

Epidemiological consequences of an incursion of highly pathogenic H5N1 avian influenza into the British poultry flock

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Highly pathogenic avian influenza and in particular the H5N1 strain has resulted in the culling of millions of birds and continues to pose a threat to poultry industries worldwide. The recent outbreak of H5N1 in the UK highlights the need for detailed assessment of the consequences of an incursion and of the efficacy of control strategies. Here, we present results from a model of H5N1 propagation within the British poultry industry. We find that although the majority of randomly seeded incursions do not spread beyond the initial infected premises, there is significant potential for widespread infection. The efficacy of the European Union strategy for disease control is evaluated and our simulations emphasize the pivotal role of duck farms in spreading H5N1.

Keywords: bird flu; H5N1; avian influenza; simulation; periodic contacts; poultry farms

1. INTRODUCTION

The Asian lineage highly pathogenic H5N1 avian influenza (HPAI) virus was first isolated in geese in China in 1996 (Xu *et al.* 1999). Subsequently, in 2003–2004, the virus was identified in eight countries in Asia (www.oie.int) resulting in over 3000 outbreaks reported to the OIE between December 2003 and February 2005 (Morris & Jackson 2005). Although most poultry sectors were affected in these countries, the low-intensity village smallholder flocks were more susceptible than larger commercial farms (Sims *et al.* 2005; Songserm *et al.* 2006). Since this time, infection has been reported in Asia, Africa and Europe. The majority of outbreaks on intensive European poultry farms have not resulted in onward transmission (www.oie.int). However, in some outbreaks, there appears to have been propagation to a very few other farms; indeed, the outbreak in the UK was likely to have arisen due to transmission from an outbreak in Hungary (Irvine *et al.* 2007). It is clear, therefore, that transmission of H5N1 can occur between farms in the intensive European poultry industry. Furthermore, in the H7N7 HPAI outbreak in The Netherlands in 2003, 255 flocks were infected, suggesting that large outbreaks are possible (Stegeman *et al.* 2004). However, extrapolation from such events to other regions is problematic due to regional differences in the poultry industries and in the characteristics of the viruses.

In the face of the threat of introduction of a major infectious disease, such as H5N1 HPAI, policymakers and animal disease control agencies need locally specific answers to the following questions: ‘what is the most likely size, duration and geographical distribution of the epidemic? What

are the critical components that exacerbate the risk of spread? What are the most effective control strategies?’ Such questions can only be addressed through detailed consideration of the specific features of the population at risk and potential transmission routes within this population. In the case of foot and mouth disease in the UK, detailed mathematical models have been used to answer these questions with varying degrees of success (e.g. Ferguson *et al.* 2001; Keeling 2005).

We evaluated the consequences of introducing highly pathogenic H5N1 avian influenza into the British poultry flock using a spatially explicit and detailed stochastic simulation model. The model included 11 754 poultry farms structured with respect to 174 slaughterhouses and 86 feed mills. Four transmission mechanisms were considered using both static and dynamic networks. In particular, the periodic nature of movements associated with feed and slaughter is represented in detail and this is a novel feature of this work.

We use this model to investigate the variation of risk with respect to species, industry sector and geographical location as well as determining the efficacy of the control strategy adopted by the British Government.

2. MATERIAL AND METHODS

(a) Data sources

The Great Britain Poultry Register (GBPR) allowed the classification of poultry premises with respect to their species. These were chickens, ducks, geese and turkeys for meat production; chickens, ducks, geese and quail for egg production, and partridge, pheasant, quail, guinea fowl and ducks for game. The GBPR also allowed classification with respect to independent producers and those belonging to large integrated companies that frequently have their own abattoirs and feed mills. Company affiliations were determined through several

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mechanisms that included both the GBPR and the ‘network database’ compiled by the UK Department for Environment, Food and Rural Affairs (Defra) from questionnaires administered to a subset of the industry, including poultry farms, slaughterhouses and catching companies. Premises excluded from our analysis were those with missing location data, those with fewer than 50 birds (which were not obligated to be on the GBPR) and those with the husbandry purposes of hatching, showing, parent stock, grandparent stock and ‘other production types’ (including pets, hobbies, schools, research, vaccine companies, pharmaceutical companies and zoos).

Poultry slaughterhouses in England, Scotland and Wales were identified using data from the Food Standard Agency (www.food.gov.uk). Location data for the premises were obtained using postcode data provided by the Meat Hygiene Service by cross reference to data supplied by Defra. Data on the species slaughtered at each site were obtained from the Meat Hygiene Service, the individual web pages of slaughterhouses (where available) and from the network database.

Data on feed mills were obtained from the Universal Feed Assurance Scheme (see www.efsis.com). Feed mills were contacted by telephone to confirm poultry feed production.

Information on the geographical profile and frequency of different movements and dangerous contacts in the industry were obtained from analysis of the network database.

The detailed structure and definition of Defra’s control policy is taken from the exotic animal disease generic contingency plan (Anon. 2005) and information on movement restrictions within control zones (CZ) from ‘controls applying to movement of poultry and eggs in a wild birds controlled zone’ from Defra’s website (<http://www.defra.gov.uk/animalh/diseases/notifiable/ai/index.htm>).

A meeting with representatives of several industry sectors was held on 8th February 2006 to gather expert opinion on a number of important issues for which other sources of data were not available.

Table 1 shows the values used to parametrize the model including the ranges used for the sensitivity analysis.

(b) *Virus model*

The propagation of H5N1 within individual poultry flocks is likely to be governed by very large reproduction numbers of the order $R_0 \approx 25$ in caged systems and $R_0 \approx 66$ in floor-reared birds (Savill *et al.* 2006). We assume that the effect of these rapid within flock dynamics can be fairly represented by farm-level transitions between susceptible, latent and infectious states. Once sufficient numbers of birds on a farm show symptoms or die, it enters a notified state at which point the presence of H5N1 is confirmed and measures to prevent further spread can be implemented.

