Impact of the implementation of rest days in live bird markets on the dynamics of H5N1 highly pathogenic avian influenza

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Live bird markets (LBMs) act as a network ‘hub’ and potential reservoir of infection for domestic poultry. They may therefore be responsible for sustaining H5N1 highly pathogenic avian influenza (HPAI) virus circulation within the poultry sector, and thus a suitable target for implementing control strategies. We developed a stochastic transmission model to understand how market functioning impacts on the transmission dynamics. We then investigated the potential for rest days—periods during which markets are emptied and disinfected—to modulate the dynamics of H5N1 HPAI within the poultry sector using a stochastic meta-population model. Our results suggest that under plausible parameter scenarios, HPAI H5N1 could be sustained silently within LBMs with the time spent by poultry in markets and the frequency of introduction of new susceptible birds’ dominant factors determining sustained silent spread. Compared with interventions applied in farms (i.e. stamping out, vaccination), our model shows that frequent rest days are an effective means to reduce HPAI transmission. Furthermore, our model predicts that full market closure would be only slightly more effective than rest days to reduce transmission. Strategies applied within markets could thus help to control transmission of the disease.

Keywords: H5N1 avian influenza; mathematical transmission model; live bird market; rest days

1. INTRODUCTION

Since December 2003 outbreaks of H5N1 highly pathogenic avian influenza (HPAI) affecting domestic poultry have been reported in 50 countries across the world [1]. The virus has also shown potential for cross-species transmission, sporadically infecting humans and other mammals [2]. Both the massive economic losses and the putative pandemic threat make H5N1 HPAI one of the greatest current public health concerns. Although interventions have been implemented, the disease is now considered to be endemic in several countries, especially in southeast Asia and Egypt. The intense measures that have enabled developed countries to eradicate past and ongoing HPAI epidemics are not appropriate in all affected areas. Therefore, locally adapted control strategies need to be designed.

Various risk factors associated with the local characteristics of poultry production in affected countries have been identified as playing a key role in the sustainability of the virus [3,4]. Among them, live bird trade and wet markets are considered to be the main pathways for disease transmission [5] as well as offering conditions for virus amplification, reassortment and cross-species transmission owing to the high density of hosts [6]. From the late 1970s, the abundance and diversity of avian influenza (AI) viruses have been recognized in live bird markets (LBMs) [7]. More recently, surveys have highlighted the diversity and abundance of low-pathogenic avian influenza (LPAI) viruses in East Asian LBMs [8–12]. Moreover, H5N1 viruses have been identified in markets where they circulated silently. Although no outbreak was reported in Vietnam prior to 2003, H5N1 virus was identified in LBMs around Hanoi in 2001 [13,14]. During the H5N1 epidemics which affected Hong Kong in 1997, birds in LBMs were found to be highly infected with the prevalence of the infection in chickens reaching 19.5 per cent [15]. LBMs have also been recognized to be a likely source of infection for domestic poultry flocks: retail marketing of live poultry was implicated as the
main source of exposure to infection on chicken farms in Hong Kong during the 2002 H5N1 epidemic [16]. Thus, LBMs may play a key role in the epidemiology of AI viruses [17] and acting as a network ‘hub’, they may be responsible for sustaining endemic infection within the poultry sector.

Following multiple outbreaks of H5N1 HPAI in Hong Kong between 1997 and 2003, control strategies were implemented across the LBM chain [18–20]. These interventions appear to have been successful as only one outbreak has been notified since 2003 [21]. Among them, rest days, during which markets are emptied and disinfected, have been associated with a significant decrease in the rate of isolation of LPAI viruses in the retail markets [22,23]. Similar observations have been noted in the United States: surveys here highlighted that rest days, frequent cleaning and disinfection are factors decreasing the risk that the market is positive for LPAI [24–26]. These observations suggest that rest days may be effective to reduce the prevalence of AI viruses in LBMs. They also indicate that the level of infection in markets is not simply the result of multiple introductions of infected birds, but the consequence of virus re-circulation and amplification within them.

