ANALYSIS OF SIMULATED OUTBREAK DATA AND SPATIAL ANALYSIS OF HIGHLY PATHOGENIC AVIAN INFLUENZA FOR PREPAREDNESS PLANNING AND POLICY

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ABSTRACT

The first objective of this research was to develop and evaluate an approach to analyze and communicate the results of a large number of simulated outbreaks of highly pathogenic avian influenza (HPAI) to decision-makers and policy-makers, using the North American Animal Disease Spread Model (NAADSM), and to make recommendations on the most effective HPAI control policy for Ontario, Canada, specifically, on the effect of stamping-out and ring-culling strategies on the magnitude of an HPAI outbreak. Negative binomial regression analysis was used to identify significant predictors of the number of farms infected for each scenario. Interaction plots were developed from the output of the negative binomial regression analysis, to facilitate communication of simulation results to policy-makers and to analyze the relationship between movement restrictions and destruction strategy. Negative binomial regression analysis was appropriate for handling the right-skewed count data of the simulated HPAI outbreaks in Ontario, while interaction plots were an appropriate visualization tool for communication to policy-makers. For policy development, the modeling results suggested that stamping-out of the infected/detected flocks, without ring-culling, in combination with movement restrictions on direct and indirect contacts, would be the most appropriate policy for Ontario.

The second objective was to compare the results of simulated outbreaks of HPAI using randomly generated point locations and flock sizes and compare the results to those obtained when real data, for Ontario, Canada, were used. The NAADSM requires farm point locations and flock sizes; however, real location data are often unavailable. Therefore random location and flock size datasets are typically used. Three datasets were developed consisting of: 1) a real-industry dataset - real flock size and location data; 2) a "random-industry" dataset - using industry data for random point locations and flock sizes; and 3) a "random-census" dataset - using Statistics Canada agricultural census data for randomly generated point locations and industry data for flock sizes. Four production types were used (commercial chicken meat, commercial eggs, commercial turkey, and hobby poultry) for the analyses. Four outbreak scenarios were investigated for comparison of the real data versus both sets of randomly generated data, considering both a weighted median and weighted maximum number of contacts per day between farms, including various control strategy options (e.g. movement restrictions and destruction strategies). Negative binomial regression analysis and a Kolmogorov-smirnov (K-S) equality-of-distributions test were carried out to determine if any significant difference existed between the three datasets. For both tests, in the majority of the scenarios, there were significant differences between the datasets. The main difference was the real data had a larger maximum number of farms infected compared to the two random datasets, when a median contact structure was used but not when a maximum contact structure was used. Overall, under the conditions set in this particular study, randomly generated flock size and location data were found to be a suitable replacement for real-industry data.

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First and foremost, thank you to my family and friends for all their support, without you I wouldn't be who I am today. Thank you to the Canadian Food Inspection Agency and the Atlantic Veterinary College for providing the funding for this research and to Dr John Vanleeuwen and Dr Javier Sanchez for their guidance. We also thank Drs Sandra Stephens and François Caya for their expertise in the development of input parameters, the Ontario Livestock and Poultry Council, Agriculture and Agri-Food Canada, and the Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA) for providing the population datasets for the simulations, and the Poultry Expert Committee for their review of the input parameters used in this study.

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Chapter 1: GENERAL INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

The Canadian poultry industry generated an annual farm gate value of $560.5 million for eggs destined for human consumption, and $1.55 billion and $278 million for chicken and turkey meat products, respectively, in 2006 (Agriculture & Agri-food Canada, 2007). In recent years, highly pathogenic avian influenza (HPAI) outbreaks have had devastating effects on the poultry industry around the world (Pozza et al., 2008), and the evolution of new antigenic strains has been impacting human health as well. Currently in Canada, the control policy for notifiable avian influenza, consisting of all HPAI and low pathogenic avian influenza (LPAI) with the H5 and H7 subtypes in domestic poultry, is to eliminate the disease through pre-emptive slaughter at a 1km radius around an infected farm and through the implementation of effective movement restrictions (CFIA, 2009a). Due to recent avian influenza (AI) outbreaks in British Columbia in 2004 and 2009 and in Saskatchewan in 2007, experts have begun to question the effectiveness of the current control policy in Canada. Policy can be defined as plans, positions or guidelines of government which influence decisions by government (Office of the Auditor General, 2003). There are many forms of policy including a broad policy which includes government-wide direction; more specific policy that is developed for more specific sectors; and operational policy that guides decisions on programs and project selection (Office of the Auditor General, 2003).

Due to past outbreak experiences and HPAI virus spread research, different approaches and methodologies have been developed to guide policy development to improve animal health. Simulation modeling is one approach which has proven an important tool for identifying effective control strategies for outbreaks of foreign animal diseases, such as HPAI (Kobayashi et al., 2007). Various platforms have been developed to simulate the spread of contagious diseases, such as AusSpread (Ward et al., 2009), Interspread Plus (Halderen et al., unpublished), and the North American Animal Disease Spread Model (NAADSM; Harvey et al., 2007).

Various issues are encountered when using disease modeling to inform policy development and decision making for incursions of foreign animal diseases. Firstly, most of the models currently used require specific farm-point locations (latitude, longitude) with farm type and number of animals present. In some cases, it is difficult to obtain exact farm-point locations for use in outbreak-simulation modeling; therefore, alternative methods need to be explored to accurately represent the real location. Limited research has been conducted to compare real-point location data and random-point location data for use in outbreak simulations. Secondly, the process of analyzing disease simulation modeling results and communicating these results in a way that can be easily grasped by decision makers and incorporated into policy can represent a major challenge. An approach has not previously been attempted.

The purpose of this literature review is to provide the reader with the background and rationale behind this thesis. We start with a review of avian influenza including its pathogenicity, its modes of transmission and recent outbreak history and control strategies. The various modeling platforms used for policy generation, such as the NAADSM, are then introduced followed by the approaches used to date to generate random point locations to represent the poultry population in these modeling platforms.

1.2 Avian influenza

1.2.1 Aetiology of the disease

In 1878, a disease of high mortality, defined as 'fowl plague', infected fowl in Italy. The association of this disease with influenza viruses, however, was not confirmed until 1955, when it was classified as HPAI (Alexander, 2000). Avian influenza viruses are negative-sense, segmented RNA viruses in the family *Orthomyxoviridae*, which has several members, including types A, B, and C influenza viruses (Swayne & Suarez, 2000). Type A influenza viruses include all avian influenza viruses and can infect a variety of animals including wild birds, domestic poultry, swine, horses, mink, seals, and humans. Types B and C influenza viruses mainly infect humans (Swayne & Suarez, 2000). Type A influenza viruses have eight RNA segments, encoding ten different proteins, which are either surface proteins or internal proteins (Swayne & Suarez, 2000). The two surface (virus envelope) proteins of interest are haemagglutinin (HA) and neuraminidase (NA), which have large antigenic variation, with 16 HA and 9 NA subtypes used to characterize the Influenza A virus (Swayne & Suarez, 2000).

HPAI viruses are not virulent for all bird species, and disease severity in any host species varies with bird species and virus strain (Alexander, 2007). In 2002, disease outbreaks of HPAI H5N1 associated with live poultry markets and chicken farms resulted in the deaths of wild birds and resident waterfowl, including little egret (*Egretta garzetta*), grey heron (*Ardea cinerea*), black-headed gull (*Larus ridibundus*), feral pigeon (*Columba livia*), and tree sparrow (*Passer montanus*) in 2 waterfowl parks in Hong Kong (Tanimura et al., 2006).

Research has shown that primary spread of LPAI viruses into poultry is a result of wild bird activity, which may or may not involve direct contact with infected waterfowl (Alexander, 2007). The evidence for the introduction of LPAI viruses carried by wild birds into poultry can be summarized as follows: (1) there is a higher prevalence of infection in poultry located on migratory waterfowl routes; (2) there is a higher prevalence of infection in poultry kept outside, such as free range turkeys; (3) surveillance studies in areas with LPAI in poultry have shown similar variation in virus subtypes as those in waterfowl outbreaks; (4) influenza outbreaks have a seasonal occurrence in high-risk areas, which coincide with migratory activity; and (5) in some documented outbreaks, there is evidence of contact with infected waterfowl at the initial infection site (Alexander, 2007).

Secondary spread of AI other than by wild bird activities among and between poultry premises is typically by mechanical transfer of feces. Spread by personnel and fomites was the most strongly suspected mechanism of spread in the 1983-1984 Pennsylvania outbreak (Alexander, 2007).

In South-east (SE) Asia, the emergence of HPAI H5N1, in 1996, and its later spread in domestic poultry and wild birds across Asia and into Europe occurred from infection of commercial geese in Guandong province, China (Alexander, 2007). Figure 1 displays outbreaks in domestic poultry, as well as cases reported in wild birds in SE Asia between November 2009 and May 2010.

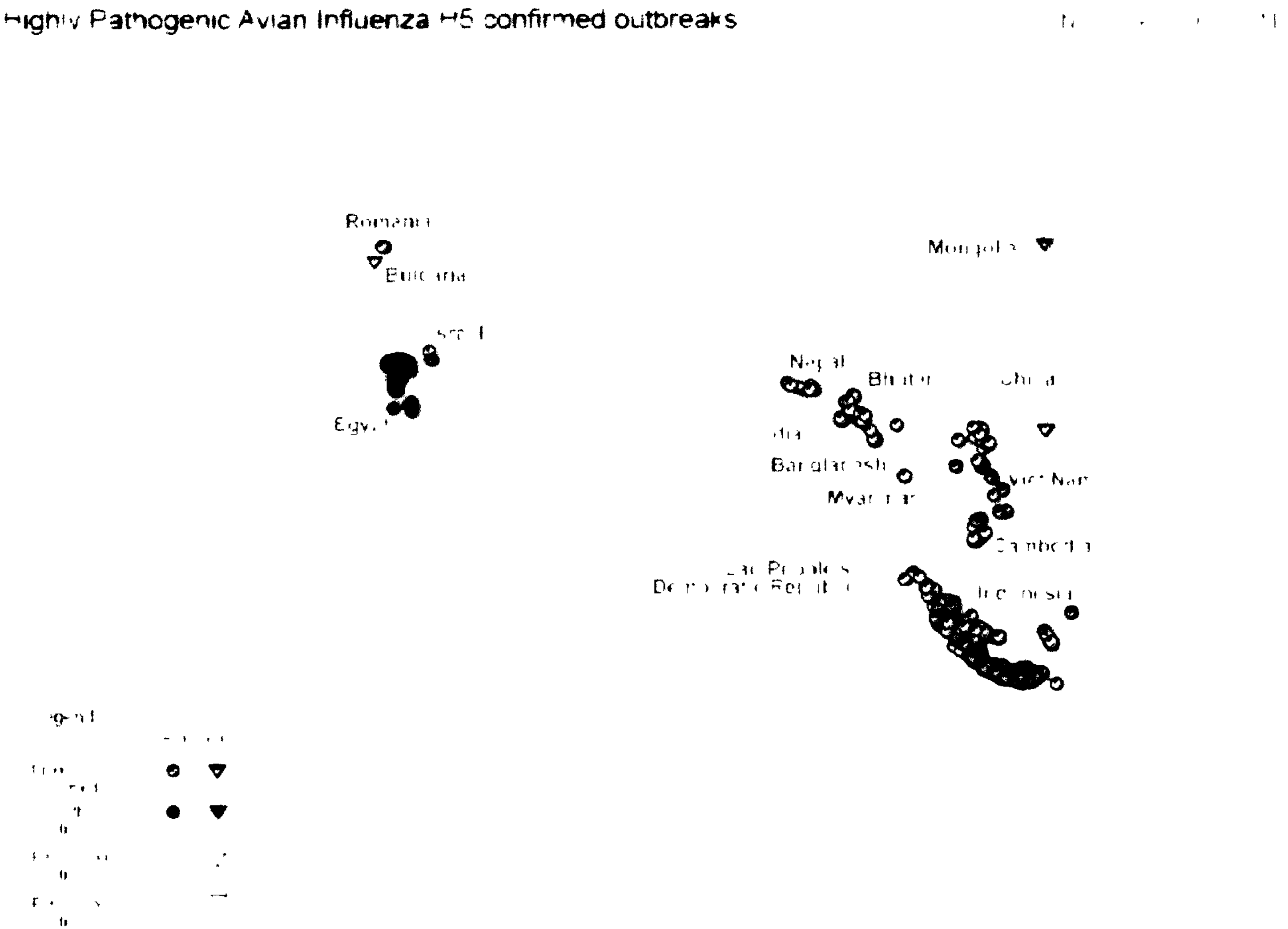

Figure 1: Confirmed cases of avian influenza HPAI H5 outbreaks among domestic poultry and wild birds between November 2009 and May 2010 (Courtesy of the World Health Organization).

1.2.2 Pathogenicity and affected species

1.2.2.1 Pathogenicity

Alexander (2007) states that Influenza A viruses can be divided into two groups; the highly virulent viruses causing highly pathogenic avian influenza (HPAI), with 100% mortality in domestic poultry and all other viruses causing a milder, mainly respiratory disease called low pathogenic avian influenza (LPAI). The HPAI viruses are restricted to subtypes H5 and H7, although not all H5 and H7 viruses cause HPAI. Furthermore, it appears that HPAI viruses typically arise through mutation of LPAI viruses that have been introduced into poultry (Alexander, 2007). The mutation of LPAI to HPAI phenotype occurs through the introduction of basic amino acids at the hemagglutinin cleavage site. This facilitates systemic virus replication in the host which causes an acute generalized disease in poultry with a mortality approaching 100% (Munster & Fouchier, 2009).

LPAI typically causes mild to no respiratory disease in poultry, though when combined with other infections or environmental conditions; it can cause more serious disease (Alexander, 2000). Chickens and turkeys are not natural hosts for AI viruses, but can easily become infected by the virus. Swayne & Suarez (2000) state that, overall, mortality rates from LPAI are low, compared to HPAI, unless accompanied by a secondary infection or unfavorable environmental conditions.

1.2.2.2 Affected species

1.2.2.2.1 Wild birds

Wild birds are frequently infected with influenza viruses, with birds from the Orders Anseriformes and Charadriiformes being the most likely carriers. Influenza viruses have been isolated from untreated lake water, where large numbers of waterfowl are found. Bird-to-bird transmission of the virus via the fecal-oral route from surface waters has been shown to occur (Reeth, 2007). Though some wild bird species are capable of carrying AI between countries or even continents, surveillance studies have found that some wild birds, namely the water birds and shore birds, in North America and Europe have a high prevalence of viruses of low virulence for poultry, though this depends on the bird species and season (Reeth, 2007). Generally, wild waterfowl and shore birds are reservoirs for LPAI where the virus replicates and then is shed in their feces, respiratory tract and GI tract, the respiratory tract has been shown to be a site of replication mainly for HPAI (Reeth, 2007; Parmley et al., 2011). Observations from a surveillance study by Yee et al. (2008) show differences in clinical signs among wild birds from the same taxonomic order, infected with HPAI H5N1, which is a highly virulent strain. Mallard ducks (*Anas platyrynchos*) have been found to carry and shed HPAI H5N1 without clinical signs for long periods of time, whereas geese (*Anser anser*), mute swans (*Cygnus olor*) and herons, such as the great blue heron (*Ardea herodias*), die from infection (Yee et al., 2008). This was contradicted in a Canadian experiment by Neufeld et al. (2009) where the adult geese did not get sick.

It is generally thought that LPAI viruses typically do not cause disease in wild birds, though this information is based mainly on experimental inoculations rather than information on natural infections in wild migratory birds. If the birds are infected, it is possible they may reallocate some of their resources to boost their immune system, impacting their migratory ability (Gils et al., 2007). In a study by Gils et al. (2007), migratory swans were fitted with a GPS-collar and tracked to obtain information about their feeding and migratory performances. Out of 25 birds, 3 were infected with a LPAI virus, and showed reduced feeding and migratory performance.

1.2.2.2.2 Domestic poultry

Galliformes, such as chickens (*Gallus gallus*), turkeys (*Melleagris gallopavo*), peafowl (*Phasianidae*) and Japanese quail (*Coturnix coturnix japonica*), have been found to be highly susceptible to influenza viruses (Reeth, 2007; Swayne & Suarez, 2000). Quail experimentally inoculated with HPAI H5N1 died within 2-3 days. Ducks experimentally inoculated with LPAI had no clinical signs, and HPAI H5N1 infection yielded mixed results, depending on the strain of virus used. One HP strain resulted in no clinical signs, while another HP strain resulted in neurological signs (Yee et al., 2008). Birds infected with HPAI are typically found dead with few clinical signs observed other than depression, recumbency and a comatose state (Swayne & Suarez, 2000).

1.2.2.2.3 Humans

Four HPAI subtypes, H5N1, H7N3, H7N7, and H9N2, with the vast majority being H5N1, have been identified in humans (Reeth, 2007). HPAI H5 and H7 virus strains have caused sporadic infections in humans in close contact with poultry, namely those that had visited a live poultry market the week prior to the onset of illness. The mortality rate associated with human infection from HPAI H5N1 is high, though infection with other HPAI viruses have has lower mortality rates (Uyeki, 2008). The first known case of HPAI H5N1 in humans was an infection in a 3-year-old child in Hong Kong in May 1997. In December 1997, 17 additional human cases were identified (Uyeki, 2008). Figure 2 demonstrates the number of human cases of HPAI H5N1 worldwide between 2003 and 2010. Reeth (2007) reports that although infection has occurred in millions of birds, HPAI H5N1 does not spread easily to humans. The World Health Organization reported 48 cases and 24 deaths in humans in 2010 and 46 cases and 23 deaths in 2011 (http://www.who.int/).

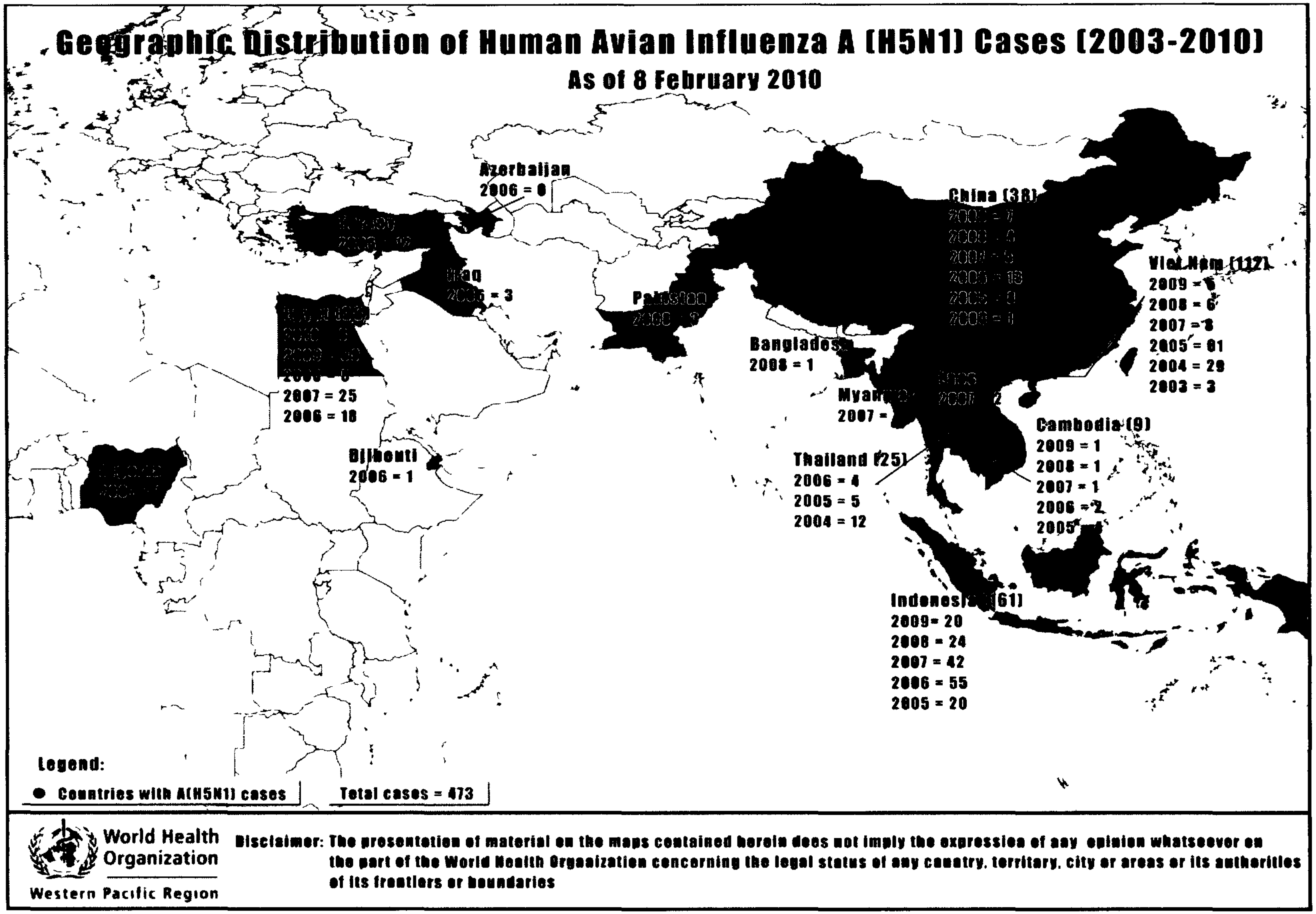

Figure 2: Cumulative distribution of human cases of avian influenza A (H5N1) from 2003-2010 (Courtesy of World Health Organization, Western Pacific Regional Office).

1.2.2.2.4 Other animals

Other species, aside from humans, domestic poultry and wild birds, can also be host species of HPAI, including; canines, felines, swine, Mustelidae, and raccoons (Procyonidae) (Yee et al., 2008). Virus transmission to felids has been repeatedly documented, with disease found in tigers in Thailand fed infected poultry carcasses, through experimental inoculation of influenza A virus (H5N1) in cats, and in cats in close contact with infected poultry (Keawcharoen et al., 2004; Leschnik et al., 2007; Rimmelzwaan et al., 2006). Keawcharoen et al. (2004) reported that during the outbreak in Thailand in December 2003, 2 tigers and 2 leopards at a zoo showed clinical signs, including fever and respiratory distress, and died unexpectedly. These tigers had been fed fresh poultry carcasses from a slaughter house later confirmed to be infected with the H5N1 virus. In October 2004, another H5N1outbreak was confirmed in tigers in a zoo in Thailand, where 147 tigers died or were euthanized. Yee et al. (2008) determined that tiger-to-tiger transmission occurred and the likely initial infection was caused by ingestion of AI-infected chicken carcasses. Furthermore, canines have been identified as a potential host for HPAI H5N1 from surveillance studies in Thailand, as well as experimental infection and natural contact studies (Yee et al., 2008; Giese et al., 2008). Songserm et al. (2006) found one dog infected with avian influenza H5N1 after ingestion of duck products obtained from an area with reported HPAI H5N1 infections in ducks. The dog had been reported as having developed high fever, panting and lethargy 5 days after ingestion before dying.

In 1979-80, 20% of harbor seals on the northeastern coast of the United States (US) died from infection with influenza A virus subtype H7N7. From 1982-83 and again in 1991-92 isolates of H4N6 and H3N3, respectively, were isolated on the New England coast from seals that had died of pneumonia (Callen et al., 1995; Horimoto & Kawaoka, 2001). The 1991-92 finding was the first isolation of an H3 subtype in seals, though it has been repeatedly seen in humans, poultry, pigs and horses (Callen et al., 1995). These viruses were antigenically and genetically related to avian viruses, indicating that transmission of AI to seals was not rare (Callen et al., 1995; Horimoto & Kawaoka, 2001).