To reflect the natural variation during the course of an epidemic, our model samples latent and notification (infectious but not reported) periods from (truncated) normal distributions. These have a standard deviation of 1 day except for notification periods for duck and goose farms, which have a standard deviation of 20 days to reflect the greater notification time scale. The values (and ranges for sensitivity analysis) for the average latency and notification periods are shown in table 1. These are obtained from the referenced literature for these parameters at the individual bird level and allow for some multiplication within the flock and delay in confirmation.

While highly pathogenic to most species, recent outbreaks of H5N1 have not killed ducks and geese rapidly. To reflect the ‘carrier’ state for these species, we assume that the average

notification time for ducks and geese is much longer than for the other species at 40 days. This figure is consistent with the literature in table 1, but to investigate the evident uncertainty in its value we assess sensitivity to this within the wide range of 20–60 days.

(c) *Transmission model*

A spatially explicit stochastic model was developed to represent the dynamics of infection between the premises recorded on the GBPR. We used both static networks and dynamic periodic contacts to represent the mechanisms of transmission. The operational structure of the poultry industry with respect to location, species and industry sectors is accounted for in detail by these structures.

With the exception of multi-species sites, the model is parametrized at the individual farm level. Multi-species sites comprise 23% of all premises and these are sub-structured to account for the additional cross-species transmission risk that they present.

Four mechanisms of disease transmission were identified. We discuss each of these in turn.

(i) *Transportation to abattoir*

For approximately 20% of slaughterhouses in the GBPR, the supplying farms are known explicitly from the network database. Using this, we defined the typical catchment radius for a slaughterhouse of a given species and type (meat or layer) as the third quartile of distances of associated premises (table 1).

The catchments for the remaining slaughterhouses were constructed by an allocation algorithm in which each farm is associated with a single slaughterhouse chosen uniformly at random from all slaughterhouses with matching species attributes and company affiliations and that lie within the typical catchment radius. If none occurs within this radius, association is made with the nearest slaughterhouse with the correct attributes. This algorithm is found to produce a very good match when tested on the subset of slaughterhouses whose associations are known.

Typically (and especially during an outbreak of H5N1), integrated producers supply their own integrated slaughterhouses and independent producers supply independent slaughterhouses. Furthermore, for practical reasons, a slaughterhouse can only deal with one species at a time which minimizes the chance of cross-species transmission by this route. This segregation with respect to species and management type is accounted for in the allocation algorithm just described.

We assume that the majority of transmission by movements to slaughter occurs between farms visited by a slaughterhouse lorry on a single day and that the biosecurity measures in place, particularly in the event of an outbreak makes between day transmission much less frequent.

Movements to slaughter are highly periodic because the time taken from hatching to slaughter shows little variation. To incorporate this periodicity, each farm is allocated a lorry visit period according to its species (table 1). The phase is set randomly for each farm at the start of each simulation. If a lorry visit coincides with a farm’s infectious period, there is potential for the infection to be spread. From expert opinion, the maximum number of farms visited on a single day by a slaughterhouse lorry is 4, which implies that the number of dangerous contacts is 0, 1, 2 or 3. We sample this distribution uniformly and choose this number of dangerous contacts

Table 1. The values of the parameters used in the model. (The values in brackets for the first 12 parameters indicate the ranges used in the sensitivity analysis.)

parameter description	value	references
minimum time before first case reported	5 (0–10) days	Elbers <i>et al.</i> (2004); Nishiguchi <i>et al.</i> (2005); Le Menach <i>et al.</i> (2006); Anon. (2007)
mean latent period (all species)	1.5 (1–2) days	Van der Goot <i>et al.</i> (2003); Swayne & Beck (2005); Tian <i>et al.</i> (2005); Gao <i>et al.</i> (2006)
mean notification period (ducks and geese)	40 (20–60) days	Perkins & Swayne (2002); Hulse-Post <i>et al.</i> (2005); Kishida <i>et al.</i> (2005); Sturm-Ramirez <i>et al.</i> (2005); Songserm <i>et al.</i> (2006)
mean notification period (partridge and pheasant)	4 (2–6) days	Perkins & Swayne (2001)
mean notification period (other species)	2 (1–3) days	Perkins & Swayne (2001); Lee <i>et al.</i> (2005); Mase <i>et al.</i> (2005a,b); Tian <i>et al.</i> (2005); Gao <i>et al.</i> (2006)
mean infectious reported period	1.5 (1–3) days	Anon. (2007)
p_L (local transmission rate at zero distance)	0.5 (0–1) days ⁻¹	See text (§2d)
p_S (transmission probability per dangerous slaughter contact)	0.25 (0–0.5)	See text (§2d)
K_F (ratio of feed to slaughter transmission probabilities per contact)	0.25 (0–1)	See text (§2d)
K_C (ratio of within company to feed transmission probabilities per contact)	0.25 (0–1)	See text (§2d)
γ (reduction factor in notification time within EUS control zones)	0.5 (0–1)	See text (§2e)
δ (reduction factor in transmission probability in EUS control zones)	0.5 (0–1)	See text (§2e)
inter-company contacts per day	3 days ⁻¹	expert opinion
maximum premises visited on single feed lorry trip	6 premises	attribute of feed lorries/feed industry
typical feed mill catchment radius	60 km	feed industry
percentage of cross-species contacts during feed visits	20%	feed industry
median period of feed lorry visits	6 days for broilers, 7 days for turkeys, 14 days for layer chickens, 30 days for meat and layer ducks and geese, 33 days for other sectors	network database
maximum premises visited on single slaughter lorry trip	4 premises	expert opinion
typical slaughterhouse catchment radius	136 km for broilers, 50 km for meat and layer ducks, 23 km for meat sector geese, 158 km for turkeys, 239 km for layer chickens	network database
median period of slaughterhouse lorry visits	52 days for broilers, 61 days for meat sector ducks, 90 days for turkeys, 1 year for other sites.	network database

randomly from the slaughterhouse catchment of the infected farm. Subject to the contact being allowed with respect to movement restrictions, the selected premises are infected with a probability p_S . Selected contacts have the phase of their periodic visits reset to match the current visit time, preventing another visit until the full period has elapsed.

