

**One-Health Simulation Modelling: Assessment of Control Strategies against the Spread of Influenza  
between Swine and Human Populations using NAADSM**

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## Abstract

Simulation models implemented using a range of parameters offer a useful approach to identifying effective disease intervention strategies. The objective of this study was to investigate the effects of key control strategies to mitigate the simultaneous spread of influenza among and between swine and human populations. We used the pandemic H1N1 2009 virus as a case study. The study population included swine herds (488 herds) and households-of-people (29,707 households) within a county in Ontario, Canada. Households were categorized as: (i) rural households with swine workers, (ii) rural households without swine workers, and (iii) urban households without swine workers. Seventy two scenarios were investigated based on a combination of the parameters of speed of detection and control strategies, such as quarantine strategy, effectiveness of movement restriction, and ring vaccination strategy, all assessed at three levels of transmissibility of the virus at the swine-human interface. Results showed that the speed of detection of the infected units combined with the quarantine strategy had the largest impact on the duration and size of outbreaks. A combination of fast to moderate speed of the detection (where infected units were detected within five to 10 days since first infection) and quarantine of the detected units alone contained the outbreak within the swine population in most of the simulated outbreaks. Ring vaccination had no added beneficial effect. In conclusion, our study suggests that the early detection (and therefore effective surveillance) and effective quarantine had the largest impact in the control of the influenza spread, consistent with earlier studies. To our knowledge no study had previously assessed the impact of the combination of different intervention strategies involving the simultaneous spread of influenza between swine and human populations.

Keywords: One-health, modelling, zoonotic diseases, influenza, pigs, humans, *NAADSM*

## **Introduction**

Pandemics caused by influenza A viruses, including the most recent outbreak involving the pandemic influenza A/H1N1 2009 (pH1N1) virus, continue to present a significant zoonotic threat to human and animal populations. Constant outbreaks of H5N1 in Asia (OIE, 2013), and recent outbreaks of a novel swine-origin H3N2 variant virus in the United States (Lindstrom et al., 2012), and bird-origin H7N9 virus in China (Gao et al., 2013, Uyeki and Cox, 2013) are examples of the current public health concerns. Many countries have developed influenza pandemic preparedness plans following the World Health Organization guidelines to prevent or mitigate the impact of future influenza pandemics (WHO, 2011). The main mitigation measures against influenza pandemics are public health measures (also known as non-pharmaceutical) and medical or pharmaceutical interventions (WHO, 2005, Ferguson et al., 2006, Halloran et al., 2008, Lee et al., 2009). Public health measures include personal hygiene such as hand washing, the use of personal protective equipment (face-masks, gloves, etc.), and social distancing measures (quarantine and isolation, school closure, restrictions on gathering at public events and on travel, etc.). The main medical interventions against influenza include anti-viral prophylaxis and treatment, as well as vaccination.

Recently, computer simulation and mathematical models have been widely used to compare or investigate the effectiveness of intervention strategies against influenza pandemics. In human populations these have included simulations that evaluate individual intervention strategies or a combination of such interventions (Lee et al., 2009, Dorjee et al., 2012). Relatively few simulation modelling studies have been reported that seek to assess the control of influenza outbreaks in animals (Dorjee et al., 2012). Only one modelling study has investigated the simultaneous spread of influenza among and between swine and human populations (Saenz et al., 2006). This is despite the fact that

swine are widely considered to be a potential host for the emergence of novel pandemic influenza strains, and frequent reports of the transmission of influenza between swine and people (Myers et al., 2006, Myers et al., 2007, Ma et al., 2009, Zimmer and Burke, 2009, Lindstrom et al., 2012). Several countries have reported the transmission of pH1N1 2009 virus from humans to swine (Nelson et al., 2012). Therefore, it is imperative to understand the transmission dynamic of influenza and the effectiveness of mitigation strategies at the swine-human interface.

Models enable researchers to simulate thousands of virtual influenza outbreaks and compare the effectiveness of control strategies under a range of scenarios, which cannot feasibly be implemented in real-world situations. The outcomes of such studies can guide and inform the development of contingency plans and policy for preparedness and response to future pandemic threats (Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Germann et al., 2006, Halloran et al., 2008, Basta et al., 2009, Gojovic et al., 2009, Tuite et al., 2010). A systematic review of models exploring effectiveness of combination strategies for pandemic influenza response in human populations concluded that the combination of several control measures proved more beneficial than the use of only one particular measure (Lee et al., 2009). Most models in human populations assessed the intervention strategies that were targeted at the individual. Few studies in humans have also investigated the spread and control of influenza at the household level (Ferguson et al., 2005, Longini et al., 2005, Wu et al., 2006, Fraser, 2007, Shaban et al., 2009). Indeed, these studies noted that targeting intervention strategies such as isolation and quarantine, or vaccination and anti-viral prophylaxis at the household level was more pragmatic and likely more effective than at the individual level. In this case, the approach is similar to the types of disease control strategy that are implemented for livestock at the farm level. Targeting intervention measures at the household level in human population offers the added advantage of ensuring that the granularity of the simulation unit is the same for both animal and human populations. This enables the

modelling of zoonotic disease spread and control between animal and human population simultaneously using readily available modelling platform like *North American Animal Disease Spread Model (NAADSM)*. *NAADSM* has built-in features to evaluate the effectiveness of the main disease control strategies against contagious diseases of livestock. These include the speed of disease detection and reporting, forward contact tracing of infected units, quarantine measure, vaccination and depopulation with or without zoning (disease control area within a specified radius around the detected units) (Harvey et al., 2007).

While the previous study (Dorjee et al., 2014) assessed the transmission dynamic of the pH1N1 at the swine-human interface, this study was aimed to further use *NAADSM* to compare different control strategies against the spread of contagious zoonotic pathogens among and between swine and human populations. Specifically it investigated the effectiveness of the speed of detection and different intervention strategies, quarantine and movement control, and ring vaccination against the simultaneous spread of pH1N1 between swine and human populations.

## **Materials and Methods**

### ***Study area and populations***

The same study area and populations described in Dorjee et al., (2014) were used for this study. Briefly a county within the province of Ontario, Canada, with relatively high density of swine farms along with the existence of a range of rural and urban areas (one city and four towns) was selected. Swine herds (SH) and household population data were extracted from the official census of 2006 (Statistics Canada, 2007b, Statistics Canada, 2007a) to ensure the correct representation of each of these populations within the model. Household populations were categorized as: (i) rural households with at least one swine worker (SWH), (ii) rural households without swine workers (RH), and (iii) urban households

without swine workers (UH). The SWH units served as the bridging population for pH1N1 virus transmission between swine and human populations. The sizes of swine herds and households were generated as described in Dorjee et al., (2014). The study population consisted of: 488 SH, 733 SWH, 7,879 RH and 21,095 UH. As the specific geographic coordinates of all units were not available in the official census data, their geo-coordinate locations were randomly assigned within the agricultural areas (SH, SWH, and RH) and urban areas (UH) of the county.