1.2.2.3 *Modes of transmission*

Transmission between and within farms can occur in a variety of ways. Within farm spread refers to spread of disease agents directly between birds or indirectly by fomites on the same farm. Between-farm spread refers to spread of the disease from an infected farm to a naïve farm, but not from infected farm to infected farm as the virus is already present on the farm. Previous attempts have been made to evaluate the transmissibility of LPAI and HPAI viruses in domestic poultry experimentally. Alexander (2007) determined that transmission was dependent on the virus strain, species of bird, and environmental factors. In order for the virus to spread easily, a sufficient amount of virus must be released by the respiratory or intestinal route (Alexander, 2007). Large quantities of virus can be excreted in the feces, contaminating lake or drinking water, which may then lead to infection by the fecal-oral route as a result of 'cloacal drinking' also known as 'cloacal drop', or by direct ingestion of drinking water contaminated with feces (Alexander, 2007). Cloacal drinking occurs when the dorsal lip of the vent of birds, which possesses a medial protuberance, becomes activated and material on the lip is taken inside the cloaca by induced contractions (Hu et al., 2004). Tsukamoto et al. (2007) looked at the effects of direct spread as well as indirect spread through airborne dissemination. Their study, along with field observations, suggested that chicken house type, number of infected chickens, and the amount of environmental contamination may have affected the virus transmission efficacy during an outbreak (Tsukamoto et al., 2007). Sedlmaier et al. (2009) looked at the risk of airborne spread through investigation of the particulate matter size within barns. They found that humans working within the barn or living nearby can inhale up to 10^4 infectious AI particles a day, putting themselves at a high risk of infection. Also, animals on nearby poultry farms could become exposed and potentially infected by inhalation of about 300 infectious AIV particles per day.

Two studies evaluated environmental transmission in wild birds through the use of simulation modeling. Rohani et al. (2009) found that a combination of direct contact and indirect environmental contact, such as shared water sources or airborne dissemination, played significant roles in the spread of an outbreak in wild waterfowl. Similarly, Breban et al. (2009) found that in addition to direct fecal-oral transmission, uptake of the virus persisting in the environment could also lead to infection. Furthermore, modeling showed that environmental transmission played a significant role in the persistence of AI and its inter-annual epidemics in wild birds (Breban et al., 2009).

Nazir et al. (2011) evaluated the persistence of the AI virus in the environment and found that AI viruses can remain infectious in duck feces for periods of time ranging from a few days (at 30 and 20 degrees) or a few weeks (at 10 degrees) to several months (at 0 degrees).

1.2.3 Recent outbreak history

1.2.3.1 International outbreak experience in domestic poultry

Since the first reported outbreak of AI in Scotland in 1959, there have been 28 reported outbreaks in poultry outside of North America, half of them being reported in the past 10 years (Capua et al., 2000; Horimoto & Kawaoka, 2001). Notable outbreaks in poultry include the Mexican and Pakistan outbreaks in 1994 and the Italian outbreak in 1999. In Mexico, in 1994, LPAI H5N2 was isolated from chickens. The virus was not eradicated by slaughter and over several months the virus mutated to an HPAI strain. After this mutation vaccination was implemented which controlled the HPAI strain, however an LPAI H5N2 strain continued to circulate. Control in Mexico relied heavily on vaccination and not on accompanying measures such as monitoring and quarantine (Lupiani & Reddy, 2008).

In Pakistan an outbreak of HPAI H7N3 in poultry farms resulted in the death of 3.2 million birds and was brought under control through vaccination only. However, in 2001, 2003 and 2004, LPAI and HPAI H7N3 outbreaks continued to re-emerge, despite vaccination, resulting in the deaths of approximately 10 million birds (Lupiani & Reddy, 2008). Also in 2003, an outbreak of H7N7 occurred in the Netherlands poultry sector and resulted in human infection with reports of conjunctivitis (Beest et al., 2010). One other notable outbreak was the H7N1 outbreak in Italy in 1999, with a reappearance of the LPAI H7N1 in 2000, which was controlled and eradicated by 2002 (Lupiani & Reddy, 2008).

1.2.3.2. American Experience

In the US, outbreaks have occurred in Pennsylvania (1983; 1996-1998), Virginia (2002), California (2000-2002) Connecticut (2003), Delaware (2004), Maryland (2004), and Texas (2004). In the Pennsylvania H5N2 outbreak in 1983, 2.5 million layer chickens from 47 flocks on 24 premises were infected, resulting in the slaughter of 17 million birds from these 24 premises. This outbreak began with an LPAI H5N2 strain that mutated into a more virulent (HPAI) strain that differed by one nucleotide (Capua et al., 2000; Horimoto & Kawaoka, 2001). Approximately 25% of the birds exhibited clinical signs of respiratory disease and a decrease in egg production (Capua & Alexander, 2004). It was believed to have originated from contacts with live-bird markets in New York. Control was with strict biosecurity measures and depopulation of infected flocks (Capua & Alexander, 2004).

In 2000-2002, an LPAI H6N2 strain of the virus was isolated from chickens in 12 different locations in California, with the chickens showing a drop in egg production and an increased mortality (Woolcock et al., 2002). In 2002, an LPAI H7N2 virus, from a live bird market, began to spill over into the industrial poultry population in the Shenandoah Valley in Virginia (Capua & Alexander, 2004). Farms in North Carolina and West Virginia were also affected. A total of 197 infected farms were diagnosed, mainly in turkeys with a total of 5 million birds destroyed, costing approximately $149 million (Capua & Alexander, 2004).

In 2003, there were 2 outbreaks of LPAI H7N2 virus in New London County, Connecticut, affecting 2.9 million table-egg layer hens (Capua & Alexander, 2004). Recovered hens and replacement pullets were vaccinated. Both of these outbreaks occurred as a result of spread from live bird markets. In February 2004, 2 farms in Delaware were confirmed infected with LPAI H7N2 (Capua & Alexander, 2004). One farm was a quasi-backyard flock of 11,000 chickens that primarily supplied live-bird markets, while the other farm was a commercial broiler operation with 85,800 birds (Capua & Alexander, 2004). In March 2004, a flock of 118,000 6-week-old broilers and a farm close to it with 210,000 2-week-old birds in Maryland were also confirmed infected. Both of the infected flocks were destroyed (Capua & Alexander, 2004).

In Gonzales County, Texas, in 2004, an HPAI H5N2 subtype was confirmed in a broiler flock of 6,608 birds (Capua & Alexander, 2004). The farm was depopulated with the source of infection being related to the Mexican H5N2 virus (Capua & Alexander, 2004).

1.2.3.3. The Canadian Experience

Canada has had limited experience with avian influenza. The first documented outbreak was a LPAI H7N1 subtype in 2000, in a flock of turkeys in Ontario (Capua & Alexander, 2004). This flock showed slightly elevated mortality and a drop in egg production. The flock fully recovered (Capua & Alexander, 2004). Other notable outbreaks include an HPAI H7N3 strain in the Fraser Valley, British Columbia (2004) (Pasick et al., 2009; Bowes et al., 2007) and Saskatchewan (2007), an LPAI H5N2 strain in Abbottsford, British Columbia (2009) and an LPAI H5N2 strain in Manitoba in 2010. During the British Columbian outbreak in the Fraser Valley in 2004, infected premises included 42 commercial flocks and 11 backyard flocks, with a total of 1.3 million birds, which were depopulated along with non-infected birds from an additional 410 commercial farms (14.9 million birds) and 553 backyard flocks (18,000 birds), within a 3km radius of each infected premise, in an effort to control the spread of the disease (Skowronski et al., 2007). This outbreak prompted the development and implementation of Canada's Inter-Agency Wild Bird Influenza Survey as the virus was believed to have originated from wild birds but the viruses circulating in wild bird populations were unknown (Bowes et al., 2004; Parmley et al., 2008). In 2007-08, an infected broiler hatching operation in Saskatchewan was depopulated (approx. 53,000 birds) after it was confirmed to be infected with HPAI H7N3, and an "infected zone" was put in place at a 3km radius of the infected farm, and a "movement restriction zone" was established at a 10km radius of the infected farm (CFIA, 2004). All restrictions were lifted as of October 31, 2008. On January 29th, 2009, a turkey farm in Abbotsford, British Columbia was infected with an LPAI H5N2 strain. The farm was quarantined and approximately 60,000 turkeys were destroyed (CFIA, 2009b). Another farm, a specialty bird breeding operation, was detected shortly after and was destroyed, with no other confirmed farms detected, leading to a total of 12,000 birds destroyed. In November 2010, LPAI

H5N2 was detected on a commercial poultry operation in Manitoba. All birds on the premise were humanely destroyed with precautionary quarantine placed on farms identified through trace-out investigation, with one hatchery also being destroyed. All restrictions were lifted in February 2011 (CFIA, 2011).

From these past outbreaks it can be said that vaccination is not the most effective method for eradicating AI in a population. The virus strains mutate easily where continuously circulating LPAI strains in wild bird populations could easily mutate to a more virulent strain that may be different from the already circulating HPAI strain. It seems that one of the most effective methods in controlling an outbreak of AI is through movement restrictions. Once the virus is detected in a population, immediate movement restrictions on direct and indirect contacts should be put into place.

1.2.4 Control strategies

Specific control strategies, such as proper biosecurity, or limiting the probability of transmission through indirect contact, should be in place at all times. The Canadian Food Inspection Agencies (CFIA) document called "Notifiable Avian Influenza (NAI) Hazard Specific Plan" (http://www.inspection.gc.ca/) states that AI viruses can survive for extended periods of time outside the host and can be spread through contact with other birds and fomites on vehicles, equipment, and people. Swayne & Suarez (2000) also emphasize that enhanced biosecurity is an important part of any AI prevention and control program. In Canada, detection of an H5 or H7 variant, regardless of whether it is LPAI or HPAI, will lead to eradication measures, due to the potential for mutation into HPAI.

The main options for control and eradication of an AI outbreak consist of one or a combination of quarantine, establishment of disease control zones to enforce movement restrictions, surveillance to determine the strains of AI present in the poultry population and to determine if the control strategies are effective and tracing of direct and indirect contacts originating from infected farms, culling of infected and exposed animals, and in some cases, vaccination. Surveillance within the commercial poultry industry allows for more effective detection of the virus if a farm becomes infected leading to a quicker response. In the wild bird population surveillance provides you with an idea of the strains circulating in the population that may pose a threat to the commercial poultry industry. Continuous surveillance during an outbreak may indicate other farms that are infected which leads to a quick response. One control strategy, stamping-out, includes culling animals that are 1) infected with the disease agent, 2) have been in contact with the infected animals or premises; or 3) are located within a predetermined distance from an infected premise (Yee et al., 2008). Movement restrictions of poultry within and outside restricted zones can be difficult to enforce in some countries due to illegal practices to satisfy the demand for meat and, as seen with the outbreaks in Canada, it was difficult to enforce due to the value of some specialty breeds of birds. Vietnamese authorities estimated that up to 70% of poultry illegally transported to China goes undetected. Quantifying these practices and the association with outbreaks in any country, however, has not been documented (Yee et al., 2008) but investigation into quantification is currently being undertaken by the CFIA and USDA. Movement restrictions on direct contacts, defined as movement or shipment of birds between flocks where one flock is infected, leading to direct contact (e.g. fecal-oral route) between infected and naïve birds, are often easier to enforce than those on indirect contacts. Indirect contacts can encompass such things as fomites on vehicles and personnel (Yee et al., 2008).

Various countries have implemented different control strategies, though no one strategy alone has been reported to eradicate the disease. AI control in the European Union, as implemented in the Italian outbreak (1999-2001), consisted of prompt identification of infected and at-risk farms, immediate movement restrictions and eradication measures (stamping-out) on infected farms, and enforcement of restrictive policies to restocking and movement of live birds, vehicles, and staff in areas at risk (Ehlers et al., 2003). During the 2003 outbreak of H7N7 in the Netherlands, infected flocks were culled with pre-emptive slaughter of any neighboring flocks (Bavinck et al., 2009).

Pozza et al. (2008) suggests that pre-requisites for successful control of an outbreak of HPAI include proper disease investigation, tracing suspect contacts, implementing proper movement control strategies, and prompt stamping-out after the disease has been confirmed. In some cases, such as in the policy in Canada, pre-emptive slaughter of contact flocks or high risk flocks have also occurred as part of a more robust control program (Pozza et al., 2008).

The primary control policy in Canada involves quarantine, stamping out of the infected farm, establishment of disease control zones and movement restrictions, tracing and surveillance and possible use of a pre-emptive slaughter program (CFIA, 2009a). In most situations, the overall purpose of an effective stamping-out initiative includes: (1) rapidly identifying all exposed premises; (2) applying strict movement control; (3) tracing and destroying all infected or potentially infected animals, products and materials; (4) decontaminating infected premises and vehicles to avoid further spread; and (5) regaining country freedom status for notifiable avian influenza without delay (CFIA, 2009a). Due to the recent Canadian outbreaks, it is important for policy-makers to determine whether this strategy is the most effective method for minimizing disease impacts and eradicating the disease, as this has not been previously explored. In order to be more effective during an outbreak policy-makers want to ensure everything is being done to efficiently and effectively eradicate the virus with a minimum cost to the industry. One of the main challenges faced in these outbreaks was compliance from owners in applying movement restrictions and following with the depopulation protocols. Due to the value of some of these birds it was difficult to enforce movement restrictions and breeder of birds with valuable genetics did not want to depopulate their flocks.

1.3 Disease modeling

1.3.1 Simulation model applications and previously used modeling tools

Modeling of simulated data can be used as a tool to determine the most effective control strategies in the event of an outbreak (Taylor, 2003). Kleijnen et al. (2005) reported that there are three basic goals in simulation analysis: 1) developing a basic understanding of a particular model or system; 2) assist with identifying important features of an outbreak that could then inform the development of robust decisions or policies; and 3) comparing the merits of various decisions or policies. In some situations, simulation modeling is used when the underlying mechanisms of a situation are not well understood, and when real-world data are limited or non-existent (Kleijnen et al., 2005).

Disease modeling, used for the study of foreign animal diseases such as Foot-and-Mouth disease (FMD), Classical Swine Fever (CSF), and HPAI in both real and simulated outbreaks, aids our understanding of a disease. Models have provided information on important elements of a foreign animal disease outbreak, though with some limitations, which depend greatly on the model being used. Simulation modeling can help identify potential risk factors for the introduction and/or spread of a contagious foreign animal disease, and can help predict the effects of implementing various control strategies during an outbreak, driving policy decisions. One key component for the use of models for policy is the ability to communicate the models and their outputs to policy-makers. One example of disease spread models that can be used as a tool during an outbreak is the stochastic model, used by Tsutsui et al. (2003), for evaluation of a FMD outbreak in Miyazaki, Japan in 2000. Japan had been free of FMD for 92 years until this particular outbreak. Once FMD was confirmed on the index farm, all animals on the farm were destroyed and the premise was disinfected. A control zone and a surveillance area were established at a 20km and 50km radius around the infected farm, respectively. From within the surveillance area, two more infected herds were detected at distances of 2km and 7km from the index farm. Once movement control measures were implemented, serological and clinical surveys were carried out on the premises that were depopulated and under surveillance. A Monte-Carlo method was used to evaluate the survey results in combination with a Reed-Frost model that simulated the spread of the disease, based on the number of days from the infection (Tsutsui et al., 2003). The model results found that herd-level sensitivity in the survey exceeded 80%, despite the conservative assumptions in the input parameters. From the detection of two infected herds by this model it was thought that the survey significantly contributed to the early eradication of FMD in Miyazaki, although the herd-level sensitivity was greatly influenced by the time of sampling post-infection. One of the main limitations of the model was that transmission between herds after imposing movement control was not considered. Animal movement in the control area was strictly prohibited for 21 days after destruction of the infected herd.

de Vos et al. (2006) used a scenario tree model for CSF, a highly contagious viral disease affecting both domestic and wild (feral) pigs, to evaluate the impacts of 257 uncertain factors. Limited data availability, low frequency of epidemics, variations in virus strains, and changes in preventive measures and control strategies resulted in a model with substantial limitations. The scenario tree model itself was used to calculate the probability of introduction of CSF into member states of the European Union so to gain more insight into the main risk factors for CSF introduction (de Vos et al., 2006).

Schoenbaum et al. (2003) compared the epidemiologic and economic consequences of different slaughter and vaccination strategies based on hypothetical outbreaks of FMD in the US. They looked at the consequences of four specific stamping-out strategies and three vaccination strategies, compared under varying conditions of herd density/sizes and rates of disease spread. A stochastic simulation model was used that allowed incorporation of other outbreaks for a variety of contagious diseases through adjustment of specific input parameters. They found that the best strategy depended on the speed of spread of FMD virus and the demographics of the susceptible population, but it is uncertain what effects were in influencing policy decisions. Furthermore, depopulation of herds in contact with infected herds was less costly than only depopulating infected herds, with depopulation in 3km rings being more costly compared to other depopulation strategies, such as stamping out only.

Sharkey et al. (2008) evaluated the consequences of introducing HPAI H5N1 into Great Britain using a spatially explicit, detailed stochastic simulation model. They successfully investigated the variation in the risk with respect to species, industry and geographical location, and determined the efficacy of the control strategies used by the British Government.

InterSpread Plus (Halderen et al., unpublished) simulates the spread of infectious diseases in populations and is an enhanced version of InterSpread (Halderen et al., unpublished), which was used extensively in the 2001 FMD outbreak in Great Britain. Interspread is a fully spatial, state-transitional model where the spread mechanisms and control options act directly on the epidemiological units. Sanson et al. (2006) developed an InterSpread Plus parameter set to evaluate FMD in New Zealand, where they found that local spread played a significant role in the spread of the disease, and movement restrictions had an impact on reducing this spread.

Another model that had been used for Johne's disease was a simulation model developed using Visual Basic v6.0® (Sergeant, 2003). This model simulated spread of Johne's disease in flocks of sheep either through local spread or through movements of replacement sheep. Control measures were also simulated using this model, such as surveillance, quarantine, and vaccination in various combinations (Sergeant, 2003). This model has potential for use for an outbreak of AI, however there was no mention of including destruction as a possibility. As destruction is a very important control factor for reducing the spread of AI the model may not be appropriate, however further investigation into the model's usefulness is required.

1.3.2 The North American Animal Disease Spread Model (NAADSM)

The NAADSM (Harvey et al., 2007) is a model framework developed to assess foreign animal disease risks, and to set up contingency plans and preparedness strategies in the event of an outbreak. NAADSM is a spatially explicit, stochastic, state-transition (moving from one disease state to the next) model developed for policy formulation in North America (Harvey et al., 2007). Although the NAADSM was developed for use in North America it has been developed with a great level of flexibility so it can be applied to any geographical area (Rivera 2009 – see ISVEE proceedings).

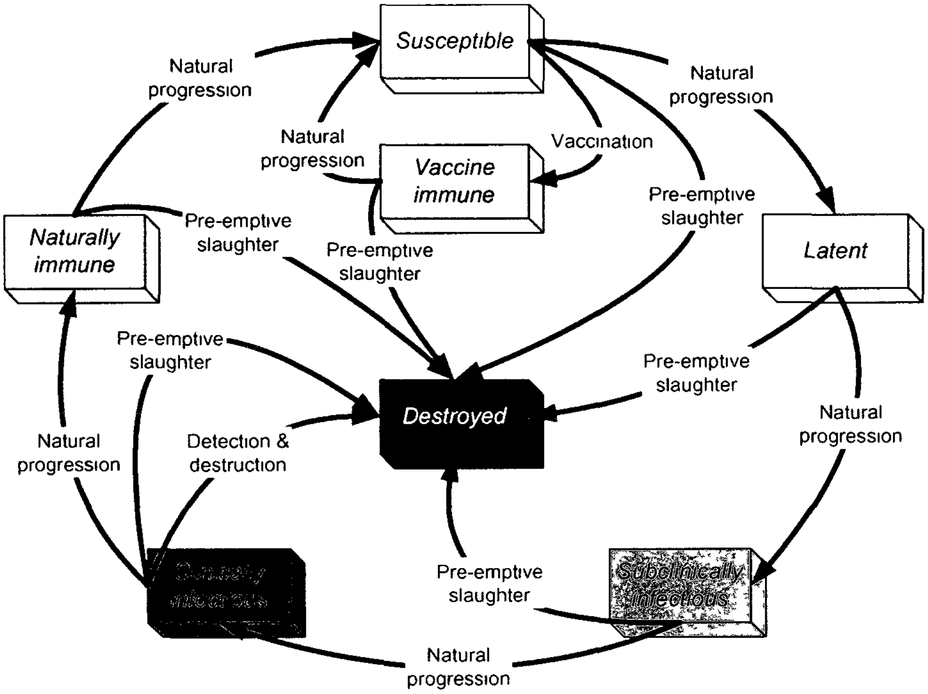

Figure 3: States and transitions simulated by the North American Animal Disease Spread Model. Without intervention, units will follow the state progression indicated in the outer loop. Upon implementation of disease control measures, intervening actions may alter the normal disease cycle, as shown inside the loop. (Provided with permission from Elseveir).

The model runs in terms of an animal aggregated unit, such as a herd or flock. These units move from one disease state into the next in a predictable cycle over a period of time (Figure 3). The cycle can be interrupted by the implementation of disease control measures (Figure 3, Harvey et al., 2007). The model contains user-established parameters that define model behavior in terms of disease progression. This involves disease spread from animal-to-animal contact; contact with contaminated personnel and equipment; airborne dissemination; and implementation of control measures such as destruction, movement restrictions, and vaccination (Harvey et al., 2007).

Production types are defined by the user and contain a group of units with similar within-herd disease transmission and similar rates of animal shipments, indirect contacts, and local spread. The production type can either be a single kind of livestock or a mixed type. When a susceptible unit is infected, it makes the transition from one disease state to the next. Direct contact spread is defined as movement or shipment of animals among units. Indirect contact spread is defined as movement of people, materials, vehicles, equipment, and animal products and is simulated in a similar manner as direct contact. A baseline rate of contact from one production type to another is independently specified for movement in each direction between each pair of production types. Similar to baseline contact rates, movement control functions are specified for each pair of source and recipient production types. An adjustment to the baseline rate of contact is based on the number of days since the initial case of disease was detected. This allows the model to mimic the implementation of movement controls over the course of an outbreak response.

Two probabilities contribute to disease detection: the probability of clinical signs being observed by the producer or veterinarian; and the probability of reporting to the authorities. Both of these probabilities can be defined for each production type. The reporting probability is a function of the number of days since the first detection in the population. The model user can then simulate the impact of improved awareness of a disease situation as an outbreak progresses.

Five disease control measures can be simulated by NAADSM (Version 3.1); quarantine, tracing, movement controls, destruction, and vaccination (Harvey et al., 2007). Units can be quarantined through various mechanisms: 1) a diseased unit is quarantined on the day immediately following detection; 2) units identified by trace-out investigations (direct/indirect) are quarantined; and 3) those units awaiting prioritized destruction are quarantined. Once the first infected farm is detected, the model can also simulate a destruction program, defined by the user, which includes the number of days from the initial detection until the destruction program begins and can be applied to detected farms only, trace-outs of detected farms or to farms in a specified vicinity of detected farms. Movement restrictions can be applied at the same time to all the farms in the study region.

The NAADSM limits the number of units that can be destroyed per day, known as the destruction capacity, based on the parameters built into the model. However, this destruction capacity does not consider the number of animals in units to be destroyed (Harvey et al., 2007). If a unit is designated for destruction but cannot be destroyed immediately, due to the maximum capacity of destruction being reached, the unit is quarantined and placed on a prioritized waiting list for destruction (Harvey et al., 2007). Three specific criteria are used to prioritize destruction, which the user ranks by importance: the production type; the reason for destruction of the particular farm; and the number of days a farm has been waiting in the destruction queue (Harvey et al., 2007). Vaccination can also be included in NAADSM but was not included in this study, as it was not of interest to the policy-makers. Briefly, a trigger is required in order to initiate vaccination in NAADSM. This trigger is based on the number of flocks detected, decided by the user. Many policies address the fact that long-live birds and flocks with high genetic values should be targeted (Dubé, unpublished). In NAADSM a vaccination ring can also be incorporated and typically varies with species. Finally a vaccination capacity is assumed.

The user-developed models can be run thousands of times, generating a distribution and a set of descriptive statistics for various outcomes, such as the median, range, standard deviation, and selected percentiles for the duration of the outbreak and number of farms infected (Harvey et al., 2007). A more detailed description of the NAADSM parameters can be found in Chapter 2.

1.4 Generating geo-location data in the absence of exact farm point locations

Mapping farm locations of animals has proven beneficial in disease outbreak control, as it provides a tool to evaluate various strategies to prevent disease spread (Norstrøm, 2001). The Geographical Information System (GIS) has an advantage over a more standard database management system in that it has a concept of spatial neighborhood, so that determination of spatial proximity between individual herds and animals can be obtained (Durr & Gatrell, 2004).

Numerous studies have looked at outbreaks by comparing the locations of infected farms with the locations of all farms at risk in the area (Ehlers et al., 2003; Ward, et al., 2008). Ehlers et al. (2003) analyzed the AI outbreak in Italy in 1999-2000, using the geographic coordinates of the farms and storing them in GIS. The analysis provided them with information to formulate contingency plans for control and eradication of AI. Spatiotemporal studies of foreign animal diseases, using GIS, can provide additional knowledge leading to detection of spatiotemporal clusters of disease, and identification of key explanatory variables and geographic areas of concern (Oyana et al., 2006).