(ii) Feed deliveries

Expert opinion suggests that premises with less than 500 birds are unlikely to have feed delivered. We allocate premises with more than 500 birds to feed mills in a similar way as premises are allocated to slaughterhouses. Within the typical catchment radius of 60 km, allocation is equally likely to feed mills with the correct attributes. Beyond this, allocation is made to the nearest feed mill with the correct attributes.

Some integrated companies have their own feed mills and farms within these companies are allocated to these feed mills. Unlike slaughterhouses, independent and integrated sector farms often use the same feed mills. Consequently, we include cross-sector interaction. It is estimated that approximately 20% of feed lorry trips contain some cross-species interaction. This species mixing is accounted for in our algorithm.

The primary transmission risk from feed lorries is between farms visited on a single trip by a single feed lorry before it returns to the feed mill where it can be disinfected. All feed lorries contain six compartments, which means that a lorry can visit up to a maximum of six premises on a single trip. Feed visits are periodic and we use a similar infection mechanism as for slaughter contacts using the feed delivery

periods in table 1. Each dangerous contact is infected with a probability p_F .

(iii) *Company transmission*

H5N1 can potentially be transmitted between farms within the same company via internal company movements (e.g. by area managers, vaccination teams, maintenance workers, etc.). There is no obvious or natural periodicity to this complex array of contacts and we represent this by a fixed contact network. All premises under the same ownership or management structure are assumed to be connected to each other by this mechanism.

If N is the number of premises owned by a given company, then we assume that the probability of contact between two premises per day is $n/(N-1)$, where n is the typical number of contacts a farm makes with other farms under the same ownership per day. Based on expert opinion, we estimate that a typical value for n is 3. The rate of infection or transmission across a dangerous contact is given by

$$\text{rate of infection} = p_C \min\left(\frac{3}{N-1}, 1\right),$$

where p_C is the average probability of transmission per dangerous contact. Here the probability of contact between two premises in very small management structures (less than four premises) is prevented from being more than 1 per day.

(iv) *Local transmission*

Local transmission encompasses risk factors that arise because farms are geographically close. The main factors are likely to be contaminated dust blown from one farm to the next or wildlife carrying contaminated dust over short distances.

We assume an underlying diffusion process to describe these mechanisms which justifies using a Gaussian kernel for the decay of risk with distance

$$\text{rate of infection} = p_L \exp\left(-\frac{(\text{distance})^2}{500}\right),$$

where p_L represents the 'rate of infection' for two farms in very close proximity. Here a distance scaling is chosen such that there is essentially no risk of infection beyond 1 km as there is no evidence of local transmission beyond this distance; from outbreaks in Europe there is no evidence to support local transmission over more than a few hundred metres (www.oie.int).

(d) *Transmission parameters*

In the absence of a propagating epidemic in the British poultry industry, the least constrained parameters used in the model (table 1) are the probabilities of transmission per dangerous contact: p_S , p_F and p_C as well as the rate of local transmission p_L .

The probability of infection per dangerous slaughter contact (p_S) could be anywhere between 0 and 1. However, the indirect contact between premises by slaughter vehicles is unlikely to transmit infection with 100% efficiency. Furthermore, in the specific case of broiler farms approximately 50% of visits by slaughter lorries result in the total depopulation of the farm after which it is typically cleaned. For sensitivity analysis, we assume that p_S is between 0 and 0.5.

We expect the probability of transmission per dangerous feed contact p_F to be less than the probability of transmission

per dangerous slaughter contact because in this case there does not have to be any direct contact between the birds and the lorries. To represent this, we define K_F by $p_F = p_S K_F$, where K_F is between 0 and 1. Similarly, we expect that the multitude of different and mainly very low-risk contacts represented by company movements p_C is lower on average than per feed contact. We define $p_C = p_F K_C$, where K_C is between 0 and 1.

The rate of local transmission for premises in close proximity is to some extent constrained by recent outbreaks in the UK and in Europe where, typically, infection does not spread. Given the evidence of recent outbreaks, a value of $p_L = 1 \text{ days}^{-1}$ would be extremely high. We investigate the sensitivity of the model to p_L in the range 0–1 days^{-1} .

Within the bounds discussed here, the actual values are essentially unknown. To facilitate investigations into the detailed variation of model output with respect to species, industry sector, geographical location and control strategies, we define our basic model with the values $p_L = 0.5$, $p_S = 0.25$, $K_F = 0.25$ and $K_C = 0.25$. The sensitivity of the model to variations in these parameters across the full range discussed above is investigated in detail.

(e) *Control strategies*

To evaluate disease control, we define four strategies.

(i) *Basic control*

This is a baseline strategy for comparison with the more stringent control measures discussed below. Here a farm is prevented from moving livestock once H5N1 is detected (i.e. upon notification). This prevents transmission via the slaughter mechanism. Tighter biosecurity is also enforced on feed and company movements. This reduces the probability of transmission by feed and company movements by a factor δ which we take to be 0.5. Sensitivity to this parameter is investigated in the full range of 0–1. The notified farm is subsequently culled on average 1.5 days after notification according to a truncated normal distribution with a standard deviation of 1 day. In line with current UK policy as defined in Defra's exotic animal disease generic contingency plan (Anon. 2005), restocking is permitted (and occurs in our model) after 56 days of disease-free status.