### ***Model structure***

#### ***North American Animal Disease Spread Model (NAADSM)***

The supercomputer version of NAADSM 3.1.24 (NAADSM Development Team, 2008) was used for the construction and simulation of the models. NAADSM is a computer modelling platform for simulating the spread and control of contagious diseases in animal populations, either of the same or different species, or production types. It uses a stochastic, spatially explicit, state-transition method. The unit of disease spread is simulated at the farm or household level. It has provisions to compare the effect of the speed of detection and effectiveness of a number of different intervention strategies, such as quarantine and movement control, ring vaccination, and depopulation. The effectiveness of these measures can be compared with or without a disease control zone of a certain radius, along with forward contact tracing. A detailed description of NAADSM has been provided by Harvey et al, (2007) as well as by Hill and Reeves (2006).

#### ***Model structure and the disease transmission***

The disease spread model structure (susceptible-exposed-infectious-recovered [SEIR]) and the parameters associated with swine farms and households have been described previously (Dorjee et al., 2014) but are provided in Tables 1 and 2 for completeness. The susceptible units consisted of herds or households that were not infected but were vulnerable to an infection; exposed/latent units were those that had been infected but were not shedding organisms; infectious units are units shedding organisms; while recovered units were those that had recovered and were immune to further infection. Permanent immunity was simulated by setting the duration of immunity to be longer than the simulated period (365 days). In addition, the same contact structure among swine herds (SH to SH), between SH and SWH, and among SWH, RH and UH as described in the previous study (Dorjee et al., 2014) were used and are reproduced in Table 3.

For the influenza spread between SH and SWH, a contact was assumed to have occurred when the swine workers came in contact with pigs on farms (SH) during the course of their daily work. Similarly, for its spread amongst households, a contact was assumed to have occurred implicitly when an individual from an infectious household established an adequate contact with individuals from other households at any place, such as schools, workplaces or other social congregations. Individuals who become newly infected through contact with infectious person outside their home in turn infect other members at home and outside their home. The influenza transmissions between infectious and susceptible units through direct and indirect (spread between SH units through contaminated fomites) contacts were simulated as a function of contact rate, the probability of infection per contact and movement distance distribution between the units.

Furthermore, all assumptions of the model, including influenza transmission between units in different disease states, their transition from one state to another, and parameters relating to disease states, contact frequencies between pairs of units, and their transmission probabilities outlined in Dorjee et al., (2014) were adopted for this study.

### ***Control strategies***

The scenarios used for the evaluation of the control strategies against the influenza spread between swine and human populations are outlined in Figure 1. Three control strategies were evaluated: (i) quarantine without zoning, where only detected units were quarantined (No-zone strategy), (ii) quarantine with zoning, where all units (both swine herd and household populations) within a zone of 3km radius were quarantined (With-zone strategy), and (iii) With-zone strategy plus ring vaccination of susceptible units (both swine herd and household populations) within a zone of 5 km radius of the detected unit. The size and duration of an influenza outbreak will depend on how soon an outbreak is detected to implement control measures, the type of control strategies, and effectiveness of implementation of these control strategies. Therefore, the effectiveness of these control strategies was compared at three levels for speed of detection (slow, moderate and fast), two levels for effectiveness of movement control of the quarantined units (less-effective and effective), and two levels for speed of commencement of ring vaccination (slow-trigger and fast-trigger). Furthermore, these control strategies were evaluated at three levels of transmissibility of the virus at the swine-human interface: (i) low animal to human - low human to animal (LL), (ii) medium animal to human - low human to animal (ML), and (iii) high animal to human - medium human to animal (HM). In total seventy two scenarios involving various combinations of speed of detection, control strategies and transmissibility of the virus at the swine-human interface were simulated.

Detection in *NAADSM* is defined as the product of two probabilities, (a) the probability of observing clinically ill and infectious units over time multiplied by (b) the probability of reporting such an observed unit over time (Hill and Reeves, 2006, Harvey et al., 2007). Each of these probabilities changes over time and it can be incorporated into the model as a linear function (Table 4 (a)). The probability of observing clinical signs would be expected to increase over time as more pigs in a swine herd or individuals in a household exhibit clinical signs. Similarly, the probability of reporting the detected infected units would be expected to increase over time due to a greater awareness following detection of the first few infected units. The fast, moderate and slow detections were defined as detection of 98% of infected units in 5, 10 and 20 days, respectively (Table 4 (a)). Not all infected units would be detected and reported. In this model, we assumed 2% of the infected units would never be detected. Furthermore, the detection was assumed to be 100% specific.

In *NAADSM* once infected units have been detected, they are quarantined and no direct contact (100% reduction in the baseline contact rate) from or to these units is allowed. However, indirect contacts from and to the detected units are allowed. In the models the influenza spread was simulated through both direct (shipment of live animals from SH to SH) and indirect (movement of contaminated fomites from farm to farm) contacts among SH units, direct contact from SWH to SH units (movement of swine workers from SWH to swine farms), and indirect contact from SH to SWH (indirect contact was assumed through movement of swine workers from a SH to SWH as swine won't be shipped to SWH), and indirect contact (an implicit assumption when individuals from different households come in contact at workplaces, shopping malls, schools or other social gatherings) among household populations (SWH, RH and UH). To accommodate movement restriction even for indirect contacts in *NAADSM* an area of five-meter radius zone was imposed around a given detected unit (SH and households) to restrict even the indirect contact to achieve the no-zone quarantine strategy (movement restriction of detected units

only). For the quarantine with-zone strategy both direct and indirect contacts of all susceptible units within the 3km radius of a detected unit were restricted. Forward contact tracing of all the direct and indirect contacts upon the detection of an infected unit was implemented for all population types. However, backward tracing was not implemented as the *NAADSM* version used for this study does not support this feature. All the direct and indirect contacts from the detected unit within 5 days (approximate maximum incubation period of the influenza infection) with a certain percentage of success were conducted (Table 4 [a]). All units successfully traced in this manner were automatically quarantined.

In this study, quarantine measures were implemented as a percentage reduction in the baseline contact rate (both direct and indirect contacts) of each detected unit, or of all units within the disease control zone (with-zone strategy). It is not expected that a 100% movement restriction will be achieved in any disease outbreak situation. Therefore two scenarios, (a) less-effective and (b) effective reflecting the effectiveness of movement restrictions of the quarantined units were investigated (Table 4 (a)). Both movement restriction strategies achieved a 100% reduction in the baseline direct contacts (SH to SH, SWH to SH contacts) for all the detected units (the default setting in *NAADSM*), 95% reduction in the baseline direct contact of undetected units within the quarantine zone, and 80% reduction in the baseline indirect contacts of each units under the quarantine. However, in the case of the “effective” strategy, the reduction in contact rates was achieved in less than 5 days, whereas the same reduction was achieved in by day 10 in the case of the “less-effective” strategy. These assumptions were based on the informed judgment of co-authors as there was no information on these parameters in the literature.