In order to simulate outbreaks using a stochastic and spatial model, such as NAADSM, for policy generation, the models require known farm locations and how many and what type of animals are on each farm. In some instances, exact farm location is mostly unknown, as in the United States, or strictly confidential, as in Canada (Riley, 2010). There are many questions surrounding the most appropriate way to geo-reference a farm point location. In some areas, the actual farm boundaries for geo-referencing have been used, such as in New Zealand, where a database has been created for national disease outbreak planning (Durr & Froggatt, 2002). Some geo-referencing methods that have been explored include: (1) deriving a point approximation of a discrete farm from the farm centroid calculated from digitized boundaries; (2) using the farm postal address postcode; (3) using a three-digit agricultural parish code that is assigned to each new farming enterprise upon registration with Department of Environment, Food and Rural Affairs (DEFRA); and (4) using farm building locations, defined as a main building or collection of buildings contained within or near the farm boundaries and used to house either the farmer, employees or animals (Durr & Froggatt, 2002). Durr & Froggatt (2002) found that the farm building was the single best practical geo-referencing point for discrete farms, in a study using data from Cornwall, England.

Tildesley et al. (2009) generated simulation experiments to help with early-outbreak decisions for FMD in the US through estimating the locations of farms for a handful of counties in the US using satellite imagery and other data sources. Their results relied on 2 weeks of outbreak data. They concluded that in the absence of location data, their methods would be used only to refine policy (Tildesley et al., 2009). Other researchers have used satellite imagery, which resulted in a large number of false positive identifications (Bruhn et al., unpublished).

Bruhn et al. (unpublished), using data from the 2002 US census of agriculture, generated farm locations using specific characteristics, such as locations in areas where actual operations of a particular size and type have a high probability of occurring. They compared their randomly generated point locations to “truth” data for Lancaster County, PA. They found it was possible to generate rudimentary poultry-operation locations nationwide using US census of agriculture data and GIS (Bruhn et al., unpublished).

With randomly generated point locations, comparisons to real data point locations can be made to determine if the size of an outbreak, based on specific scenarios, is comparable. This will allow countries that lack the point locations of their farms to confidently use randomly generated point locations to determine the potential size of an outbreak based on different control measures.

1.5 Simulation output analysis techniques

In a complex model, a large number of simulated scenarios can have many input parameters that have a highly significant impact on the outcome. This creates numerous significant interactions, which are difficult to interpret (Kleijnen, 1995b). Fraedrich et al. (2000) suggests using a typical statistical ‘goodness of fit’ test, including t-tests, chi-square tests, and regression analysis, as methods for analyzing the output from a simulation model. Fraedrich et al. (2000) also suggests that using a t-test on the differences between the measured and predicted results of a linear regression versus the sums will improve the power of the study more than other regression tests. Identifying the non-informative variables can be done by evaluation of insignificant correlation coefficients between the exogenous variables and the residuals, using both parametric and non-parametric methods (Fraedrich et al., 2000).

Regression analysis can generalize results from a simulation, characterize the input/output behavior, provide an estimate of the effects of the parameters in the regression and give a good estimate of the main effects and interactions among factors (Kleijnen, 1995a). The influence of key model parameters on the model output is of great interest, as this may indicate specific threshold points or particular parameters that may have a great impact on the outcome (Harvey et al., 2007).

When deciding which analysis technique is most appropriate for a particular analysis of the output from a simulation model, it is important to consider all possible methods and their associated assumptions that need to be met. In linear regression, the specific assumptions include: homoscedasticity, normality of residuals, and linearity of the outcome-predictor association. Homoscedasticity implies constant variance of predictors at different levels of the outcome variable (Dohoo et al., 2003). With outbreak data consisting of an outcome of counts, from 'rare' events, that are strongly right-skewed due to a large number of outbreaks with 1 or 2 farms infected, but occasional large numbers of farms infected, a linear regression is not appropriate because most of its assumptions are violated. The next possible option is a Poisson distribution typically used to model counts of 'rare' events (Dohoo et al., 2003). Poisson distributions are evaluated by analysis of the residuals, assessing the overall fit of the data to the distribution, evaluating overdispersion, and checking for influential points or outliers. The assumption behind the Poisson model is that the mean and the variance of the number of events are equal, after taking into account the effects of the predictors in the model (Dohoo et al., 2003). If there is overdispersion, it can be dealt with by fitting a model that allows the variance to be larger than the mean, such as a negative binomial regression model (Dohoo et al., 2003). Negative binomial regression fits models of count data, with strongly skewed outcomes.

1.6 Model communication and visualization

Policy-makers typically create a robust policy, using the worst case scenario that is useful across a broad range of scenarios. Kleijnen et al. (2005) state that to communicate results from a simulation effectively to policy- and decision-makers, graphical tools allow multi-dimensional visualization of the results and are generally more informative than tables and equations.

Graphical methods, such as scatter plots, illustrate whether a factor has a positive or negative effect on the outcome. Scatter plots are also appropriate for studying interactions. By definition, if the predicted line for factor A and an outcome for one level of factor B is not parallel to that of another level of factor B, an interaction is present and should be explored further (Kleijnen, 1995a). Graphical visualization is very subjective when determining if the lines are parallel. This limitation is removed through the use of regression analysis (Kleijnen, 1995a). Scatter plots can show how two responses are related, though they are not as useful with large datasets, because with numerous data points, the scatter plot will not necessarily show where the majority of the data are clustered, due to overlapping points (Kleijnen et al., 2005). Non-parametric visualization methods, for presentation to policy-makers, include contour and surface plots and non-parametric methods of ranking. Contour and surface plots are typically used to represent 3-dimensional surfaces, using geographical coordinates. Non-parametric methods, such as ranking, have the advantage that there are no assumptions that need to be met and it can sometimes be used to obtain a quick answer. One of the main disadvantages of this method is that it is difficult to make quantitative statements about the actual differences between populations (Dohoo et al., 2003).

1.7 Objectives of research

The research in this thesis focuses on two primary objectives. The first objective is to develop and evaluate an approach to analyze and communicate the results of a large number of simulated outbreaks of HPAI to decision-makers and policy-makers, using the NAADSM, in order to make recommendations on the current HPAI control policy in Canada, specifically, on the effect of stamping-out strategies on the magnitude of an HPAI outbreak. The second objective is to compare the results of simulated outbreaks of HPAI using randomly generated point-locations (latitude, longitude) and flock sizes versus real-point location and flock size data for the poultry industry in Ontario, Canada.

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Chapter 2: Analysis of a large number of simulated outbreaks of highly pathogenic avian influenza in Ontario, Canada, from the North American Animal Disease Spread Model

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2.1 Abstract

The North American Animal Disease Spread Model (NAADSM) is a model framework developed to simulate the spread of highly contagious diseases of livestock and poultry such as foot-and-mouth disease (FMD) and highly pathogenic avian influenza (HPAI). The objectives of this paper were to develop and evaluate an approach to analyze and communicate the results of a large number of simulated outbreaks of HPAI to decision-makers and policy-makers, using the NAADSM, and to make recommendations on the most effective HPAI control policy for Canada, specifically, on the effect of stamping-out and ring-culling strategies on the magnitude of an HPAI outbreak. The current control policy for HPAI in Canada consists of quarantine of infected/detected farms, establishment of disease control zones to impose movement restrictions, tracing of the movements to and from infected/detected farms, stamping-out the infected/detected flock while pre-emptively culling those flocks with exposed birds which may include all neighboring flocks within a 1km radius (ring-culling). Locations and production data for 2487 commercial and 7140 non-commercial poultry farms were provided by industry and provincial government sources in Ontario, Canada. A total of 21,060 scenarios, defined as different combinations of parameters for various epidemiological conditions and control measures, were created to simulate the number of poultry farms that would become infected as a result of an incursion of HPAI. Each scenario was parameterized in NAADSM and replicated 1000 times, generating the mean and 95th percentile for the number of farms infected at the end of the outbreak for each scenario. Negative binomial regression analysis was used to identify significant predictors of the number of farms infected for each scenario. Interaction plots were developed from the output of the negative binomial regression analysis, to facilitate communication of simulation results to policy-makers. Three parameters were selected for the interaction plots: the probability of transmission through indirect contact, farm density, and detection rate. Each selected parameter was stratified at various levels. Negative binomial regression analysis was shown to be appropriate for handling the right-skewed count data of the simulated HPAI outbreaks in Ontario, Canada, while interaction plots developed from the negative binomial regression analysis, were an appropriate visualization tool for communication to policy-makers. From a policy development perspective, the modeling results suggested that stamping-out of the infected/detected flocks, without ring culling, in combination with movement restrictions on direct and indirect contacts, would be the most appropriate policy for Ontario.

Keywords

Highly pathogenic avian influenza; simulation modeling; control strategies; validation; NAADSM; policy

2.2 Introduction

Highly pathogenic avian influenza (HPAI) has become exceedingly important world-wide due to the economic losses it has caused the poultry industry and the human disease arising from the development of new antigenic strains, such as HPAI H5N1 (Pozza et al., 2008). Control of foreign animal diseases, like HPAI, requires that policy be in place in order to respond quickly and effectively in the event of an outbreak. The current control policy for HPAI in Canada consists of quarantine of infected/detected farms, establishment of disease control zones to impose movement restrictions, tracing of the movements to and from infected/detected farms, stamping-out the infected/detected flock while pre-emptively culling those flocks with exposed birds which may include all neighboring flocks within a 1km radius (ring-culling).This policy has been developed following an outbreak in British Columbia, in 2004 in the Fraser Valley, caused by the highly pathogenic strain H7N3 (Bowes et al., 2004; Lupiani & Reddy, 2008). Since then, outbreaks have taken place in Saskatchewan in 2007, also caused by an HPAI H7N3 strain (CFIA, 2008), and in Abbottsford, British Columbia in January 2009 (CFIA, 2009) and Manitoba in November 2010 (CFIA, 2011), caused by a LPAI H5N2 strain.

Simulation modeling has become an important tool for identifying effective control strategies for outbreaks of foreign animal diseases, such as HPAI (Kobayashi et al., 2007). Taylor (2003) stated that "models aid our understanding of complex systems, assisting in predictions of the effect of changing or modifying different components in a system, analyzing and explaining the behavior of a complex system, and determining the importance of various elements of a system". A study by Sharkey et al. (2008) used a spatially explicit, detailed stochastic simulation model to investigate the variation of risk in an outbreak of HPAI in Great Britain and to re-evaluate the policy of the British government.

The North American Animal Disease Spread Model (NAADSM) is also a spatially explicit, stochastic, state-transition model developed for contingency plans and preparedness strategies in the event of an outbreak of a foreign animal disease in North America (Harvey et al., 2007). In this model, a herd or flock moves from one disease state into the next in a predetermined cycle over a period of time, which can be interrupted by disease control measures (Harvey et al., 2007). The model contains many user-established input parameters that define: 1) model behavior in terms of disease progression; 2) disease spread from flock to flock via direct contact; 3) indirect and localized dissemination; and 4) implementation of control measures such as tracing, surveillance, destruction, movement restrictions, and vaccination (Harvey et al., 2007). Each scenario or combination of input parameters can potentially produce a different number of infected farms.

With a large number of possible scenarios from a complex model, that has many input variables, such as the NAADSM, analysis of input factors associated with the output would lead to complex and numerous significant interactions, which are difficult to interpret, because of the relationship between the variables. Kleijnen (1995) suggested that regression analysis should be used for analysis of the output from the simulation models, as well as scatter plots, for a better understanding of these interactions.

The objectives of this research were to develop and evaluate an approach to analyze large numbers of NAADSM simulated HPAI outbreak scenarios in Ontario, Canada, for communication to policy- and decision-makers, and to make recommendations about the current HPAI control policy in Canada, specifically, the effect of a stamping-out destruction strategy on the potential size of an HPAI outbreak.

2.3 Materials and methods

2.3.1 Model description

2.3.1.1. Population dataset and model scenarios

Farm identification, production type, number of birds and location (latitude, longitude) data were provided by the Ontario Livestock and Poultry Council (OLPC) for all commercial poultry operations in Ontario in 2006. The Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA) provided the farm identification, production type, location (latitude, longitude) data, number of barns and number of birds for each non-commercial and turkey farm, also for 2006. A total of 2,487 commercial and 7,140 non-commercial poultry farms were included in each scenario (all provided by Dubé, unpublished).

Using NAADSM Version 3.1 (www.naadsm.org), 1000 iterations of each of the possible 21,060 disease outbreak scenarios were conducted, to generate the expected mean number of farms infected during an outbreak for each scenario in Ontario, Canada (Dubé, unpublished). Each scenario represented a different combination of the input parameters (Table 1). An explanation of the 21, 060 scenarios is provided below.

From Table 1, 540 scenarios were generated by multiplying 10 categories of probabilities of transmission through indirect contact, 3 detection speeds, 3 destruction strategy methods, 3 movement restriction levels based on percent of contact rate by day, and 2 subclinical spread levels. These 540 scenarios were multiplied by 34 different randomly selected flocks (which consisted of a mixture of different production types and densities) where the infection began, giving a total 18,360 scenarios. However, multiple flocks could become infected simultaneously at the beginning of the simulation. Therefore the level of initial infection could be a single farm initially infected (described above) or multiple farms, increasing in increments of 5 up to 50 (Table 1). Therefore 2700 additional scenarios were generated by multiplying the 10 additional categories of initial infection by 10 probability levels of transmission through indirect contact, 3 detection speeds, 3 destruction strategy methods, and 3 movement restriction levels. For these additional scenarios, only 1 level of subclinical spread was assumed, that the subclinically infected flocks could spread the disease, to allow for multiple farms to be initially infected at the start of the simulation. Combining the 18,360 and 2700 scenarios gave 21,060 total scenarios. Additional detail of each of these parameters is provided below.

Table 1: Variables used to build various infection outbreak simulation scenarios for HPAI in Ontario, Canada, based on poultry farm data from 2006

Factor	Description	Levels
Transmission Probability	Probability of transmission following an indirect contact with an infected flock	1 = 1-10% 2 = 11-20% 3 = 21-30% 4 = 31-40% 5 = 41-50% 6 = 51-60% 7 = 61-70% 8 = 71-80% 9 = 81-90% 10 = 91-100%
Detection Rate	Categorized time period to detect a first case in the population	1 = slow detection = 15-21 days 2 =moderate detection = 8-14 days 3 = fast detection = within 7 days
Destruction Strategy	Categories of destruction methods where stamping-out means destruction of infected/detected herds and tracing of direct contacts, and ring-culling means destruction of herds within a specific distance from infected/detected herds (1km and 3km)	1 = Stamping-out 2 = Stamping-out & ring-culling 1km 3 = Stamping-out & ring-culling 3km
Movement Restrictions	Categories of movement restrictions intended to reduce contact rates of direct/indirect contact	0 = no restrictions 1 = less effective restrictions on indirect contacts 2 = effective restrictions on indirect contacts
Subclinical Spread	Ability of subclinically infected flocks to spread infections through direct/indirect contact	0=cannot spread 1=can spread
Initial Infection	Number of infections starting the NAADSM simulation	1 = single infection 2 = 5 infections 3 = 10 infections 4 = 15 infections 5 = 20 infections 6 = 25 infections 7 = 30 infections 8 = 35 infections 9 = 40 infections 10 = 45 infections 11 = 50 infections

*Type of initially infected flock	Poultry production groups of units with similar within-flock disease transmission and similar rates of animal shipments, indirect contacts, and airborne dissemination.	1 = chicken meat multiplier breeder 2 = chicken meat multiplier breeder pullets 3 = chicken meat broiler 4 = meat spikers (roosters) 5 = turkey meat multiplier breeder 6 = turkey meat multiplier breeder pullets 7 = turkey meat broilers 8 = egg multiplier breeder 9 = egg multiplier breeder pullets 10 = table egg producer 11= mixed
*Farm Density (where the initially infected flock(s) is located)	Categories of density calculated through the number of commercial farms per sq-km for each county.	1 = Very low < 25th percentile 2 = Low 25th to 49th percentile 3 = Moderate 50th to 75th percentile 4 = High > 75th percentile 5 = Mixed

*Note: Variables were used to produce probability of transmission

2.3.1.2. Simulation of disease transition and animal movement and contact

Farm units were classified into one of a number of specific disease states, where a unit consists of a production type, defined by the user, which encompasses a group of units with similar within herd disease transmission and similar rates of animal shipments, indirect contacts, and airborne dissemination (when applicable). The incubation period for the disease was varied, ranging from a few hours up to 7 days, depending on the production type (Dubé, unpublished). A flock was considered infectious as soon as the first bird began shedding and was therefore capable of spreading the infection to other flocks through direct and indirect contact (Dubé, unpublished).

Disease spread was assumed to be a function of frequency of contact by both direct and indirect routes. Direct contact was defined as movement of birds from one farm to another and probability of transmission with direct contact was assumed to be 100%, while the probability of transmission from indirect contact ranged from 1 to 100%, and included movement of equipment, people and other fomites from farm to farm. A direct contact rate was calculated for each production type to represent the frequency of movements of birds off of the premises. This rate was calculated on a per day basis, required by the NAADSM, using the length of the production cycle by production type and the number of barns per farm, estimated by expert opinion from the industry, government, veterinarians and poultry specialists. For example, direct contact between table egg producers would be calculated as follows. One contact was assumed per barn per production cycle with table egg producers having 1 barn per premise, as provided by the Egg Farmers of Ontario. So, 1 contact/barn/production cycle was divided by the 18 week production cycle length for birds of a table egg producer, giving 0.056 contacts per week (1/18) or 0.0079 contacts per day (1/126). On a yearly basis, the contact rate would be 2.9 (0.0079*365).

A list of all possible indirect contacts was generated and experts were consulted, using surveys, to classify each contact into 3 risk categories: low, medium and high. High-risk indirect contacts were included in the simulations, which involved direct contact between people and birds or the inside of the barns in which they were housed, or other activities that were expected to lead to virus transmission, such as catching crews and vaccination crews. Medium and low-risk indirect contacts were not included because they were thought to have a low probability of transmission and most likely had a lower number of contacts than high-risk indirect contacts. Examples of medium-risk indirect contacts included government inspectors, processing representatives, and maintenance workers, who might enter the barn but do not have contact with the birds. Examples of low-risk indirect contacts included marketing board representatives and service people including gas, power and electric companies, who would not likely enter the bird housing component of the barns.

Frequency of high risk indirect contacts between flocks was also calculated using the length of the production cycle, by production type, and the number of barns per farm. For this calculation to be done, expert opinion was solicited through a poultry expert committee composed of veterinarians with a solid knowledge of the poultry industry. High risk indirect contact values allocated by the experts for chicken multiplier breeders, chicken meat broilers, and chicken table egg layers were later validated by a questionnaire to producers (data not shown).

A third spread option included was localized spread. This option consisted of unidentified mechanisms (either direct or indirect) that could act locally to spread infection, assuming a probability of infection of 0.01 at 1km from an infected premise, decreasing exponentially (Dubé, unpublished). As direct contact from the infected farm to a naïve farm was assumed to always result in transmission of the infection and localized spread was held constant in the NAADSM analysis, they were not included in the negative binomial regression analysis.

2.3.1.3. Simulation of disease detection

In the NAADSM, disease detection represented both the probability of a veterinarian or producer detecting the presence of HPAI on the premise, based on clinical signs, and the overall awareness of the producers in the study region to HPAI (Dubé, unpublished). Once the first case was detected, it was assumed that other producers were informed, and were therefore more likely to inspect their flocks for suspicion of HPAI, increasing awareness. Based on these assumptions, speed of disease detection was identified as a categorical variable, outlined in Table 1.

2.3.1.4. Simulation of movement controls and destruction

The control strategies investigated included movement restrictions (on direct and indirect contacts) and destruction strategies, which were applied to all premises in the study region once HPAI was confirmed in a flock (Dubé, unpublished). Movement restrictions were defined as reducing contact rates during an outbreak as compared to "normal" days (pre-outbreak) of direct and indirect contacts (Table 1). These restrictions were categorized as: 1) no restrictions on direct and indirect contacts (100% movement); 2) less effective restrictions on indirect contacts with restrictions on direct contacts; and 3) effective restrictions on indirect contacts and direct contacts. Less effective and effective movement restrictions on indirect contacts referred to the decrease in the percent of movement over time. With less effective movement restrictions at day 0 there was 100% movement, on day 2 there was 90% movement, on day 5 there was 75% movement, day 7 there was 60% movement and on day 10, 30% movement. For effective movement restrictions at day 0 there was also 100% movement, day 1 had 65% movement, day 2 had 35% movement, day 4 had 15% movement, and only 5% movement by day 5.

Three destruction strategies were also included: 1) stamping-out of the infected/detected farms and tracing/testing of direct contacts; 2) stamping-out with ring-culling of flocks within 1 km from infected/detected farms; or 3) stamping-out with ring-culling of flocks within 3 km from infected/detected farms. Based on the HPAI and low pathogenic avian influenza (LPAI) outbreaks in British Columbia (BC), as stated in the Notifiable Avian Influenza Hazard Specific Plan by the Canadian Food Inspection Agency (CFIA), it is critical that slaughter decisions be made to allow clinical and pre-clinical flocks to be destroyed within 24 hours of detection (CFIA, 2007). Therefore, a 1 day delay was utilized in the NAADSM to start destruction of the first infected flock (Dubé, unpublished).

2.3.2. Statistical analysis

An initial descriptive statistical analysis was carried out on the 2 outcomes of interest, mean number and 95th percentile of farms infected at the end of the outbreak, as well as correlation coefficients among the predictor variables. Input parameters from the scenarios were used as predictors in the statistical analysis (Table 1). All predictors were initially assessed for unconditional association with the outcomes. Predictors were deemed unconditionally associated with the outcomes if they had a p-value <0.15, and were then eligible for inclusion in the multivariable model building. Using Stata 10.0 (www.stata.com/stata10/), negative binomial regression analysis was used to determine significant predictors for the outcomes. Comparable to linear regression models, negative binomial regression models are suitable for analysis of strongly right-skewed count data. All predictors were assessed for confounding and all possible two-way interactions. Confounding was considered present if the coefficient of the risk factor of interest changed more than 20% when the potential confounder was added to the model.

The stepwise forward selection process of the significant explanatory variables for model-building followed the methodology described by Dohoo et al. (2003), and was validated using a backward elimination process to further test the association of the predictors with the mean number and 95th percentile of farms infected.

The negative binomial model was validated through overdispersion analysis and a deviance chi^2 goodness-of-fit test, using the deviance residuals.

2.3.3 Interaction plot analysis

Predictive values were obtained from the negative binomial models to visualize the interaction between movement restrictions and destruction strategies. The interaction plots were stratified on a low (40%), moderate (60%) and high (90%) probability of transmission through indirect contact, low, moderate, and high farm density, and slow, moderate and fast detection to gain a better understanding of the effects of the probability of transmission through indirect contact, farm density, and detection as well as the interaction between movement restrictions and destruction strategies. The stratified plots were also compared to each other to determine if there were any major differences present, such as differences between a low and a high probability of transmission.

The values chosen for the probability of transmission through indirect contact were from the initial baseline scenarios developed by Dubé (unpublished), chosen to represent high, moderate and low probability of transmission via indirect contact.

2.4 Results

2.4.1. Statistical Analysis

The outcomes had a strong right skew and consisted of a large number of scenarios resulting in zero, one, and two farms infected (Figures 1 & 2). The distribution for the outcomes, mean number of farms infected and 95th percentile had medians of 8 and 28, ranges of 0 to 3308 and 1 to 3530.05, and interquartile ranges of 112 and 203.45, respectively.

For both the unconditional and multivariable analyses, all predictors were significantly associated with the outcomes, and there was no significant correlation among the predictors. The final models (n=2 for the 2 outcomes) included the following predictors: flock type initially infected, farm density within the county where the initially infected flock was located, probability of transmission through indirect contact, subclinical spread of the infection, number of initially infected flocks, speed of detection, and a two-way interaction between destruction and movement restrictions.

Due to the categorical nature of the predictors investigated, reference levels for each predictor were needed for interpretation. For example, with density of farms in a given area there were 4 levels, or categories, including very low density, low density, moderate density and high density. In order to evaluate these levels a reference level, in this case a very low density area, was used for comparison. Thus the count ratios in the final models are relative to a baseline model consisting of a single chicken broiler farm initially infected and located in a moderate density area in Ontario, where there was subclinical spread of the disease and the premise had a moderate probability of transmission through indirect contact, with a moderate rate of detection.