(ii) *Control zones*

These add 3 km protection zones and 10 km surveillance zones to the basic control (BC) strategy. Nominally, these are minimum radii, but in practice this has corresponded to British Government strategy. A protection zone remains in place around a notified and culled farm for 21 days, after which it becomes absorbed into the surveillance zone surrounding it. The surveillance zone remains in place for a further 9 days. Again these are nominally minimum values, but these have been used in practice and we use them to define this strategy in our model.

Within CZ, surveillance is increased and we assume that this leads to a reduction in the time to notification by a factor γ , which we take to be 0.5, and sensitivity to this parameter is investigated in the full range from 0 to 1. Biosecurity is also increased, which reduces the probability of transmission by feed, slaughter and company movements by a factor δ . There is no impact on the rate of local transmission because transmission by, for example, contaminated dust spread by air or by wildlife is extremely difficult to prevent by temporary disease control measures.

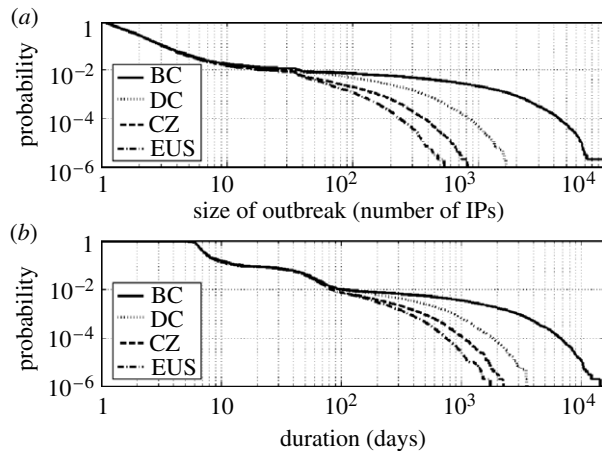


Figure 1. The probability of an outbreak reaching a given (a) size (the number of infected premises (IPs)) and (b) duration in days. The duration is defined as the time from initial infection to the culling of the final IP. Here BC is compared against the EUS. Also shown are the effects of DC and CZs applied individually. Each of these graphs is based on 1 million simulations each initiated at a single premises selected uniformly at random.

Apart from movements to designated slaughterhouses, which we assume present no risk of transmission, protection zones enforce a total ban on livestock movement. This has the effect of stopping transmission by movements associated with slaughter. Surveillance zones enforce a partial ban on livestock movements which is represented in the model by allowing transmission (at a reduced rate) between premises in the same surveillance zone but disallowing contacts across surveillance zone boundaries.

(iii) Dangerous contact tracing

Dangerous contact tracing (DC) adds the tracing and isolation of dangerous contacts to the BC strategy. This is represented in the model by imposing a livestock movement ban on all premises that have had a feed or slaughter contact with a notified farm during its infectious period. Biosecurity and surveillance are also increased in the same way as they would be in a control zone. We assume that these measures remain in place for 30 days.

(iv) European union strategy

European union strategy (EUS) is the strategy recommended by the European Union and adopted by the British Government for controlling avian influenza. In our model, it is represented by the simultaneous operation of CZ and DC as they are described above.

3. RESULTS

(a) Size, duration and control strategies

Using the values of our basic model, we found that the size of epidemic was limited to the initial infected premises (IPs) in the majority of simulated outbreaks (73%). The additional impact of EUS on the probability of outbreaks of fewer than approximately 30 IPs was minimal (figure 1a).

Figure 1b shows the probable duration of epidemics defined as the time from the first infection to the culling of the last infected premises. We find that 99% of outbreaks are over within 100 days, regardless of control strategy. The apparent absence of epidemics lasting less than 5 days is a reflection of our assumption that this is the minimum

time from the first infection in Britain to its detection and control. The average time to first detection in our simulations is 9.8 days although there is considerable variability, particularly due to infections initiated in duck and goose farms which can take a long time to detect. This value is consistent with the outbreak on a turkey farm in England detected in February 2007 (Anon. 2007) that took between 7 and 10 days to identify.

Although all outbreaks are eventually brought under control, regardless of control strategy, some can persist for many years and these are essentially endemic. The principle effect of EUS is to reduce the probability of rare, large outbreaks. Figure 1 also demonstrates that CZ (protection and surveillance zones) have a larger individual impact than DC.

(b) Geographical distribution of risk

The geographical distribution of risk from a propagating epidemic is shown in figure 2b. This illustrates the frequency of infections per farm for 1 million randomly seeded simulations using the BC strategy. EUS had little impact on this distribution except for scale. The areas at greatest risk are in the east of England, particularly East Anglia as well as Lincolnshire and South Yorkshire. Comparison with the farm density map (figure 2a) shows that this is not a trivial function of farm density. Several regions, including the English–Welsh and the Devon–Somerset borders and the northwest of England were at relatively low risk, despite being areas of high poultry farm density.

(c) Variation of risk with industry sector

The chance of an outbreak being large is very dependent on the sector of the poultry industry in which it is seeded (table 2). In general, we find that infections seeded in the meat sector present a higher risk than those in the layer or game sectors. Where comparisons can be drawn, we find that infections initiated in the integrated sectors are more likely to result in more than 50 IPs than those initiated in the independent sectors.

