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JOURNAL OF THE ROYAL SOCIETY Interface

J. R. Soc. Interface (2008) **5**, 1409–1419
doi:10.1098/rsif.2008.0133
Published online 13 May 2008

Detection of mortality clusters associated with highly pathogenic avian influenza in poultry: a theoretical analysis

Nicholas J. Savill*, Suzanne G. St. Rose and Mark E. J. Woolhouse

Centre for Infectious Diseases, Ashworth Laboratories, Institute of Immunology and Infection Research, University of Edinburgh, The King's Buildings, West Mains Road, Edinburgh EH9 3JT, UK

Rapid detection of infectious disease outbreaks is often crucial for their effective control. One example is highly pathogenic avian influenza (HPAI) such as H5N1 in commercial poultry flocks. There are no quantitative data, however, on how quickly the effects of HPAI infection in poultry flocks can be detected. Here, we study, using an individual-based mathematical model, time to detection in chicken flocks. Detection is triggered when mortality, food or water intake or egg production in layers pass recommended thresholds suggested from the experience of past HPAI outbreaks. We suggest a new threshold for caged flocks—the cage mortality detection threshold—as a more sensitive threshold than current ones. Time to detection is shown to depend nonlinearly on R_0 and is particularly sensitive for $R_0 < 10$. It also depends logarithmically on flock size and number of birds per cage. We also examine how many false alarms occur in uninfected flocks when we vary detection thresholds owing to background mortality. The false alarm rate is shown to be sensitive to detection thresholds, dependent on flock size and background mortality and independent of the length of the production cycle. We suggest that current detection thresholds appear sufficient to rapidly detect the effects of a high R_0 HPAI strain such as H7N7 over a wide range of flock sizes. Time to detection of the effects of a low R_0 HPAI strain such as H5N1 can be significantly improved, particularly for large flocks, by lowering detection thresholds, and this can be accomplished without causing excessive false alarms in uninfected flocks. The results are discussed in terms of optimizing the design of disease surveillance programmes in general.

Keywords: avian influenza; mathematical model; surveillance

1. INTRODUCTION

Surveillance is at the centre of any strategy in the prevention, control and eradication of human, livestock and wild animal infectious diseases (Weinberg 2005; King *et al.* 2006). With the increasing emergence of new infectious diseases into often large naive populations, the rapid detection and characterization of these diseases is crucial in preventing potentially catastrophic epidemics. Four examples where the lack of early detection has caused socially and economically disastrous epidemics are foot-and-mouth disease in the UK in 2001 (Anderson 2002; Haydon *et al.* 2003), SARS in East Asia in 2003 (Ho & Su 2004), highly pathogenic avian influenza (HPAI) H7N1 in Italy in 1999 (Capua & Marangon 2000) and HPAI H7N7 in The Netherlands in 2003 (Elbers *et al.* 2004*a*). In particular to HPAI, the escalating number of epidemics of HPAI viruses in domestic poultry around the world, the endemicity of H5N1 virus in poultry in southern China (Li *et al.* 2004) and its potential mutation into a human transmissible form have heightened the awareness of rapid detection of infection in poultry and humans (Ferguson *et al.* 2004; Food and Agriculture Organisation and World Organisation for Animal Health 2005; Kuiken *et al.* 2005; Capua & Alexander 2006).

At present, there is little quantitative understanding of how long it takes to detect the effects of HPAI infection in commercial poultry flocks, and how such time to detection is affected by various factors such as flock size, species, age and housing. It is important to know this for several reasons. First, in an epidemic situation, it is vitally important to trace contacts between farms on which infection has been notified and farms that are at risk of infection. Fast and efficient tracing of contacts is essential in the combat of such diseases. Knowing the temporal window during which a farm is infectious focuses limited resources on tracing farms at risk. Second, national planning for disease control requires a good understanding of disease dynamics on farms in order to inform models of the transmission dynamics between farms. Some key

*Author for correspondence (nick.savill@ed.ac.uk).

Received 4 April 2008
Accepted 23 April 2008

parameters for such models are time to detection and farm latent and infectious periods, all of which can be inferred from well-parametrized mathematical models.

How HPAI infection is detected in a flock will depend on how rapidly the disease kills clinically apparent birds. If death is sudden with little or no clinical signs, then rapidly rising mortality may be the first indication that something is amiss. If clinical signs are more apparent, then decreased food and water intake or reduced egg production in layers may be the first indication. Deciding whether something is wrong with a flock is made difficult by the day-to-day variation in bird deaths, food and water usage and egg production. Even in healthy commercial poultry flocks, a small number of deaths are expected. Typical daily mortalities are approximately 0.01–0.15% (McMullin 2006; Elbers *et al.* 2007).

To guide the decision of whether to consult veterinary practitioners and inform the authorities, several thresholds have been recommended in The Netherlands as a temporary precaution due to HPAI outbreaks in Italy (Elbers *et al.* 2004*a*) and during and after the severe HPAI outbreaks in The Netherlands in 2003 (Elbers *et al.* 2004*a*, 2005, 2007). Currently, the recommended thresholds for chickens are (Elbers *et al.* 2007)

— greater than 0.5% mortality over two consecutive days for floor-reared layers and broilers,
— greater than 0.25% mortality over two consecutive days for caged layers, and
— food or water intake or egg production in layers down 5% over two consecutive days.

An additional weekly mortality detection threshold of 3% was instigated by the Dutch authorities during and after the 2003 outbreak (Elbers *et al.* 2004*a*).

There are two important constraints on setting the level of a detection threshold. First, they should not be too high otherwise they could lead to infections going unnotified for several critical days. The key to controlling avian influenza—as well as many other human and animal infectious diseases—is rapid reporting so that control measures can be quickly implemented. Second, they should not be too low otherwise false alarms in uninfected flocks will occur. Too many false alarms would overstretch diagnostic laboratories, thus creating long waiting times for critical test results. This situation needs to be avoided, especially during an epidemic.

The aim of this paper is to study, using mathematical models, the relationship between detection thresholds and false alarm rate in uninfected flocks and the trade-off between lowering detection thresholds to speed detection in infected flocks and increasing false alarm rate in uninfected flocks.

During this work, it became clear that the above detection thresholds were not able to detect infection rapidly in caged systems. In such systems, it is likely that infection will be detected when many birds appear dead within a single cage (Tsukamoto *et al.* 2007). The above detection thresholds are generally too insensitive to pick up such cases. Therefore, in addition to the above thresholds, we include a fourth which we call the *cage mortality detection threshold*. This threshold is defined as at least one cage containing more than a given proportion of dead birds. Later in this paper we suggest a value for this proportion.