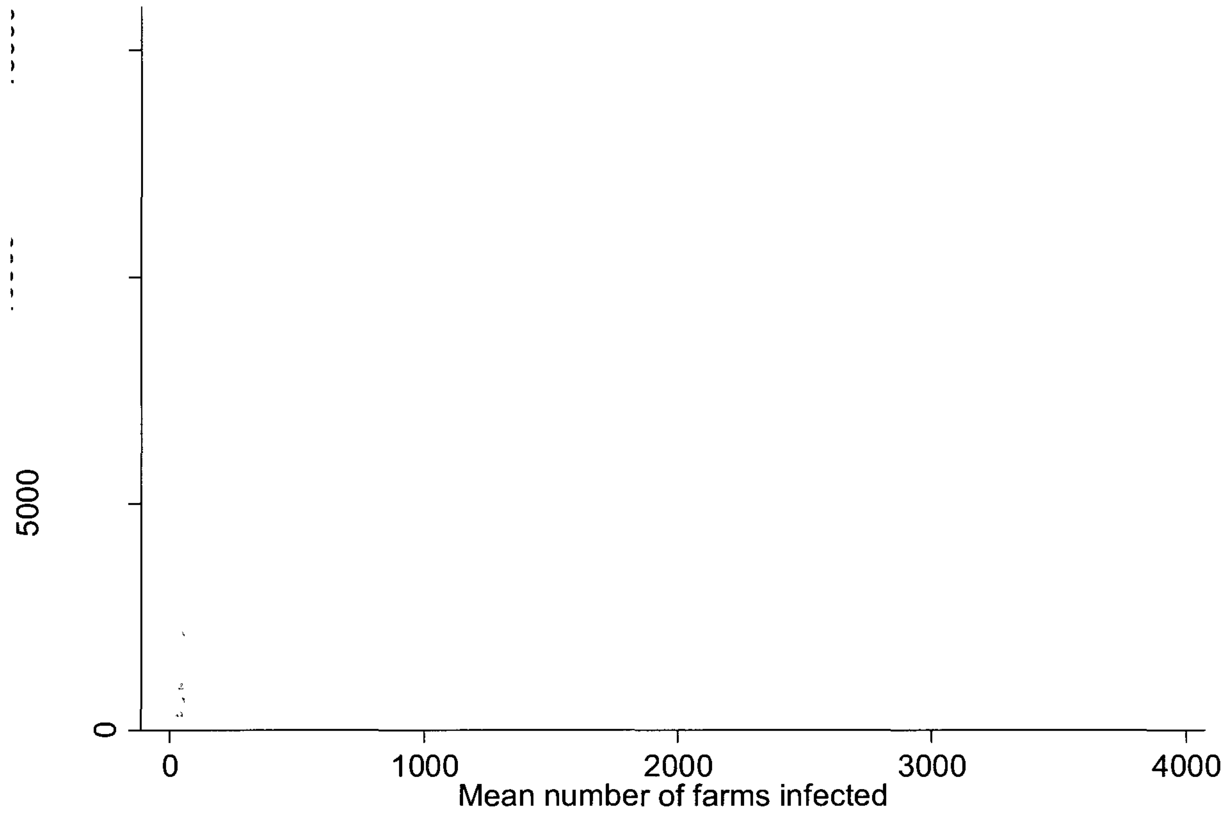


Figure 1: Histogram of the distribution of the mean number of farms infected

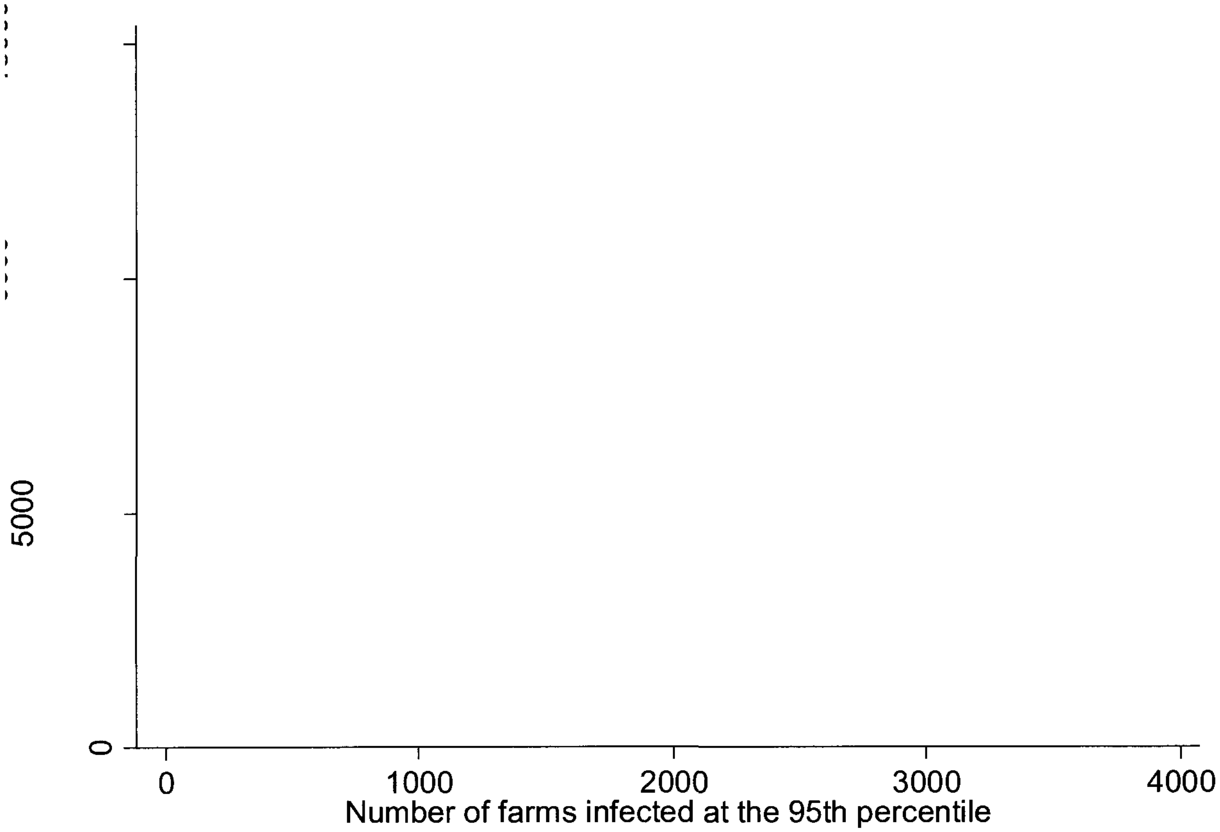


Figure 2: Histogram of the distribution of the number of farms infected at the 95th percentile

In the final models, compared to introduction into a chicken broiler farm, introductions into any other production types generally reduced the mean number of farms infected, with count ratios below 1, with the exception of the mixed type group, which was a mixture of farm types with mixed densities and multiple farms initially infected (Table 2). When the infected farm could not subclinically spread the disease through direct and indirect contact, fewer farms were infected compared to being able to subclinically spread the disease. For example, if 30 farms were infected because the initially infected farm could subclinically spread the disease, when the infected farm could not subclinically spread the disease, only 26 farms become infected. It was expected that the mixed farm type group and mixed density would have had a significant impact on the size of the outbreak as they were a combination of flock types with various densities within counties. The type and density were unknown for some areas, therefore they were assumed to be mixtures.

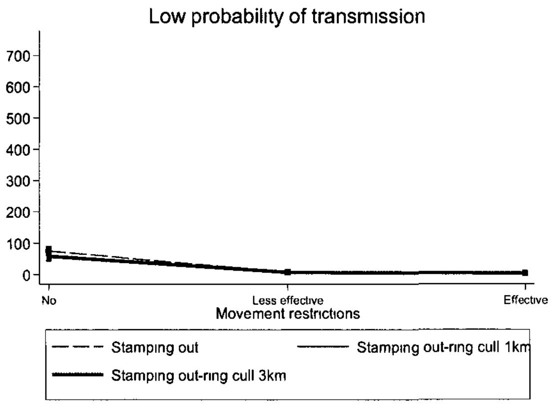
The data were tested for overdispersion and goodness of fit as well as an analysis of the residuals completed. The likelihood ratio test had a chi-squared value of $2.3 \times 10^{0.6}$, with a p-value of <0.05. This indicates that a Poisson model was not a good fit for the data and a negative binomial regression analysis corrected the problems of overdispersion, making it a better fit.

2.4.2. Interaction plot analysis

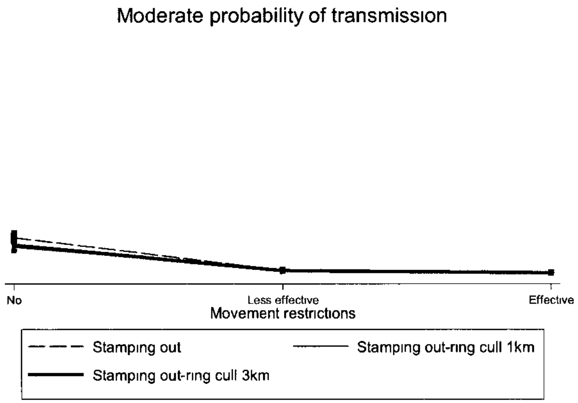
Because of the interaction between movement restrictions and destruction, interaction plots were necessary for the interpretation of these variables (Figures 3&4). The interaction plots, developed from the negative binomial regression analysis, were found to be an appropriate visualization tool for communication to policy-makers, as described below.

Table 2: Count ratios, standard errors, p-values, and confidence intervals for the predictors used in the determination of the association among the mean (and 95th percentile) number of farms infected and various control strategies

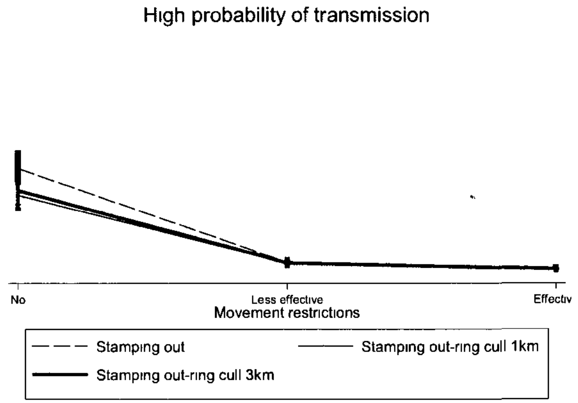
Variable	Count Ratio		Standard Error		P-Value		Confidence Intervals			
	Mean	95th%	Mean	95th%	Mean	95th%	Mean	95th%	Mean	95th%
Farm Type										
Chicken meat broilers	Reference	-	-	-	-	-	-	-	-	-
Chicken meat multiplier breeders	0.191	0.333	0.033	0.032	<0.05	<0.05	0.179	0.313	0.203	0.355
Chicken meat multiplier breeder pullets	0.165	0.348	0.038	0.037	<0.05	<0.05	0.153	0.323	0.178	0.374
Chicken meat spikers	0.073	0.147	0.037	0.035	<0.05	<0.05	0.068	0.138	0.079	0.158
Table egg layers	0.232	0.416	0.033	0.032	<0.05	<0.05	0.217	0.391	0.247	0.443
Egg layer multiplier breeders	0.965	0.859	0.026	0.026	0.176	<0.05	0.917	0.816	1.016	0.905
Egg layer multiplier pullets	0.224	0.342	0.052	0.049	<0.05	<0.05	0.203	0.311	0.248	0.377
Turkey broilers	0.379	0.698	0.054	0.050	<0.05	<0.05	0.341	0.633	0.421	0.771
Turkey multiplier breeders	1.027	0.965	0.024	0.024	0.272	0.139	0.980	0.921	1.076	1.012
Turkey multiplier pullets	0.888	0.760	0.038	0.038	<0.05	<0.05	0.825	0.707	0.956	0.818
Mixed type	17.187	5.527	0.060	0.064	<0.05	<0.05	15.269	4.873	19.345	6.269
Cannot subclinically spread the disease	0.130	0.168	0.017	0.016	<0.05	<0.05	0.126	0.163	0.135	0.174



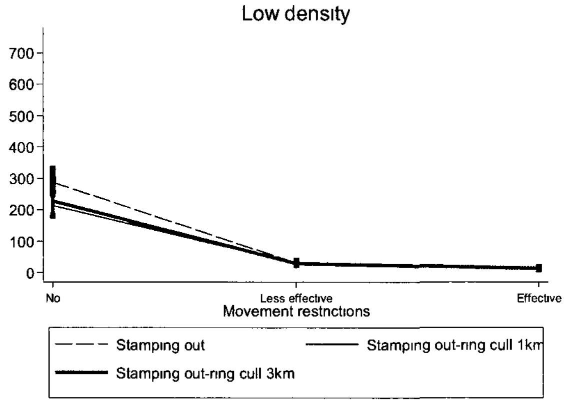
a. Effect of MR and destruction on the number of farms infected when there is a low probability of transmission via indirect contacts



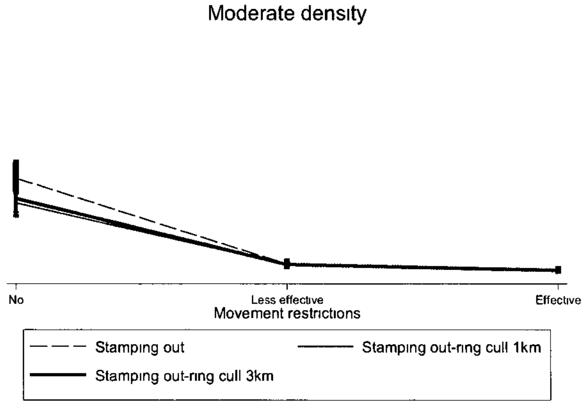
b. Effect of MR and destruction on the number of farms infected when there is a moderate probability of transmission via indirect contacts



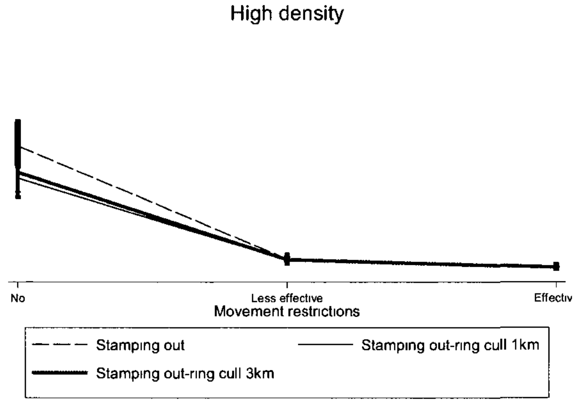
c. Effect of MR and destruction on the number of farms infected when there is a high probability of transmission via indirect contacts



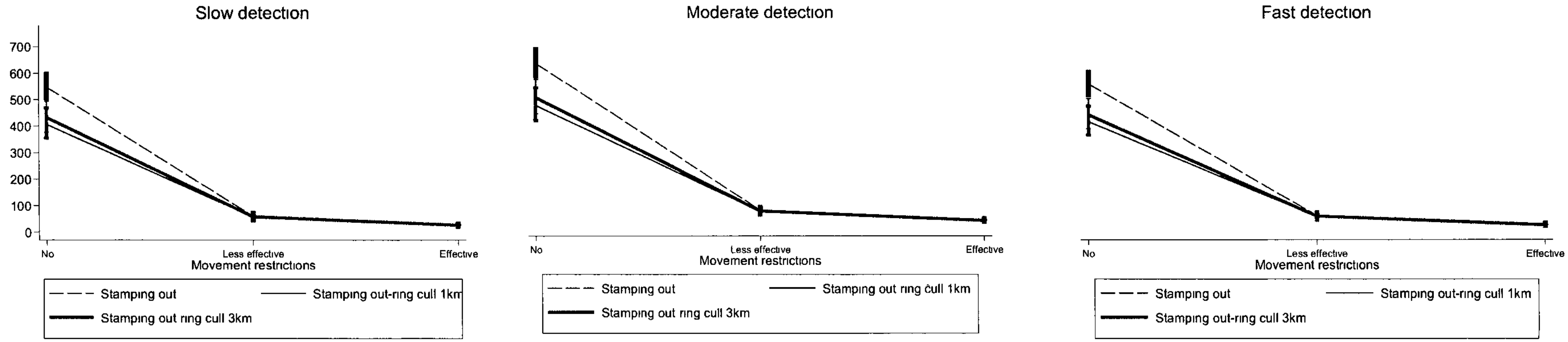
d. Effect of MR and destruction on the number of farms infected when the initially infected farm is in a low density area



e. Effect of MR and destruction on the number of farms infected when the initially infected farm is in a moderate density area



f. Effect of MR and destruction on the number of farms infected when the initially infected farm is in a high density area

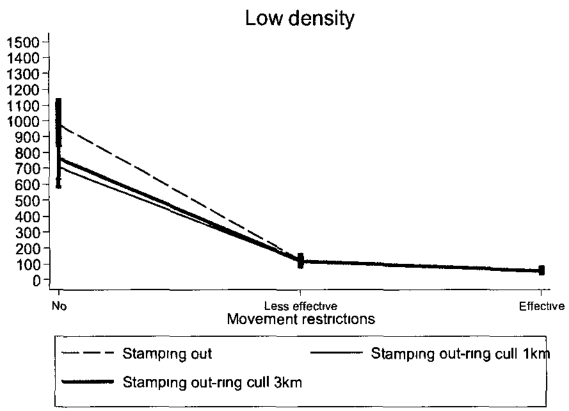


g. Effect of MR and destruction on the number of farms infected when the initially infected flock was detected slowly

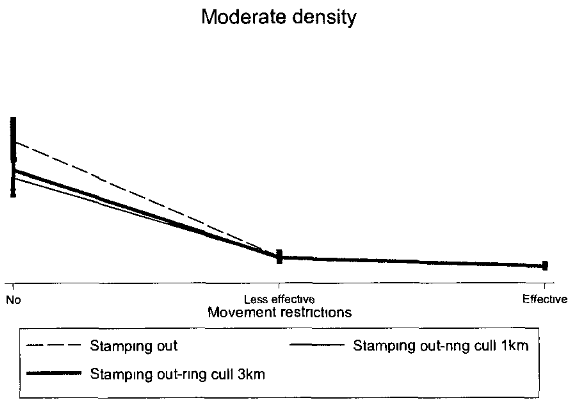
h. Effect of MR and destruction on the number of farms infected when the initially infected flock was detected at a moderate speed

i. Effect of MR and destruction on the number of farms infected when the initially infected flock was detected quickly

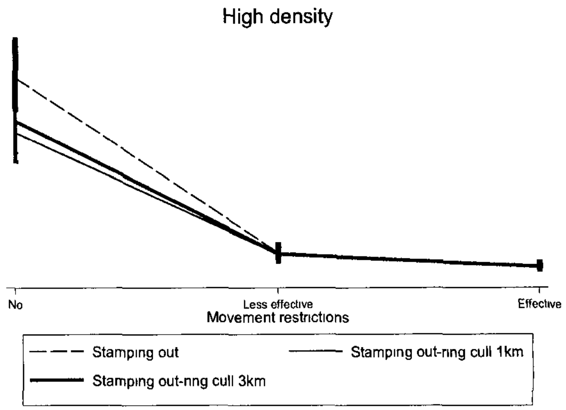
Figure 3- Interaction plots between movement restrictions (MR) and destruction strategies ($p<0.05$) for a high, moderate and low probability of transmission from indirect contact, low, moderate and high density, and slow, moderate and fast detection from the final negative binomial model of associations with the **mean** number of farms infected



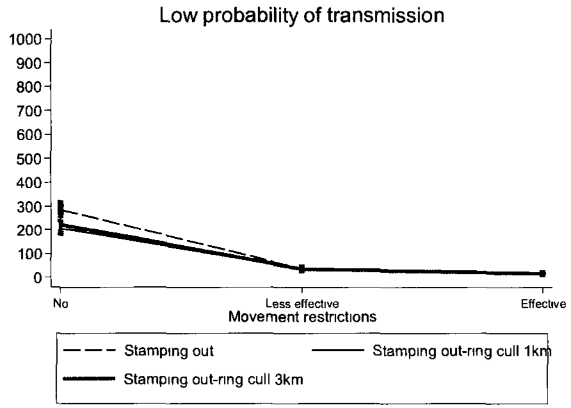
a. Effect of MR and destruction on the number of farms infected when the initially infected flock was in a low density area



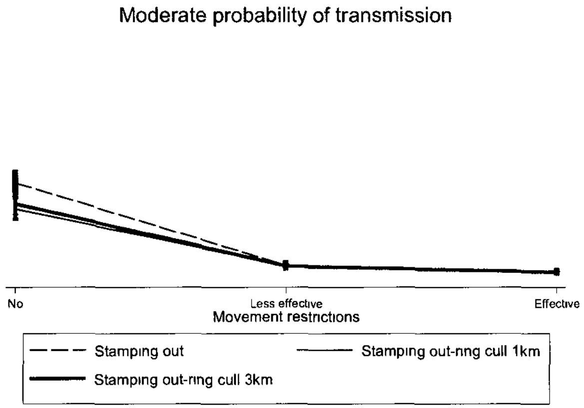
b. Effect of MR and destruction on the number of farms infected when the initially infected flock was in a moderate density area



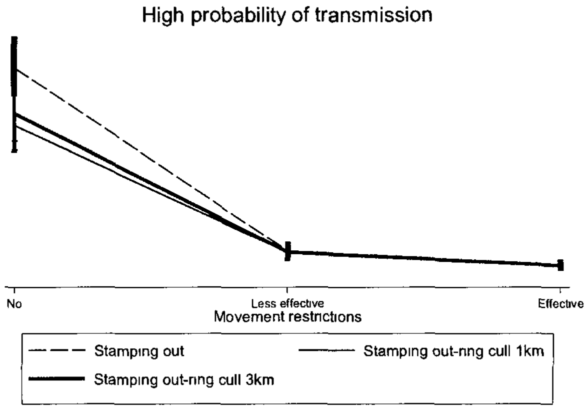
c. Effect of MR and destruction on the number of farms infected when the initially infected flock was in a high density area



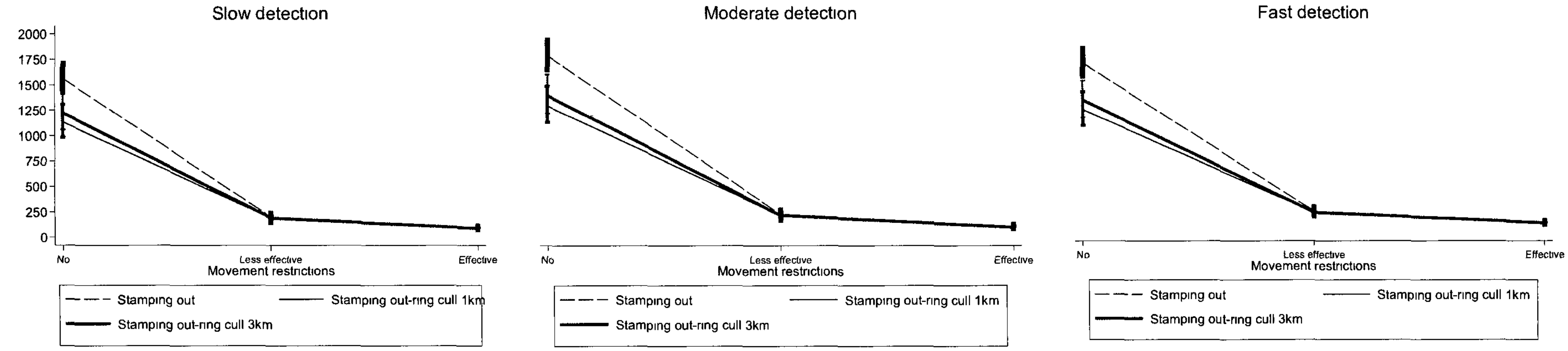
d. Effect of MR and destruction on the number of farms infected when there is a low probability of transmission via indirect contact



e. Effect of MR and destruction on the number of farms infected when there is a moderate probability of transmission via indirect contact



f. Effect of MR and destruction on the number of farms infected when there is a high probability of transmission via indirect contact



i. Effect of MR and destruction on the number of farms infected when the initially infected flock was detected slowly

h. Effect of MR and destruction on the number of farms infected when the initially infected flock was detected at a moderate speed

i. Effect of MR and destruction on the number of farms infected when the initially infected flock was detected quickly

Figure 4- Interaction plots between movement restrictions and destruction strategies ($p<0.05$) for a high, moderate and low probability of transmission from indirect contact, low, moderate and high density, and slow, moderate and fast detection from the final negative binomial model of associations with the number of farms infected **at the 95th percentile**

2.4.2.1 Probability of transmission through indirect contact

The trends between the mean number of farms infected and the 95th percentile were found to be similar. In Figure 3, the model demonstrates that a high probability of transmission through indirect contact resulted in a larger outbreak and the presence of movement restrictions, compared to the baseline parameters, consisting of a low probability of transmission through indirect contact, in a moderate density area, with a single chicken farm initially infected, with a moderate detection rate, no movement restrictions, and a stamping-out only destruction strategy. For instance, a high probability of transmission resulted in 50.8 (46.0, 56.3) farms infected at the end of the outbreak, compared to the baseline (same as above) with a low probability of transmission through indirect contact, which resulted in only 30.8 (28.6, 33.2) farms infected (Table 3; Figure 3). The trend was similar for the 95th percentile, although the number of farms infected at the end of the outbreak was substantially larger (Table 4; Figure 4).