For the control strategy incorporating ring vaccination, the speed of initiation of the vaccination was evaluated using a slow and fast response (Figure 1). In the slow-trigger scenario, the ring vaccination of

all susceptible units within a radius of 5 km was triggered upon detecting 25 or more infected units. The fast-trigger began upon detecting 5 or more infected units (Table 4 (b)). A seven day delay in the onset of the immunity from the time of vaccination for SH (Lange et al., 2009) and households (Bresson et al., 2006, Leroux-Roels et al., 2007, Milne et al., 2010) was assumed. Furthermore, the vaccine was assumed to be 100% protective with permanent immunity. The daily ring vaccination capacity increased from 20 units to a maximum of 300 units per day within five days of starting vaccination for all populations.

For each simulated outbreak, the infection was seeded (index case) into a single randomly selected swine herd (latent state). Each scenario was run for 1,000 iterations. Each of the iterations ran until no infected units remained in the populations or until 365 days had been simulated in the case of persistence of the infection. In all scenarios the randomly selected index swine herd was kept fixed. This was a choice limited by the version of *NAADSM* 3.1.24 (*NAADSM* Development Team, 2008) used in this study since it had no feature of seeding the infection randomly in a population at each iteration.

### ***Statistical analyses***

The models' outcomes were assessed in terms of the duration of the outbreak and total number of infected units. Summary statistics of these outcomes under each scenario of speed of detection, quarantine, movement restriction and ring vaccination strategies were generated. Furthermore, the effects of these control strategies at the three levels of the transmissibility of the virus at the interface were evaluated by fitting the survival and negative binomial regression models, for outbreak duration and number of infected units, respectively. Fitting these multivariable models allowed for assessment of interaction effects among control strategies on the outcomes.

An accelerated failure-time (AFT) survival model (using the generalized linear model function) was fitted with outbreak duration as the outcome variable, and the input parameters as the predictor variables. The predictors were entered into the model as categorical variables. The speed of detection was coded as 1 = Slow, 2 = Moderate, and 3 = Fast, quarantine strategy was coded as 1 = No-zone and 2 = With-zone, movement restriction as 1 = Less-effective and 2 = Effective, ring vaccination strategy as 1 = No-vaccination, 2 = Slow-trigger and 3 = Fast-trigger. All meaningful 2-way interactions among the predictors were evaluated and retained in the model if they were significant at  $P < 0.05$  and if the difference in the predicted duration of the outbreak between any levels of the interaction term was greater than one-week duration. This criterion was used because even a small difference between the two interaction terms could be statistically significant simply due to large sample size. Akaike Information Criterion (AIC) and Cox-Snell residual plots were used to select the best fitting AFT parametric model and to evaluate the overall fit of the model, as described in Dohoo et al., (2009). Residuals were evaluated using deviance residual and plotting it against the fitted values or individual predictors.

The effect of the predictors on the size of the outbreak was assessed using a negative binomial regression model. All predictors were entered into the model as described in the survival model above. Instead of building a separate model for each population type, the size of outbreak in each population type was combined into a common outcome variable, and the population type was entered into the model as a categorical predictor (coded as 1 = SH, 2 = SWH, 3 = RH, and 4 = UH). All meaningful two-way interactions among the predictors were examined and retained if they were significant at  $P < 0.05$  and if the difference in the predicted number of infected units between any levels of the interaction term was  $>10$  units. Model diagnostics and residuals were evaluated based on the deviance residual.

The results of the survival and the negative binomial regression models were presented in terms of predicted margins of median epidemic duration and number of infected units at the specific representative values of the covariates. All analyses were implemented in Stata version 12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

## **Results**

### *Outbreak duration*

The AFT survival model with log-logistic distribution fitted the data best. All the control strategies had statistically significant effects on the outbreak duration. The time ratios of the final model of different control strategies are presented in Table 3. The difference in the median duration of outbreaks between with and without ring vaccination (ring vaccination category 2 or 3, versus 1) was 5 days, which was practically not a meaningful difference, although it was statistically significant ( $P < 0.05$ ). As such, the ring vaccination strategy variable was excluded from the final model. Significant interactions between the effects of speed of detection and quarantine strategy, and between speed of detection and movement restriction strategy on the outbreak duration were observed. These effects were similar at all the three levels of the transmissibility of the virus at the interface. Therefore, only the results at the high transmissibility (HM) are presented. The interaction plot of speed of detection and quarantine strategy showed that the effect of these two control strategies depended upon each other (Figure 2). At the slow speed of detection, the outbreak duration was 4 times longer (208 days, 95% CI 207–286 days) when no quarantine zone was used compared with when a 3km quarantine zone was used. However, at the moderate or fast speed of detection, the outbreak duration were approximately similar (<4 days) between the two quarantine strategies (Figure 2[a]). At no-zone quarantine strategy, the outbreak duration was 6–8 times longer (238–239 days) when the speed of detection was slow than when it was moderate or fast. However, this difference was relatively smaller (34–40 days longer) when a quarantine

zone of 3km was imposed (with-zone quarantine strategy) (Figure 2[a]). These effects were similar at both the levels of the effectiveness of movement restriction strategy (which is a covariate in the final model) (Figure 2[a] and 2[b]). Similar interaction effects between the speed of detection and the movement restriction strategies on the duration of outbreak were observed but of much lesser magnitude at both levels of the quarantine strategies (Figure 3[a] and 3[b]). The overall duration was much shorter when a 3km quarantine zone was imposed compared with when a detected units only were quarantined (no-zone quarantine strategy (Figure 3[a] versus 3[b])).

### *Outbreak size*

The overall percentages of units infected was <1% (median values) for all the population types. The overall 95<sup>th</sup> percentile of units infected was: SH 10%, SWH 11%, RH 3% and UH 1%. The multivariable negative binomial regression results showed that all the control strategies, except the vaccination strategy ( $P = 0.172$ ) had a statistically significant effect on the size of the outbreak in all the population types. All two-way interactions between the control strategies and population type on the size of outbreak were significant. Furthermore, the interactions between the speed of detection and quarantine strategy or movement restriction strategy were significant. These effects were again similar at all three levels of the transmissibility of the virus at the interface. Therefore, only results at the high transmissibility of the virus (HM) are presented. The count ratios of the number of infected units under different control strategies and their interaction terms are presented in Table 6. The interaction effect between the speed of detection and quarantine strategy on the size of outbreak suggested that imposing quarantine zone around the detected units was beneficial only at the slow detection level (Figure 4). No difference in the size of the outbreak was observed between the two quarantine strategies at the moderate or fast detection levels. These effects were similar in all the population types at both the levels of movement restriction strategies. However, the magnitude of difference between

the two quarantine strategies on the size of the outbreak at slow detection was smaller at the effective than at less-effective movement strategies; less by 33 and 174 units in SH and UH populations, respectively.

Similarly, the size of outbreak between the two movement restriction strategies was significantly different at the slow detection level, with no difference observed in moderate or high detection levels (Figure 5). Furthermore, the difference in the effect was observed only at the no-zone quarantine strategy. No difference between the two movement restriction strategies was observed at all levels of the detection at the with-zone quarantine strategy (Figure not shown).

#### *Model and residual diagnostics*

The smallest and largest deviance residuals of the AFT survival model were -3.43 and 5.10 respectively. However, less than 1% of the iteration had the deviance residuals above or below  $\pm 3$ . The deviance chi-squared goodness-of-fit test of the negative binomial model did not indicate any lack of fit ( $P = 0.999$ ).