Note that we are assuming in this paper that detection means farmers becoming aware of a problem in their flocks. The period from when a farmer becomes aware of a problem to when the authorities declare an HPAI infection is subject to a completely different set of issues, as exemplified by other HPAI epidemics (Capua & Marangon 2000; Elbers *et al.* 2004*a*; Tsukamoto *et al.* 2007), and ones we will not consider here.

2. METHODS

2.1. Relationship between detection thresholds and false alarm rate in uninfected flocks

A mortality detection threshold gives the minimum proportion of birds that must die within a given number of days to trigger detection. Let α be that minimum proportion and T the number of days. If the flock size is N birds, then the minimum number of birds that must die is αN, where αN is rounded up to the nearest integer. Assuming that the daily background rate of bird deaths, b, is constant over a production cycle, then the probability of a bird dying in T days is $1-\exp(-bT)$. The probability of αN birds dying in T days is given by the binomial distribution with parameters N and $p=1-\exp(-bT)$. We require the probability, $P(\alpha, T, b, N)$, of at least αN deaths in T days; this is given by $1-D(\alpha N-1;\ N,\ 1-\exp(-bT))$ where D is the binomial cumulative density function.

First, consider the weekly mortality detection threshold α_{w}. Mortality is calculated each day over the last 7 days. Therefore, if the production cycle lasts C days, then mortality is calculated $C-6$ times during the production cycle. The expected number of false alarms during the production cycle, f_{w}, is therefore

$$(C-6)P(\alpha_{\mathrm{w}};\ T=7, b, N)=f_{\mathrm{w}}. \tag{2.1}$$

Given C, α_{w}, T, b and N, it is a simple matter to calculate f_{w} using the regularized incomplete beta function. We also want to solve the equation for α_{w} given f_{w}. This cannot be done analytically, and so a numerical technique is required. In this paper, we use the bisection method with a tolerance of 10^{-10}.

For the daily mortality detection threshold α_{d}, mortality has to be greater than some threshold on two consecutive days. Thus, the value of the threshold that causes f_{d} false alarms per production cycle is found by solving the equation

$$(C-1)P^2(\alpha_{\mathrm{d}};\ T=1, b, N)=f_{\mathrm{d}}. \tag{2.2}$$

In caged systems, the death of most birds within an infected cage will be readily detected. We propose a cage mortality detection threshold α_{c}, such that if there are n birds per cage, then the death of more than $\alpha_{\mathrm{c}}n$ birds in a single cage will trigger detection. Deaths of all birds within a cage are likely to occur in less than a week. Therefore, the value of the threshold that causes

Table 1. Model parameters and their values.

parameter	description	H5N1	H7N7
viral subtype parameters			
L	minimum duration of latent period in hours	24; Shortridge *et al.* (1998)	24; van der Goot *et al.* (2005)
	mean duration of latent period in hours	36	48
	maximum duration of latent period in hours	48	72
A	minimum duration of asymptomatic period in hours	24; Shortridge *et al.* (1998)	94; van der Goot *et al.* (2005)
	mean duration of asymptomatic period in hours	33	151
	maximum duration of asymptomatic period in hours	42	209
S	minimum duration of symptomatic period in hours	6; Shortridge *et al.* (1998)	0; van der Goot *et al.* (2005)
	mean duration of symptomatic period in hours	6	12
	maximum duration of symptomatic period in hours	6	24
p_S	probability of clinical signs	0.5; Shortridge *et al.* (1998)	1; Elbers *et al.* (2007)
μ_f	mean infectiousness of virus excreted in faeces in 1 hour	0.0027; derived from Tiensin *et al.* (2007)	0.067; derived from van der Goot *et al.* (2005)
μ_a	mean infectiousness of airborne virus excreted in 1 hour	0.00027; derived from Tiensin *et al.* (2007)	0.0067; derived from van der Goot *et al.* (2005)
d	percentage reduction in faeces infectiousness per hour	5%; Shortridge *et al.* (1998)	5%; Shortridge *et al.* (1998)
flock and housing parameters			
b	daily background mortality	0.05%; McMullin (2006) and Elbers *et al.* (2007)	
z_f	dispersal distance (number of cages) of infective faeces	1; this paper	
z_a	dispersal distance (number of cages) of airborne virus	1; this paper	
detection threshold parameters			
c	times per day birds are checked	2	
α_d	daily mortality	0.5%; Elbers *et al.* (2004*a*)	
α_w	weekly mortality	3%; Elbers *et al.* (2005)	
α_c	cage mortality	50%; this paper	
α_s	clinical signs	5%; Elbers *et al.* (2004*a*)	

f_c false alarms per production cycle is found by solving the equation

$$(C-6)P(\alpha_c; T=7, b, N=n) = f_c. \qquad (2.3)$$

2.2. Individual-based model of HPAI transmission in infected flocks

The model we use for HPAI transmission in infected flocks is the same as in previous work (Savill *et al.* 2006). It is an individual-based model. Each bird has parameter values randomly chosen from appropriate distributions, and we track the infection status of each bird. Birds are assigned a latent period, an asymptomatic period, a symptomatic period and infectiousness rates for virus excreted in faeces and exhaled. All model parameters are given in table 1.

In terms of the model, floor-reared birds are a special case of caged birds with just one cage.

The status of the birds and the infectiousness of faeces are updated every hour. At hour 0, we assume that a small amount of infective faeces (equal to the amount of infective faeces one bird excretes in an hour) enters a single cage in a caged system or is deposited on the floor in a floor-reared system. The rate of infection, r_i, of susceptible bird i in cage j is given by bird susceptibility multiplied by the infectiousness of infective faeces and airborne virus in that cage and divided by the number of birds per cage (thus assuming frequency-dependent transmission), i.e.

$$r_i = s \cdot \frac{T_{f,j} + T_{a,j}}{n}, \qquad (2.4)$$

where s is bird susceptibility; n is the number of birds per cage; $T_{f,j}$ is the infectiousness of infective faeces in cage j; and $T_{a,j}$ is the infectiousness of airborne virus in cage j. Bird susceptibility, s, is set to 1 with no loss of generality if we assume susceptibility to infection via the faecal–oral and respiratory routes is the same.