With stamping-out only, scenarios with a high probability of transmission through indirect contact, and effective movement restrictions on indirect contacts and restrictions on direct contacts, resulted in a reduction in the mean number of farms infected by 48.5 (44.0, 53.6) farms (Table 3; Figure 3), compared to the baseline (as above) with no movement restrictions. Under the same conditions, for the 95th percentile, the number of farms infected would be reduced by 1192.1 (1087.3, 1308.3) farms (Table 4; Figure 4). There was no significant difference between the destruction strategies found, therefore a stamping-out only strategy (no ring-culling) would be an appropriate control strategy in this situation (Figures 3 & 4).

Table 3: Summary of the reduction in the **mean** number of farms infected from 1000 iterations based on the probability of transmission through indirect contact, farm density area where the initially infected flock resided, and detection speed for less effective and effective movement restrictions on indirect contacts and restrictions on direct contacts with stamping-out only

Parameter	Number of farms infected		
	No movement restrictions on direct or indirect contacts	Less effective movement restrictions on indirect contacts with restrictions on direct contacts	Effective movement restrictions on indirect contacts with restrictions on direct contacts
Probability of transmission			
Low	30.8 (28.6, 33.2)	3.3 (2.9, 3.8)	1.4 (1.3, 1.6)
Moderate	36.3 (33.3, 39.7)	3.9 (3.4, 4.5)	1.7 (1.5, 2.0)
High	50.8 (46.0, 56.3)	5.5 (4.7, 6.4)	2.4 (2.0, 2.8)
Farm Density			
Low	55.8 (48.2, 64.2)	6.0 (4.9, 7.3)	2.6 (2.1, 3.2)
Moderate	59.0 (50.7, 68.8)	6.4 (5.2, 7.8)	2.7 (2.2, 3.4)
High	78.4 (66.0, 93.2)	8.4 (6.7, 10.6)	3.6 (2.9, 4.6)
Detection Speed			
Slow	139.1 (129.2, 149.8)	15.0 (13.2, 17.1)	6.4 (5.6, 7.4)
Moderate	122.6 (112.9, 133.1)	13.2 (11.5, 15.2)	5.7 (4.9, 6.6)
Fast	108.1 (99.9, 117.0)	11.7 (10.2, 13.3)	5.0 (4.4, 5.8)

Table 4: Summary of the reduction in the mean number of farms infected (**at the 95th percentile level**) from 1000 iterations based on the probability of transmission through indirect contact, farm density area where the initially infected flock resided, and detection speed for less effective and effective movement restrictions on indirect contacts and restrictions on direct contacts with stamping-out only

Parameter	Number of farms infected		
	No movement restrictions on direct or indirect contacts	Less effective movement restrictions on indirect contacts with restrictions on direct contacts	Effective movement restrictions on indirect contacts with restrictions on direct contacts
		Probability of transmission	
Low	864.4 (803.5, 929.8)	109.3 (95.9, 124.6)	51.4 (45.0, 58.7)
Moderate	970.1 (891.4, 1056.6)	122.7 (106.4, 141.6)	57.7 (49.9, 66.7)
High	1267.5 (1151.7, 1396.6)	160.3 (137.4, 187.1)	75.4 (64.5, 88.2)
		Farm Density	
Low	1324.9 (1154.8, 1524.8)	167.5 (137.8, 204.3)	78.7 (64.6, 96.3)
Moderate	1416.5 (1219.6, 1649.8)	179.1 (145.5, 221.1)	84.2 (68.3, 104.2)
High	1758.3 (1486.5, 2085.4)	222.3 (177.4, 279.4)	104.5 (83.2, 131.7)
		Detection Speed	
Slow	2721.7 (2527.5, 2933.6)	344.1 (301.6, 393.1)	161.7 (141.5, 185.3)
Moderate	2418.9 (2228.2, 2629.9)	305.9 (265.9, 352.4)	143.8 (124.7, 166.1)
Fast	2138.0 (1975.5, 2317.0)	270.3 (235.7, 310.5)	127.1 (110.6, 146.4)

2.4.2.2. Farm density

In Figure 3, the model demonstrated that when the initially infected farm was located in higher farm density areas, it resulted in a larger outbreak, compared to the baseline consisting of a very low density area, with a moderate probability of transmission through indirect contact, a single chicken farm initially infected, a moderate detection rate, with no movement restrictions, and a stamping-out only destruction strategy. For instance, in a high density area where the initially infected farm was located, 78.4 (66.0, 93.2) farms were infected at the end of the outbreak compared to a low density area with 55.8 (48.2, 64.2) farms infected (Table 3; Figure 3). The trend was similar for the 95th percentile, although the numbers are substantially larger (Table 4; Figure 4).

Again, there was no significant difference between destruction strategies, therefore a stamping-out only strategy was an appropriate control strategy in this situation. With stamping-out only and either a low or moderate farm density, and effective movement restrictions on indirect contacts and restrictions on direct contacts, the number of farms infected was reduced by 53.2 (46.1, 61.0) and 56.3 (48.4, 65.4) farms, respectively (Table 3; Figure 3), compared to no movement restrictions. In high farm density areas, with effective movement restrictions on indirect contacts and restrictions on direct contacts, the number of farms infected was reduced by 74.7 (63.1, 88.6) farms (Table 3; Figure 3), compared to no movement restrictions.

2.4.2.3 Speed of detection

A smaller outbreak resulted when HPAI was detected quickly (within 7d), compared to the baseline, which consisted of a slow detection rate, and a moderate farm density area, with a moderate probability of transmission through indirect contact, a single chicken farm initially infected, with no movement restrictions, and a stamping-out only destruction strategy (Figure 3). For instance, when the disease was detected quickly only 108.1 (99.9, 117.0) farms were infected at the end of the outbreak, compared to the baseline (as above) with a slow detection rate resulting in 139.1 (129.2, 149.8) farms infected (Table 3; Figure 3). The trend was similar for the 95th percentile though the numbers were once again more substantial (Table 4; Figure 4).

When the initially infected flock was detected slowly, moderately or fast, effective movement restrictions on indirect contacts and restrictions on direct contacts, resulted in a reduction in the number of farms infected by 139.1 (123.5, 142.4), 116.9 (108.0, 126.6), and 103.1 (95.6, 111.3) farms, respectively, compared to no movement restrictions (stamping-out only) (Table 3; Figure 3). For the same conditions, for the 95th percentile, for slow, moderate and fast detection, the number of farms was reduced by 2559.9 (2386.1, 2748.3), 2275.2 (2103.5, 2463.8), and 2011.0 (1865.0, 2170.6) farms, respectively (Table 4; Figure 4).

2.4.3. Multiple initially infected flock analysis

A separate model (data not shown) was fitted using multiple farms initially infected as a predictor. This predictor represented mixed farm types and different density values, which were collinear with multiple farms initially infected, therefore farm type and density, were removed from the model. Briefly, results show that as the number of farms initially infected increased, at the start of the simulation, the resulting number of farms infected at the end of the outbreak was also higher, compared to only a single farm initially infected. For instance, five farms initially infected caused 3.16 times more farms to be infected at the end of the outbreak simulation, compared to a single farm initially infected, when there were no movement restrictions, a stamping-out-only destruction strategy, subclinically infected farms could spread the disease, a moderate probability of transmission through indirect contact (60%), and a slow detection rate (21 days). For example, compared to the baseline with, for instance, 30 farms infected at the end of the outbreak, having 5 farms initially infected would result in 95 farms infected at the end of the outbreak. The rest of the model was similar to the model with only one farm initially infected, and therefore it is not described here further.

2.5 Discussion

The negative binomial regression model was an appropriate tool for analysis of a large number of simulated outbreaks, with the right-skewed outcome closely fitting the negative binomial distribution. Results show that all production types, when compared to chicken broilers, generally reduced the mean number of farms infected. This result was most likely due to the contact structure defined in the NAADSM for each production type. Chicken broilers tend to have higher direct and indirect contact rates than other production types due to their short production cycles, which may increase the likelihood of infection. This is different from chicken layers because layers remain on one farm for the duration of their life until they are no longer high egg producers, in which case this would result in slaughter. In the model by Sharkey et al. (2008), the key risk factor for a wide-scale outbreak was the presence of infection in high-risk sectors such as meat duck farms, similar to the current study with chicken broilers. This emphasizes that identifying these high-risk sectors and preventing transmission to them is essential for reducing the risk of such large-scale outbreaks (Sharkey et al., 2008).

The ability of the infected flock to spread the disease without detection from clinical signs (subclinically) through direct and indirect contact resulted in a larger outbreak than if the infected premise could not subclinically spread the disease. Most likely undetected transmission is occurring in this case, leading to an increased mean number of farms infected, as unaware infected farmers do not restrict bird movement. Realistically, during an outbreak, subclinical farms would be a source of spread of the disease, due to the inability to detect disease transmission from a lack of clinical signs.

Separate analysis of the effect of the number of initially infected farms on the outcome showed that as the number of initially infected farms increased, the number of farms infected at the end of the outbreak also increased. This was expected, though it is unlikely that in an outbreak of HPAI, multiple farms would be initially infected, such as 5 farms or more, depending on the time of detection. Also, the appropriate control strategies (effective movement restrictions and a stamping-out only strategy) for resolving the outbreak remained the same regardless of the number of farms initially infected.

The probability of transmission through indirect contact was influential to virus spread. A higher probability of transmission through indirect contact resulted in a larger number of farms infected. As previously stated, this form of transmission occurs through things like fomites from movement of people and vehicles between farms, which can be controlled through proper biosecurity measures. The notifiable avian influenza (NAI) hazard specific plan, put forth by the CFIA, specifically states that an outbreak can be spread due to poor biosecurity measures (CFIA, 2007). These suggestions coincide with the findings in the current study. It was also suggested that the introduction of the virus in Saskatchewan (2007) was caused by transmission through either wild bird contact, contaminated drinking water from a nearby dug-out, or farm workers (CFIA, 2008). The current study and insights gained from previous outbreaks indicated that transmission from indirect contacts is extremely important for virus spread and therefore warrants more stringent regulations.

Initiating outbreaks in areas of higher density in a given area resulted in an increase in the number of farms infected, though the increase was not as large as expected. Previous outbreaks show that high density areas are more susceptible to disease spread due to a higher potential for direct and indirect contacts (Nishiguchi et al., 2007). Conversely, Sharkey et al. (2008) found that some high farm density areas of Great Britain had a relatively low risk of infection while other high farm density areas produced large scale outbreaks, providing variable results. The results from the current study and results from previous studies could be due to many factors, such as the extent of local spread in the current study. Localized spread represented unknown spread mechanisms, direct or indirect, such as contact with wild birds, which depended on the type of production facility. A probability of infection of 0.01 at 1km was used, which may not encompass all possible unknown spread mechanisms. Sharkey et al. (2008) used a similar localized spread value, as well as a range of other probabilities up to 0.5 at 1km. They found similar results, also indicating the difficulty in defining the level of localized spread, as it is not easy to quantify spread by wild birds or other animals, vehicles and people. Sharkey et al. (2008) states that other contributing factors may include species on farm, distance between farms, locality of feed mills and slaughter houses, and the industry structure, as well as other geographical, demographical and epidemiological factors for a given area. These factors would need to be considered when determining the contact structure of industry for movement restrictions.

There was a reduction in the number of farms infected when the speed of detection changed from slow through moderate to fast. Previous studies demonstrated that earlier detection resulted in more effective use of the control strategies (Pozza et al., 2008). In the NAADSM, it was assumed that baseline awareness was moderate or good, and that clinical signs caused farmers to detect the disease quickly.

Movement restrictions on direct and indirect contacts were found to have the largest impact on the size of the outbreak, compared to the other parameters in the model. Increasing movement restrictions on indirect contacts referred to restricting movement of people and vehicles from infected premises to naïve premises. Restrictions on direct contacts referred to restricted movement of birds from farm to farm. Both contacts were found to play an important role in the size of an outbreak, and through the use of movement restrictions, the number of farms infected were greatly reduced. Pozza et al. (2008) states that pre-requisites for a successful control intervention include prompt restriction measures on suspected flocks, indicating the need to involve movement restrictions in any outbreak control program.

Stamping-out of the infected/detected flock was an appropriate destruction strategy (no ring-culling required). Many countries have a stamping-out policy in place in the event of an outbreak, however, containment of the infection on individual farms or in zones is also extremely important (Swayne & Suarez, 2000). The guidelines put forth by the World Animal Health Organization (OIE) state that the basis of HPAI eradication through stamping-out is to immediately impose movement restrictions on the infected area followed by slaughter of all infected and potentially infected birds (Martin et al., 2006). This is highly dependent on the area, as demographics, geography and epidemiological considerations need to be taken into account (Sharkey et al., 2008). Current Canadian policy states that a stamping-out strategy and pre-emptive slaughter of neighboring flocks with ring-culling at 1km in combination with effective movement restrictions, is the best method for control and eradication of virus spread between flocks (CFIA, 2004). The results of the current study indicate that, in the event of an outbreak, stamping-out of the infected/detected flock, with no ring-culling, combined with effective movement restrictions on direct and indirect contacts, would be the most effective control policy.

The main limitation in simulations, such as this, is they depend on various assumptions for each variable. In order to make these assumptions, information is required from the industry, which may be difficult to obtain. The main limitation of the current study was the difficulty in covering all aspects of a potential outbreak, as each outbreak is unique and some parameters are difficult to quantify. This study was the first of its kind on an Ontario poultry population using the NAADSM, making comparisons difficult. While the NAADSM has been used for modeling FMD outbreaks, little work has been completed on avian influenza, and therefore further research is required to refine model assumptions and gain a better understanding of HPAI virus movement. Newer versions of NAADSM have resulted in various errors being corrected and slight modifications to the model, therefore it would be of interest to see if there are any differences in the results between the version of NAADSM used in the current study and a newer version of the model.

Future directions of this research should include analysis of other outcomes, such as the duration of an outbreak, comparison to randomly generated farm location data, and analysis involving other provinces and states.

2.6 Conclusion

The outcomes, mean number of farms and 95th percentile, had a strong right skew, consisting of a large number of scenarios with only 1-2 farms infected at the end of the outbreak, making a negative binomial regression analysis the most appropriate analytical tool. Interaction plots, developed from the negative binomial regression analysis, were appropriate for use as a visualization tool for communication of results to policy-makers. This was determined from presentation of the results to policy-makers, which was well received with the concepts being easily understood.

This novel approach revealed that, from a policy development perspective, destruction of the infected/detected flocks only was appropriate, in combination with effective movement restrictions on direct and indirect contacts (no ring-culling required). This finding, however, may be subject to change, depending on the geography and demographics of an area.

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Chapter 3: Comparison of randomly generated location and flock size data versus real data for outbreak simulations of highly pathogenic avian influenza using the North American Animal Disease Spread Model

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3.1 Abstract

The purpose of this research was to compare the results of simulated outbreaks of highly pathogenic avian influenza (HPAI) using randomly generated point locations and flock sizes and compare the results to those obtained when real location and flock size data, for Ontario, Canada, were used. Farm identification, point locations (latitude, longitude), number of birds, number of barns, and production types were provided by the Ontario Livestock and Poultry Council (OLPC) regarding all commercial poultry production, including all chicken and egg production types, in Ontario (2006). The Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA) provided the farm identification, production type, location (latitude, longitude), number of barns and number of birds for the commercial turkey farms, and the same data were provided from the Ontario Farm Business Registry (OFBR) for the hobby producers. Three datasets were developed consisting of: 1) the real-industry dataset - real flock size and location data (from Chapter 2); 2) the "random-industry" dataset - using OLPC and OMAFRA data for random generation of point locations and flock sizes; and 3) the "random-census" dataset - using Statistics Canada agricultural census data for 2006 for randomly generated point locations and OLPC and OMAFRA data for flock sizes. Farms were categorized into 4 production types (commercial chicken meat, commercial eggs, commercial turkey, and hobby poultry) for the analyses, because the census data were recorded in this manner. Four outbreak scenarios were investigated for comparison of the real data versus both sets of randomly generated data, considering both a weighted median number of contacts per day between farms, and a weighted maximum number of contacts per day, including various control strategy options (e.g. movement restrictions and destruction strategies). Negative binomial regression analysis and a Kolmogorov-Smirnov (K-S) equality-of-distributions test were carried out, to determine if any significant difference existed between the three datasets. For the negative binomial regression analysis, in the majority of the scenarios, there were significant differences between the datasets. This was most likely due to the large number of iterations, suggesting a significant difference even if that difference was very small, as seen in the current study. For the K-S test there were significant differences between the 3 datasets in all scenarios. The significant differences found in the K-S test may be due to a small difference in only one part of the curve. The real data tended to produce larger outbreaks as compared to the two random datasets. However, these discrepancies were considered minimal from a policy development perspective, as a robust policy is typically created. Overall, under the conditions set in this particular study, both the random-census and random industry datasets were suitable replacements for the real-industry data. The findings in this study were only for an outbreak of HPAI in Ontario, due to data availability, and therefore further simulations should be done for other provinces.

Keywords

Highly pathogenic avian influenza; simulation modeling; random allocation; NAADSM; policy

3.2 Introduction

Highly pathogenic avian influenza (HPAI), a negative-sense RNA virus, has been impacting poultry production systems throughout the world, and transmission to humans has also been occurring, leading to increased public concern for its control (Yee et al., 2008). The outbreak experience in North America in the past has been limited, but it has raised awareness about the potential impact of a serious outbreak, and therefore governmental organizations have developed contingency plans and policies in preparation for an outbreak. Under this context, simulation modeling has become an extremely important tool for predicting potential consequences in the event of an outbreak, and for providing insight into the most important methods of control and eradication of the virus (Harvey et al., 2007).

The North American Animal Disease Spread Model (NAADSM) was developed for particular use in North America to assist in policy development and decision-making around disease incursions. NAADSM is a herd-based, spatially explicit, state-transition simulation model for the spread of highly contagious diseases of animals (Harvey et al., 2007). Harvey et al. (2007) describes NAADSM as having user-established parameters that define the model's behavior in terms of: disease progression; disease spread through animal-to-animal contact; contact with contaminated personnel or equipment; airborne dissemination; and the implementation of control measures such as movement restrictions, destruction and vaccination strategies. In the current version of NAADSM, the unit of concern is a herd or a flock, and this is represented by a production type (e.g. broilers) and a given size (e.g. number of birds), which is geographically represented by its latitude and longitude.

In Canada, the exact location of the farm and the number of birds on each farm is confidential and this information is usually not accessible by regulatory agencies, except when facing an outbreak situation. Three specific studies looked at appropriately generating data when farm information is unavailable, though no comparisons were made to real data. This type of random point generation has never been compared to real location data, in Canada. Freier, et al.

(2007), used summarized data provided by the United States Department of Agriculture (USDA) Census of Agriculture to randomly generate farm locations for simulations. The summarized data contained county-level information about the number of farms and animals per farm for each commodity. Dot density maps that showed the location of randomly placed farms were created, utilizing exclusion zones for areas where a farm was unlikely to be situated, such as lakes and urban areas.

Tildesley et al. (2010) explored the use of estimated farm locations and spatial clustering for disease transmission in place of real location data in the United Kingdom (U.K.) for foot-and-mouth disease (FMD). They concluded that parameterizing the model to match epidemic behavior, and using aggregate county-scale data were appropriate methods for determining optimal control measures in the event of an outbreak of FMD. They also noted that clustering of farms played a significant role in the model parameterization (Tildesley et al., 2010).

Bruhn et al. (unpublished) derived the number, type and size of farms in the USA from the USDA Census of Agriculture's county totals. These authors stated that the USDA has simulated farm and animal populations for North Carolina in the past, using six spatial constraints that were not mentioned in the paper. However, the authors of that study reported that their approach only achieved moderate success, due to inaccuracies in the public domain lists of farms, and because of difficulties in converting rural route addresses to geocodable locations. Bruhn et al. (unpublished) also found that it was possible to generate rudimentary poultry-operation locations nation-wide, using the USDA Census of Agriculture data and geographic information systems (GIS) which were reasonable substitutes for actual farm locations, and with further customization of poultry subtypes and sizes, the data would be more realistic (Bruhn et al., unpublished).

For the NAADSM model, flock size is another input parameter that requires investigation when randomly generating a dataset to be used in the absence of real data. It is important to ensure that random allocation of flock sizes to the flock locations is done accurately. In the study by Bruhn et al. (unpublished), the farms in Delaware were mostly broiler farms, and the authors estimated the number of birds for each farm based on the size and number of poultry houses on each Delaware farm from the 2002 USDA Census of Agriculture. However, difficulties in producing appropriate flock sizes for the different types of poultry were encountered due to the fact that numerous farms raised multiple types of poultry, such as broilers, layers and pullets. This made it difficult to give point locations to individual production types. This specific challenge was not encountered in the current study as it was assumed that there was only one production type on each farm.

The main objective of this manuscript was to compare the number of flocks affected under simulated HPAI outbreak scenarios when randomly generated point locations and flock size data were used versus real locations and flock size data provided by the poultry industry in Ontario, Canada.

3.3 Materials and Methods

3.3.1 Data sources and generation of random locations and flock sizes

Three datasets representing Ontario in 2006 were created for comparison, as described below.

3.3.1.1 Real-Industry dataset

Farm identification, production type, flock size and point location (latitude, longitude) data were obtained from the Ontario Livestock and Poultry Council (OLPC) for the commercial poultry production, from the Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA) for the commercial turkey farms, and from the Ontario Farm Business Registry

(OFBR) for the hobby farms. A total of 8,773 commercial (n=2,186) and non-commercial farms (n=6,587) were included in the simulations (Table 1).

The real-industry dataset used in the current study was modified from the dataset used in Chapter 2 which consisted of 10 production types. To generate a dataset that was comparable to the random location datasets, these 10 production types were collapsed into 3 specific types: commercial chicken meat (including chicken meat multiplier breeder pullets, chicken meat multiplier breeders, meat spikers used to stimulate the hens and chicken broilers), commercial turkey meat (including turkey multiplier breeder pullets, turkey multiplier breeders, and turkey broilers), commercial chicken egg (including egg multiplier breeder pullets, table egg multiplier breeders, table egg layer pullets, and table egg producers (layers)), plus a 4th production type called hobby farms, which consisted of all backyard hobby farms in the province. The main characteristics of the 3 main production types are the commercial chicken meat consist of those chicken production types used in meat production, the commercial chicken egg type are those used specifically in the production of eggs and the turkey meat type consists of those production types that produce turkey meat. The real point locations (latitude, longitude) and flock sizes were maintained from the original dataset (as described in Chapter 2) and entered into NAADSM Version 3.1 (http://www.naadsm.org/download/versions).