The smallest and largest deviance residuals of negative binomial regression were -4.14 and 9.62 respectively. However, less than 1% of the iterations had the deviance residuals above or below  $\pm 3$ .

Therefore the numbers of outlying residuals were within the acceptable range. Excluding these iterations with outlying residuals had negligible impact on the estimates of both the models. No patterns in the distribution of these outlying residuals were observed in terms of the covariate patterns.

Therefore these residuals might explain the extent of the stochastic variation over and above those explained by the predictors in the models.

## Discussion

This study investigated the effectiveness of key control strategies against the simultaneous spread of the influenza between swine and human populations using the *NAADSM* modelling platform. We used pH1N1 virus as a case study because it is easily transmissible between human and swine populations (Howden et al., 2009, Nelson et al., 2012). Simulations of thousands of virtual disease outbreak events under a defined set of input parameters in the model offer a useful tool to compare effective intervention strategies. Results from such studies can provide guidance for making policy decisions and developing disease contingency plans and preparedness for future pandemic threats. To our knowledge (Dorjee et al., 2012) no study has investigated the combination of intervention strategies in situations involving influenza spread between swine and human populations simultaneously.

The results of this study showed that under the assumptions given in the models, differences in speed of detection had the largest effect on the size and duration of the outbreaks. They suggested that a fast to moderate speed of detection (98% detection within 5 to 10 day period) combined with the quarantine of detected units alone (No-zone quarantine strategy) would control the outbreak in 30–40 days with only a single SH unit and no household unit infected in most instances (Figure 2 and Figure 4). If the detection of the majority of infected units (41–98% of the units) was delayed by 11–20 days, the implementation of the zone-based quarantine strategy (in which both the infected and susceptible units within a 3km radius of the detected infected units are quarantined) was a better alternative strategy. It could be argued that even the slow detection defined in this study was relatively effective because in reality it might take weeks to a few months to recognize a novel influenza virus originating in swine to be of potential pandemic threat. Its effective transmission from person to person would have to be known before serious public health intervention measures are initiated. However, if control measures were implemented in a manner defined in this study for any serious influenza outbreak in swine,

irrespective of knowing its potential pandemic threat to people, the outbreak can be contained within the swine population alone. This would mitigate the likelihood of occurrence of future influenza pandemics. The transmission of the influenza from swine to swine workers can be prevented following strict personal hygiene and protective equipment, including anti-viral prophylaxis in the case of influenza outbreaks, preventing serious threat to human health (Hayden, 2001, Ramirez et al., 2006, McCaw and McVernon, 2007, Handel et al., 2009).

A similar time-frame for speed of detection and implementation of control measures was used for pandemic influenza spread in humans by Longini et al (2005), where delay times of 7, 14, or 21 days after the detection of the first case were investigated. However, Ferguson et al (2005) used the threshold of 20 or more cases (individuals rather than households) to initiate the implementation of the control strategies, as opposed to a delay measured in days. The finding that speed of detection has the largest impact on the modelled outcomes in this study was consistent with these other studies that compared the similar control strategies targeted at the household level and used zones of a certain radius around infected cases (Ferguson et al., 2005, Longini et al., 2005, Shaban et al., 2009).

Given the assumptions in the model, including the speed of detection and the movement restriction levels defined in this study, it was apparent that the ring vaccination strategy did not offer an additional beneficial effect. This also suggests that in the presence of an effective surveillance system which detects any disease spread rapidly, combined with effective quarantine and movement restriction, a vaccine will have limited value as an additional response measure. As an appropriate vaccine may not be available during the early phase of the emergence of a novel virus, focusing on rapid detection and effective quarantine measures may be practical and sufficient. However, as the disease transmission and

contact parameters used in this study were based on a number of assumptions rather than having been calibrated to real outbreak data, this finding must be interpreted cautiously. Ring vaccination may also entail additional costs to swine producers and public health authorities, and may effectively increase the contact rates through increasing movements of people during the vaccination process. However, other indirect benefits such as reducing panic in people (by doing something), in addition to the direct benefits associated with increased herd immunity should be taken in consideration. Therefore, additional sensitivity analysis to assess the effect of vaccination, particularly in the circumstances of delayed speed of detection, reduced effectiveness of movement restriction (that is the compliance rate of quarantine measures) at a wide range of reproductive numbers or varied rates of transmissibility of the virus, should be explored in future studies.

For this study we have compared the effect of control strategies under the scenario of the pH1N1 seeded (index case) in a swine farm only, due to time constraint and due to the fact that a novel influenza virus may most likely originate in animal than human populations. However, it would be worthwhile for future studies to investigate the effects of similar control strategies under scenario where the virus was seeded in a human population.

In this study the control strategies were targeted at the farm or household levels, in contrast to most studies in human populations where control strategies are targeted at the individual level (Germann et al., 2006, Nuno et al., 2007, Yasuda and Suzuki, 2009, Tsai et al., 2010, Tuite et al., 2010). However, other studies have highlighted the importance of investigating the spread and control strategies targeted at the household level together with zones of certain radius (Ferguson et al., 2005, Longini et al., 2005, Wu et al., 2006, Fraser, 2007). These studies justify such approaches on the basis that most

influenza transmission occurs within households and that cases tend to be clustered within localities. Furthermore, they highlight the fact that anti-viral treatment and prophylaxes, as well as quarantine measures, are more practical and effective if targeted at the whole household and/or a zone of a certain radius, rather than at the individual level. For these reasons the need to estimate influenza spread parameters, such as the reproduction number at household level, had been emphasized (Cauchemez et al., 2004, Ferguson et al., 2005, Fraser, 2007). Therefore, a choice as to the granularity of simulation unit and approach to control strategy evaluation adopted in this study, were consistent with the approaches highlighted as being important by a number of other authors.

The results of this study indicated that NAADSM is a feasible platform on which to model the simultaneous spread and control of contagious zoonotic diseases between swine and human populations. The main limitation of this study was the lack of empirical data on pH1N1 outbreaks in a usable form at the swine herd or household levels, to calibrate the model when comparing different intervention strategies. Information on contact frequencies between SWH, RH and UH were not available so assumptions were based on the informed judgement of co-authors, which may have introduced bias in the estimates. The contact rates among households were assumed to be equal to the average daily contact rate of an individual person for UH units, or half this rate for SWH and RH units. This may have underestimated the spread of the disease because each household has, on average three members, and therefore the actual contact rate between households would likely be higher. Furthermore, the references (Mossong et al., 2008, Lee et al., 2010) from which these contact rates were extracted did not specify what proportion of any daily average contact rate related to contacts between members of the same household, or among and between different household/occupational groups (e.g. swine workers, rural non-swine workers or urban households). Therefore, the magnitude and direction of any introduced bias on the estimates of the spread of the disease in these populations could not be

predicted. Future work could examine the effects of these parameters on the modelled spread of the virus through more extensive sensitivity analysis. The roles of other occupational groups such as veterinarians, abattoir workers and transport operators who come into contact with swine, and who may play an important role in influenza spread, were not considered. Similarly the role of live swine markets was not considered. These limitations may have underestimated the spread of influenza in the study populations to a certain extent. Nevertheless, this study provides useful insights into the effect of strategic combinations of intervention measures, with findings that were similar to those arising from studies that have modelled influenza spread only in human populations.