While it is therefore clear that measures implemented in LBMs and further along the market chain could help to control the spread of the disease, it remains unclear what factors allow lethal H5N1 viruses to circulate without detection in LBMs. It has been assumed that the lack of detection in Hong Kong LBMs in 1997 was owing to cross-reactive cellular immunity induced by an H9N2 virus, which would have protected chickens from H5N1 virus infection [26]. According to these findings, reduction in individual chicken susceptibility would then allow H5N1 viruses to be sustained. However, an alternative explanation could be that the rapid turnover of the chicken population means that transmission in LBMs is never detected because the birds do not remain long enough to show symptoms. Here we use a mathematical model of H5N1 transmission within a LBM system similar to that described in Hong Kong retail LBMs [23], to ask if factors related to the management of poultry can create conditions for silent perpetuation of H5N1 viruses in a population of highly susceptible birds. The model incorporates opening/closing times of the market, cohorts of birds and transmission via direct contact or via environmental contamination from infectious faeces. We then use a stochastic meta-population model that mimics the vertical market flow system in place in Hong Kong to determine the likely impact of control strategies implemented within the market chain on the transmission of H5N1 HPAI within poultry sectors if the LBM system was responsible for virus amplification, and to assess which aspects of the system need to be understood and further quantified to determine the success of interventions implemented in LBMs.

2. METHODS

Our models are based on the Hong Kong LBM chain. Although this is a unique and well-managed market system compared with others in regions where the disease is probably endemic, this LBM chain is well described in the literature and is thus a good candidate for investigating the potential of LBMs to sustain the disease and to assess the impact of interventions.

2.1. Within-market model

2.1.1. Functioning of the market and management of poultry. A day is divided into two periods: during the first half of the day the market is open and during the second half it is closed. As only chickens are sold in Hong Kong LBMs [23], and because we are most interested in highly susceptible birds, we restrict our analysis to chickens. All birds are assumed to be introduced into the market when it opens, thus we define a cohort as a group of birds introduced simultaneously into the market, and the turn-over period \( T \), as the maximum time needed for a cohort to be sold. Figure 1 illustrates how the probability that a bird remains in a market evolves as a function of time for a turn over period of 1.5 days.

2.1.2. H5N1 virus transmission process. Within markets, birds pass through three infection states: susceptible (S), infected but not infectious (E) and infectious (I). When birds become infectious, they are first asymptomatic and subsequently develop clinical signs. All birds are assumed to die at the end of the infectious period. The latent and infectious period distributions are given in figure 1c,d. These periods are the sum of a fixed minimum duration and an additional stochastic integer duration generated from a binomial distribution with parameters \( B(n,p) \) as specified in table 1.

Infectious birds are assumed to contaminate their environment by releasing faeces at each time step. Faeces infectiousness decreases exponentially with time at a rate \( \Theta \). Therefore, during the infectious period of a bird, disease is transmitted directly through contact with susceptible birds and indirectly through the contaminated environment (figure 1b). Transmission continues after the death of the infectious bird via the remaining environmental reservoir. The infectiousness via each route of transmission can therefore be expressed as:

\[
inf_{\text{contact}} = \int_{t=0}^{t=T_{\text{inf}}} \beta dt = \beta T_{\text{inf}}, \tag{2.1}
\]

\[
inf_{\text{env}} = \int_{t=0}^{t=T_{\text{inf}}} \frac{dH}{dt} \int_{t=0}^{t=H} \beta \eta (1-\Theta)^i dt = T_{\text{inf}} \int_{t=0}^{t=H} \beta \eta (1-\Theta)^i dt, \tag{2.2}
\]

where \( T_{\text{inf}} \) is the infectious period, \( H \) is the length of time the faeces remains infectious, \( \beta \) is the per unit time rate of transmission and \( \eta \) the relative rate of transmission from the environmental reservoir compared with \( \beta \). In equation (2.2), the integral refers to the exponential decay of faeces dropped each day that the bird is infectious, which extends the infectious period in the environment beyond the infectious...
Figure 1. Illustration of the within-market model. (a) Probability that a bird introduced at time $t = 0$ remains in the market as a function of time. In green: period during which the market is open for trading. In red: period during which the market is closed for trading. (b) Within-market SEI model. (c) Assumed distribution of the latent period (solid line, latent period). (d) Assumed distribution of the infectious period (dotted line, infectious period).

Table 1. Parameter values.