Our simulations assume frequency-dependent transmission. Density-dependent transmission would lead to R decreasing as birds die during the outbreak because birds would experience fewer contacts. However, because very few birds die before detection, the change

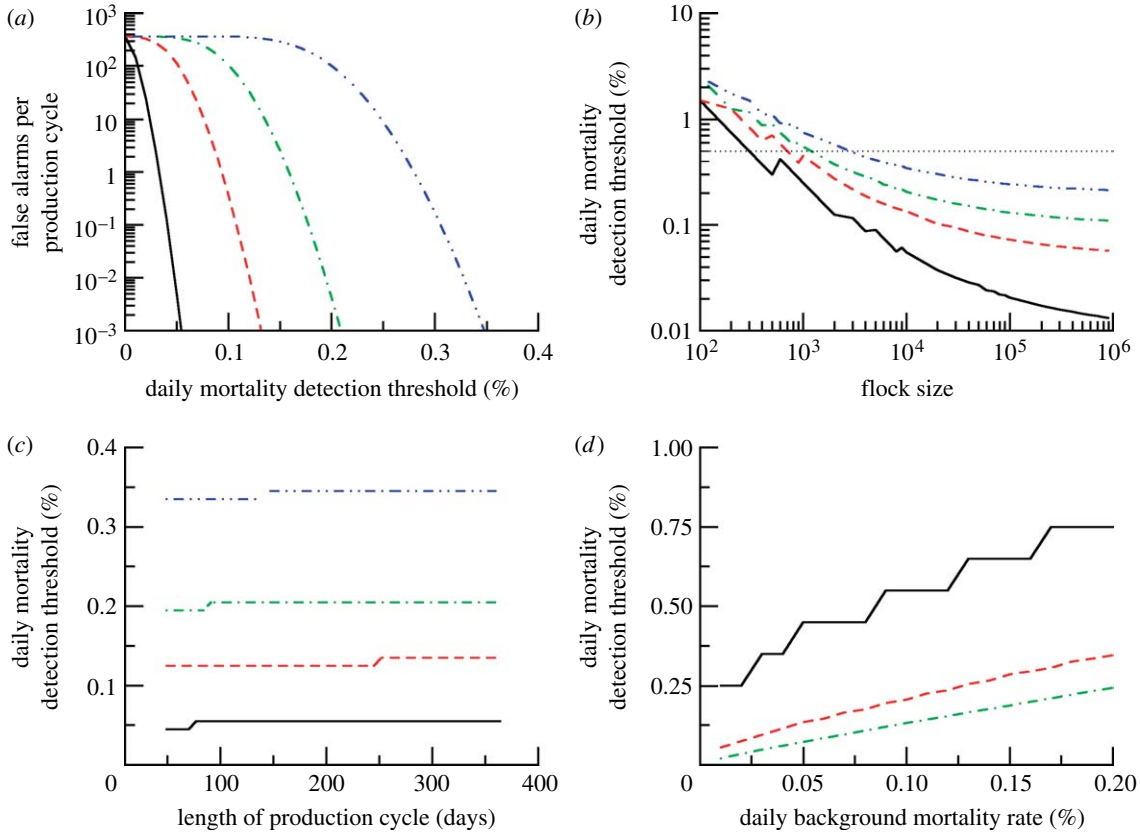

Figure 1. (*a*) Expected number of false alarms per production cycle against daily mortality detection threshold for various background daily mortality rates for a flock of 10 000 birds and production cycle of 365 days. (*b*) The values of the daily mortality detection threshold against flock size that give one false alarm per 1000 production cycles for various background daily mortality rates and a production cycle of 365 days. (*c*) The values of the daily mortality detection threshold against the length of the production cycle that give one false alarm per 1000 production cycles for various background daily mortality rates and a flock of 10 000 birds. (*d*) The values of the daily mortality detection threshold against daily background mortality rate that give one false alarm per 1000 production cycles for various flock sizes and a production cycle of 365 days. (*a–c*) Black solid line, 0.01% background daily mortality rate; red dashed line, 0.05%; green dot-dashed line, 0.1%; blue double dot-dashed line, 0.2%. (*d*) Black solid line, 1000 birds; red dashed line, 10 000; green dot-dashed line, 100 000.

in R would be negligible. Hence, our results would not be affected if we had chosen density-dependent transmission instead.

Once bird i becomes infected, it is latent (asymptomatic and non-infectious) for L_i hours. It then becomes asymptomatic and infectious for A_i hours. We assume that the infectiousness of birds is constant throughout the infectious period. At the end of the asymptomatic period, birds have a probability p_S of becoming symptomatic, otherwise they die. Symptomatic bird i is infectious for S_i hours and then dies. We assume that dead birds are not infectious. We consider two cases of HPAI for which we have some data: H5N1 and H7N7. H5N1 is characterized by rapid death within 2–4 days with few apparent clinical signs before death and virus excretion 1 day after infection (Shortridge *et al.* 1998; Tsukamoto *et al.* 2007). With very little other data to proceed on, we assume that a bird's latent period in hours is randomly drawn from the distribution 24+Binomial(24, 0.5) that gives a minimum latent period of 24 hours, a maximum of 48 hours and a mean of 36 hours (table 1). A bird's asymptomatic period in hours is drawn from the distribution 24+Binomial(18, 0.5). Birds have a 50% chance of showing clinical signs—reduced food or water intake or egg production in layers—and if they do, they die after 6 hours. A more detailed quantitative analysis of the H7N7 virus from the Dutch 2003 epidemic has established that the latent period in chickens is approximately 1–2 days (modelled as 24+Binomial(48, 0.5)) and the infectious period is 6.3 days with a 95% CI from 3.9 to 8.7 days (modelled as 94+Binomial(115, 0.5); van der Goot *et al.* 2005). Elbers *et al.* (2007) noted that infected farms in the Dutch 2003 epidemic experienced some reduced food and water intake the day before mortality began to rise. We therefore allow all birds to become symptomatic with the symptomatic period distributed as Binomial(24, 0.5).

At the beginning of a simulated hour, we reduce the infectiousness of infective faeces, T_f, in all cages by a proportion d. The default value of d models the loss of infectiousness in wet faeces at 25°C (Shortridge *et al.* 1998). We next calculate the infectiousness of any new faeces that have been excreted by all infectious birds in each cage, which, for cage j, is given by

$$T_{f,j}^{\text{new}} = \sum_{i \in \text{infectious bird in cage } j} E_{f,i}, \qquad (2.5)$$

where $E_{f,i}$ is the infectiousness of faeces excreted by infectious bird i in 1 hour.

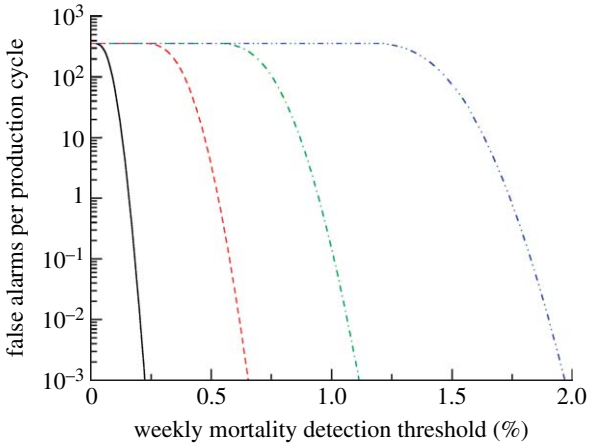

Figure 2. Expected number of false alarms per production cycle against weekly mortality detection threshold for various background daily mortality rates (black solid line, 0.01%; red dashed line, 0.05%; green dot-dashed line, 0.2%; blue double dot-dashed line, 0.5%) for a flock of 10 000 birds and production cycle of 365 days.