Table 1: Summary of flock number and flock size range for each production type in each of the 3 datasets

		Random-census	Random-industry	Real-industry*
Broiler chicken meat	Number of farms	1387	1387	1387
	Flock size range	46, 195358	1, 188646	1, 188646
Egg	Number of farms	528	528	528
	Flock size range	246, 279890	687, 396883	687, 396883
Turkey	Number of farms	6587	6587	6587
	Flock size range	410, 148186	286, 158382	286, 158382
Hobby	Number of farms	271	271	271
	Flock size range	75, 75	75, 75	75, 75

*The real-industry data consisted of 10 commercial production types (4 chicken types, 3 egg types, and 3 turkey types) where each of those types had its own range of flock sizes

3.3.1.2 Random-Industry dataset

From the real-industry dataset of 8773 farms, the total number of flocks for each of the 4 -production types within each census division in Ontario was determined (Table 1). These data were entered into Quantum GIS, and random points representing the location of a specific type of farm were generated using the FTools extension, which is a widely used advanced set of spatial tools used to extend the functionality of Quantum GIS (http://www.ftools.ca/). These points were randomly generated within the known census divisions, and were constrained by agricultural land use only (Statistics Canada, 2011). A minimum distance between farms of 0.5km was assumed as a constraint as well. Geographic coordinate values (latitude, longitude) were then added to these randomly generated farm location points to allow for data input into NAADSM.

Flock sizes for these farm location points were the same flock sizes used in the real-industry dataset.

3.3.1.3 Random-Census dataset

The total numbers of commercial chicken meat, commercial chicken egg, and turkey meat farms, within each census division, were obtained from the Statistics Canada website (www.statcan.gc.ca/). However, though the data were from 2006 as well, the number of farms provided by Statistics Canada was different from the real data; therefore in order to make the datasets as comparable as possible, the total number of farms within each census division in the census dataset was adjusted to reflect the true data based on production type. This ensured that there were 2186 commercial farms in both the real, random-industry, and random-census datasets (Table 1). The differences may be due to the method of data collection, as Statistics

Canada typically rounds the number of farms to the nearest five. The farm locations generated for the random-industry dataset were also used for the random-census dataset.

Since hobby farm information was not provided by Statistics Canada, the total number of farms and minimum and maximum flock sizes of those farms were taken from the real-industry dataset. Locations for these hobby farms were also randomly generated within the given census divisions, using the same methods mentioned above in the random-industry dataset section.

Random flock sizes were again generated using the minimum, mode, and maximum number of birds for each of the 4 production types within each census division, as provided by OLPC and OMAFRA, assuming a Pert distribution, in ModelRisk (www.vosesoftware.com/). Random flock sizes were generated from this distribution and randomly assigned to each farm location, for all four production types, across all census divisions.

3.3.2 Simulation modeling and input parameters

Each dataset was entered into NAADSM, and 1000 iterations of outbreak simulations were conducted, using the following scenarios, to determine the total number of farms infected with HPAI when the outbreak was finally eradicated.

3.3.2.1. Outbreak scenarios

For ease of interpretation of results among datasets, only four outbreak scenarios, with two stochastic contact structures each, were investigated for each dataset (Table 2). The scenarios were developed so that all input parameters related to each scenario remained the same throughout the 1000 iterations. The control parameters used in these scenarios were adapted from the parameters created by Dubé (unpublished) and found to be important in Chapter 2, when no movement restrictions were in place. Details are provided below.

Table 2: Summary of the 4 outbreak scenarios of HPAI used for comparison of the real-industry, random-industry, and random-census datasets

Scenario	Initially infected flock	Census division location of initially infected flock	Movement restrictions*	Destruction strategy**
1. T-Eff-1km	Turkey	3531	Effective restrictions	Stamping-out with 1km ring-culling
2. CM-N-1km	Chicken Meat	3531	No restrictions	Stamping-out with 1km ring-culling
3. T-Eff-3km	Turkey	3529	Effective restrictions	Stamping-out with 3km ring-culling
4. CM-N-3km	Chicken Meat	3529	No restrictions	Stamping-out with 3km ring-culling

* Effective restrictions indicate that on day 0, there is 100% contact between farms and indirect contacts, but by day 5 of the outbreak, there is only 5% contact occurring between farms and with indirect contacts.

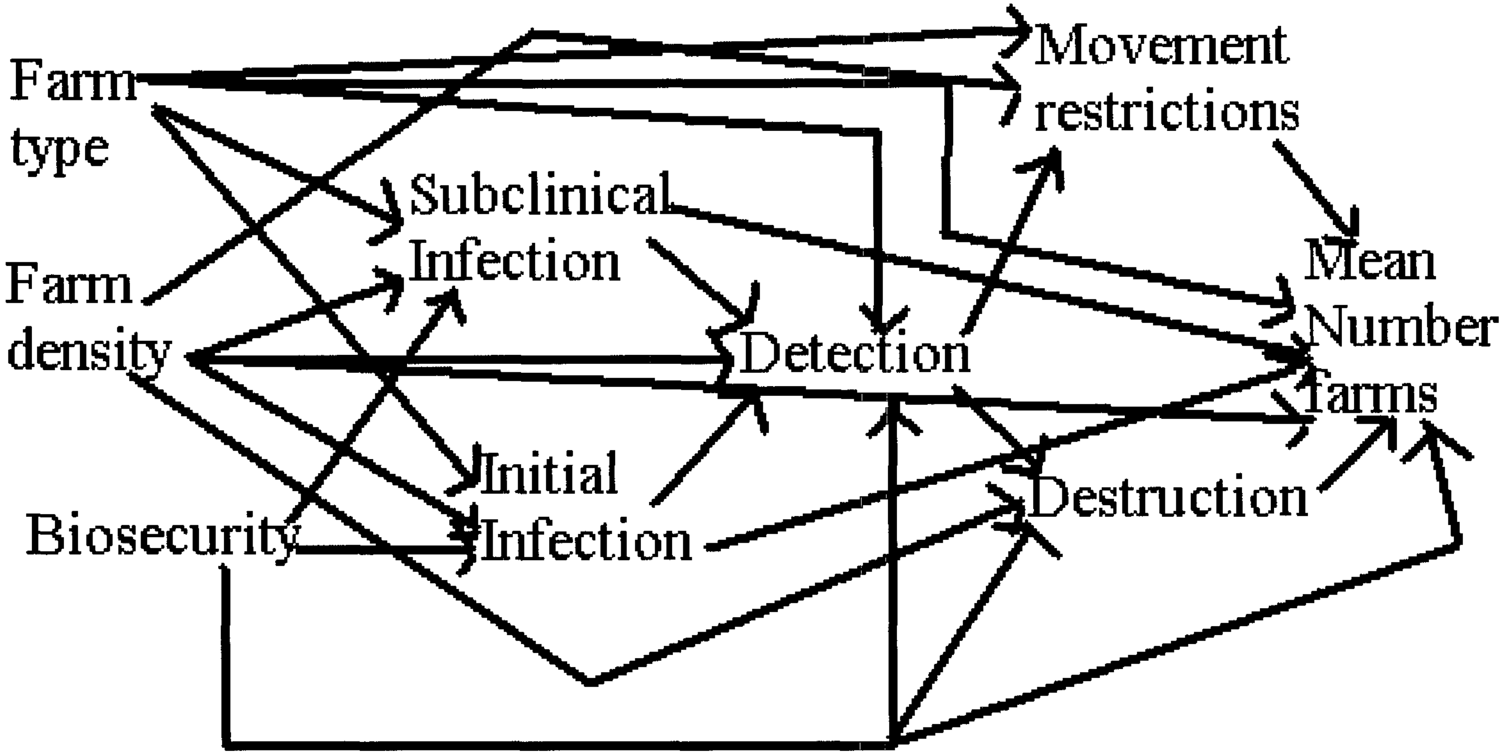
** Stamping-out is defined as depopulation of the infected/detected flock with pre-emptive ring-culling of either 1 or 3km.

In the assembly of the 4 scenarios, by design, only one farm was initially infected at the start of each simulation, from a census division with high study farm density, for each of the datasets. We purposively chose one of two different production types to initiate the outbreak, a commercial chicken meat farm or a commercial turkey meat farm, to allow us to see whether type of production made any difference in the results among the datasets.

Regarding control strategies, the rate of direct and indirect contacts can be affected when movement restrictions are applied. Once HPAI is confirmed in a flock, movement restrictions can be applied to all farms in a study region (Dubé, unpublished). In NAADSM, movement restrictions can be modeled by reducing the baseline contact rate specified by each production type combination for direct and indirect contacts. For example, if there was a rate of 1 direct or indirect contact per farm per day prior to implementation of movement restrictions, it would go down to 1*0.4=0.4 if movement restrictions were deemed to be reduced to 40% of their original value (Dubé, unpublished). In the current study, for ease of interpretation (because we were more interested in comparing datasets for certain control strategies than comparing control strategies themselves), and based on Chapter 2 results, one of two levels of movement restrictions (none or effective restrictions on direct and indirect contacts) were applied to all premises in the study regions, for a given scenario, once HPAI was confirmed in a flock (Table 2).

Culling detected flocks and 1) flocks in direct contact with an infected flock, 2) flocks within a specified distance around an infected flock, and/or 3) flocks that had indirect contact with an infected flock were all options for the destruction strategies for the model input parameters, as described in Chapter 2. In the current study, again for ease of interpretation, only two levels of destruction strategies were included here, stamping-out with a 1 km ring-cull or stamping-out with a 3 km ring-cull (Table 2).

Other variables held constant regardless of the scenario included a moderate probability of transmission through indirect contact (50%), one farm initially infected to start the outbreak, the farm can subclinically spread the disease through shedding the virus in the feces, moderate farm density in the area where the initially infected flock was located, and a moderate speed of detection (14d), as described in Chapter 2 (Figure 1).



*Subclinical infection is the ability of a farm to subclinically spread the infection
**Initial infection is the number of farms initially infected with the virus at the start of the simulation
***Biosecurity is equivalent to the probability of transmission via indirect contact

Figure 1: Conceptual diagram depicting the suspected interactions and associations between all input parameters used in the NAADSM model for HPAI

3.3.2.2. Frequency of contacts (weighted contact)

For each of the three datasets and scenarios, two sets of contact frequency structures were developed for input into NAADSM, a weighted median value and a weighted maximum value, for each production type, calculated from the direct and indirect contact structures used by Dubé (unpublished). The direct contact structure used by Dubé (unpublished) was calculated as the frequency of contacts per day, which required the following information: length of production cycle by production type, and number of barns per farm. For example, the original dataset consisted of 5 different turkey production types, but in the current study, these 5 types needed to be collapsed into one commercial turkey type. For turkey multiplier breeders, from the original dataset, there were 0.015 direct contacts/d/farm and 28 turkey multiplier breeder farms total. The weighted average was calculated using the 0.015 contacts/d/farm multiplied by the total number of turkey multiplier breeder farms (28 farms) divided by the total number of turkey farms in Ontario, which was 302 total turkey farms (0.015* (28/302)). The weighted average in this example was 0.0014 contacts/d/farm. The weighted median and maximum was then calculated using the weighted average.

For the indirect contacts, only different types of high risk indirect contacts were included, such as, catching crews, vaccination crews, and feed representatives. For example, movement of catching crews was assumed to be divided into breeders and non-breeders, and a catching crew could start in the morning on a table egg multiplier breeder pullet farm and also go to a meat type multiplier breeder later on the same day. The daily rates of indirect contacts per source farm was then determined. The number of barns per premises was again used in the calculation of these rates. The weighted indirect contact frequencies were calculated the exact same way as the example given above for the direct contacts.

The total number of scenarios included in this study was 24: 3 datasets*4 outbreak scenarios*2 contact structures and a total of 1000 iterations were run for each scenario.

3.3.3. Descriptive and Statistical Analysis

For the 1000 iterations of each scenario and dataset, the minimum, 5th percentile, median, 95th percentile and maximum number of farms infected were determined. These descriptive statistics were determined for both the weighted median and the weighted maximum contact structures.

For each of the three datasets, cumulative probability plots for the 1000 iterations were generated for comparison of the outcomes, number of farms infected, for the four scenarios and two contact structures. The K-S equality-of-distributions test was applied to aid in the determination of any existing significant differences among these distributions. This test is often used to decide if a sample comes from a population with a specific distribution, by testing the similarities between two distributions, the specific distribution in question, and another distribution.

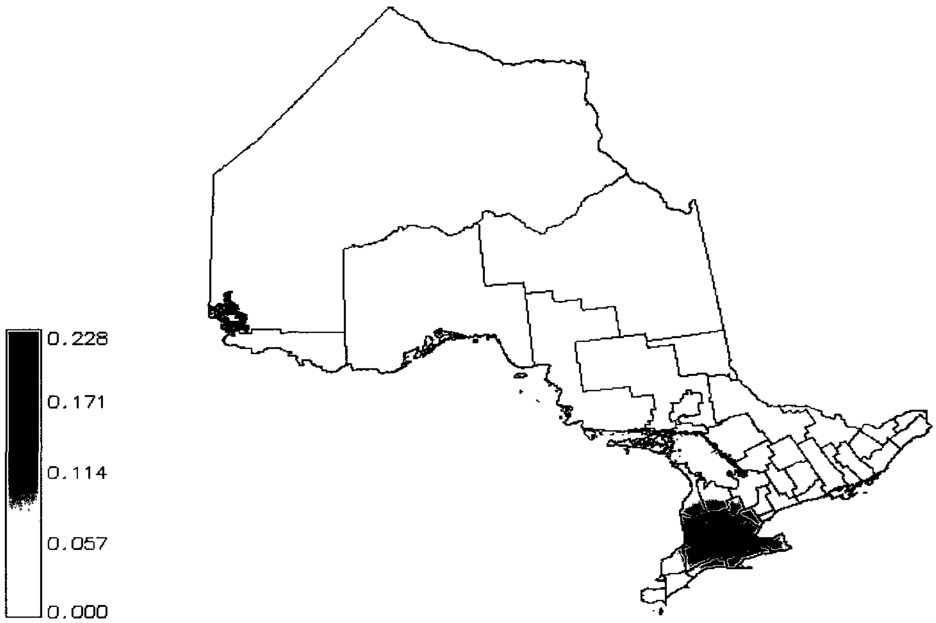
In addition, a negative binomial regression analysis was used to determine if a significant difference existed between the 3 datasets for the 4 scenarios and 2 contact structures. An initial descriptive analysis was carried out on the outcome of interest, number of farms infected at the end of the outbreak, as well as correlation coefficients among the predictor variables, which included random-census, random-industry and real-industry.

All predictors were initially assessed for unconditional association with the outcome. Predictors were deemed unconditionally associated with the outcomes if they had a p-value <0.15, and were then eligible for inclusion in the multivariable model building. Using Stata 10.0, a negative binomial regression analysis was used to determine significant predictors for the outcomes. All predictors were assessed for confounding and all possible two-way interactions. Confounding was considered present if the coefficient of the risk factor of interest changed more than 20% when the potential confounder was added to the model. The stepwise forward selection process of the significant explanatory variables for model-building followed the methodology described by Dohoo et al. (2003), and was validated using a backward elimination process to further test the association of the predictors with the number of farms infected. Overall, 8 models were developed for the 4 scenarios and the two contact structures, and each model consisted of 3000 iterations (1000 iteration for each of the 3 datasets).

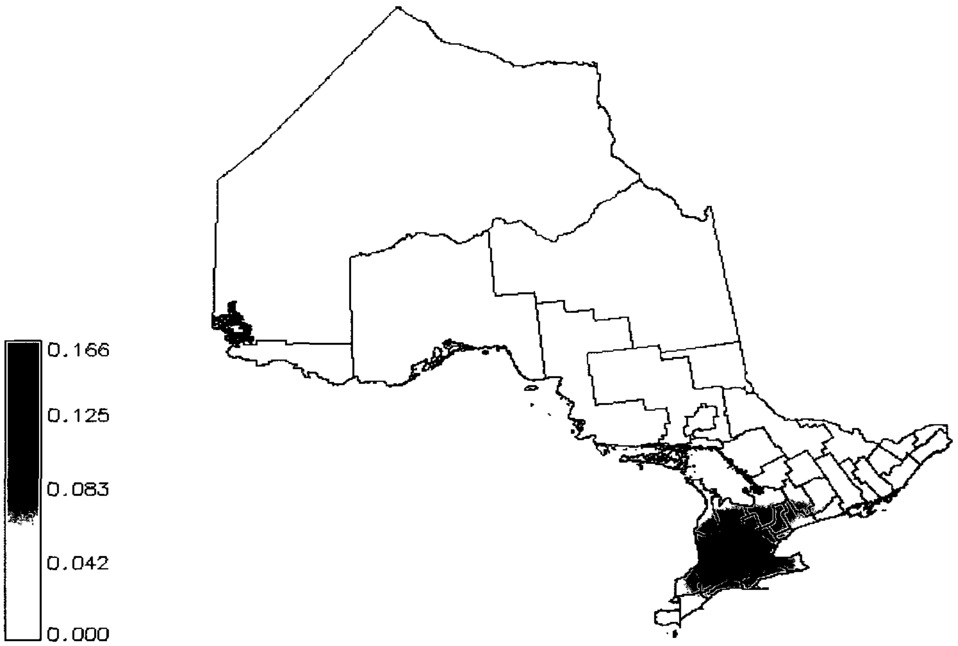
The negative binomial model was validated through overdispersion analysis and a deviance chi2 goodness-of-fit test, using the deviance residuals.

3.4 Results

The kernel density maps depicted in Figure 2 display the spatial distribution of the real and randomly allocated farms for all four production types used in this study. It was observed that the total number of farms was spread out over a larger area in the randomly generated point locations compared to the real-industry data.



Real density farms/km2



Random density farms/km2

* Random points were generated using the FTools extension from census division data entered into Quantum GIS

**The random location graph represents the two random datasets (random-census and random-industry) as the locations of the two datasets were similar

Figure 2: Kernel density maps for comparison of the real-industry, random-census and random-industry farm locations

3.4.1. Weighted median and maximum frequency contacts

The results indicate a vast difference in number of infected farms between the two types of contact structures, with the weighted maximum contact structure resulting in many more farms becoming infected at the end of the outbreak compared to the weighted median contact structure.

For the weighted median contact structure, comparison of the 1000 iterations between the random-census, random-industry and real-industry datasets showed similar minimum and median counts for the number of farms infected at the end of the outbreak (Table 3). However, the maximum count in the real-industry dataset was approximately 2-3 times larger than the random-census and random-industry datasets, across all scenarios (Table 3). Overall, the random-census and random-industry datasets had similar maximum counts. The 5th percentile was zero in nearly every situation for each dataset; while the 95th percentile counts were overall much lower than the maximum counts.

For the weighted maximum contact structure, again similar minimum and median counts for the number of farms infected at the end of the outbreak was observed within all datasets (Table 4), even though scenarios 2 and 4 (CM-N-1km & CM-N-3km) had higher median counts than scenarios 1 and 3 (T-Eff-1km & T-Eff-3km) for all datasets. For scenarios 1 (T-Eff-1km) and 3 (T-Eff-3km), where there were effective movement restrictions on direct and indirect contacts, there were more than double the maximum number of farms infected in the real-industry dataset, compared to the random-census and random-industry datasets, which were similar. The 5th percentile was again zero in nearly every situation for each dataset, however the 95th percentile counts were only slightly lower than the maximum counts for scenarios 2 and 4

(CM-N-1km & CM-N-3km), while scenarios 1 and 3 (T-Eff-1km & T-Eff-3km) were ¼ to ½ the maximum counts.

Table 3: Ranges and percentiles of the number of farms infected with HPAI, from 1000 iterations, for scenarios 1-4, for the real-industry, random-industry, and random-census datasets using a median contact structure

Scenario	Dataset	Minimum	5th percentile	Median	95th percentile	Maximum
1. T-Eff-1km	Real-industry	0	0	1	5	12
	Random-industry	0	0	0	1	4
	Random-census	0	1	1	4	8
2. CM-N-1km	Real-industry	0	0	0	6	14
	Random-industry	0	0	0	1	5
	Random-census	0	0	0	1	4
3. T-Eff-3km	Real-industry	0	0	0	1	17
	Random-industry	0	0	0	1	4
	Random-census	0	0	0	1	6
4. CM-N-3km	Real-industry	0	0	0	2	18
	Random-industry	0	0	0	1	6
	Random-census	0	0	0	1	5

Table 4: Ranges and percentiles of the number of farms infected with HPAI, from 1000 iterations, for scenarios 1-4, for the real-industry, random-industry, and random-census datasets using a maximum contact structure

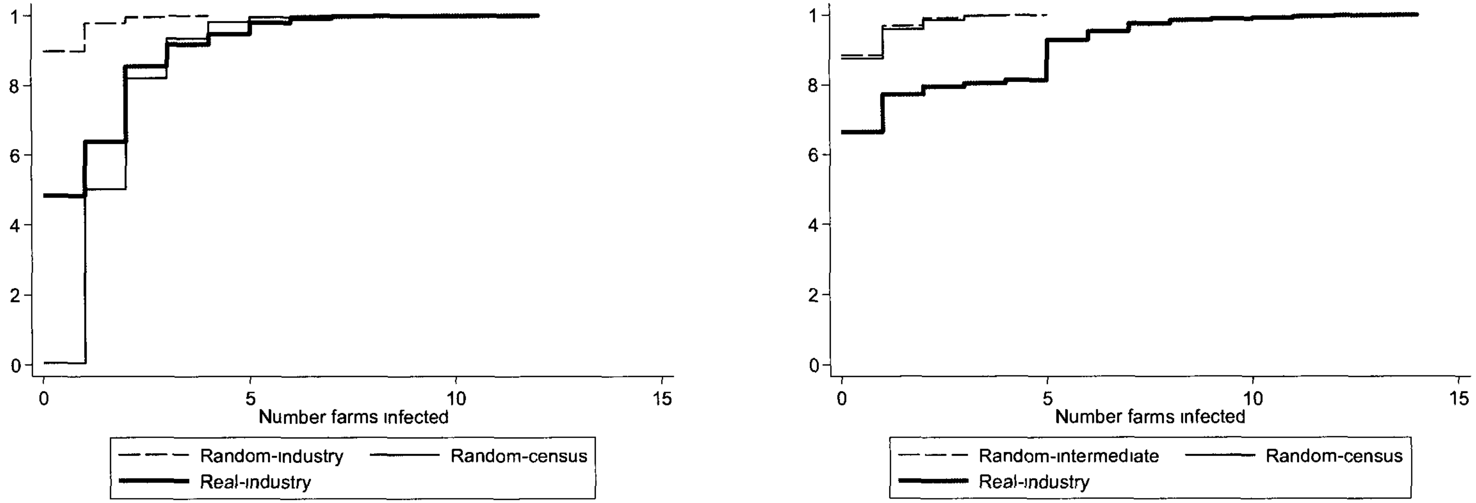
Scenario	Dataset	Minimum	5th percentile	Median	95th percentile	Maximum
1. T-Eff-1km	Real-industry	0	0	5	39	126
	Random-industry	0	0	2	14	33
	Random-census	0	1	7	29	66
2. CM-N-1km	Real-industry	0	0	1830	1885	1923
	Random-industry	0	0	1636	1716	1764
	Random-census	0	0	1600.5	1686	1741
3. T-Eff-3km	Real-industry	0	0	2	37	165
	Random-industry	0	0	2	12	41
	Random-census	0	0	2	17	51
4. CM-N-3km	Real-industry	0	0	1789	1877	1918
	Random-industry	0	0	1566	1693	1747
	Random-census	0	0	1540.5	1665	1745

3.4.2. Weighted median and maximum cumulative ascending probability

The cumulative ascending probability plots show the percentage of iterations with a number of infected farms equal or less than a specific number. For example, in Figure 3, scenario 1 (T-Eff-1km), for the random-census dataset, 100% of the iterations contained 8 or less infected farms at the end of the outbreak, while 50% of the iterations (the median) had 1 or less infected farms at the end of the outbreak. For the random-industry dataset, 100% of the iterations contained 4 infected farms or less, while the real-industry dataset showed 100% of iterations consisted of 12 infected farms or less at the end of the outbreak. Meanwhile, 90% of the iterations, for the random-industry, and 50% of the iterations (the median), for the real-industry, had 1 or less infected farms at the end of the outbreak.