A number of *NAADSM's* general limitations were outlined in Dorjee et al., (2014). In addition, when modelling control strategies some of the limitations include: it assumes the detection is 100% specific (no false positives), no capability for tracing the contacts of detected units backward, units are quarantined permanently till the end of the simulation period, and there is no capability to assess the effects of school or workplace closure along with the quarantine of households. Imposing permanent quarantine measures for swine herds may be realistic but this is not the case for households, particularly when the duration of the outbreak is prolonged. In human studies the members of infected households have typically been quarantined for 7–21 days (Ferguson et al., 2005, Ferguson et al., 2006, Wu et al., 2006). The *NAADSM* version used in this study does not have a specific feature to evaluate the effectiveness of the anti-viral treatment or prophylaxis measures. The feature evaluating the ring vaccination can be used to mimic anti-viral prophylaxis by setting the delay time to immunity to one day following vaccination. However, this approach would mean that it would not be possible to assess the effectiveness of the anti-viral and the ring vaccination strategies simultaneously. In addition, ring vaccination or anti-viral treatment would be assumed to be 100% protective, which is not likely realistic. Finally, it should be noted that it was not the intention of this study to provide quantitative predictions

(given that several assumptions had to be made in the absence of empirical data); rather the study attempted to provide a better qualitative assessment of the impacts of combining various control strategies. Therefore, the reader should interpret the findings of this study in terms of relative magnitude rather than focusing on the quantitative outputs of the models.

## **Conclusion**

This study demonstrated that effective quarantine, based on the early detection of infected units alone, would have the largest impact in limiting influenza outbreaks in swine populations with negligible spread to humans, under the assumptions present in this model. A moderate speed of detection (98% detection within a 5 to 10 day period) combined with quarantine of the detected units alone (i.e. without the implementation of any zone-based quarantine strategy) would control the outbreak in 30–40 days with only a single SH unit and no household units becoming infected in most instances. If the detection of the majority of infected units (41–98% of the units) was delayed by 11–20 days, the implementation of a zone-based quarantine strategy (in which both the infected and susceptible units within a 3km radius of any detected infected units are quarantined) was a better strategy. The modelling approach and the exploration of effectiveness of a combination of key control strategies assessed in this study is suitable for modelling contagious zoonotic pathogens as they spread among and between animal and human populations. Furthermore, this study demonstrated that *NAADSM* offers a feasible and readily useable platform for such an undertaking. It is recommended that concerted efforts should be made to collect relevant information on influenza outbreaks in swine and human populations to better parameterize such models at the farm and household levels, which could greatly improve future modelling work.

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Table 1. 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 <sup>a</sup>	Fixed value of 1 <sup>b</sup>	<sup>a</sup> (Brookes et al., 2010, Lange et al., 2009, Vincent et al., 2010);
Subclinical infectious (day)	0–6 <sup>a</sup>	BetaPERT(0, 3, 6) <sup>b</sup>	<sup>b</sup> Generated from the individual-level parameters using WH 0.9.5 software†;
Clinical infectious (day)	1–15 <sup>a</sup>	BetaPERT (5; 25;45) <sup>b</sup>	<sup>c</sup> (Blaskovic et al., 1970, Desrosiers et al., 2004);
Immune period (day)	365–840 <sup>c</sup>	Fixed value 366 <sup>d</sup>	<sup>d</sup> 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 (Reeves et al., 2013).

Parameters were extracted from the references with the same superscripts.

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

†WH 0.9.5 is the software that simulate within-herd disease transmission stochastically and generates herd-level durations of disease states (Reeves et al., 2013). Parameters were extracted from the references with the same superscripts.

Table 3. 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
<b>Swine to swine</b>				
SH-SH (Direct contact)	0.06 <sup>a</sup>	BetaPERT(0.8, 20, 100) <sup>b</sup>	1 <sup>c</sup>	<sup>a</sup> (Christensen et al., 2008, Bates et al., 2001) and unpublished data from Ontario Veterinary College; <sup>b</sup> Assumption based on the informed judgement of co-authors;
SH-SH (Indirect contact)	0.196 <sup>a</sup>	BetaPERT (0.8, 20,100) <sup>b</sup>	0.01 <sup>b</sup>	
<b>Swine to human</b>				
SH-SWH	1 <sup>d</sup>	Uniform(0.1, 0.5) <sup>b</sup>	(0.024/0.3/ 1 <sup>d</sup>	<sup>c</sup> Assumed based on based on experimental studies (Brookes et al., 2010, Lange et al., 2009, Vincent et al., 2010); <sup>d</sup> Bases on the assumptions explained in the main text;
<b>Human to swine</b>				
SWH-SH	1 <sup>d</sup>	Uniform(0.1, 0.5) <sup>c</sup>	(0.024/ 0.3/1) <sup>d</sup>	<sup>e</sup> Assumed once/week based on the informed judgement of the co-authors and multiplied by half the individual contact rate from Lee et al., (2010) and Mossong et al., (2008); <sup>f</sup> Derived from $R_0$ value of pH1N1 2009 as explained the text. <sup>g</sup> Assumed 5 times/week based on the informed judgement of the co-authors and multiplied by half the individual contact rate from Lee et al., (2010) and Mossong et al., (2008); <sup>h</sup> Assumed once/year based on the informed judgement of the co-authors and multiplied by the individual contact rate from Lee et al., (2010) and Mossong et al., (2008); <sup>i</sup> Assumed twice/year based on the informed judgement of the co-authors and multiplied by the individual contact rate from Lee et al., (2010) and Mossong et al., (2008); <sup>j</sup> Based on the individual contact rate from Lee et al., (2010) and Mossong et al., (2008)
<b>Human to human</b>				
SWH-SWH	0.857 <sup>e</sup>	BetaPERT(0.5, 20, 100) <sup>b</sup>	(0.024) <sup>f</sup>	
SWH-RH	4.286 <sup>g</sup>	BetaPERT(0.1, 10, 30) <sup>b</sup>	(0.024) <sup>f</sup>	
SWH-UH	0.857 <sup>e</sup>	BetaPERT(1, 30, 65) <sup>b</sup>	(0.024) <sup>f</sup>	
RH-SWH	0.857 <sup>e</sup>	BetaPERT(0.1, 10, 30) <sup>b</sup>	(0.024) <sup>f</sup>	
RH-RH	4.286 <sup>g</sup>	BetaPERT(0.01, 20, 100) <sup>b</sup>	(0.024) <sup>f</sup>	
RH-UH	0.857 <sup>e</sup>	BetaPERT(1, 30, 65) <sup>b</sup>	(0.024) <sup>f</sup>	
UH-SWH	0.036 <sup>h</sup>	BetaPERT(1, 30, 65) <sup>b</sup>	(0.024) <sup>f</sup>	
UH-RH	0.071 <sup>i</sup>	BetaPERT(1, 30, 65) <sup>b</sup>	(0.024) <sup>f</sup>	
UH-UH	12.893 <sup>j</sup>	BetaPERT(0.01, 10, 30) <sup>b</sup>	(0.024) <sup>f</sup>	

Key: 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.