With BC, an infection in the integrated duck meat sector carries a 69% chance of spreading to 50 or more premises. A naïve estimate gives a basic reproduction ratio for this sector of around $R_0 = 1/(1 - 0.69) = 3.23$. This risk is only reduced to 37% ($R_0 = 1.59$) by EUS.

A major feature of the species representation in our model is the difference in time to notification. In the case of ducks and geese, this is considerably longer than for the other species and this is used to reflect the carrier state in these species. To investigate this further, we ran simulations where the notification time for ducks and geese was reduced to an average of 5.5 days with a standard deviation of 1 day. The impact of this on the probability of large outbreaks is dramatic as illustrated by the final column of table 2. Outbreaks of more than 50 IPs are almost completely removed by removing the carrier state in ducks and geese.

(d) Transmission mechanisms

When the mechanisms of transmission were evaluated, we found that for BC, 54% of all infections were attributable to local transmission, 9% to feed, 7% to slaughter and 30% to within company contacts. For EUS, these proportions change to 74% for local

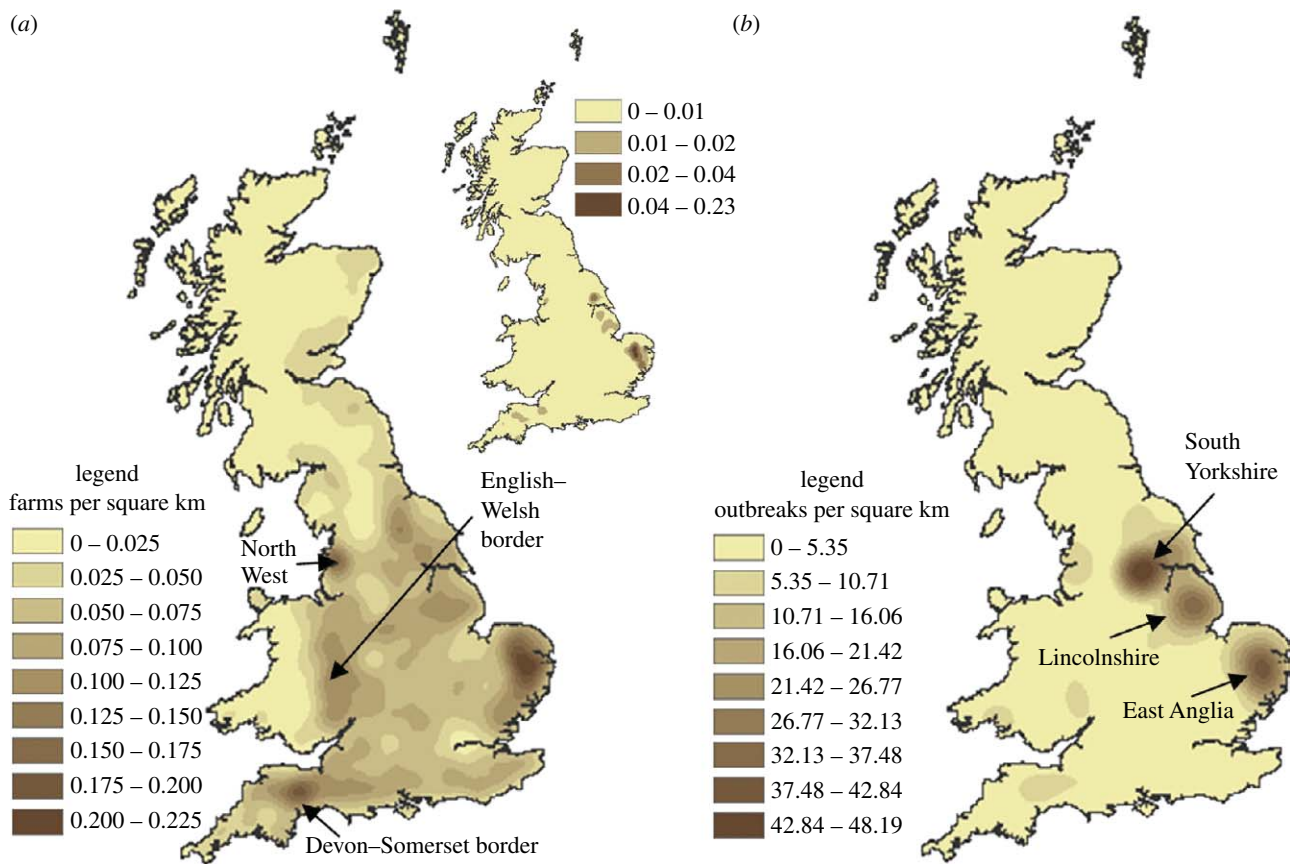


Figure 2. (a) Density map of the poultry farms in Britain representing the number of premises per square kilometre. (Insert illustrates the density of duck meat farms with a rescaled legend.) (b) Geographical distribution of the frequency of infections per farm per million randomly seeded simulations. The initial infected case in each simulation is excluded. Multiple infections of the same premises in a single simulation due to restocking were counted once. The simulations used to generate the figure employed the BC control strategy.