Faeces are spread equally among neighbouring cages a distance z_f cages away. We have no estimate for how far faeces can be spread in caged flocks; we assume spread to only contiguous cages, although faeces could be moved farther distances on egg belts and feed tracks, for example. It is known that the spread of infection is slower in caged systems than in floor-reared systems (Shortridge *et al.* 1998; Sims *et al.* 2003*a*; Elbers *et al.* 2007; Tsukamoto *et al.* 2007).

Also, at the beginning of each simulated hour, we calculate the infectiousness of airborne virus exhaled in each cage. Virus exhaled by birds in cage j is given by

$$T_{a,j}^{\text{new}} = \sum_{i \in \text{infectious bird in cage } j} E_{a,i}, \qquad (2.6)$$

where $E_{a,i}$ is the infectiousness of airborne virus excreted by an infectious bird i in 1 hour. Airborne virus is assumed to spread equally among neighbouring cages a distance z_a cages away.

We assume that airborne virus is less infectious than that in faeces (Shortridge *et al.* 1998; Tsukamoto *et al.* 2007). There is no quantitative estimate for the relative infectiousness of these transmission routes, so we assume that transmission via faeces is 10 times more likely than through inhalation. (Analysis not shown here demonstrates that our results are insensitive to transmission route.) We assume that $E_{f,i}$ and $E_{a,i}$ vary among birds. Their true distributions are unknown, so we assume that they are normally distributed with means μ_f and μ_a and standard deviations $0.25\mu_f$ and $0.25\mu_a$, respectively. The results in this paper are robust to the width of these distributions. We use an estimate of $R_0 = 2.5$ for H5N1 (Tiensin *et al.* 2007) and $R_0 = 208$ for H7N7 (van der Goot *et al.* 2005) to determine mean faeces infectiousness.

The flock is checked $c = 2$ times per day, once in the morning and once in the evening. A tally of dead birds is kept. Detection can occur in the following ways.

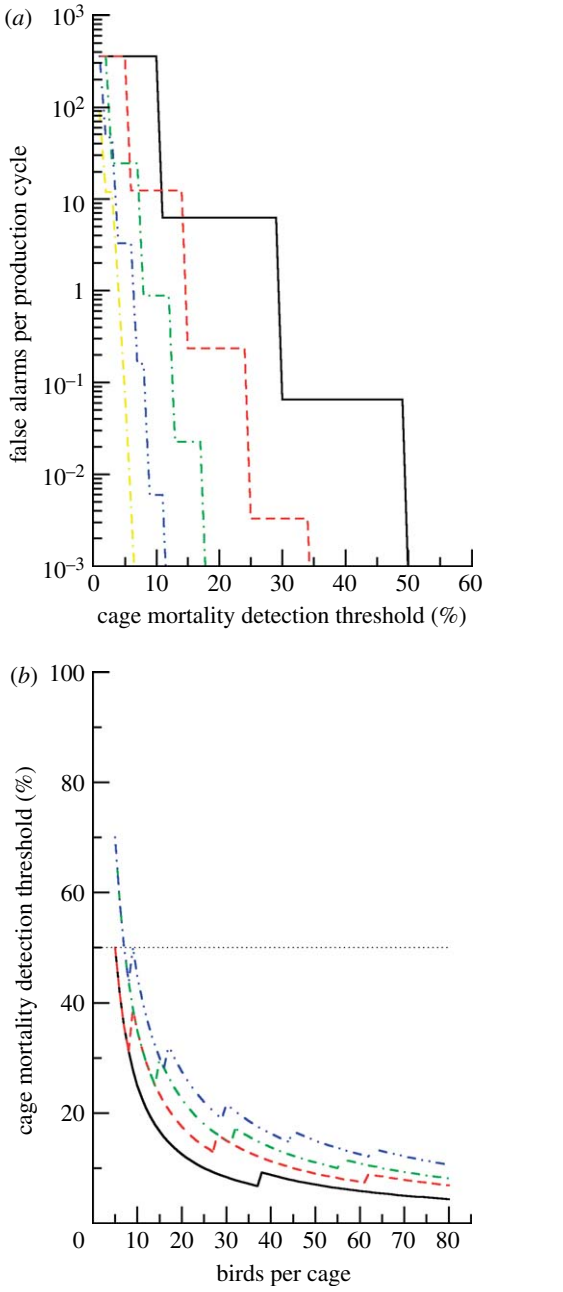

Figure 3. (*a*) Expected number of false alarms per production cycle against cage mortality detection threshold for various numbers of birds per cage (black solid line, 5; red dashed line, 10; green dot-dashed line, 20; blue double dot-dashed line, 40; yellow dot-dashed line, 80), a background mortality of 0.05% and a production cycle of 365 days. (*b*) The values of the cage mortality detection threshold against birds per cage that give one false alarm per 1000 production cycles for various background daily mortality rates (black solid line, 0.01%; red dashed line, 0.05%; green dot-dashed line, 0.1%; blue double dot-dashed line, 0.2%) and a production cycle of 365 days.

— Mortality greater than α_d in two consecutive 24 hour periods.
— Mortality greater than α_w within the last 168 hours.
— Reduction in food or water intake or egg production in layers of α_s over two consecutive days. This is found by dividing the number of symptomatic birds by the number of birds alive.
— A single cage with at least $\alpha_c n$ dead birds.

As well as death by infection, birds also die of other causes at a rate b per day. McMullin (2006) noted mortality rates between 0.05 and 0.1% per day for broilers and 0.014% per day for breeding birds and commercial layers. Elbers *et al.* (2007) estimated a mean mortality of 0.03% for caged layers, 0.04% for organic layers, 0.07% for broilers, 0.04% for up to 11-week-old turkeys and 0.1% for greater than 15-week-old turkeys.

3. RESULTS AND DISCUSSION

3.1. Relationship between detection thresholds and false alarm rate in uninfected flocks

We first examine the relationship between false alarm rate and the daily detection threshold in uninfected flocks. Figure 1*a* shows the expected number of false alarms per production cycle as the daily mortality detection threshold is varied for different background mortality rates and a flock size of 10 000 birds (equation (2.2)). The most striking result is the sensitivity of false alarm rate to the detection threshold. Taking a background mortality of 0.05% as an example (red dashed line), for detection thresholds up to 0.093%, a flock is expected to have at least one false alarm during its production cycle. To achieve, say, a 1000-fold reduction in false alarm rate to 0.1% only requires the threshold to rise to 0.13%. This graph demonstrates that setting a detection threshold high enough makes the chance of a false alarm negligible; setting it slightly too low and false alarms become very frequent. The current recommended threshold of 0.5% means that false alarms will never happen for typical background mortality and for a flock of 10 000 birds. Note that these and the following results are independent of the characteristics of any AI subtype because we are examining uninfected flocks.