Table 4 (a). Parameters of control strategies used for simulation models of the simultaneous spread of pandemic influenza H1N1 2009 virus between swine and human populations in a county in Ontario, Canada

Parameters	Parameter values						
		Swine herd			Household		
1. Speed of detection	Day	Slow	Moderate	Fast	Slow	Moderate	Fast
(a) Probability of observing clinical signs given the number of days that a unit is clinically infectious*	0	0	0	0	0	0	0
	1	0.1	0.4	0.7	0.1	0.4	0.8
	3	0.2	0.6	0.9	0.3	0.7	0.95
	5	0.25	0.8	0.99	0.5	0.9	0.99
	10	0.5	0.99	-	0.8	0.99	-
	15	0.9	-	-	0.9	-	-
	20	0.99	-	-	0.99	-	-
(b) Probability of reporting an observed clinical unit given the number of days since any unit was first detected *	0	0	0	0	0	0	0
	1	0.1	0.25	0.7	0.1	0.25	0.7
	3	0.5	0.6	0.9	0.5	0.6	0.9
	5	0.7	0.9	0.99	0.7	0.9	0.99
	10	0.8	0.99	-	0.8	0.99	-
	15	0.9	-	-	0.9	-	-
	20	0.99	-	-	0.99	-	-
(c) Probability of the overall detection [(a)*(b)]	0	0	0	0	0	0	0
	1	0.01	0.1	0.49	0.01	0.1	0.56
	3	0.1	0.36	0.81	0.15	0.42	0.86
	5	0.18	0.72	0.98	0.35	0.81	0.98
	10	0.4	0.98	-	0.64	0.98	-
	15	0.81	-	-	0.81	-	-
	20	0.98	-	-	0.98	-	-
<b>2. Quarantine strategy</b>		Radius			Radius		
(a) No-zone strategy - quarantine of detected units only (however a zone of this radius was imposed to control the indirect contacts between SH to SH, and SH to SWH, and among household units)	-	0.005 km			0.005 km		
(b) With-zone strategy – quarantined all units within a zone of this radius around the detected units.	-	3 km			3 km		
<b>3. Effectiveness of movement control (fraction of baseline contact rate over time)</b>	Day	Less-effective	Effective		Less-effective	Effective	
(a) Movement restriction of direct contacts of undetected units within the disease control zone (With-zone strategy only) <sup>§</sup>	0	1.0	1.0		1.0	1.0	
	1	0.7	0.5		0.7	0.5	
	3	0.5	0.2		0.5	0.2	
	5	0.3	0.05		0.3	0.05	
	10	0.05	-		0.05	-	
(b) Movement restriction for indirect contacts upon detection for both No-zone and With-zone strategy)	0	1.0	1.0		1.0	1.0	
	1	0.7	0.5		0.7	0.5	
	3	0.5	0.3		0.5	0.3	
	5	0.3	0.2		0.3	0.2	
	10	0.2	-		0.2	-	
<b>4. Forward contact tracing</b>		Trace success (%)			Trace success (%)		
(a) Probability of trace success for the movement that occurred within five days of detection for direct contacts		0.95			1.0		
(b) Probability of trace success given days before the detection for indirect contacts		0.6			0.7		

\*These cumulative probability distributions were converted to a daily probability distribution using spreadsheet provided by Neil Harvey of the University of Guelph and entered into the models. <sup>§</sup> This applies to the direct contacts of undetected units of swine herds (SH) and swine worker households to SH contact (SWH to SH contact) under with-zone strategy, as the direct contacts of all detected units were automatically quarantined with 100% effectiveness as a default setting in NAADSM. The contacts between between pairs of households were simulated by indirect contact.

Table 4 (b). Parameters of vaccination strategies used for simulation models of the simultaneous spread of pandemic influenza H1N1 2009 virus between swine and human populations in a county in Ontario, Canada

Parameters	Parameter value for both swine herds & Households		
	No-vaccination	Slow-trigger	Fast-trigger
<b>5. Vaccination</b>			
(a) Threshold level to start vaccination	-	≥25 units detected	≥5 units detected
(b) Whether to vaccinate all unit types	-	Yes	Yes
(c) Delay to immunity following vaccination of units (all units)	-	7 days	7 days
(d) Vaccine immune period	-	Permanent	Permanent
(e) Radius of the ring vaccination	-	5 km	5 km
(f) Number of units vaccinated per day (all units)	-	Day	Capacity/day
		0	20
		3	150
		5	300
		10	300

Table 5. Time ratios of a multivariable accelerated failure time survival model assessing the control strategies against the simulated influenza spread between swine and human populations in a county in Ontario, Canada

Predictors (input parameters)	Time ratios (95% CI)	P-values
1. Speed of detection		
Slow	Baseline	
Moderate	0.155 (0.152–0.159)	<0.001
Fast	0.117 (0.114–0.119)	<0.001
2. Quarantine strategy		
No-zone	Baseline	
With-zone	0.262 (0.257–0.266)	<0.001
3. Effectiveness of movement restriction		
Less effective	Baseline	
Effective	0.833 (0.822–0.845)	<0.001
4. Speed of detection * quarantine strategy		
Slow * No-zone	Baseline	
Moderate * With zone	3.514 (3.434–3.596)	<0.001
Fast * With zone	3.931 (3.846–4.017)	<0.001
5. Speed of detection * Effectiveness of movement restriction		
Slow * Less-effective	Baseline	
Moderate * Effective	1.075 (1.054–1.096)	<0.001
Fast * Effective	1.114 (1.093–1.136)	<0.001

Table 6. Count ratios of a multivariable negative binomial regression model assessing the control strategies against the simulated influenza spread between swine and human populations in a county in Ontario, Canada

Predictors (input parameters)	Count ratios (95% CI)	P-values
<b>1. Population type</b>		
Swine herds (SH)	Baseline	
Swine worker households (SWH)	1.58 (1.51 – 1.65)	<0.001
Rural non-swine worker households (RH)	2.59 (2.48 – 2.72)	<0.001
Urban non-swine worker households (UH)	1.97 (1.87 -2.07)	<0.001
<b>2. Speed of detection</b>		
Slow	Baseline	
Moderate	0.02 (0.02 -0.02)	<0.001
Fast	0.00 (0.00 - 0.00)	<0.001
<b>3. Quarantine strategy</b>		
No-zone	Baseline	
With zone	0.04 (0.03 -0.04)	<0.001
<b>4. Effectiveness of movement restriction</b>		
Less effective	Baseline	
Effective	0.86 (0.83 – 0.88)	<0.001
<b>5. Population type * speed of detection</b>		
SH * Slow	Baseline	
SWH * Moderate	1.03 (0.99 – 1.07)	0.184
SWH * Fast	0.99 (0.95 – 1.04)	0.693
RH * Moderate	0.48 (0.46 – 0.50)	<0.001
RH * Fast	0.11 (0.10 – 0.11)	<0.001
UH * Moderate	0.34 (0.32 – 0.35)	<0.001
UH * Fast	0.04 (0.03 -0.04)	<0.001
<b>6. Population type * quarantine strategy</b>		
SH * No zone	Baseline	
SWH * With zone	1.13 (1.08 – 1.17)	<0.001
RH * With zone	0.85 (0.82 – 0.89)	<0.001
UH * With zone	0.69 (0.66 – 0.73)	<0.001
<b>7. Population type * Effectiveness of movement restriction</b>		
SH * Less effective	Baseline	
SWH * Effective	0.86 (0.83 – 0.90)	<0.001
RH * Effective	0.88 (0.85 – 0.92)	<0.001
UH * Effective	0.72 (0.70 – 0.76)	<0.001
<b>5. Speed of detection * quarantine strategy</b>		
Slow * No-zone	Baseline	
Moderate * With zone	12.46 (12.04 – 12.88)	<0.001
Fast * With zone	30.56 (29.27 – 31.91)	<0.001
<b>6. Speed of detection * Effectiveness of movement restriction</b>		
Slow * Less effective	Baseline	
Moderate * Effective	1.05 (1.02 – 1.08)	0.002
Fast * Effective	0.97 (0.94 – 1.01)	0.180

