rural and/or urban populations.

Model assumptions, limitations and feasibility of NAADSM

In common with other modelling studies in this domain, a reasonable number of assumptions have to be made. While some of these assumptions are implicit in *NAADSM*, others were made due to the lack of information and/or for the purpose of practicality of model implementation. In the following section, we discussed these assumptions and/or limitations of the model and how they impact on our assessment of the feasibility of using *NAADSM* for modelling directly transmitted zoonotic diseases. In other words, what could have been done, and how might that have influenced our results and conclusions of this study.

NAADSM simulates diseases spread for a static and closed population (that is no addition or removal of farms or households occurs during the simulation, and unit sizes are fixed throughout the simulation). However, this is a reasonable assumption given that the duration of the simulation chosen was 1 year (as opposed to a number of years), and it is a most common assumptions made across in many comparable studies. One of the main limitations imposed by the design of *NAADSM* is the use of farms and households as the unit of simulation. While this is the most common approach to model livestock diseases at a farm level, most modelling studies of human populations are simulated at the individual person level. However, some studies have suggested modelling disease spread at the household level as a suitable alternative, especially for diseases such as pandemic influenza (Ferguson et al., 2005; Longini et al., 2005; Wu et al., 2006; Fraser, 2007). This level of aggregation has been justified on the basis that most influenza transmission occurs within a household. In addition, it is more practical and effective to target implementation of both public health and pharmaceutical intervention measures at the household level and/or all households within a zone of a certain radius, rather than at the individual level.

We also assumed all units (farms or households) were 100% susceptible to the influenza virus. A corollary of the limitation of using farm or household as the unit of simulation is that once a single animal on a farm or a person in a household become infectious, the entire unit itself is considered infectious. In reality, all animals on a farm may not become infected, though studies have shown that the large majority of animals do become infected during influenza outbreaks in farms (Howden et al., 2009; OIE, 2009–2010; Pasma and Joseph, 2010). Even the household secondary attack rates of pH1N1 were estimated in the range of 13–50% (Cauchemez et al., 2009; Ghani et al., 2009; Yang et al., 2009; van Gemert et al., 2011). In addition, the probability of transmission is likely to be influenced by the within-farm or within-household prevalence of disease, but this effect was not accounted-for in the current study. The effect of animal shipment size on the transmission probability for direct contacts between SH units was also not considered. In reality, we would expect the transmission to be influenced by both within-farm prevalence and shipment size. These assumptions might have overestimated the spread of the disease in the populations.

Theoretically, it is possible to simulate a disease spread at the individual person level in *NAADSM* by making a size of unit ('herd/household') as one and number of units equal to a total population of an area, assigning location of units among members of the same household in very close geographic proximity, and using the 'local area spread' mechanism rather than direct contact. However, this will be difficult to implement because of the huge number of units and may increase the simulation time required considerably. Therefore, simulation of a disease spread at the household-level seems more appropriate, at least for contagious diseases like influenza. Currently, there is paucity of information on how long household remain infectious, household to household transmission, contact rates among households, which are required to parameterize household-level model more accurately. A work similar to the one reported by van Gemert et al. (2011) would be useful for this purpose.

Another main limitation of *NAADSM* is that it is not possible to assign more than a single location to each unit, in contrast to some human disease spread models where an individual can be assigned to two or more locations, such as the home, school/workplace, community or other places of social gathering (Haber et al., 2007; Das et al., 2008; Milne et al., 2010; Ohkusa and Sugawara, 2009; Lee et al., 2010b). However, simulating these locations explicitly in a model is important only if a study is aimed at specifically assessing the impact of these locations on the spread and intervention measures of diseases. In addition, our model could not incorporate the heterogeneities in terms of social demographics such as age, gender, immunity status, occupations, etc. The contact rates, risk and susceptibility to an infection may vary significantly among these variables, as was observed for pH1N1 (Cauchemez et al., 2009; Yang et al., 2009; van Gemert et al., 2011). It is difficult to predict the direction of bias due to lack of information on these demographic values and disease transmission parameters. It is possible to incorporate social structure in the model by using *NAADSM*'s feature for inclusion of different species of animals or production types. However, this would potentially result in a large number of pairs of combinations between these variables.