For illustrative purposes, we fix the false alarm rate at 1 per 1000 production cycles, and examine how the threshold varies with flock size (figure 1*b*), length of production cycle (figure 1*c*) and background mortality rate (figure 1*d*).

Figure 1*b* shows the daily mortality detection threshold such that the false alarm rate is 1 per 1000 production cycles for varying flock size and background mortality rates. As flock size increases and background mortality decreases, the minimum threshold drops. For a given flock size and background death rate, a threshold above the curve will give less than one false alarm per 1000 production cycles and a threshold below the curve will give more than one false alarm per 1000 production cycles. Thus, the currently recommended threshold of 0.5% would cause more than one false alarm per 1000 production cycles for flocks with less than approximately 1000 birds and typical background mortalities of 0.05%. The discontinuities in the curves are not artefacts or numerical errors; they are due to the detection threshold α_{d}, which is a continuous parameter, being transformed into a discrete number of birds, i.e. $\alpha_{\mathrm{d}}N$.

Figure 1*c* shows that daily mortality detection thresholds (for one false alarm per 1000 production cycles and a flock size of 10 000 birds) is insensitive to the length of the production cycle. This is because the number of false alarms during a production cycle is linearly related to the length of the production cycle, and a linear change in false alarm rate (at approx. 1 per 1000 production cycles) can be accomplished with very small changes to the detection threshold (figure 1*a*).

Figure 1*d* shows the sensitivity of the daily mortality detection threshold against background mortality for a false alarm rate of 1 per 1000 production cycles and varying flock sizes. For small background death rates (typical of commercial poultry flocks), the detection threshold for a given false alarm rate rises approximately linearly with the background death rate.

We next turn to the weekly mortality detection threshold. Figure 2 shows the expected number of false alarms per production cycle as the weekly mortality detection threshold is varied for different background mortality rates and a flock size of 10 000 birds. The qualitative results are the same as for daily mortality detection thresholds except that the thresholds are, of course, higher. All the results that apply to the daily mortality detection threshold similarly apply to the weekly threshold.

Finally, we examine the cage mortality detection threshold. Figure 3*a* shows how the false alarm rate depends sensitively on the cage mortality detection threshold for various numbers of birds per cage (usually between 5 and 80 birds) and a background mortality of 0.05%. The fewer birds per cage, the higher the threshold required to maintain a given false alarm rate. A threshold of 50% gives one false alarm per 1000 production cycles for five birds per cage. We propose that this could be used as a potential threshold value.

Figure 3*b* shows how the cage mortality detection threshold changes for varying number of birds per cage such that the false alarm rate is 1 per 1000 production cycles for different background mortality rates. The threshold increases approximately linearly with the background mortality rate for a given number of birds.

3.2. Sensitivity analysis of time to detection in infected flocks

In this section, we analyse how the mortality and symptoms detection thresholds affect the time to detection in commercial poultry flocks infected with either H5N1 or H7N7. Furthermore, we explore whether time to detection can be improved by lowering detection thresholds without compromising false alarm rate in uninfected flocks.

Figure 4*a* shows how time to detection varies with daily mortality detection threshold for different flock sizes (1000–100 000 birds) and a background mortality rate of 0.05% in H5N1-infected flocks. For a given threshold, time to detection rises logarithmically with flock size. This is owing to the longer time it takes for a certain proportion of the birds to die given the same initial infection of a small amount of infective faeces as flock size increases. At the current recommended threshold (shown by the vertical dotted line), flocks of 1000 birds are detected around day 5 post-infection, whereas flocks of 100 000 birds are detected around day 25 post-infection. The black dashed lines demarcate

regions of different false alarm rates in uninfected flocks (calculated using equation (2.2)). At the current recommended threshold, flocks of 1000 birds have a false alarm rate of approximately 10^{-6}. Larger flock sizes have much smaller false alarm rates.

The main result one can draw from figure 4*a* is that the daily mortality threshold can be lowered from its current recommended value while still keeping false alarm rate negligible. This is particularly true for larger flocks: time to detection for flocks of 100 000 birds can be improved from 25 days to approximately 10 days while keeping the false alarm rate less than 1 in 1000 per production cycle.

Time to detection versus weekly mortality detection threshold exhibits quantitatively and qualitatively similar results as for the daily mortality threshold (figure 4*b*). It might appear strange that detection can occur in less than a week. However, the definition of the weekly threshold is greater than 3% mortality *within* a week. In our simulations, such high rates of mortality often occur within a single day. Such a rapid rise in mortality is often observed in HPAI outbreaks (Bean *et al.* 1985; Barr *et al.* 1986; Capua & Marangon 2000; Sims *et al.* 2003*b*; Selleck *et al.* 2003; Ellis *et al.* 2004; Kwon *et al.* 2005; Department of the Environment, Food and Rural Affairs 2007; Elbers *et al.* 2007; Tsukamoto *et al.* 2007). Note that combining detection thresholds does not act synergistically to improve detection. Detection occurs whenever the first threshold is passed.

Time to detection for H7N7 (figure 4*d*,*e*) is less variable than for H5N1 due to its higher estimated R_0. Improvements in time to detection, by reducing detection thresholds, are therefore less pronounced; for example, only a day or two's improvement for flocks of 100 000 birds.

Time to detection using only the symptoms detection threshold takes very much longer than with mortality thresholds for H5N1 due to the short symptomatic period (figure 4*c*). Even for H7N7, where we have assumed that most birds show clinical signs, time to detection is several days longer than with mortality thresholds (figure 4*f*). This is not surprising given that the recommended symptoms threshold is 10 times less sensitive than the daily threshold. Presumably this threshold was set so high owing to the greater daily variation in food and water intake and egg production, compared with daily variation in mortality.

Figure 5*a* shows the time to detection of H5N1 in caged birds versus the cage mortality detection threshold. For five birds per cage, time to detection is approximately 4 days and is almost independent of the cage mortality detection threshold. However, for 80 birds per cage, time to detection rises from 4 days for a less than 10% mortality threshold to 60 days at an 80% mortality threshold. Moreover, time to detection can be significantly improved without compromising on false alarms; for all the numbers of birds per cage, time to detection can be reduced to approximately 4 days while still maintaining a false alarm rate of less than 10^{-6} per production cycle.

For H7N7 in caged birds, there is less change in time to detection with cage mortality detection threshold due to its higher estimated R_0 than H5N1. As for floor-reared birds, there is only a few days' improvement in time to detection as the detection threshold is reduced.