<table>
<thead>
<tr>
<th>parameter</th>
<th>description</th>
<th>value (unit)</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>time parameters</td>
<td>$d_t$ step-time</td>
<td>0.1 (days)</td>
<td></td>
</tr>
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<td>market parameters</td>
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<td></td>
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<tr>
<td>$N_w$</td>
<td>number of wholesale markets</td>
<td>1</td>
<td>[23]</td>
</tr>
<tr>
<td>$N_r$</td>
<td>number of regional markets (or clusters)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>$T_w$</td>
<td>time spent at wholesale market</td>
<td>0.5 (days)</td>
<td></td>
</tr>
<tr>
<td>$T_r$</td>
<td>turn-over period in regional markets</td>
<td>1.5 (days)</td>
<td></td>
</tr>
<tr>
<td>farm parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$N_i$</td>
<td>number of farms per cluster</td>
<td>30</td>
<td>a</td>
</tr>
<tr>
<td>$N_b$</td>
<td>flock size</td>
<td>5000</td>
<td>a</td>
</tr>
<tr>
<td>$T_{cycle}$</td>
<td>length of time of a cycle</td>
<td>100 (days)</td>
<td></td>
</tr>
<tr>
<td>$T_{repop}$</td>
<td>length of time between two successive cycles</td>
<td>21 (days)</td>
<td></td>
</tr>
<tr>
<td>infection parameters</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$T_{latent}$</td>
<td>latent period</td>
<td>$0.1 + B(4,0.5)dt$ (days)</td>
<td>[46]</td>
</tr>
<tr>
<td>$T_{inf}$</td>
<td>infectious period</td>
<td>$1.5 + B(10,0.5)dt$ (days)</td>
<td>[46]</td>
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<tr>
<td>$T_{asympt}$</td>
<td>asymptomatic infectious period</td>
<td>1 (day)</td>
<td>a</td>
</tr>
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<td>$\xi$</td>
<td>environmental contamination ratio</td>
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<td>a</td>
</tr>
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<td>$R_0^p$</td>
<td>within-farm basic reproduction number</td>
<td>5</td>
<td>a</td>
</tr>
<tr>
<td>$p_0^a$</td>
<td>prevalence of infectious birds in regional market at the equilibrium</td>
<td>19.5%</td>
<td>[15]</td>
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<tr>
<td>$r^w/r$</td>
<td>ratio between $r^w$ ($r$ within cluster only) and $r$</td>
<td>0.1</td>
<td>a</td>
</tr>
<tr>
<td>$H$</td>
<td>length of time the faeces remain infectious</td>
<td>4 (days)</td>
<td>[47]</td>
</tr>
<tr>
<td>$\Theta$</td>
<td>decay rate in faeces infectiousness per time-step</td>
<td>10%</td>
<td>[47]</td>
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<tr>
<td>intervention parameters</td>
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<td></td>
</tr>
<tr>
<td>$D_m$</td>
<td>daily mortality threshold for suspicion in farms</td>
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<tr>
<td>$T_{stamping}$</td>
<td>delay between suspicion and interventions in farms</td>
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<td>a</td>
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<tr>
<td>$\Sigma$</td>
<td>proportion of efficiently vaccinated poultry per cycle</td>
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<td>[31]</td>
</tr>
<tr>
<td>$\Omega$</td>
<td>length of time from vaccination to immunity</td>
<td>14 (days)</td>
<td>[48,49]</td>
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*Further details on these parameter estimates are provided in electronic supplementary material, S2.
period of the bird. For a stable population size and an infectious period going to its end without being stopped owing to selling and slaughtering, the basic reproduction number $R_0$ (i.e. expected number of secondary cases following the introduction of a primary case in a susceptible population) is then defined as:

$$ R_0 = (\inf_{\text{contact}} + \inf_{\text{env}}) N_0, $$

where $N_0$ is the initial number of susceptible birds in the market. We can thus define the environmental contamination ratio $\xi$ as the proportion of infectivity, which is mediated by the environment:

$$ \xi = \frac{\inf_{\text{env}} N_0}{R_0} = \frac{\beta \eta T_{\inf} N_0}{R_0} \int_{t=0}^{t=H} (1 - \Theta)^t dt. $$

Thus, knowing $\xi$ and $R_0$, we can calculate $\beta$ and $\eta$:

$$ \beta = \frac{R_0}{T_{\inf} N_0 (1 + \eta \int_{t=0}^{t=H} (1 - \Theta)^t dt)} $$

$$ \eta = \frac{\xi}{(1 - \xi) \int_{t=0}^{t=H} (1 - \Theta)^t dt}. $$

The infection process is stochastic and density-dependent. Homogeneous mixing is assumed.