Table 2. The chance of epidemics exceeding 50 IPs depending on the sector of the poultry industry in which they are initiated. Each result is based on 100 000 simulations initiated at single IPs selected uniformly at random from the premises within each sector. The risks are ordered with respect to the results for BC. Also shown are simulations with BC where the carrier state in ducks and geese is removed. The risk from sectors with less than 30 premises is not assessed.

species	industry	management	BC (%)	EUS (%)	BC, no carrier state (%)
duck	meat	integrated	69	37	0.005
duck	meat	independent	7.7	3.1	0.001
goose	meat	independent	1.8	0.57	0
turkey	meat	integrated	1.5	0.22	0.002
duck	layer	independent	0.75	0.20	0
chicken	meat	integrated	0.58	0.22	0.003
chicken	layer	integrated	0.58	0.23	0.001
turkey	meat	independent	0.26	0.056	0
partridge	game	independent	0.24	0.073	0
chicken	meat	independent	0.21	0.058	0.008
quail	layer	independent	0.16	0.058	0
goose	layer	independent	0.16	0.016	0
pheasant	game	independent	0.16	0.056	0
duck	game	independent	0.15	0.049	0
chicken	layer	independent	0.14	0.048	0
guinea fowl	game	independent	0.082	0.022	0
quail	game	independent	0.003	0.002	0

transmission, 5% for feed, 2% for slaughter and 19% for within company contacts. The significant percentage reduction in transmission via slaughter contacts shows the effect of banning the movement of livestock for dangerous contacts and premises within CZ. The higher percentage of local transmission with EUS reflects its

relative impact on slaughter, feed and company movements but lack of impact on local transmission. This analysis indicates that the majority of transmission events are due to local transmission. However, from a disease control perspective, this exaggerates its importance as we now illustrate.

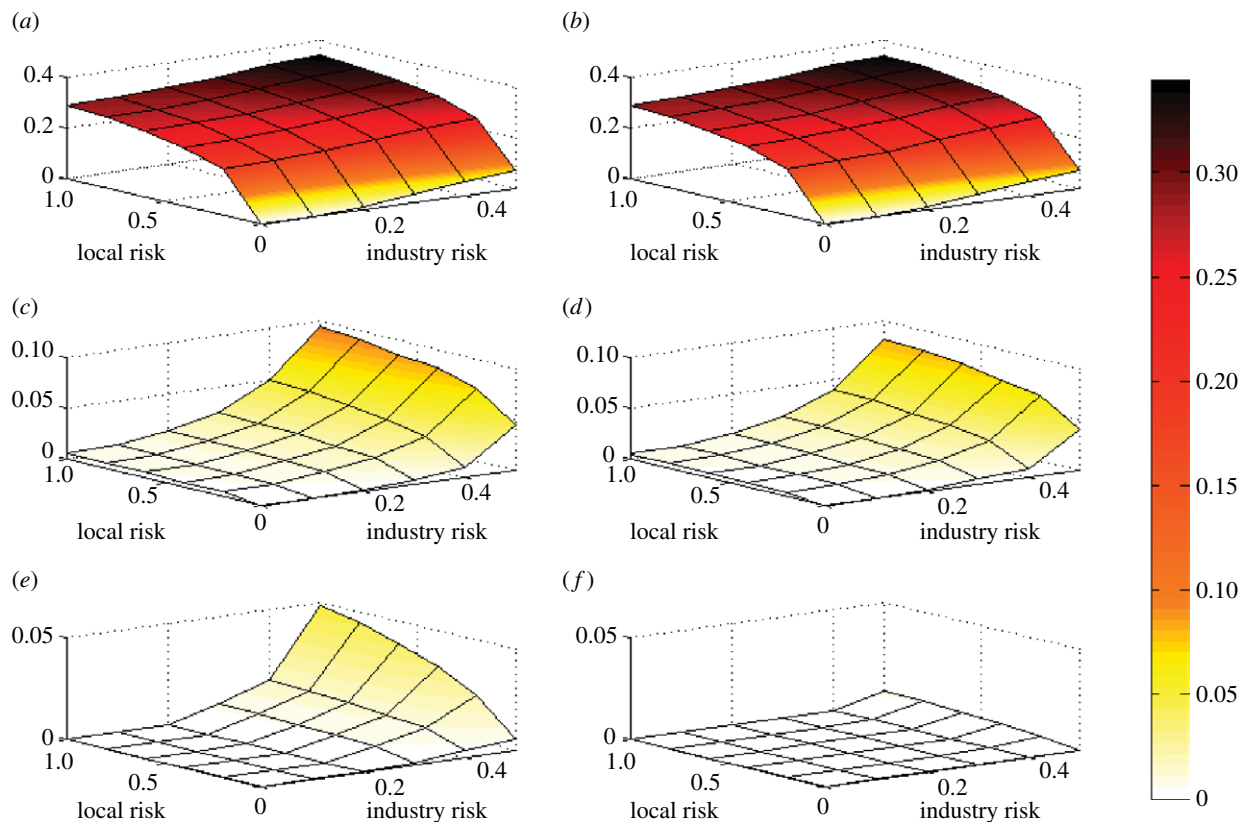


Figure 3. The probability of outbreaks of more than 1 IP (*a,b*), more than 10 IPs (*c,d*) and of endemic infections (*e,f*) (defined here as more than 3000 IPs) for both BC (*a,c,e*) and EUS (*b,d,f*) as a function of local and industry risks. Each plot on the mesh is based on 100 000 stochastic simulations, each one initiated at a single premises selected uniformly at random.

The transmission parameters are largely unknown within their upper and lower bounds and it is essential to study the impact of varying these. We have argued that the three industry-related transmission probabilities satisfy $p_S > p_F > p_C$. While there is no clear direct relationship between these parameters, it is useful here to define a quantity η that we call ‘industry risk’, which we use to parametrize the different probabilities by $p_S = \eta$, $p_F = \eta^2$ and $p_C = \eta^3$. This represents a cut through parameter space corresponding to variations in the risk associated with industry-related contacts. Our basic model parameters then correspond to $\eta = 0.25$.

Figure 3 illustrates how the probabilities of outbreaks of different sizes vary with respect to local risk (defined as p_L) and industry risk in the boundaries specified in table 1. Here our basic model parameters occupy the central point $\eta = 0.25$, $p_L = 0.5$.