A whole host of factors related to virus subtype, host species, management practices and housing units, density and conditions (Tsukamoto *et al.* 2007) not considered in this paper determine R_0. Instead of varying specific factors to determine their effect on time to detection, we can simply vary R_0 via changes in faeces infectiousness. Figure 6 demonstrates that time to detection is independent of R_0 for floor-reared flocks of approximately 1000 birds and for caged birds with less than approximately 20 birds per cage. For larger flock sizes and more birds per cage, detection can vary from days to weeks depending on the value of R_0. For a given R_0, the longer time to detection of H7N7 compared with H5N1 is due to its longer latent and infectious periods.

4. CONCLUSION

HPAI outbreaks have been increasing in frequency over the past 10 years resulting in the deaths of millions of poultry and huge economic losses for affected countries (McLeod *et al.* 2005). Surveillance systems of avian influenza in wild and domestic birds have thus become internationally important front line tools in preventing, detecting, controlling and eradicating epidemic and endemic diseases in poultry (Capua & Alexander 2006).

In this paper, we have focused on the use of surveillance to detect the effects of HPAI infection on commercial poultry flocks, namely rapidly rising mortality, clinical signs, reduced food and water intake and reduced egg production in layers. It is important that detection and confirmation by virus isolation occur as rapidly as possible as amply demonstrated by the H7N1 HPAI outbreak in Italy in 1999 (Capua & Marangon 2000) and the H7N7 HPAI outbreak in The Netherlands in 2003 (Elbers *et al.* 2004*a*), and the successful control of many H5N1 incursions into Asia and Europe in recent years.

To aid detection and reporting, several flock-level mortality and symptoms thresholds have been established by the Dutch authorities (Elbers *et al.* 2004*a*, 2005, 2007). We analysed the relationship between the values of these thresholds and the rate at which they cause false alarms in uninfected flocks due to background levels of mortality. We show that the false alarm rate is sensitive to the various detection thresholds. The implication is that it is better to set a detection threshold slightly too high rather than too low. We show that for a given false alarm rate (e.g. 1 per 1000 production cycles), detection thresholds vary in a nonlinear fashion with flock size and number of birds per cage and background mortality rate, but are insensitive to the length of the production cycle.

We examined how quickly the effects of HPAI infection can be detected in commercial poultry flocks with three different mortality detection thresholds and a symptoms detection threshold. Floor-reared birds are detected by mortality passing either a daily or weekly mortality detection threshold. Time to detection depends logarithmically on flock size. This is the case

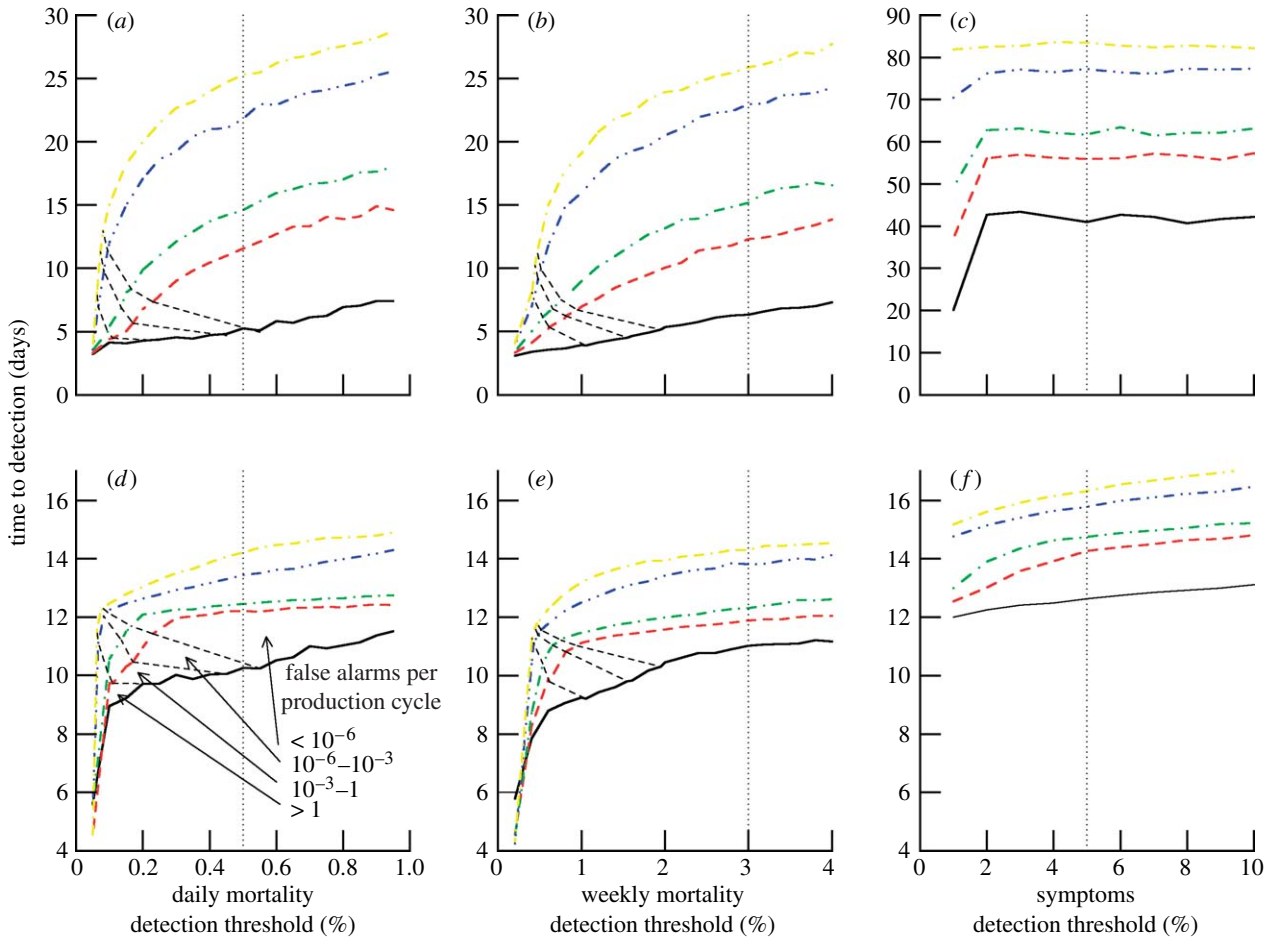

Figure 4. Time to detection in floor-reared birds for (*a–c*) H5N1 and (*d–f*) H7N7 against (*a,d*) daily mortality, (*b,e*) weekly mortality and (*c,f*) symptoms detection thresholds for different flock sizes (black solid line, 1000; red dashed line, 5000; green dot-dashed line, 10 000; blue double dot-dashed line, 50 000; yellow dot-dashed line, 100 000). Values are averaged over 100 simulations. Vertical dotted lines represent current recommended thresholds. The black dashed lines in (*a–e*) demarcate regions of different false alarm rates in uninfected flocks. From left to right, the regions are greater than 1, between 10^{-3} and 1, between 10^{-6} and 10^{-3} and less than 10^{-6} false alarms per production cycle. Note the different *y*-axis scales.

when the initial contamination is small, for example infective faeces brought into a flock on someone's clothing. For a large contamination, for example by contaminated food or water, time to detection may be more rapid and independent of flock size.