### 2.1.3. Scenarios

We initially assume a turn-over period of 1.5 days [23] with birds introduced every day. We then adjust $\beta$, $\eta$ and the proportion of introduced birds that are infected to get an average prevalence of infectious birds during open time equal to 19.5 per cent [15], assuming either that (i) virus is not amplified (i.e. $\beta = 0$ and $\eta = 0$) or that (ii) virus is amplified in the market. We then assess the impact of variations in the frequency of bird introduction into the market and the turn-over period on the prevalence of symptomatic birds and mortality. One thousand iterations are run for each parameter combination. We defined silent spread by the number of chickens showing symptoms or dying. This value would reflect a sufficiently low level of morbidity and mortality, which could be considered normal and attributable to other causes (e.g. stress associated with transport). We could not find threshold values for morbidity and mortality rate in the literature, hence, we assume that the mortality rate on any given time in a day would have to be close to 0 per cent and morbidity lower than 3 per cent for the virus circulation to remain undetected.

### 2.2. Meta-population model

#### 2.2.1. Structure of the market chain

A vertical market system with a unidirectional flow of poultry comparable to the one in use in Hong Kong is assumed [23]; from farms all poultry are stored in a unique wholesale market before being transferred to regional markets (figure 2). There are no poultry movements directly
from farms to regional markets. Each farm rears 5000 broiler chickens with a cycle length of 100 days according to an all-in-all-out system. When a cycle ends, the infectious reservoir, if present, is then assumed to be removed through disinfection. The mortality owing to causes other than HPAI is considered to be negligible. New birds are introduced, and old birds leave the wholesale market simultaneously.

2.2.2. Infection process between populations. Between flocks, the infection can spread by (i) commercial poultry movements across the market chain from farms to the wholesale market, and from the wholesale market to regional markets, or by (ii) indirect contacts between farms, between farms and regional markets, and between regional markets (figure 2).

Thus, the force of infection applied to birds within a farm (or a market) depends on the number of infectious chickens \( \lambda^F \) (or \( \lambda^M \)) and the environmental load \( \psi^F \) (or \( \psi^M \)) within this farm (or this market), and the environmental load in other farms and markets. Farms are clustered around each regional market, with each cluster composed of one regional market and \( N_f \) farms (table 1). In the simulations presented here, we model a single wholesale market, and 30 clusters composed of the regional market and associated farms. The rates of transmission differ within and between clusters (figure 2): \( \gamma_f, \gamma_m \) are the rate of transmission between farms, and between farms and markets belonging to the same cluster, respectively. \( \Gamma_f, \Gamma_m \) and \( \Gamma_{mn} \) are the rate of transmission between farms, between farms and markets and between markets belonging to different clusters, respectively.

In farm \( i \) in cluster \( j \) with \( S^S_{ij}(t) \) susceptible birds at time \( t \), the number of newly infected birds at \( t + dt \) is given by a stochastic binomial variable \( B(\lambda^F_{ij}(t), S^S_{ij}(t)) \), where \( \lambda^F_{ij}(t) \) is the force of infection (i.e. the rate at which poultry gets infected between \( t \) and \( t + dt \)) defined by:

\[
\lambda^F_{ij}(t) = 1 - \exp\left\{-\delta^F_{ij}(t)dt\right\}.
\]

Here \( \delta^F_{ij}(t) \) is the instantaneous hazard of infection:

\[
\delta^F_{ij}(t) = \beta^F \left[ \rho^F_{ij}(t) + \eta^F \psi^F_{ij}(t) \right] + \gamma_m \sum_{k \neq i} \psi^M_{ik}(t) + \left[ \gamma_m \sum_{k \neq i} \psi^M_{ik}(t) \right]
\]

\[
+ \left[ \Gamma_m \sum_{k \neq i} \psi^M_{ik}(t) \right] + \left[ \gamma_m \sum_{k \neq i} \psi^M_{ik}(t) \right].
\]

In equation (2.8), the first component is the within-farm infection process, the second the hazard of infection from other farms in the same cluster, the third the hazard of infection from farms in other clusters, the fourth the hazard of infection from the market in the same cluster and the fifth the hazard of infection from markets in other clusters.