A key conclusion from figure 3 is that large outbreaks cannot occur with local transmission alone. Even with very high local risk ($p_L = 1$), the largest simulated outbreak in the absence of industry transmission was 71 and 36 IPs for BC and EUS, respectively. These results indicate that local transmission is not as important as it appears from a simple count of the number of infections it causes.

Large outbreaks can occasionally occur without local transmission provided that there is very significant industry risk (figure 3*e*). However, it is evident that the combined effect of local and industry contacts presents the greatest threat of major outbreaks.

The additional effect of EUS in minimizing the risk of spread of H5N1 from the initial IP is negligible (figure 3*a,b*). Figure 3*c,d* illustrates that the effect of EUS in reducing the risk of an outbreak of greater than 10

IPs is also small. Figure 3*e,f* compares the risk of endemic infections for BC and EUS and this indicates that EUS has a sizable additional impact. Endemic infections can occur because farm restocking, which happens in the model after 56 days of disease-free status, allows re-infection to occur. In practice, this policy would probably be reviewed in a major outbreak.

(e) Sensitivity and uncertainty analysis

The 12 parameters included in the sensitivity analysis (table 1) were sampled 1000 times within their respective ranges using a Latin hypercube sampling algorithm (Blower & Dowlatabadi 1994) to optimize the sampling of parameter space. For the variables that represent the mean μ of a normal distribution, the standard deviation σ is scaled accordingly to keep the ratio μ/σ constant. For each of the 1000 parameter samples, 10 000 stochastic simulations were generated, each one initiated on a single IP chosen uniformly at random.

For each of the 1000 samples, we determined the probability of an outbreak spreading beyond the initial IP. The distribution in values is shown for the BC strategy in figure 4*a*. The mean probability is found to be 0.27 and the median is 0.28. The most extreme probability found for an outbreak spreading beyond the initial case is 0.39 and the lower bound approaches zero when the transmission coefficients are small. EUS was found to have no impact on these values.

Partial rank correlation coefficients (PRCCs; Blower & Dowlatabadi 1994) were calculated for each of the control parameters. Irrespective of whether EUS or BC was used, the most influential parameters on the probability of the outbreak spreading beyond the first IP were found to be p_L

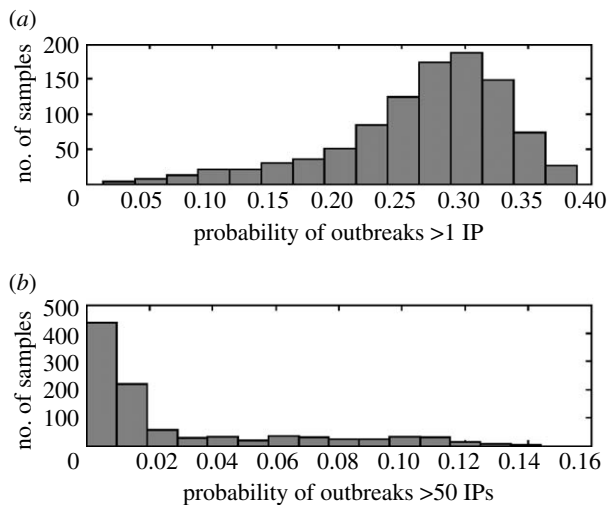


Figure 4. Distribution of probabilities for outbreak sizes varying with respect to changes in parameter values for (a) outbreaks of more than 1 IP and (b) outbreaks of more than 50 IPs. These were evaluated with 10 000 simulations for each data point and with the BC control strategy.

(PRCC=0.92) and the minimum time to first notification (PRCC=0.78). Other significant factors are the other transmission mechanisms p_s (PRCC=0.55), K_F (PRCC=0.53) and K_C (PRCC=0.44).

When the probability of a large outbreak (defined here as greater than 50 IPs) was investigated we found that for BC, the mean and median probabilities were 0.028 and 0.012, respectively, and the most extreme value observed in the 1000 samples was 0.14 (figure 4b). The impact of EUS on these results reduced the chance of a large epidemic to a mean of 0.021 with a median of 0.008 and an extreme upper bound of 0.13.

A PRCC analysis with the BC strategy shows that the probability of large outbreaks is most sensitive to p_s (PRCC=0.81) and K_F (PRCC=0.79) as well as K_C (PRCC=0.67). To a lesser extent, it is also dependent on the notification time in ducks and geese (PRCC=0.33) and p_L (PRCC=0.31). EUS had little impact on these values except that the PRCC value for the biosecurity factor δ becomes notable (PRCC=0.33).

4. DISCUSSION

The output of this simulation model provides policy-makers and national animal disease control authorities with important information. The number, sector and geographical location of infected farms inform the advanced deployment of equipment and personnel required for culling and disposal.

In our model, 73% of randomly seeded incursions of highly pathogenic H5N1 avian influenza did not spread beyond the initial infected premises. This is in contrast to the experience of the 2003 H7N7 HPAI outbreak in poultry flocks in The Netherlands, in which 255 flocks were infected (Stegeman *et al.* 2004) and to models based on this outbreak (Le Menach *et al.* 2006), which reported a mean of 184 infected farms (95% CI 34–294). Similarly, analysis of data from four HPAI outbreaks (H7N7 in Italy, H7N7 in two areas in The Netherlands and H7N3 in Canada) suggest that even in the face of control measures the reproductive number often remains close to or above 1, highlighting the potential for propagating epidemics

(Garske *et al.* 2007). However, our conclusion that most outbreaks will be confined to a single case is found to be very insensitive to parameter variation. Furthermore, this finding is consistent with limited current experience of H5N1 HPAI in Britain (Irvine *et al.* 2007) and in other intensive poultry industries in Europe (www.oie.int).