Our analysis indicates that current recommended thresholds could be lowered in order to shorten time to detection in floor-reared birds. For H7N7, which has a high estimate of R_0 of 208 (van der Goot *et al.* 2005), approximately 12–24 hours can be gained without compromising on false alarms in uninfected flocks. For H5N1, which has a much lower estimate of R_0 of approximately 2.5 (Tiensin *et al.* 2007), time to detection can be improved by days, or even a few weeks for large flock sizes, without compromising on false alarms.

Although we included a detection threshold for clinical signs, clinical signs were never detected before rising mortality in our simulations. This is not surprising since the daily and weekly mortality detection thresholds are 10 times more sensitive than the symptoms threshold. In fact, using clinical signs as a detection threshold is problematic. Clinical signs of HPAI are extremely variable, depending on species, age, virus subtype and the presence of other diseases. Infected birds may die with no obvious signs or they may show many diverse clinical signs (Elbers *et al.* 2004*b*). This dramatic variation would introduce too much error into detection and probably contribute to an increase in false alarms. Elbers *et al.* (2007) reported that a decrease in food or water intake was often seen in H7N7-infected flocks a day before rising mortality was observed, although at what level was not noted. They suggested that the observation of clinical signs within a flock should trigger closer scrutiny of the flock in order to respond rapidly to rising mortality if it occurs.

During this work, we realized that the recommended detection thresholds were too insensitive to trigger early detection in caged systems. We therefore recommend an additional mortality detection threshold for caged systems. The reason a cage mortality detection threshold is more sensitive than other thresholds is that deaths are spatially clustered in a small subgroup of the flock and are therefore easier to observe. A value of approximately 50% dead birds in a single cage should be easily detected in commercial caged flocks and prevents excessive false alarms in uninfected flocks (figure 2). Time to detection is generally faster than in floor-reared flocks because most early deaths occur in small easily monitored cages

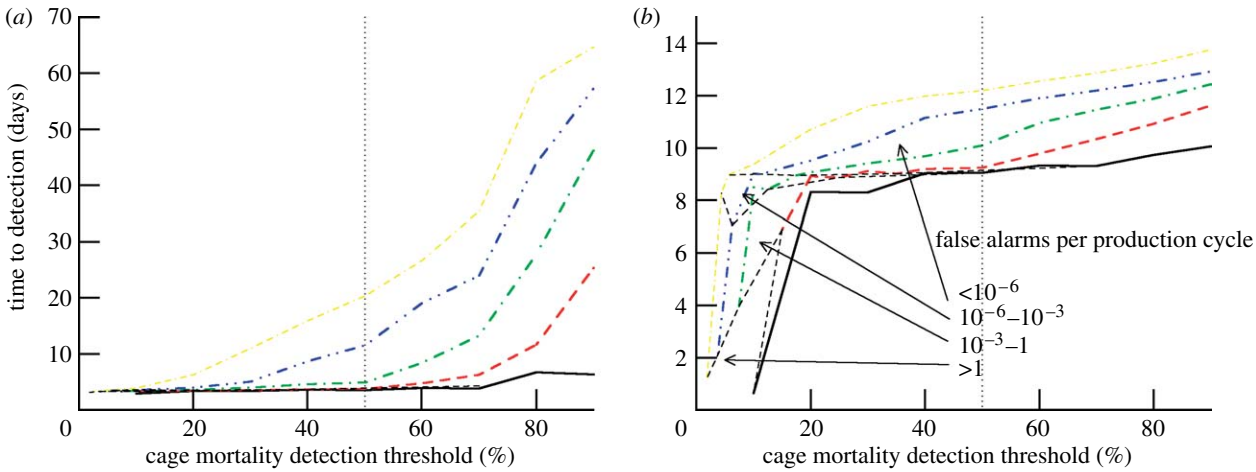

Figure 5. Time to detection in caged birds for (*a*) H5N1 and (*b*) H7N7 against cage mortality detection threshold for different numbers of birds per cage (black solid line, 5; red dashed line, 10; green dot-dashed line, 20; blue double dot-dashed line, 40; yellow dot-dashed line, 80). See the legend of figure 4 for the explanation of regions of differing false alarm rates (the regions in the H5N1 plot are mostly hidden below the five birds per cage (black solid) curve). Note the different *y*-axis scales.