<p><b>Transmissibility of the virus at the swine-human interface</b></p> <p>1. Low = 0.024 2. Medium = 0.3 3. High = 1.0</p>	<p><b>Control strategies</b></p>	<p><b>Speed of detection</b></p> <p>1. Slow = 11-20 days 2. Moderate= 6-10 days 3. Fast = 1-5 days</p>	<p><b>Effectiveness of movement restriction</b></p> <p>1. Less-effective = requiring 10 days to achieve 80% (direct<sup>§</sup>) and 95% (indirect<sup>¥</sup>) contact reduction 2. Effective = requiring 5 days to achieve 80% (direct<sup>§</sup>) and 95% (indirect<sup>¥</sup>) contact reduction</p>	<p><b>Ring vaccination (≤5 km radius)</b></p> <p>1. No-vaccination 2. Slow-trigger = start ≥25 units infected 3. Fast-trigger = start ≥5 units infected</p>
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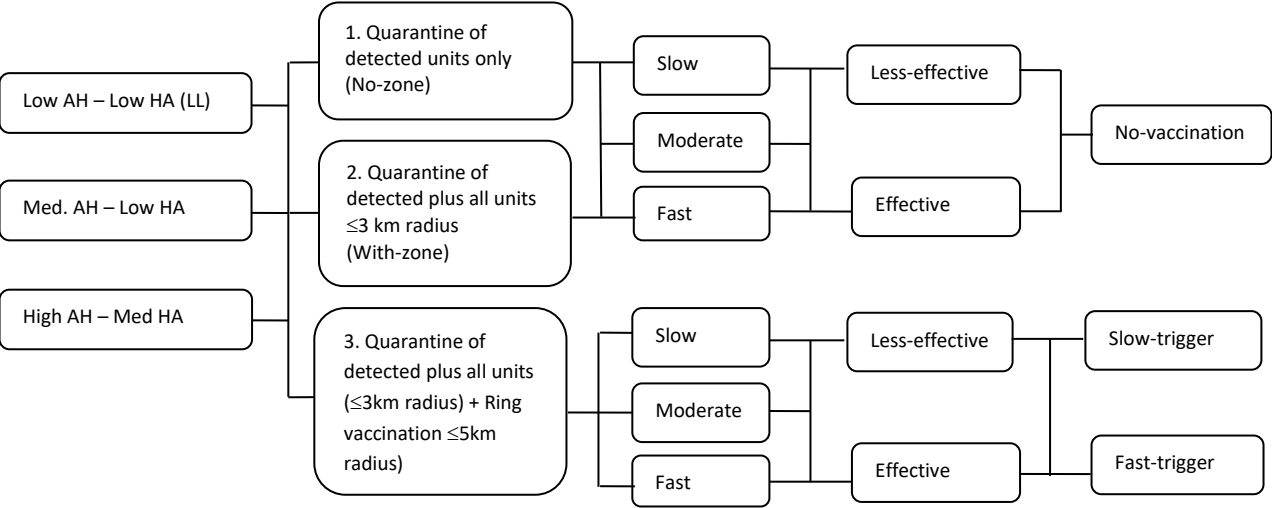


Figure 1: The description of scenarios used for assessing the control strategies against the simultaneous spread of pandemic influenza H1N1 2009 virus between swine and human populations in a county of Ontario, Canada. The infection was seeded in a single randomly selected swine herd. Key: AH = animal to human, HA = human to animal.

<sup>§</sup> Direct contacts refer to shipment of live pigs from one farm to another (SH to SH), movement of swine workers from swine worker household to swine farms (SWH to SH).

<sup>¥</sup> Indirect contacts refer to movement of contaminated fomites (equipment, feeds, etc) from farm to farm (SH to SH contacts), movement of swine workers from swine farms to swine worker households (SH to SWH contact), and contacts among people from different households at workplaces, shopping malls, and other social congregations (contacts amongst SWH, RH and UH)

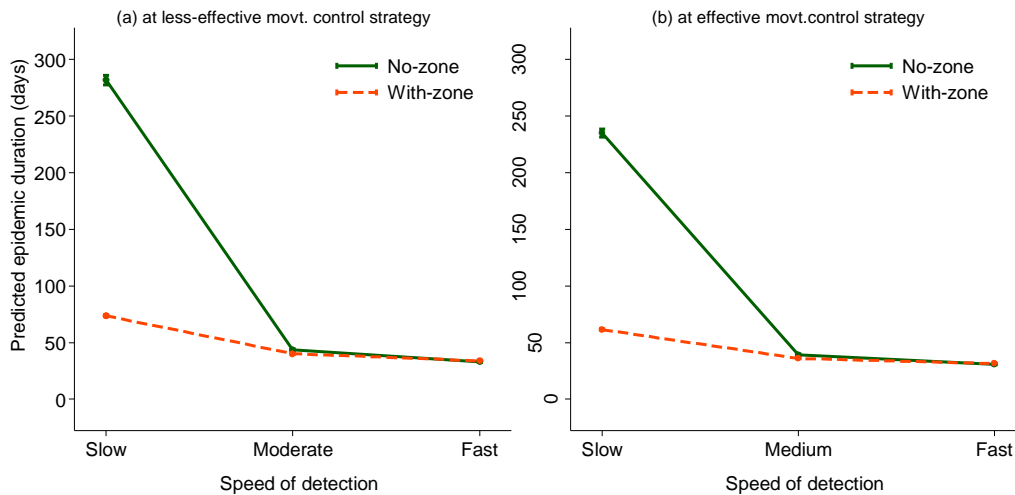


Figure 2: The interaction effect of the speed of detection and quarantine strategy on the duration of the outbreaks: (a) less-effective movement control, and (b) effective movement control strategy. The error bar shows the predicted 95% confidence intervals of the duration of the outbreaks. Only the results of high animal to human – medium human to animal (HM) transmissibility of the virus are shown. Key: No-zone = quarantine of the detected units only; With-zone = quarantine of all units within the 3km radius of the detected units; Less-effective movement restriction = 100% decrease in the baseline direct contact of all detected units, 95% decrease in the baseline direct contacts of undetected units within the quarantine zone and 80% decrease in the indirect contacts, all within 5 days; Effective movement restriction = same levels of decrease in the baseline contact rates as less-effective movement restriction but all achieved within 10 days.