Similarly in a regional market \( c \):

\[
\lambda^M_{c}(t) = 1 - \exp\left\{-\delta^M_{c}(t)dt\right\},
\]

with the hazard of infection \( \delta^M_{c}(t) \) given by:

\[
\delta^M_{c}(t) = \beta^M \left[ \rho^M_{c}(t) + \eta^M \psi^M_{c}(t) \right] + \gamma_m \sum_{t} \psi^M_{c}(t)
\]

\[
+ \left[ \Gamma_m \sum_{k \neq i} \psi^M_{ik}(t) \right] + \left[ \Gamma_m \sum_{k \neq i} \psi^M_{ik}(t) \right].
\]

Here the first component is the within-market infection process, the second the hazard of infection from farms in the same cluster, the third from farms in other clusters and the fourth from markets in other clusters.

At the wholesale market, the force of infection is assumed to depend only on within-market infection process.

We assume that \( \Gamma_m = \Gamma_{mn} \) and \( \gamma_m / \gamma_m = \gamma_m / \gamma_m \).

Both models were implemented in BERKELEY MADONNA v. 8.4.14 [28].

2.2.3. Outcomes. We calculate the flock reproduction number \( r \), defined as the expected number of secondary cases (market or farm) per single infected case in a fully susceptible population, using the approach advocated by Diekmann & Heesterbeek [29]. The reproduction number assesses the potential for infection to be sustained: if it is greater than 1, the epidemic will almost always spread, whereas if it is less than 1 the infection is more likely to go extinct. We denote \( r^f \) and \( r^m \) to be the flock reproduction number when the market chain has been removed (i.e. markets are no longer infectious), and when the transmission is only mediated by markets (i.e. no farm-to-farm transmission, \( \gamma_f = \Gamma_f = 0 \)), respectively. \( r, r^f \) and \( r^m \) were calculated using R software v. 2.7.1 [30]. A full expression for \( r \) is given in electronic supplementary material, S1.

2.2.4. Parameters. The parameters for the model were derived from the published literature, the grey literature (including for example FAO reports) and from field observations made by the authors. Their assumed values and sources are summarized in table 1. Supplementary information on parameter values are provided in electronic supplementary material, S2. Sensitivity analyses to key parameter assumptions are given in electronic supplementary material, S3.

2.2.5. Scenarios. The flock reproduction number \( r \) is assumed initially to be equal to five. The ratio between \( r^f \) and \( r^m \) is denoted as \( f/m \), such that if \( f/m \) is low, the routes of transmission involving markets are more important than the ones involving only farms (i.e. the main source of infection of farms is markets). By contrast, if \( f/m \) is high, the routes of transmission involving markets are less important than the ones involving only farms (i.e. the main source of infection of farms is other farms).

Three scenarios corresponding to three different values of \( f/m \) are then considered:

- almost all farm outbreaks are owing to market-to-farm transmission (\( f/m = 0.05 \));
— most farm outbreaks are owing to market-to-farm transmission ($J/m = 0.5$); and
— most farm outbreaks are owing to farm-to-farm transmission ($J/m = 2$).

$P^{m}$ is defined as the mean prevalence of infectious birds in market during the open period. For a turn-over period of 1.5 days, $P^{m}$ will depend only on $\beta$ and $\eta$. We define $R^{m}_{0}$ as the corresponding basic reproduction number in the market assuming the same $\beta$ and $\eta$ (i.e. the population size is stable, the infectious period would go to its end, and would not be stopped owing to selling and slaughtering, as defined in §2.1). Three scenarios corresponding to three different values of $P^{m}$ are then considered:

— market 1: $P^{m} = 19.5\%$, $R^{m}_{0} = 16.8$;
— market 2: $P^{m} = 37.8\%$, $R^{m}_{0} = 40$; and
— market 3: $P^{m} = 43.1\%$, $R^{m}_{0} = 80$.