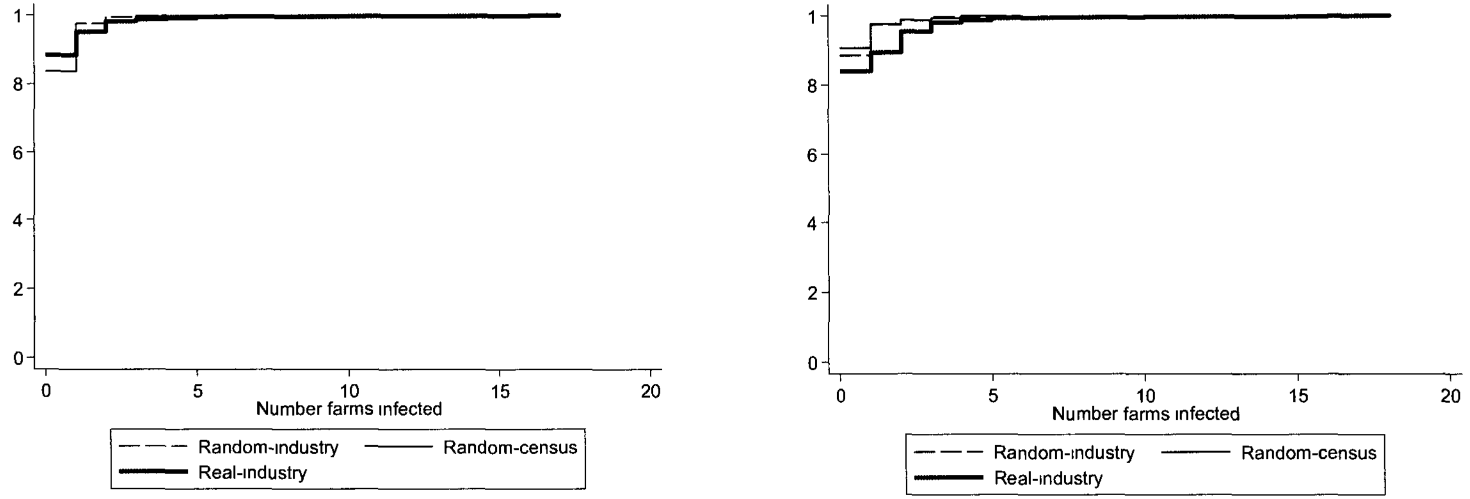
For the weighted median contact structure, scenario 1 (T-Eff-1km) shows similar patterns between the real-industry and random-census datasets, with 50% of the iterations consisting of 1 farm or less infected at the end of the outbreak, while the random-industry dataset had 90% of the iterations with 1 farm or less infected at the end of the outbreak. In scenario 2 (CM-N-1km), the random-industry and random-census datasets show similar patterns, but the real-industry data was different. In scenarios 3 (T-Eff-3km) and 4 (CM-N-3km), all three datasets show very similar patterns, though the real-industry dataset had 3-4 times more farms infected at the end of the outbreak compared to the random-industry and random-census datasets (Figure 3).

For the maximum contact structure, scenarios 1and 2 (T-Eff-1km & CM-N-1km) show similar patterns between all three datasets in the cumulative ascending probability plots. For scenario 3 (T-Eff-3km), the random-industry and random-census datasets show very similar patterns (Figure 4). The real-industry dataset shows a similar pattern but has an approximately 3-4 times larger maximum number of farms infected compared to the random-census and random-industry datasets. For scenario 4 (CM-N-3km), the random-industry and random-census datasets have very similar patterns, whereas the real-industry dataset had approximately 200 more farms infected.



T-Eff-1km

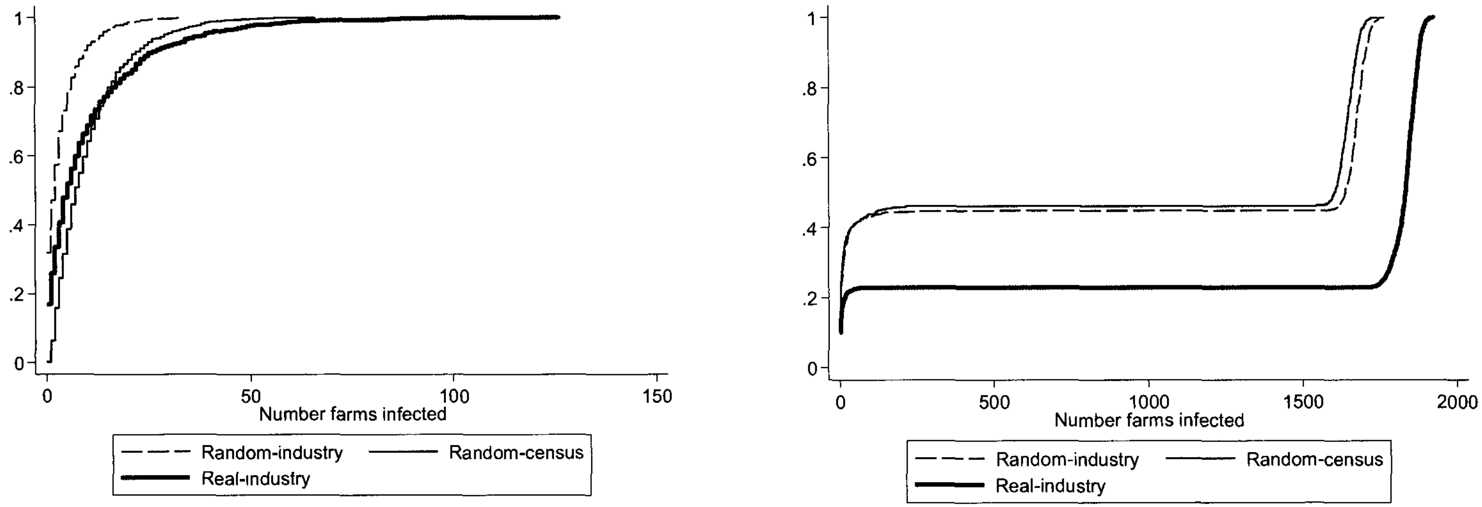
CM-N-1km



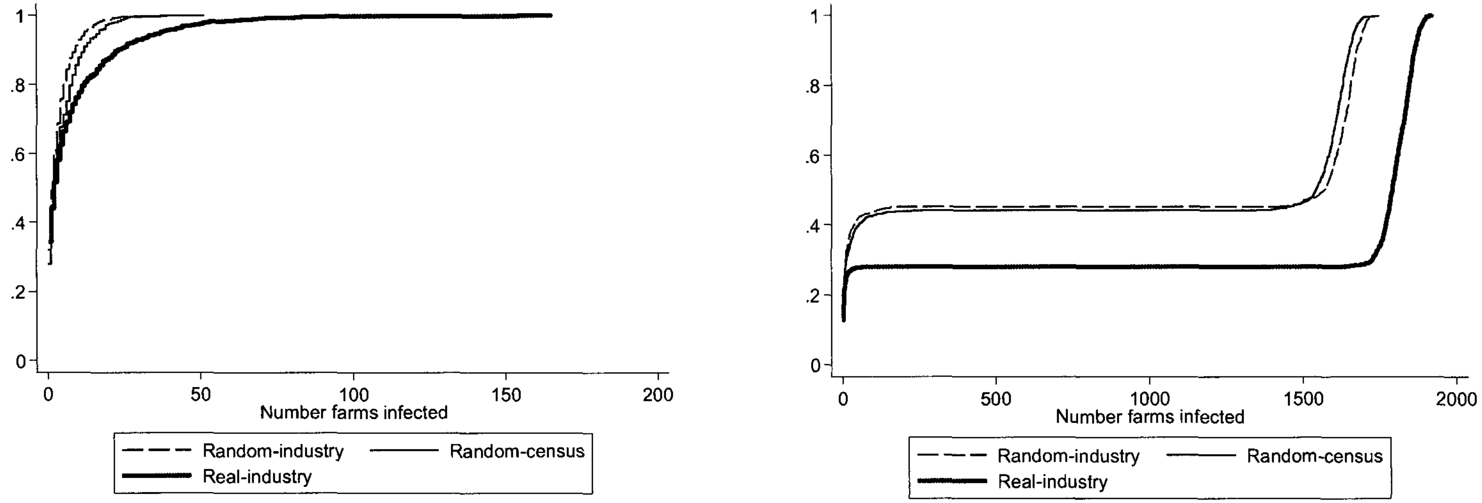
T-Eff-3km

CM-N-3km

Figure 3: Cumulative ascending probability plots of HPAI outbreaks comparing the real-industry, random-industry and random-census datasets for the weighted median contact structure of the 4 scenarios



T-Eff-1km CM-N-3km



T-Eff-3km CM-N-3km

Figure 4: Cumulative ascending probability plots of HPAI outbreaks comparing the real-industry, random-industry and random-census datasets for the weighted maximum contact structure (worst case scenario) of the 4 scenarios

3.4.3. Statistical analysis

3.4.3.1. Kolmogorov-Smirnov equality-of-distribution test

The K-S equality-of-distribution test further demonstrates that the random-census and random-industry datasets were significantly different from the real-industry dataset ($p<0.05$), for every scenario, for both the median and maximum contact structure. Therefore, one portion of the curve showed a difference for the number of farms infected between the datasets.

3.4.3.2 Negative binomial regression analysis

The outcome, number of farms infected at the end of the outbreak, had a strong right skew and consisted of a large number of iterations resulting in zero and one farms infected (Figure 5 & 6). The distribution for the outcome had means of 0.507 (for the median contact structure) and 532.017 (for the maximum contact structure), medians of 0 and 8, respectively, and ranges from 0 to 18 and 0 to 1923, respectively. All predictors were significantly associated with the outcome. The eight final models, for the 4 scenarios and 2 contact structures, contained the outcome, number of farms infected, and three predictors, which was the 3 datasets (Real-industry, Random-census and Random-industry).

For the median contact structure, the random-census and random-industry datasets were found to be significantly different ($p<0.05$) from the real-industry dataset in all scenarios except scenario 3 (T-Eff-1km), where the random-census dataset was not significantly different from the real dataset ($p=0.899$). The magnitude of the differences in the scenarios where a significant difference was found ranged from 0.107 (95%CI: 0.089, 0.129) to 1.468 (95%CI: 1.357, 1.587), seen in scenario 1 (CM-N-1km). Therefore the random-census and random-industry datasets resulted in an outbreak that was between 0.107 and 1.468 times that of the real-industry dataset (Table 5).

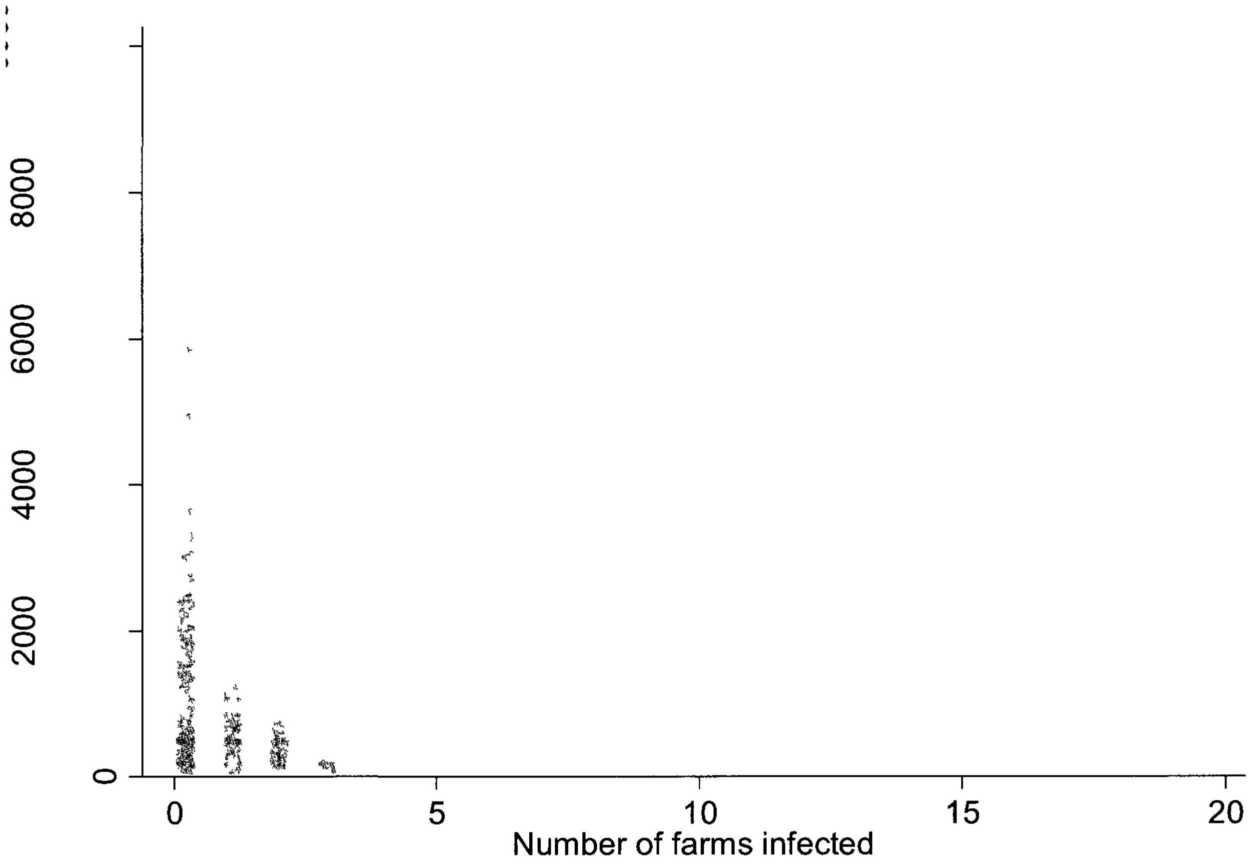


Figure 5: Histogram of the distribution of the number of farms infected with HPAI for the median contact structure, across all simulated datasets

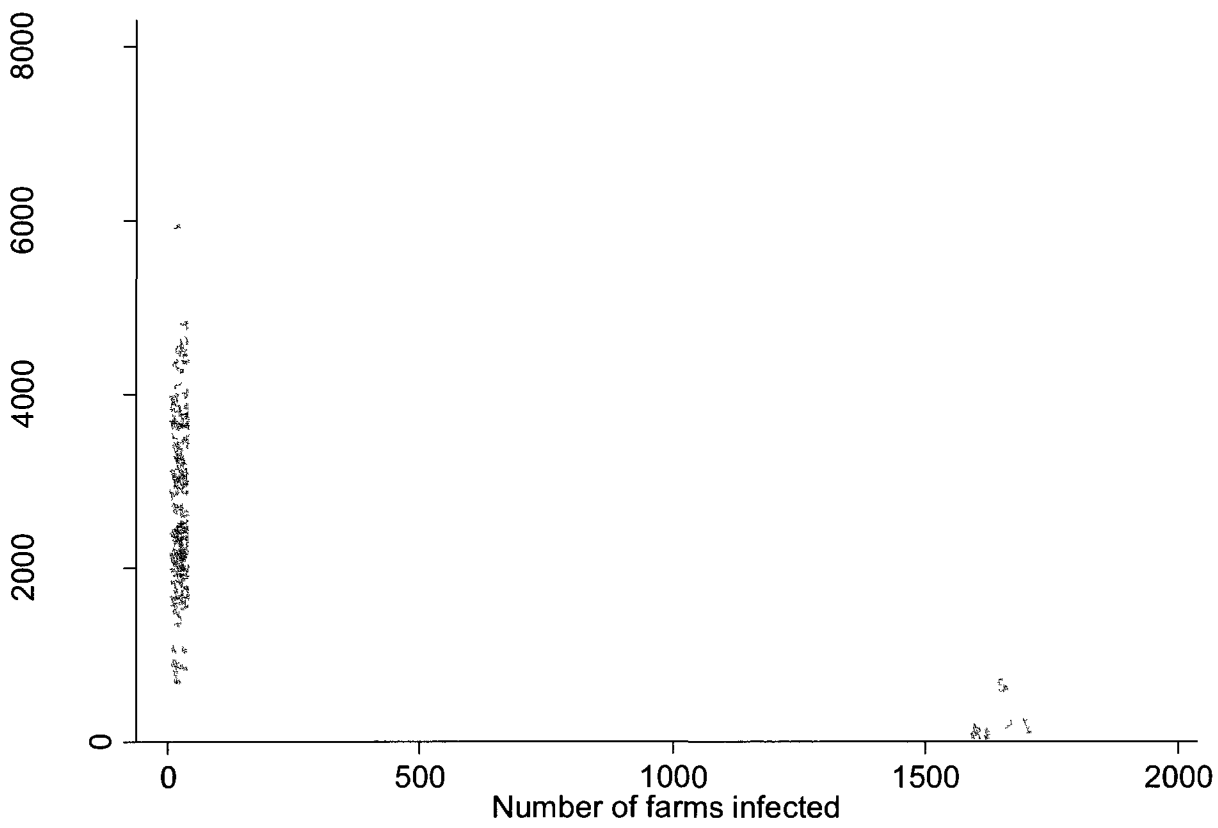


Figure 6: Histogram of the distribution of the number of farms infected with HPAI for the maximum contact structure, across all simulated datasets

Table 5: Negative binomial regression count ratios and confidence intervals for comparison of the 2 random datasets to the real-industry dataset (baseline), across each scenario, for the weighted median contact structure

	Real-industry	
Scenario 1 (T-Eff-1km)	Count ratio (CI)	P-Value
Random-census	1.468 (1.357, 1.587)	<0.05
Random-industry	0.107 (0.089, 0.129)	<0.05
Scenario 2 (CM-N-1km)		
Random-census	0.135 (0.106, 0.172)	<0.05
Random-industry	0.118 (0.092, 0.151)	<0.05
Scenario 3 (T-Eff-3km)		
Random-census	0.983 (0.755, 1.279)	0.899
Random-industry	0.636 (0.480, 0.841)	<0.05
Scenario 4 (CM-N-3km)		
Random-census	0.344 (0.255, 0.465)	<0.05
Random-industry	0.410 (0.306, 0.549)	<0.05

For the maximum contact structure, the random-census and random-industry datasets were found to be significantly different ($p<0.05$) from the real-industry dataset in all scenarios except in scenario 1 (CM-N-1km), where the random-census dataset was not significantly different from the real dataset ($p=0.921$). The magnitude of the differences in the scenarios where a significant difference was found was consistently less than 0.7 (Table 6). Therefore the size of the HPAI outbreak in the random-census and random-industry datasets were 0.7 times that of the real-industry dataset.

The data were tested for overdispersion and goodness of fit, as well as an analysis of the residuals, for the two contact structures. The data did not fit the Poisson model well, with evidence of overdispersion, as seen with the likelihood ratio test where the chi-squared value was 2704.00 for the median contact structure, and 5.7e+06 for the maximum contact structure, with a p-value of <0.05 for both. The problem of overdispersion has therefore been corrected by using a negative binomial regression model in place of a Poisson model.

Table 6: Negative binomial regression count ratios and confidence intervals for comparison of the 2 random datasets to the real-industry dataset (baseline), across each scenario, for the weighted maximum contact structure

	Real-industry	
Scenario 1 (T-Eff-1km)	Count Ratio (CI)	P-Value
Random-census	0.995 (0.901, 1.098)	0.921
Random-industry	0.339 (0.306, 0.376)	<0.05
Scenario 2 (CM-N-1km)		
Random-census	0.630 (0.537, 0.739)	<0.05
Random-industry	0.657 (0.560, 0.771)	<0.05
Scenario 3 (T-Eff-3km)		
Random-census	0.540 (0.473, 0.617)	<0.05
Random-industry	0.401 (0.350, 0.469)	<0.05
Scenario 4 (CM-N-3km)		
Random-census	0.691 (0.586, 0.813)	<0.05
Random-industry	0.690 (0.586, 0.812)	<0.05

3.5 Discussion

With the increasing use of spatially explicit models to inform policy decisions, it is important to have the most accurate and realistic population data as possible. USDA researchers have simulated farm and animal populations in areas such as North Carolina, using specific spatial constraints, but have had only moderate success, due to inaccuracies in the public domain lists and because of difficulties in converting rural route addresses to geocodable locations (Bruhn et al., unpublished). Bruhn et al. (unpublished) created spatial data with generated point locations of animal operations from publicly available data, using the number and type of operations from the 2002 USDA Census of Agriculture. Similarly, the current study obtained the number and type of operations from the 2006 Statistics Canada Census of Agriculture to aid in the generation of random point locations within each census division in Ontario. It was specified, in the current study, that poultry operations could not be located in water, in the middle of cities, or on public land, and were constrained within areas of agricultural land use, similar to other studies that generated estimated farm locations (Bruhn et al. 2007; Freier et al., 2007).

The kernel density plots showed more farm spread across census divisions in the random location dataset (which was the same for both the random-census and random-industry dataset) compared to the real-industry dataset (Figure 2). This may have resulted in a decreased number of farm-to-farm contacts resulting in an underestimation in the size of the outbreak, because naïve farms would not be as likely to come into contact with infected farms. Tildesley et al. (2010) stated that for infectious diseases to occur, where transmission is over short distances, spatial structure plays three specific roles: 1) hosts that are far from sources of infection are at very little risk; 2) local transmission and depletion of susceptible hosts can dramatically reduce the speed of epidemic growth; and 3) local control measures can be applied using spatial proximity as a method of targeting at-risk hosts. In the current study, a minimum distance of

0.5km was enforced between farms during the random generation of farm locations. This may have also affected the spread of disease between farms, resulting in an underestimated maximum number of farms infected at the end of the outbreak. Previous studies have shown that farms located closer to infected premises are more likely to become infected with the disease, as well as farms that are in direct contact with infected farms (Nishiguchi et al., 2007). Allowing for this type of spatial dynamic may make the random location and flock size dataset more comparable to the real dataset. One way of achieving more accurate spatial distribution of randomly generated farm locations is to use a higher resolution spatial area of farm location to start the random generation process. Therefore, we suggest that in future simulations, the census subdivision be used as opposed to the census division, as an attempt to correct the density distribution problems seen in the current study.

Bruhn et al. (unpublished) found that it was possible to generate poultry-operation locations nationwide using USDA Census of Agriculture data and GIS, but without formal assessment of the locations' suitability. The current study showed that by using Statistics Canada census data, random farm locations and flock sizes could be generated, and these locations supplied a reasonable surrogate for actual farm locations through statistical analyses; however the kernel density maps showed differences that may have had a big impact on the results. The generalizability of successfully generating point locations should be strengthened by comparing random and real datasets for other Canadian provinces and jurisdictions, where real data are available for comparison.

Any differences seen between the random and real datasets was likely due to the random distribution of farms within census divisions, as demonstrated in Figure 2. It can be difficult selecting the most appropriate method for geo-referencing data. Durr & Froggatt (2002) states that the most critical piece of data for any outbreak is the location where that outbreak began, which is most effectively represented as a point location. When addressing the question of how to effectively generate farm locations when data are absent, all possible avenues need to be explored. Farms could be identified in a number of ways, such as: 1) farm centroids calculated from digitized boundaries; 2) farm postal code; 3) the three digit agricultural parish code; or 4) farm building locations from satellite imagery (Durr & Froggatt, 2002). In the current study, farm locations were generated as a random farm point location within agricultural land use, in each census division for Ontario, and it was assumed that each farm point location was an entire farm, not individual buildings on the farm, based on the source of the data. Durr & Froggatt (2002) found that the farm building was the single best practical geo-referencing point for discrete farms, if possible, but only if the type of farm is not essential. In the current study, farm type was important, because different farm types would have different contact structures.

The weighted minimum and maximum contact structures were found to have some differences in the magnitude of the outbreak. For the weighted median contact structure, the maximum number of farms infected was approximately two times larger in the real-industry data compared to the random-census and random-industry datasets (Table 3). The maximum weighted contact frequency had more comparable maximum number of farms infected between the real-industry and the two random datasets in scenarios 2 (CM-N-1km) and 4 (CM-N-1km), however in scenarios 1 (T-Eff-1km) and 3 (T-Eff-3km) the maximum number of farms infected in the real-industry dataset was approximately double the number for the random-census and random-industry datasets (Table 4). In the 4 scenarios chosen, this indicates that the median contact structure is more likely to underestimate an outbreak than the maximum contact structure. This requires further investigation through simulation of more scenarios.

Overall, the random-industry and random-census datasets produced quite similar outbreak results to the real-industry dataset, as shown by the cumulative probability plots and Tables 3 and 4. The similarity between the random and real datasets in all aspects of the outbreaks, with the exception of the maximum number of farms infected, is useful for the generation of a robust policy, as most policies are built on the overall outbreak picture (minimum, mean, maximum number of farms infected, etc.) and with a robust policy the differences in the maximum number of farms infected is not as important. This overall picture was similar to the real-industry dataset and therefore is useful when real data is unavailable. However, policy makers will have to realize that this approach would not provide an evaluation of the worst case scenario.