Critically, however, our model also demonstrates that there is the potential for rare large-scale outbreaks infecting thousands of premises. A key risk factor for large-scale outbreaks is the presence of infection in high-risk sectors and particularly in duck meat farms. This emphasizes that preventing transmission to high-risk sectors is fundamental to reducing the risk of large outbreaks.

It appears that the role of ducks in propagating large outbreaks, a feature also noted elsewhere (Morris & Jackson 2005; Songserm *et al.* 2006), could be attributed to the delay in notification, used to reflect the ‘carrier state’ reported for this species (Hulse-Post *et al.* 2005). However, the risk from infections in ducks in the layer or game sectors or from geese, which also possess the carrier state, is not so evident (table 2). This implies that other structural differences between the industry sectors are important. Nevertheless, the carrier state is clearly a fundamentally important factor. The impact of removing this carrier state in ducks and geese is found to be dramatic and this essentially removes the chance of an outbreak spreading to more than 50 premises even with only a BC strategy in place. The value of such surveillance is reflected in Defra’s recent decision to undertake serological sampling of birds on duck and geese farms (and other high-risk premises) within the PZ and SZ (J. Wilesmith 2007, personal communication). This monitoring (if successful, adequate and timely) is likely to have substantial impact on the probability of large epidemics, whether they arise in the duck sector or in other sectors.

Geographically, the areas of Britain at greatest risk from a propagating epidemic are found to be in East Anglia, Lincolnshire and south Yorkshire. The observed variation in risk is not a trivial function of the density of poultry farms in the respective areas. Data from Thailand demonstrate a strong association between H5N1 HPAI outbreaks and the abundance of free-ranging ducks (Gilbert *et al.* 2006). Given the high risk associated with duck farms in our results, a similar effect may have been expected. However, the presence of duck farms accounts for relatively little of the variation observed, although there does appear to be some association with the presence of duck meat farms (figure 2). There are many epidemiological, demographic and geographical factors contributing to regional variation in risk in our model. These include differences in the species present on farms, proximity of the farms to each other, locality of the slaughterhouses and feed mills as well as the structures of the companies and the locations of integrated and independent producers. These factors together contribute to the clustering of poultry industry activity in specific areas that gives rise to higher localized basic reproduction numbers.

Our model provides some justification for the additional control strategies involved in EUS. Longer-range industry movements are found to be essential for large epidemics and the tracing and isolation of these contacts is a feature of EUS. Local spread, when combined with industry transmission, makes large outbreaks much more likely

and EUS uses CZ to limit its impact. We found that the principal effect of EUS is to minimize the risk of very large outbreaks and endemic infections. However, we note that for large outbreaks, significant resources would be needed to implement this policy effectively.

Of the two aspects of EUS modelled here, CZ are found to have a larger individual impact than DC. We note that the efficacy of DC is reduced owing to the periodic nature of feed and slaughter contacts; if infection is transmitted by a periodic contact, the maximum time elapses before the next similar contact by which time the farm is likely to have been notified and isolated. In November 2006, a statutory requirement for the creation of a *restricted zone* (RZ), around the PZ and SZ, came into force (Anon. 2006a). The area of the RZ is variable and aims to include important epidemiological niches and administrative zones. Within this zone, there is a discretionary power to impose further restriction of movement of poultry and other captive birds, eggs, vehicles used for poultry or poultry products and mammals. We did not model the effect of this additional zone as it has been introduced since the development of this model. Furthermore, the lack of formal rules governing the extent of the RZ makes it difficult to include in models. However, its effect is likely to further reduce the likelihood of large epidemics.

Our analysis focuses on the risk factors associated with the mechanistic operation of the poultry industry. Possible variations in the infectivity and susceptibility of individual farms due, for example, to differences in species, size, biosecurity measures, husbandry practices, shared personnel, production type and the mechanism of H5N1 transmission are difficult to quantify and are excluded. We also assumed time-independent infectivity. These are aspects of the model which could be improved with greater understanding of H5N1 transmission.

The British poultry industry has a hierarchical structure consisting of production sector farms as well as a relatively small number of more elite sites (comprising hatcheries, and parent and grandparent stock) whose net effect is to supply young birds to the production sector farms (H. Hellig, personal communication). These elite sites have a relatively high level of biosecurity and are excluded from our present analysis which focuses on transmission among the premises in the production sector. In the unlikely event that one of these elite sites becomes infected, the impact on the production sector premises that it supplies could be dramatic and the rapid identification and isolation of those sites supplied by it is clearly essential for disease control. Sites with less than 50 birds are also excluded from our analysis as such sites are not required to be on the GBPR (Anon. 2006b). These backyard sites are less integrated into the major structure of the industrialized poultry industry and we do not consider them to be important hubs for propagation of infection, but regard them as potential background infections in a similar way to infected wildlife.

There is currently little evidence to suggest that local transmission carries H5N1 over distances greater than approximately 1 km and our local risk kernel reflects this. During the outbreak on a single farm in England in 2007, there was no transmission to the 78 farms within the 3 km protection zone or 70 farms within the 10 km surveillance zone (Anon. 2007). However, although clinical signs were

only noted in birds from one house on the farm involved in this outbreak, the virus was detected in birds from 3 of the other 21 populated houses (Irvine et al. 2007) indicating the potential for short-range transmission, also modelled by our risk kernel. However, given the influential importance of local transmission in our model, future evidence of longer-range local transmission events would necessitate revision of our conclusions.

The major conclusions of our model are found to be robust with respect to very wide parameter variation. To a large degree, this is a feature of the detailed representation of the mechanisms of transmission which accounts for the periodicity in feed and slaughter movements and provides accurate representations of their respective catchments. From a methodological viewpoint, the use of periodic transmission mechanisms on dynamic contact networks is a novel feature of this work.

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