The impact of the following control strategies on $r$ is assessed:

— Early detection of outbreaks in farms and stamping out: an outbreak is detected if the mortality rate exceeds 1 per cent during two successive 24 h periods, 2 days after which birds are culled out, the farm is emptied and the infectious reservoir is assumed to be removed through disinfection and/or isolation.

— Vaccination in farms: 50 per cent of chickens are vaccinated at the start of each cycle [31]. The vaccine is assumed to be fully protective two weeks after vaccination.

— Rest days in LBMs: rest days are synchronized in the wholesale and regional markets. The day before a rest day ($-1 < t < 0$), no birds are introduced into the wholesale market, which is disinfected so that the infectious reservoir, if present, is assumed to be removed. When the regional markets are closed ($t = -0.5$), the remaining birds are slaughtered and the infectious reservoir is assumed to be removed via disinfection. On the rest day ($0 < t < 1$), the regional markets remain empty. Birds are then re-introduced into the wholesale market at $t = 0.5$ and these birds move on to regional markets at $t = 1$.

— LBM closure: the LBM chain is removed from the system and thus transmission occurs only directly between farms.

3. RESULTS

3.1. Within-market model

If the virus is not amplified in the market (i.e. $\beta = 0$ and $\eta = 0$), to reach a prevalence of infectious birds of 19.5 per cent as measured in Hong Kong [14], we require 24.2 per cent of the birds introduced each day to be infected or infectious for a turn-over period $T_{r} = 1.5$ (the time from birds entering to leaving the market). Under such a scenario, the maximum prevalence of symptomatic birds is 10.6 per cent and the cumulative mortality rate reaches 3 per cent during the open period. Thus, in this scenario, we would expect disease to be detectable in the market through screening for clinical signs.

In contrast, if the virus can be amplified in the market, the introduction of a single infected bird followed by the daily introduction of susceptible birds can lead to a prevalence of infectious birds of 19.5 per cent on average during the open period varying from 18.7 to 22 per cent according to the time of day. The prevalence of symptomatic birds throughout the open period however remains lower than 1.8 per cent (figure 3a) and hence HPAI-related mortality is
unlikely to be observed in the market. Thus, in this scenario, transmission in the market is very likely to be silent.

For a prevalence of infectious birds of 19.5 per cent and a turn-over period now increased to 2.5 days, the mean prevalence of infectious birds varies within the same range. The peak prevalence of symptomatic birds in this scenario now reaches 4.8 per cent (figure 3c), and the detection of virus circulation owing to observation of sick birds is thus more likely than for $T_f = 1.5$.

If we instead assume that birds are introduced every 2 days, the dynamics are dramatically modified. On one day out of two, the prevalence of infection varies between 0 and 3.4 per cent for a turnover period $T_f = 1.5$ days, and between 8 and 10.9 per cent for $T_f = 2.5$ days. On this day, the prevalence of symptomatic birds remains equal to zero. On the other day, the prevalence of infectious birds has a peak at 52.3 and 37.9 per cent for $T_f = 1.5$ and 2.5 days, respectively, while the morbidity rate has a peak at 3.5 per cent for $T_f = 1.5$ days, and at 4.9 per cent for $T_f = 2.5$ days (figure 3b,d). Thus, under these scenarios we would expect to observe disease signs if the market is observed sufficiently frequently.

For all four scenarios, the overall mortality rate in the market is low and would not be distinguishable from background rates of non-disease-associated mortality, the cumulative mortality over the open period remaining lower than 0.4 per cent.

3.2. Meta-population model

Figure 4 compares the impact of control strategies applied in farms (stamping out and vaccination) with rest days in LBM’s on the flock reproduction number $r$. For $f/m = 0.05$ (almost all farm outbreaks are owing to market-to-farm transmission) (b,e,h) For $f/m = 0.5$ most farm outbreaks are owing to market-to-farm transmission. (c,f,i) For $f/m = 2$ most farm outbreaks are owing to farm-to-farm transmission. (a,b,c) For market 1, the mean prevalence at the market $P_m$ is 19.5%, and the corresponding basic reproduction number $R_m^0$ assuming the same $\beta$ and $\eta$ is 16.8. (d,e,f) For market 2, $P_m = 37.8\%$ and $R_m^0 = 40$. (g,h,i) For market 3, $P_m = 43.1\%$ and $R_m^0 = 80$. Cull., culling out; vacc., vaccination; 6m, rest days every six months; 1w, rest days once a week; cl, the market chain is closed.
rest days becomes linear and the benefit of more frequent rest days is lost (figure 4c,f,i). As expected, the impact of rest days on the reduction of \( r \) is smaller as \( f/m \) is increased. Although rest days applied every 10 days in LBMs are enough to reduce \( r \) below 1 when \( f/m = 0.05 \), they would need to be implemented in combination with stamping out or vaccination to decrease \( r \) below this threshold when \( f/m = 0.5 \) or 2.