From the regression analyses, the outbreak results from the randomly generated data were significantly different than from the real-industry dataset, showing an underestimation of the maximum number of farms infected. The significant difference was most likely due to the large number of iterations/observations. The main reasons for the differences in the datasets are most likely related to the way the random points were generated and the density of the farms, within census divisions. As previously mentioned, the use of the census subdivision may create a more similar density distribution to the real-industry data. The K-S equality-of-distributions test also showed that there was a significant difference ($p<0.05$) between all three datasets, in all 4 scenarios, for both the median and maximum contact frequencies. This test, however, is not without its limitations, as (1) it only applies to continuous distributions; (2) it tends to be more sensitive near the center of the distribution than at the tails; and (3) the most serious limitation is that the distribution must be fully specified (NIST/SEMATECH e-Handbook of Statistical Methods, 2010). As this test compares two distributions, the significant differences seen between the datasets, may be attributed to a small portion of distribution of the outcome from the random-census or random-industry datasets being different from the distribution of the outcome from the real-industry datasets. The rest of the graph may be the same for both datasets.

Another limitation of this study, aside from obtaining an appropriate spatial distribution, included the difficulty in generating the most appropriate flock size for each farm using Statistics Canada data, as there was a large amount of data missing. To adjust for this large amount of missing data the minimum, mode and maximum values from the real-industry data were used, generating a distribution where flock sizes could be randomly selected and assigned to each flock, as seen with the random-industry data. The random-industry dataset consisted of the same number of farms and the same census divisions as the real dataset, and the flock sizes were estimated from the industry provided information. By randomly selecting flock sizes for each flock, within each production type, by individual census divisions, it was thought that the random-industry dataset would be more comparable to the real dataset as all the parameters were the same except the farm location, distance between farms, and flock size. However, in general census data is more readily available than industry data, which is considered confidential.

3.6 Conclusions

Generation of the random-census and random-industry data resulted in a larger farm spread across the province resulting in a difference in farm density within the census divisions compared to the real-industry data. This could have had a major impact on the size of the outbreaks seen in the 4 outbreak scenarios. It is therefore suggested that the use of the census subdivision, which is a smaller land parcel than the census division, be investigated in future simulations instead of the census division, as it may correct some of the differences in the density of farms in each area resulting in more comparable outbreaks and greater similarity with the real-industry data. Differences were seen between the random-census and random-industry datasets compared to the real-industry dataset for the maximum number of farms infected for most scenarios, with the random-census and random-industry datasets underestimating the maximum size of the outbreaks. A robust policy is created for outbreak preparedness and therefore relies more on the entire outbreak picture than the maximum number of farms infected. As seen in this study, all other aspects of the outbreak (minimum, 5th percentiles, median, and 95th percentiles) were comparable in all 3 datasets. Therefore, random-census and random-industry point location data and flock sizes were found to be an appropriate representation of the real-industry dataset for simulation of an outbreak of HPAI in Ontario, making them useful in policy generation when real data is unavailable. However, due to data availability, the use of census data may be more practical as industry data is typically considered confidential. The 2 contact frequencies assessed showed that the median contact frequency more often underestimated the outbreak than the maximum contact frequency, therefore it may be more appropriate to use a maximum contact frequency in future simulations. However, this theory requires further investigation with the evaluation of more outbreak scenarios. The results apply specifically to Ontario, Canada, as other provinces have different demographics, geography and epidemiological conditions; therefore further research is required to determine if this random generation approach has a potential use in other areas.

3.7 References

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Chapter 4

Summary and Conclusions

4.1 Introduction

As each outbreak of highly pathogenic avian influenza (HPAI) is unique, pre-outbreak preparedness is important. The World Organization for Animal Health (OIE) focuses on such factors as early detection through wild bird and domestic poultry surveillance, and a rapid response through disease surveillance and specific control strategies to quickly and effectively eradicate the disease (Martin et al., 2006). The appropriateness of control strategies that are implemented in an outbreak are dependent on various demographic, geographic and epidemiological factors, therefore each country should develop its own outbreak policy. No one control strategy alone has proven effective at eradicating a disease (Yee et al., 2008). The current policy for controlling an outbreak of highly pathogenic avian influenza (HPAI) in Canada consists of destruction of the infected/detected flock, with pre-emptive ring-culling of exposed or high-risk flocks within a 1km radius of the infected/detected flock (CFIA, 2009).

Disease spread simulation modeling can help identify potential risk factors for the introduction and/or spread of a contagious foreign animal disease, and can help predict the effects of implementing various control strategies during an outbreak, driving policy decisions. For HPAI, these risk factors include the proximity to an infected flock, sharing of farm equipment, movement of birds and fomites between farms, and contact with wild birds (Nishiguchi et al., 2007).

One key component for the use of animal disease spread models for policy is the ability to communicate model study results and the model themselves and their outputs to policy-makers. Due to the complexity of these models, finding the most effective method of presenting outputs from modeling studies can be very difficult to achieve. In order to have an effective policy, decision makers must fully understand findings of simulation studies as well as the models themselves. A disease spread model developed to simulate the spread of highly contagious diseases of animals is the North American Animal Disease Spread Model (NAADSM). This stochastic, spatial, state-transition model is comparable to previously developed outbreak models, such as InterSpread Plus (Harvey et al., 2007). However, this model was developed to specifically support policy development and decision-making for potential disease incursions in North America (Harvey et al., 2007). NAADSM requires, among other input parameters, point locations (latitude, longitude) and farm sizes in order to run a simulation, which can be limiting, depending on data availability. Some research has been done to test the efficacy of randomly generated point locations compared to real farm locations, with limited success (Bruhn et al., unpublished).

The main objectives of this thesis were 1) to find an appropriate method for analysis of a large number of outbreak scenarios for HPAI, in order to determine which control strategies were most important to minimizing the number of farms infected during the outbreak; 2) to identify an effective way to communicate those results to decision-makers for use in policy generation; and 3) to determine if census data are comparable to industry based data in simulation models of HPAI, so that it may be used in the absence of real location and flock size information.

4.2 Analysis of a large number of simulated outbreaks (Chapter II)

The specific objectives of this chapter were to develop an approach to analyze large numbers of NAADSM simulated HPAI outbreak scenarios in Ontario, Canada, and communicate these results effectively to policy-makers. Information included in the analysis was provided by the Ontario Livestock and Poultry Council (OLPC) and Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA) for a total of 2,487 commercial and 7,140 non-commercial poultry farms, respectively.

A total of 21,060 disease outbreak scenarios were developed, which were entered into NAADSM and run 1000 times each, to obtain the mean number of farms infected and 95th percentile at the end of the simulated outbreak scenario for Ontario, Canada. Each scenario represented a different combination of input parameters, with movement restrictions (e.g. no movement restrictions) and destruction strategies (e.g. stamping-out with ring-culling at a 1km radius) being the primary focus. The outputs from the scenarios were analyzed using a negative binomial regression model to determine which input parameters were most effective at reducing the size of an outbreak. Predictive values were obtained from the negative binomial regression analysis to generate interaction plots of the control measures and the outcome (mean number of farms infected). Interaction plots were stratified on a low (40%), moderate (60%) and high (90%) probability of transmission through indirect contact, and on a low (between the 25th-49th percentile), moderate (between the 50th-75th percentile), and high (>75th percentile) farm density, and slow (15-21d), moderate (8-14d) and fast (<7d) detection speed to gain a better understanding of the effects of transmission via indirect contacts, speed of detection, and farm density in the area where the initially infected flock was located, as well as the interaction between movement restrictions and destruction strategies. These plots were generated as a method of presenting the results of the model for communication to policy-makers.

Due to the shape of the distribution of the outcome, a negative binomial regression analysis was found to be the most appropriate analytical tool as a large number of the outbreak scenarios ended with just 0-1 farms infected (right-skewed data) and did not fit a normal, Poisson, or other type of distribution.

Scatter plots have also been used in other studies, but as an alternative, the interaction plots, developed from the negative binomial regression analysis, were used instead and found to be an appropriate and better visualization tool for communication of these results to policy-makers, as these results were presented to policy-makers and were well received. These interaction plots provided a simple and effective way to show the significant difference between, for example, no movement restrictions compared to effective movement restrictions on direct and indirect contacts, and the effect these control measures had on the outcome. They also provide important information on the effectiveness of various control strategies during an outbreak of AI.

4.3 HPAI Policy in Canada (Chapter II)

Due to the lack of previous HPAI outbreak experience, there has not been a lot of research challenging the current control policies for HPAI in Canada and elsewhere. A large portion of studies have been conducted on data from previous outbreaks to determine if the control strategies used at the time of that past outbreak were the most effective methods. Simulations based on previous outbreaks are one tool that may be used to determine the effectiveness of various control strategies on potential future outbreaks. Using the negative binomial regression analysis and interaction plots, the most appropriate outbreak policy for Ontario, Canada was determined in the current study. As mentioned, the current HPAI control policy in Canada states that effective movement restrictions (on direct and indirect contacts) and destruction of infected/detected flocks, within a 1km radius, are required.

Using the mean number of farms infected from the 21,060 scenario outputs and a negative binomial regression analysis, destruction strategies and movement restriction (on direct and indirect contacts) were specifically investigated. Movement restrictions were defined as reducing contact rates during an outbreak, as compared to "normal" days (pre-outbreak) of direct and indirect contacts. These restrictions were categorized as: 1) no restrictions on direct and indirect contacts (100% movement); 2) less effective restrictions on indirect contacts with effective restrictions on direct contacts; and 3) effective restrictions on indirect and direct contacts. Less effective and effective movement restrictions on indirect contacts referred to the decrease in the percent of movement over time. Three destruction strategies were included: 1) stamping-out (destruction) of the infected/detected farms and tracing/testing of direct contacts; 2) stamping-out with ring-culling of flocks within 1 km from infected/detected farms; or 3) stamping-out with ring-culling of flocks within 3 km from infected/detected farms. Other studies have also included vaccination programs in their outbreak analysis but that was not the focus of this study, as the current Canadian outbreak policy does not include vaccination in its control program.

The results from this study showed that the current Canadian policy is not necessarily the best solution. The most appropriate strategy was destruction of the infected/detected flocks only (i.e. no ring-culling required), in combination with effective movement restrictions on direct and indirect contacts. Without effective movement restrictions on direct and indirect contacts, in the case with slow, moderate and fast detection speeds and a low, moderate and high probability of transmission, there was a significant difference found between the destruction strategies used. Therefore, if effective movement restrictions on direct and indirect contacts could not be achieved the recommendation for the current Canadian policy would be similar to the current policy.

Some of the issues with the use of effective movement restrictions is the compliance from the farmers. Farms with valuable genetic stock or show breeds do not want to restrict movement on their farms and do not want to lose valuable genetics from depopulation. This is not something that is easily modeled. Another issue is this may not be the most appropriate policy for other provinces, whose province and industry demographics may be completely different from Ontario. For instance, Prince Edward Island does not have a large poultry industry and the majority of their stock is shipped to other provinces, instead of staying within the province, which could result in the outbreak spreading to other provinces. This must be taken into consideration, therefore simulation scenarios may need to be evaluated for each province individually.

Also, being able to subclinically spread the infection led to a larger number of farms infected than when farms could not subclinically spread the disease, though the ability to subclinically spread could potentially be affected if vaccination were implemented. Poultry farm density in the area of the initially infected flock did not affect the number of farms infected at the end of the outbreak, but the level of transmission from indirect contacts, reflecting the level of biosecurity in the flock, did. This may have been due to the uncertainty with the level of local spread, such as from unknown sources like wild birds and airborne transmission. Numerous factors cause each outbreak to be unique, making accurate predictive simulations difficult because it is hard to predict what will be the primary contributing factor in an outbreak. Policies in other countries consist of slightly different methods of control of an outbreak of HPAI, as each country has a different industry structure, with different demographics and environment;

therefore it is inappropriate to compare the results from the current study to other studies. Other findings from the final model indicated that initial infection of other poultry operation types, compared to chicken broilers, and resulted in fewer total farms being infected. The assumptions and information applied in the models for policy generation would vary greatly between countries.

Findings from this study were specific to Ontario, Canada; results may differ between provinces within Canada, therefore one policy for all of Canada may not be appropriate. It may be more appropriate to develop a policy for each province, as they all differ in their demographics, although the industry structure is very similar. Further research is required to determine if this model provides similar results across all provinces, as each province has its own specific geography, demographics and productions systems/types, which may cause simulation results to vary.

4.4 Randomly generated point locations and flock sizes vs. real data in Ontario (Chapter III)

With the determination that NAADSM is useful in policy generation and may be used for other foreign animal diseases, the specific parameter requirements for the development of scenarios for HPAI were considered. NAADSM requires specific flock locations (latitude, longitude) and flock sizes. The majority of previous simulation studies used available location and flock size data stored from earlier outbreaks, or randomly generated data when no detailed data were available. Little comparison has been made between real location data and randomly generated data to ensure that the use of randomly generated location and flock size data are appropriate in the absence of real data. The specific objective of this part of the project was to compare the NAADSM results of 4 simulated HPAI outbreak scenarios using 2 datasets with randomly generated point locations and flock sizes, based on information from Statistics Canada census data and industry data versus a third dataset consisting of real industry data for Ontario, Canada, to determine if random location and flock size data could be used in the absence of real location and flock size data for policy development.

The real-industry data were obtained from the Ontario Livestock and Poultry Council (OLPC) and the Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA), which consisted of 2,186 commercial farms, while the 6,587 non-commercial poultry farm data were obtained from the Ontario Farm Business Registry (OFBR). This dataset was the same dataset used in Chapter 2 which consisted of 10 production types, but was collapsed into 3 specific commercial production types (chicken meat, egg, and turkey) plus a 4th type, which included all non-commercial backyard hobby farms. The collapsing was to ensure that the farms for the real industry-based dataset were comparable to the random-census and random-industry datasets. The real point locations (latitude, longitude) and flock sizes were maintained in this dataset.

The random-industry dataset was formed from the same farms seen in the real-industry dataset but with randomly generated point locations and flock sizes, within known census divisions, constrained by agricultural land use. A minimum distance between farms of 0.5km was also assumed. Geographic coordinate values (latitude, longitude) were then added to these randomly generated farm locations to allow for data input into NAADSM. The flock sizes used in this dataset was the same as those in the real-industry dataset.

The random-census data were obtained from the Statistics Canada Census of Agriculture for 2006 (www.statcan.ca), with farm locations for the chicken meat, egg, and turkey production types being randomly generated within known census divisions, constrained by agricultural land use, and a minimum distance between farms of 0.5 km. Hobby farm information was not provided by Statistics Canada, therefore information on those farms were taken from the real-industry dataset. Random flock sizes were generated in a similar fashion to that of the random-industry dataset.

Four scenarios were selected based on the results from the original dataset used in Chapter 2, using two separate stochastic frequency contact structures developed from the original dataset (weighted median and weighted maximum) and were each run 1000 times in NAADSM. In the assembly of the 4 scenarios, only one farm was initially infected at the start of each simulation, from a census division with high study farm density, a commercial chicken meat farm or a commercial turkey farm. In the scenarios, for ease of interpretation, only 2 destruction strategies were compared, stamping-out with 1km ring-culling or stamping-out with 3km ring-culling, as destruction is one of the main control strategies of interest from a policy development perspective. The diameters used for ring culling were based on data collected from previous outbreaks, though any size ring-culling can be included. Only two types of movement restrictions were included; no restrictions or effective movement restrictions (on direct and indirect contacts). All other parameters identified as important in Chapter 2, were held constant.

The output from these simulations were then compared, between the three datasets, using cumulative ascending probability plots, a Kolmogorov-Smirnov equality-of-distributions test and a negative binomial regression analysis. Differences between the two contact frequencies were also investigated.

Differences were seen between the two weighted contact frequencies used. The maximum contact frequency, which would be the worst case scenario, resulted in a much larger outbreak than the median contact frequencies, which was more comparable to the real-industry data. This suggests that in future simulations, where contact data is unavailable, the weighted maximum contact frequencies may be more appropriate than the median contact frequency. By using the worst case scenario, for the number of direct and indirect contacts between farms a more robust policy can be formulated to ensure preparedness if the number of contacts were the maximum possible.

The cumulative ascending probability plots, for the weighted median contact structure, in scenario 1 (T-Eff-1km) showed similar patterns between the real-industry and random-census datasets, while the random-industry dataset showed a different pattern. In scenario 2 (CM-N-1km), the real-industry dataset looked different than the random-industry and random-census datasets. In scenarios 3 (T-Eff-3km) and 4 (CM-N-3km), all three datasets had very similar patterns. For the maximum contact structure, scenarios 1and 2 (T-Eff-1km & CM-N-1km) showed similar patterns between all three datasets in the cumulative ascending probability plots. For scenarios 3 (T-Eff-3km) and 4 (CM-N-3km), the real-industry dataset had a similar pattern to the random-census and random-industry datasets but a larger maximum number of farms infected. In the 4 scenarios chosen, this indicates that the median contact structure is more likely to underestimate an outbreak than the maximum contact structure. This requires further investigation through simulation of more scenarios.

The differences may also be attributed to the random location of the flocks. Differences were seen between the kernel density maps for the real-industry and two randomly generated datasets in the spread of the farms and the randomly generated point locations. The kernel density plots showed a wider distribution of farms across census divisions in the random location dataset (which was the same for both the random-census and random-industry dataset) compared to the real-industry dataset. This may have resulted in a decreased number of farm-to-farm contacts resulting in an underestimation in the size of the outbreak, because naïve farms are less likely to come into contact with infected farms.

The negative binomial regression model found significant differences between the datasets in the majority of the scenarios, with few exceptions, and the Kolmogorov-Smirnov equality-of-distributions test showed a significant difference between all three datasets, in every scenario. The significant differences seen in the negative binomial regression analysis was most likely due to the large number of simulations done, making it more likely to find a significant difference between datasets, even when these differences were very small. For the median contact structure, in scenario 1 (T-Eff-1km), there were significant differences seen between the random-census and real-industry dataset as well as between the random-industry and real-industry dataset. The random-census data had 1.468 (1.357, 1.587) times more farms infected at the end of the outbreak compared to the real-industry dataset. In scenario 3 (T-Eff-3km), there was no significant difference between random-census and real-industry datasets ($p=0.899$). For the maximum contact structure, in scenario 1(T-Eff-1km), there were no significant differences between the random and real datasets ($p=0.921$). In scenario 3, there were significant differences between the real and random datasets ($p<0.05$). The random-census dataset resulted in 0.540 (0.473, 0.617) times more farms infected than the real-industry dataset.

The significant differences from the Kolmogorov-Smirnov equality-of-distributions test was most likely due to a discrepancy observed in one part of the curve but the rest of the curve was the same. Due to the inaccuracies of these tests, caused by the large amount of data, and the need for a robust policy a visual examination may be more appropriate in the comparison of datasets for use in policy decisions. The differences between the datasets were in the maximum number of farms infected, and using a maximum contact structure this difference was only by a couple of hundred farms. This is not a large difference when considering a robust policy.

There were similarities between the datasets for the 5th, median and 95th percentile of the number of farms infected, for each scenario (for both of the contact structures), as well as with the patterns in the cumulative ascending probability plots. The current study showed that by using Statistics Canada census data, random farm locations and flock sizes could be generated, and these locations supplied a reasonable surrogate for actual farm locations through statistical analyses; however the kernel density maps showed differences that may have had a big impact on the results. Therefore, it is recommended to investigate the use of the census subdivision as a means of random point location generation in future studies. Also, the random-census is more applicable for use as it is more readily available to the public, but if industry data is available the farm sizes and number of flocks is more closely reflective of the true data. The generalizability of successfully generating point locations should be strengthened by comparing random and real datasets for other Canadian provinces and jurisdictions, where real data is available for comparison.

4.5 Conclusions

Kleijnen et al. (2005) reported that there are three basic goals in simulation analysis: 1) developing a basic understanding of a particular simulation model or system; 2) using the results of the model to develop robust decisions or policies; and 3) comparing the merits of various decisions or policies. In some situations, simulation modeling is used when the underlying mechanisms of a situation are not well understood, and when real-world data are limited or non-existent (Kleijnen et al., 2005).

With the current threat posed by various foreign animal diseases, simulation modeling has become the key to enhancing our understanding of how an outbreak operates, and how Canada and other countries can regain their disease-free status in the event of an outbreak. Without simulation modeling, we would have to rely solely on previous outbreak experience. By relying solely on previous experience, we would be making the major assumption that all outbreaks act the same no matter where in the world they occur. This does not take into consideration the geography, epidemiological factors, and demographics of each individual area. Therefore a national policy for Canada may not be appropriate as we are not considering any regional differences that may exist. With disease spread simulation modeling, we can input a large number of potential scenarios to develop a more robust policy, and make more informed guesses as to the control measures needed in the event of an outbreak. The difficulty, however, lies in presenting these results to policy-makers. The interaction plots provide another communication tool, and can be used in place of other types of plots, and have proven to be effective, as the results have been presented to policy-makers and were well received. NAADSM has been specifically developed for North America in order to aid in policy generation, and the current study has shown that, although data access may be difficult, NAADSM may be useful for determination of the best methods for control and eradication for a more robust policy. One of the main things that should be changed in order to better represent real life situations is the use of census subdivisions to ensure adequate generation of farm locations.

With little experience in avian influenza outbreaks, the results of this study will be useful for the Canadian Food Inspection Agency (CFIA), as well as the United States Department of Agriculture (USDA). Exploration into the most effective way to generate random data, however, will initially be required before using NAADSM for simulations of HPAI in each area if real location and flock size data are unavailable. While most differences in the number of infected farms between datasets were small, it cannot be assumed that randomly generated location and flock size data provide a robust outcome, as seen in the current study, where the maximum number of infected farms could be 3-4 times larger in the real data compared to the randomly generated data, particularly when a weighted median contact structure is applied. NAADSM can however provide information for the formulation of a robust policy for North America, specifically Canada, when location and flock size data are available.

The use of NAADSM to produce a large number of potential outbreak scenarios reinforces those control strategies previously thought to have an impact in an outbreak situation, as well as introduces the idea that maybe "less is more", as seen with the destruction strategies. Determining the most appropriate control strategies for an outbreak, is the most important part of the planning involved in outbreak preparedness and policy. Applying movement restrictions may seem to be common sense, but showing that destruction with no ring-culling is just as effective as destruction with ring-culling at a 1km radius saves on resources and reduces the amount of deaths resulting from the outbreak. The model also indicates other, possibly not as obvious parameters that are important, such as the density of farms within the area where the outbreak started, and the transmission from indirect contacts, such as fomites from catching crews and vaccination crews.

Though useful in simulation of foreign animal disease outbreaks for policy and preparedness, simulation models are not without their limitations. Simulation models, including NAADSM, require the user to make several assumptions in regards to a potential outbreak. This requires information from industry, government, and experts on the disease. Though great efforts are made to ensure the model is as realistic as possible, no outbreak is the same, and unforeseen impacts may occur. NAADSM cannot cover all possible avenues of disease spread, including wildlife inputs, abattoirs, and markets, though every effort is made to include as many different scenarios as possible. These other sources could have major implications in disease spread and may need to be taken into account when building scenarios for simulation. Common sense dictates that if you reduce the contacts between farms, there is less of a chance of disease spread; therefore people may argue against the need for simulating an outbreak at all. However, as previously mentioned, there are many parameters that play a role in an outbreak and a simulation model may implicate a specific parameter that may not have been previously considered as important. Simulation modeling provides the user with a starting point in terms of understanding virus spread and important methods of control.

As with simulation modeling, generation of random locations and flock sizes have their limitations and assumptions. It is important to use information about locations and flock sizes that are appropriate and from a reliable resource. Though Statistics Canada does not provide specific data about farm location and flock size, in the province of interest, it does provide an excellent and reliable overall picture of the industry, making it an appropriate choice for use in simulations in NAADSM. Generation of random locations in smaller geographic areas (such as census subdivisions) is another avenue that requires exploration, as the findings in this study show that there was a noticeable difference between the density distribution of farms for the real and random location datasets. This is specific for Ontario, Canada, and therefore should be tested with other Canadian provinces.

In the future, simulations should be completed in other provinces, as well as analysis with other outcomes, such as duration of an outbreak. Also, other methods of generating random flock locations and distances between farms need to be explored and compared to real data in other areas. Using smaller land parcels, such as census subdivisions, also available from Statistics Canada, for the random generation of data may also provide a more comparable dataset.

Overall, the use of NAADSM simulations for preparedness against the potential threat of an HPAI outbreak has proven valuable when real data were available, as well as when data were absent (mostly) and we were relying on random locations and flock sizes. However, it is important to obtain as much information as possible from the industry, government and experts in the area of interest to ensure the simulations are as realistic and useful as possible.

4.6 References

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