Our model could not incorporate or explore the effect of different contact network structure as the version of *NAADSM* used in this study simulated disease spread as a function of contact rate, transmission probabilities and spatial distance (that is based on a spatial kernel with higher probability of contact between infectious and susceptible units that are in close geographical proximity) between source and recipient units. In actuality farms, households or people only contact a fixed number of units or individuals in a population, and units in close geographical proximity may not necessarily have any contact between one another to facilitate the influenza spread. Indeed, close spatial proximity between two units become largely irrelevant unless a disease spreads locally through aerosol transmission. Furthermore, contact networks in both human and farm populations exhibit scale-free and/small-world topologies (Dubé et al., 2008; Rahmandad and Sterman, 2008; Buttner et al., 2013; Dorjee et al., 2013b); characteristics which will influence the speed and extent of disease spread in a population. In the absence of specific contact network structures, the speed and extent of influenza spread may have been underestimated in this study. As this is one of the major limitations of *NAADSM*, future version of it needs to incorporate flexibility to model different contact network structures.

While some swine workers are likely to live in towns, we were not able to assign SWH locations to be in town due to the inability of *NAADSM* to incorporate such contact network structures explicitly. As we artificially restricted the geographic locations of SWH within a radius of 0.1–0.5 km of SH and limited contact distance to a maximum of 0.5 km, this might have underestimated the spread between SWH and other household types. However, we believe the magnitude of the bias is likely to be small as the majority of farms are family operated enterprises in this county (based on co-authors informed judgment), and due to the fact that swine workers spend most of the day on these farms. We also assumed that swine workers work every day of the week. While this may be true for family owned operators, some swine workers will likely to take 1 or 2 days off, and therefore, it is likely that we have overestimated the contact frequency and thereby the disease spread.

For simplicity, all swine farms were treated as a homogeneous population as we did not have information on a number of different farm types and their contact parameters. In reality, epidemic size and length of disease outbreak will likely vary by farm type (farrowing, grower, finishing, etc.) as has been observed for classical swine fever (Dürr et al., 2013). This might have biased the disease spread to a certain extent but the magnitude and direction of bias could not be determined due to lack of information on the contact and transmission parameters between different production types. We also did not consider the contacts between populations of the county being modelled and neighbouring counties, which is not realistic as some movements of infected and susceptible populations between counties would be expected. Other occupational groups such as veterinarians, abattoir workers, and swine transporters, who come into contact with swine, may play an important role in influenza spread but these groups were not considered in this study. Therefore, this would have underestimated the disease spread in the populations.

Information on contact frequencies between SWH, RH and UH were not available with assumptions being based on the informed judgement of co-authors, which may have introduced some bias in the estimates. Future works could examine the effects of all these parameters on the modelled spread of the virus through more extensive sensitivity analysis.

The effect of seeding the infection randomly in a population at different locations could not be assessed as the version of *NAADSM* used in this study lacks this feature. It would be expected that the speed and extent of spread including stochastic 'die-out' fraction would be influenced to a certain extent by the density of population around the index unit. We could have manually selected few index units randomly at different location to investigate this effect but due to time constraints it could not be carried out.

Observations from this study suggest that *NAADSM* provides a feasible platform for modelling directly transmitted contagious zoonotic diseases between animal and human populations under simplifying assumptions similar to those adopted in this study. Overall, *NAADSM* provides a sophisticated, flexible and user-friendly software platform. It is particularly useful to people with a biology background who do not possess strong mathematical or computer programming skills (as are typically required to make appropriate use of other modelling software). Building model structures and specifying parameters relating to transmission and control strategies can be easily achieved within *NAADSM* as it requires only the specification of parameter values in the form of fixed values, probability density functions or relational functions. The software also has features to generate graphs, summary statistics, and to compare outcomes across as a range of different scenarios. Furthermore, *NAADSM* has features to assess all key intervention strategies either alone or in combination. These are relevant from a regulatory perspective but are equally applicable to exploring issues relating to the public health. Another limitation of the personal computer version of *NAADSM* was the time taken to simulate the spread of disease in populations of a significant size. Despite being run on a relatively powerful personal computer the simulation for this study (with 30 195 units) took 4 days to complete 100 iterations. If *NAADSM* could be developed further to address the limitations highlighted in this study, its capability for modelling zoonotic diseases could be greatly enhanced.

Conclusion

In conclusion, this is a unique one-health modelling study which investigated the simultaneous spread of pH1N1 both within and between swine and human populations. It provided useful insights into how manipulating the transmission dynamics of pH1N1 at the swine–human interface can alter the spread of an influenza epidemic in swine and/or human populations, and illustrated the beneficial effects of targeted vaccination of swine workers. Minimizing transmissibility at the swine–human interface through appropriate mechanisms including targeted vaccination should form key components of all pandemic contingency measures for zoonotic influenza. This study also serves as a benchmark for future studies to improve the modelling approaches of zoonotic influenza including other directly transmitted zoonotic diseases further through enhanced surveillance and collection of quality information to parameterize models accurately. This study also illustrated that *NAADSM* is a feasible and relatively flexible platform for modelling a spread of directly transmitted zoonotic influenza between swine and human populations under certain simplifying assumptions.

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