We consider the impact of combined interventions for different epidemiological scenarios. In the first, which we term market 1 we set our model parameters to a market prevalence \( P^m = 19.5\% \) and a corresponding reproduction number in the market of \( R^m_0 = 16.8 \). In this scenario, vaccination plus stamping out will always achieve a reduction of \( r \) under its threshold of 1. This strategy is less efficient as \( f/m \) increases (i.e. the extent of farm-to-farm transmission increases). For scenarios with prevalence of infectious chickens lower than 19.5 per cent, the impact of rest days, stamping out and vaccination, applied alone or in association, shows similar trends as for a prevalence of 19.5 per cent. We then consider two higher prevalence scenarios: market 2, where \( P^m = 37.8\% \) and \( R^m_0 = 40 \) and market 3, where \( P^m = 43.1\% \) and \( R^m_0 = 80 \). In these scenarios, vaccination shows an opposite pattern: it has a greater impact on \( r \) as \( f/m \) increases. Compared with rest days, stamping out plus vaccination is less effective when \( f/m \) is low: for \( f/m = 0.05 \), an equivalent reduction in the reproduction number \( r \) to that achieved by stamping out plus vaccination can be achieved with rest days alone implemented every five and three weeks for market 3 and market 2, respectively. In contrast, if farm-to-farm transmission dominates (\( f/m = 2 \)), then vaccination plus stamping out will be a much more effective policy than frequent rest days or market closure. For all values of \( f/m \) and \( P^m \), monthly rest days implemented in combination with stamping out and vaccination could reduce \( r \) below its threshold of one.

Market closure appears to be only slightly more effective than weekly rest days. Indeed, in all scenarios in which market closure results in \( r \) falling below the threshold value of one, weekly rest days also achieve this reduction. Moreover, as the degree of farm-to-farm transmission (\( f/m \)) increases and the relation between \( r \) and rest day frequency becomes linear, the difference between \( r \) in a system with weekly rest days and \( r \) in a system without markets becomes smaller: for \( f/m = 0.05 \), this difference is equal to 0.31, for \( f/m = 0.5 \) and \( f/m = 2 \), this difference is 0.06 and less than 0.01, respectively.

4. DISCUSSION

Our results show that a high prevalence of infection in LBMs could occur if virus is amplified within the market following the introduction of a single infectious bird. For a short turn-over period, our model predicts that infected birds will be sold and slaughtered before showing disease signs or dying of the infection, regardless of the prevalence level. Thus, there is the potential for the virus to circulate silently within the LBM depending only on the relative balance between the time a bird remains in the market system and the duration of asymptomatic shedding. Furthermore, in such a system, most infectious birds will be slaughtered before dying from the disease, and a high proportion of infected birds will be slaughtered even before becoming infectious. This shortens the average infectious period. To maintain high virus prevalence, a high rate of transmission is thus required, and both the contact rate and the susceptibility of birds must be high. Therefore, cross-immunity, which reduces bird susceptibility and virus shedding, would not necessarily create conditions for HPAI endemicity in LBMs at high prevalence level, contrary to the hypothesis proposed by Seo & Webster [27].