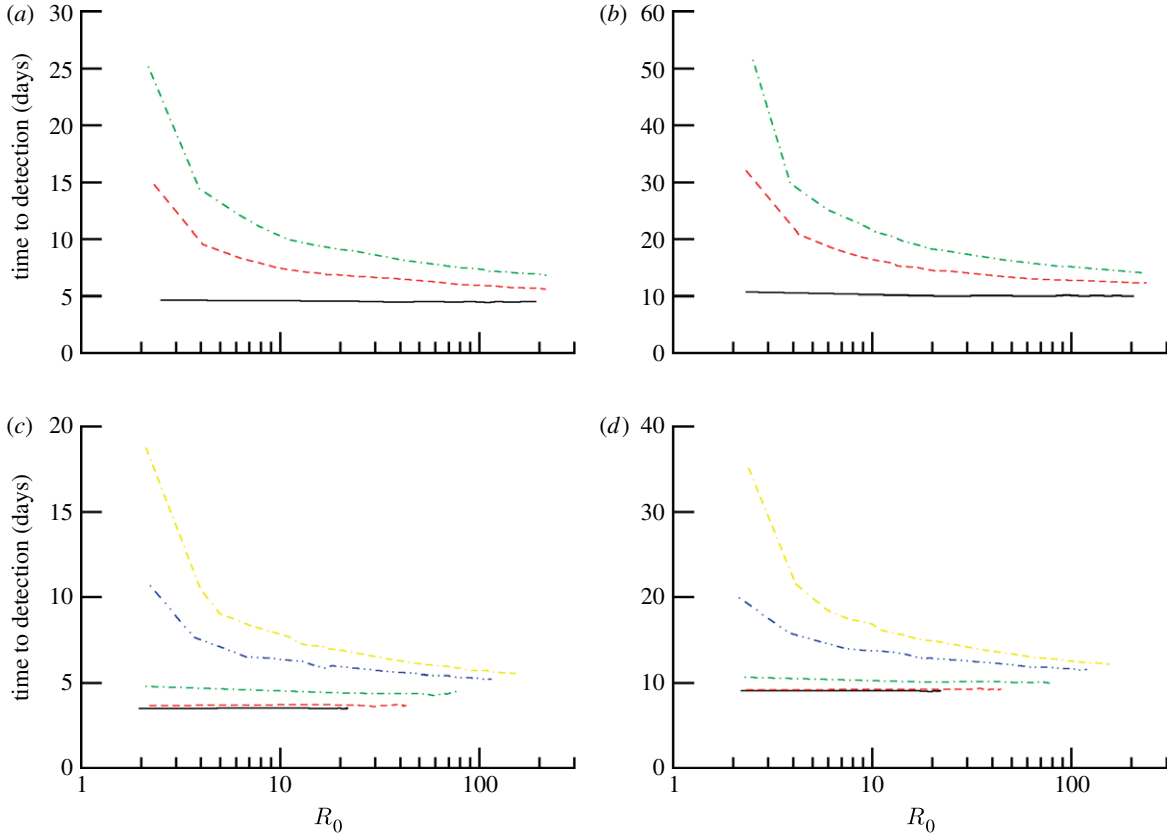

Figure 6. Time to detection against R_0 for (*a*,*b*) floor-reared birds and (*c*,*d*) caged birds for (*a*,*c*) H5N1 and (*b*,*d*) H7N1 for different flock sizes (black solid line, 1000; red dashed line, 10 000; green dot-dashed line, 100 000) or birds per cage (black solid line, 5; red dashed line, 10; green dot-dashed line, 20; blue double dot-dashed line, 40; yellow dot-dashed line, 80) and detection thresholds set to current recommendations. Note the different *y*-axis scales.

rather than a large open area containing thousands of birds. As for floor-reared birds, time to detection can be improved by lowering the detection threshold without compromising on false alarms. For H7N7, we predict an improvement of only a few days when there are more than approximately 20 birds per cage and there is little improvement at lower densities. For H5N1, we predict that very little improvement can be made for less than approximately 20 birds per cage; however, several weeks can be taken off time to detection for higher densities.

Our results indicate that time to detection is sensitive to changes in R_0 for $R_0<10$ and relatively insensitive above 10 (figure 6); the smaller R_0 is, the longer detection takes. However, for low R_0, time to detection is also sensitive to mortality detection thresholds, particularly for larger flock sizes in floor-reared birds and high numbers of birds per cage in

caged systems; thus, by lowering detection thresholds, we predict that time to detection can be improved by days or even weeks without compromising on false alarms in uninfected flocks. When R_0 is high, we predict that time to detection can be improved by only a day or two, and only then for large flock sizes or high numbers of birds per cage.

There have been two recent H5N1 outbreaks in the UK both in turkeys: one in January 2007 and another in November 2007. The epidemiological investigation of the January outbreak found that a shed of 7119 turkeys became infected somewhere between 22 and 25 January. Some birds were 'off colour' on 27 January and mortality was 0.18, 2.2 and 12% on 30 January, 31 January and 1 February, respectively. Disease was notified on 1 February. Based on current recommended mortality thresholds, notification occurred on the appropriate day. Our model predicts that detection would have occurred approximately 11–12 days post-infection in chickens, or approximately during the week beginning 4 February: at least 3 days after actual detection. This discrepancy could be because turkeys are generally more susceptible to AI compared with chickens (Tumpey *et al.* 2004; Balicer *et al.* 2007). Alternatively, multiple turkeys may have been initially infected as the route of infection was likely to have been contaminated wild birds or rodents entering the shed. Unfortunately, the epidemiological investigation of the November outbreak was unable to trace the source of infection. This meant there was no estimate of when the turkeys were initially infected.

Although reducing the detection thresholds to improve time to detection is theoretically possible, in practice there are some difficulties. To calculate thresholds for a certain false alarm rate for a particular flock is not simple. However, pre-printed tables or graphs such as in figure 2 can be easily referred to in a commercial situation. Moreover, we have assumed a constant death rate of birds over a production cycle, which implies that the number of bird deaths is binomially distributed. In reality, chickens and layers have a peak in mortality in the first week post-hatch and thereafter layer mortality tends to be low throughout rear and production with a slight rise as the birds age. Chicken mortality tends to rise again more rapidly towards week 5 in the production cycle. However, it is feasible that detection thresholds can be adjusted throughout the production cycle to take these predictable variations into account.

In reality, the use of mortality detection thresholds may not be strictly adhered to by farmers. Elbers *et al.* (2007) have noted that some farmers still ignore the early detection system put in place during the H7N7 epidemic in The Netherlands. Moreover, rising mortality can be caused by other avian diseases and stress conditions leading to a hesitation to notify. Notwithstanding this, the results we describe here have relevance in informing the implementation of an early detection system. It gives policy makers a quantitative and scientific base on which to make decisions on surveillance and control. It feeds into mathematical models of between-flock transmission that are used to inform contingency planning, and contact tracing in an epidemic can be refined based on our estimates of time to detection.

Elbers *et al.* (2007) have highlighted the necessity for good quantification of mortality with respect to flock size as a means for rapid diagnosis of AI. We wholeheartedly agree with this sentiment, and would add that more and better quantification and reporting of all aspects of poultry rearing and key epidemiological parameters such as latent and infectious periods and transmission rates are paramount for developing evidence-based surveillance, control and prevention strategies.

Figure 6 highlights and reiterates that imperfect prophylactic vaccination that reduces R_0 to just above 1 can have serious consequences for disease control (Savill *et al.* 2006). Time to detection can be significantly increased compared with non-vaccinated birds with much higher R_0. This suggests that disease could spread through flocks undetected for many weeks before mortality rises above the threshold. This makes between-flock transmission much more likely and control of an epidemic orders of magnitude more difficult. It may also increase the risk of transmission to humans.

This work also has more general implications. The problem of detecting HPAI infection in commercial poultry flocks illustrates the principle that, for any disease detection system based on proxy indicators (e.g. mortality clusters), the optimal design is a function of the demography and structure of the host population. Quantitative approaches such as those developed here are therefore likely to be useful in informing the design of surveillance programmes for emerging infectious diseases in any host population, including humans.

We would like to thank Nick Sparks from the Scottish Agricultural College, Arjan Stegeman from Utrecht University, Armin Elbers from the Central Institute for Animal Disease Control (CIDC) at Wageningen University, David Swayne, USDA and the late Howard Hellig for their kind help and useful discussions. This work was funded by the Department for Environment, Food and Rural Affairs under the Avian Influenza Epidemiological Modelling and Economic Assessment initiative and by the Scottish Funding Council under the Interdisciplinary Centre for Human and Avian Influenza Research initiative.

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