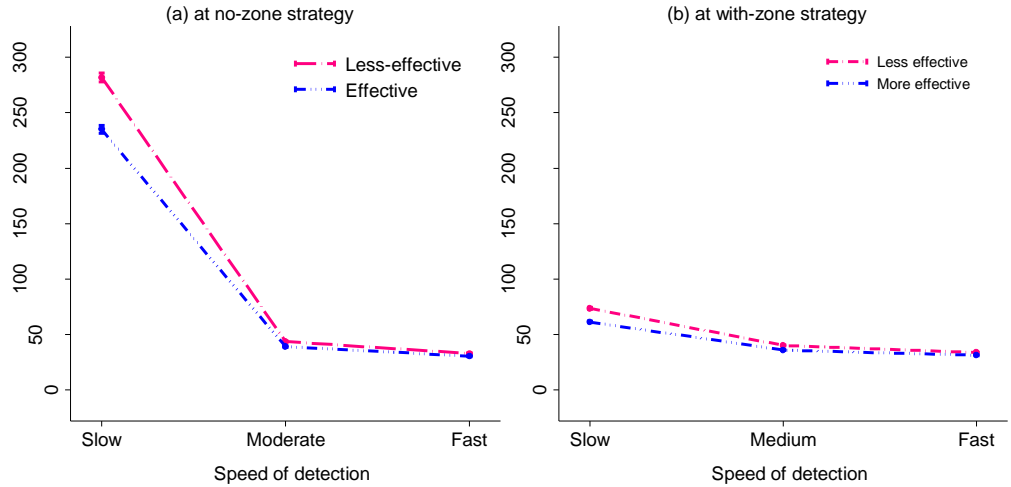


Figure 3: The interaction effect of the speed of detection and movement restriction strategy on the duration of the outbreaks at: (a) no-zone , and (b) with-zone quarantine strategy. The error bar shows the predicted 95% confidence intervals of the duration of the outbreak. Only the results of high animal to human – medium human to animal (HM) transmissibility of the virus are shown. Key: refer to Figure 2.

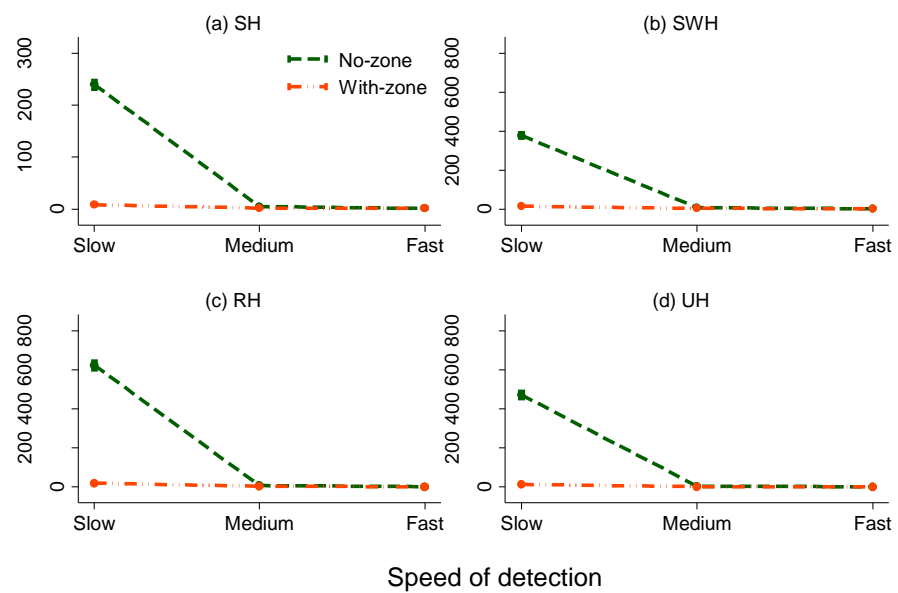


Figure 4: The interaction effects of speed of detection and quarantine strategy on the size of the outbreaks. The error bars show the predicted 95% confidence intervals of the size of the outbreaks. Only the results of high animal to human – medium human to animal (HM) transmissibility of the virus at the Less-effective movement restriction strategy is shown. Key: SH = swine herds; SWH = swine worker households; RH = rural non-swine worker households; UH = urban households; No-zone = quarantined detected units only, With-zone = quarantined all units within 3 km radius of the detected infected units.

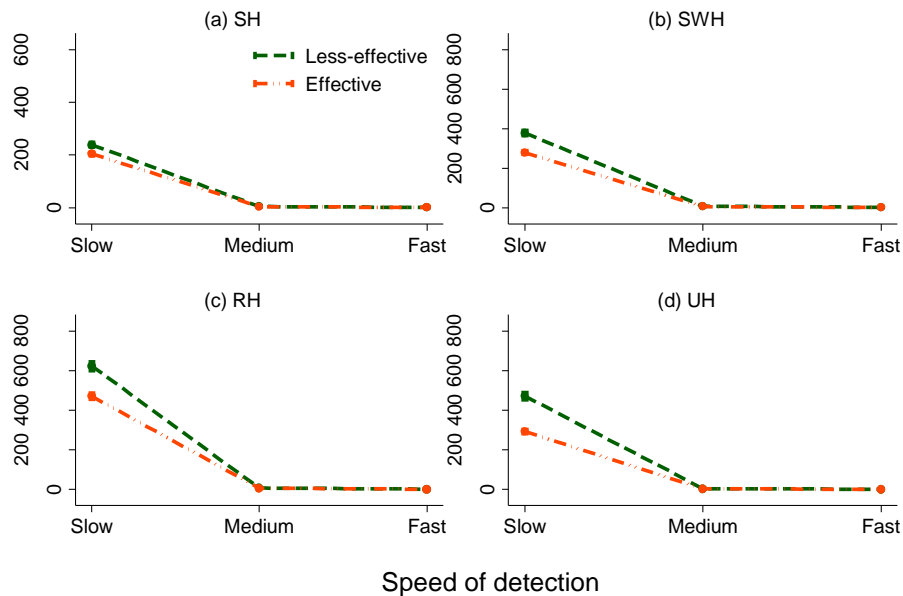


Figure 5: The interaction effects of speed of detection and movement restriction strategy on the size of the outbreaks. The error bars show the predicted 95% confidence intervals of the size of the outbreaks. Only the results of high animal to human – medium human to animal (HM) transmissibility of the virus at No-zone quarantine strategy are shown. Key: SH = swine herds, SWH = swine worker households, RH = rural non-swine worker households, UH = urban households; Less-effective movement restriction = 100% decrease in the baseline direct contact of all detected units, 95% decrease in the baseline direct contacts of undetected units within the quarantine zone and 80% decrease in the indirect contacts, all within 5 days; Effective movement restriction = same levels of decrease in the baseline contact rates as less-effective movement restriction but all achieved within 10 days.