In several surveys in which H5N1 viruses were detected in LBMs, the virus isolation rate was much less than in Hong Kong in 1997 [8,13,18,32]. This may be owing to issues related to sampling and conservation methods, to recent introduction of the virus or to major differences in market structure and functioning. In the model and parameters presented here, the market setting is very favourable for virus amplification: the market is open every day and all day long, bird density is high, new birds are introduced every day and the turn-over period is 1.5 days. This kind of setting might not be encountered frequently in developing countries. Therefore, in less favourable settings, the prevalence of infectious birds could be expected to be lower than that observed in Hong Kong, and sustainability of the virus circulation might even be questionable. Indeed, Egyptian and Vietnamese village markets are only open a few days in a month (Egypt, G. Fournié, 2007; Vietnam, G. Fournié, 2009, personal observation). In Cambodian markets, birds remain just a few hours in, the turn-over period being lower than the latent period [33]. Thus, these LBMs would not be able to sustain the disease, and their level of infection would be the direct result of the introduction of infected birds. The prevalence of infectious birds would therefore be low and a large number of birds would need to be sampled to detect the virus. However, because of environmental contamination, markets may remain infectious for a few days even if infectious birds have spent just a few hours in the market. In this case, sampling of the environment may be more suitable than individual bird sampling. Therefore, further research on the structure and the functioning of LBMs in regions where the disease is endemic is needed. Collecting information on the LBM features we identified and integrating them to this model will help to identify markets and market systems that are likely to sustain silent virus circulation as well as to define appropriate surveillance strategies within these markets.

The results from our meta-population model show that rest days implemented in LBMs can have a strong impact on disease dynamics within the poultry sector. Depending on the characteristics of the system, especially the relative importance of transmission routes involving markets compared with those involving farms only, rest days can be more effective than control strategies applied in farms to reduce disease transmission. Moreover, as rest days will target other transmission routes, their effect acts in synergy with stamping out and vaccination. However, if vaccination
coverage and efficacy is sufficient to interrupt transmission and hence prevent the disease from becoming endemic in markets, this strategy would lead to a drastic reduction in market infectivity. Thus, vaccination could be highly efficient where market-to-farm transmission is high. For scenarios in which most transmission occurs from market-to-farm (low values of \( f/m \)), the impact of rest days on \( r \) is amplified as the time between two successive rest days decreases. In fact, if rest days are implemented sufficiently frequently, virus amplification can be halted in the market before it reaches endemic levels and as a result, the infectivity from the market to other flocks will be drastically reduced.

To date, models aiming at assessing the impact of interventions on HPAI transmission in domestic poultry have focused on farm-to-farm contact patterns. Indeed, these models focused on poultry production systems, which were generally in developed countries including the UK [34–37] and the Netherlands [38], where there is limited live bird trading. Therefore, in these models, strategies applied in farms (early detection and stamping out, vaccination) have a much greater impact on transmission. However, in systems where live bird trading is well developed, this route of transmission needs to be taken into account to avoid overestimating the impact of measures implemented on farms. Moreover, the effectiveness in the field and the cost-effectiveness of these interventions still need to be evaluated. Effectiveness of stamping out to reduce transmission mainly relies on the early report of the disease by farmers. Failing to implement expensive incentive policies leads to late detection of outbreaks and under-reporting, as observed in Egypt [39,40]. In developing countries, optimum vaccination coverage might be difficult to achieve owing to practical and cost-benefit problems [41]. Even if sufficient levels of vaccination are achieved, this can result in decreased clinical signs and longer infectious periods resulting in less intense but prolonged outbreak waves. For scenarios in which most transmission occurs from market-to-farm (low values of \( f/m \)), the impact of rest days on \( r \) is amplified as the time between two successive rest days decreases. In fact, if rest days are implemented sufficiently frequently, virus amplification can be halted in the market before it reaches endemic levels and as a result, the infectivity from the market to other flocks will be drastically reduced.

The Hong Kong market system is unique; it is highly structured and homogeneous, yet most countries where H5N1 is a recurrent problem have a heterogeneous poultry sector and a much more complex market chain. The impact of control strategies implemented in LBMs could thus vary. Moreover, further issues could be encountered when implementing these interventions in the field. The structure of the market itself (e.g. floor type, multiple entries) can make disinfection programmes difficult to implement and the flow of traders difficult to control. The number of LBMs is very large in some countries and it would be unrealistic to attempt rest days and disinfection in all of them. Rather, the most at-risk and suitable markets would need to be identified and these hygienic measures adapted to local contexts. Therefore, including further data on the different market systems in AI-affected countries within model parameters could help to elucidate the potential impact of rest days as well as to define their optimal frequency in terms of their impact on circulating HPAI virus.

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