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Models of highly pathogenic avian influenza epidemics in commercial poultry flocks in Nigeria and Ghana

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Abstract

State-scale and premises-scale gravity models for the spread of highly pathogenic avian influenza (H5N1) in Nigeria and Ghana were used to provide a basis for risk maps for future epidemics and to compare and rank plausible culling and vaccination strategies for control. Maximum likelihood methods were used to fit the models to the 2006–2007 outbreaks. The sensitivity and specificity of the state-scale model-generated probabilities that any given state would be involved in an epidemic were each 57 %. The premises-based model indicated that reactive, countrywide vaccination strategies, in which the order in which flocks are vaccinated was strictly determined by known risk factors for infection, were more effective in reducing the final size of the epidemic and the epidemic impact than vaccinating flocks at random or ring vaccination. The model suggests that an introduction of highly pathogenic avian influenza (H5N1) into Ghana had a high chance (84 %) of causing a major outbreak. That this did not happen was most probably a result of the very swift Ghanaian response to news of the first introductions.

Keywords

Avian influenza; Nigeria; Ghana; Mathematical model; Control

Introduction

We describe two gravity models for the spatial spread of highly pathogenic avian influenza (H5N1) in Nigeria: one for the spread of the infection between the country's 36 states and the Federal Capital Territory, and one for the spatial spread between poultry farms in Ogun. We also use the second model to examine the H5N1 outbreak in Ghana. Our goal is to use the 2006–2007 H5N1 outbreaks to quantify the spatial spread of H5N1 in Nigeria to provide methods for creating risk maps for infection that are sensitive to the date and location of first introduction (Boender et al. 2007) and to better inform future control. This is of relevance to Nigeria where a future H5N1 infection involving 10 % of the commercial birds is estimated to cost about US \$245 million with worse scenarios costing around US \$700 million (Fasina et al. 2008).

Materials and methods

Gravity model of the spread of infection between Nigerian states

The model—The 2006–2007 H5N1 outbreak in Nigeria was reported as the number of outbreaks in each state each month (OIE 2008). This determined the time step (1 month) and the spatial scale (by state) of the gravity model. A metapopulation format represented the spread of H5N1 between states (Matthews et al. 2003) and assumed that aerial spread and the movement of animals and fomites result in what is called “gravity transmission” (Erlander and Stewart 1990). The numbers of birds in each state were found in Adene and Oguntade (2006). The probability of transmission of H5N1 from an infected to an uninfected state was a function of the centroid distance between the patches (determined using *Google Earth* WGS4 data¹) and the number of birds in each state. Specifically, the probability, $P_{jk}(\delta, \rho)$, that the j th state will be infected in the k th month by any infected state i was:

$$P_{jk}(\delta, \rho) = 1 - \prod_{i \in A(k)} \exp \left(-N_i N_j \left(\frac{\delta}{d_{ij}} \right)^\rho \right)$$

where i is an infected state from the set of infected states $A(k)$ during month k of the epidemic, j is a susceptible, uninfected state from the set of susceptible, uninfected states, d_{ij} is the distance (in kilometers) between states i and j , and N_i and N_j are the total numbers of birds in those states (Rorres et al. 2010, 2011). The constants δ and ρ were estimated by fitting the model to the OIE outbreak data: δ is the distance at which the probability is $1-1/e$ (or about 63 %) that one infectious animal will infect one susceptible animal (in another state) in 1 day; ρ determines whether the decay from probability 1 to probability 0 is gradual (small ρ) or step like (large ρ , Rorres et al. 2010).

Monte Carlo methods (Metropolis and Ulam 1949) were used to model the transition of each state from “susceptible” (having no current or previous reports of H5N1 in the state) to “infectious” (having a current report of H5N1—or a previous report within the last 2 months) and finally to “recovered” (the outbreak in that state had been contained). The Nigerian authorities implemented control procedures once an infected farm was detected (Ekong et al. 2007), and states continued to report new cases for an average of 2 months.

Fitting the model—We estimated the values of δ and ρ using a maximum likelihood method to fit the model to the OIE 2006–2007 Nigerian outbreak data on which month any given state reported an outbreak (Rorres et al. 2010—method 1). The number of outbreaks in each state was used later on to assess model validity. We estimated ρ and δ separately for dry and wet seasons (November–March, and April–October, respectively; Williams et al. 2008). We took account of the fact that Nigerian outbreaks of H5N1 in 2006 and 2007 were the result of two (possibly three) separate introductions (Cattoli et al. 2009).

Validity of the between-states gravity model—To evaluate the validity of the fitted model, we replicated the initial conditions of the 2006 H5N1 Nigerian outbreak. The scenario was simulated 10,000 times to estimate the probability that any given state experienced an outbreak. We hypothesized that the probability of a state being involved in an outbreak (estimated from the model) and the severity of the outbreak in that state (measured by the number of affected premises reported each month) should be correlated—the correlation providing a measure of the model validity. The model-generated probabilities

¹http://www.nationsonline.org/oneworld/map/google_map_nigeria.htm

were treated as the outcome of a diagnostic test whose cutoff point had yet to be determined and examined using a receiver operating characteristic (ROC) analysis in which a “severe” state outbreak was defined as involving 10 or more flocks.

Gravity model of transmission between poultry premises in Ogun, Nigeria

The map of poultry premises—Farm locations were not available for Nigeria, but we can draw useful conclusions about disease control even from spatial models using approximate maps (Riley 2010; Tildesley et al. 2010). Therefore, we created synthetic maps of the locations of the larger companies, hatcheries, and smallholder semicommercial premises (sectors 1, 2, and 3, respectively) in Ogun. Ogun experienced a large epidemic in 2007 and had been the subject of poultry surveys that established the proportional distribution of flock sizes (Bamiro et al. 2006) as well as the total number of sector 2 premises (Adene and Oguntade 2006). We estimated the total number of sector 2 and 3 farms in Ogun (714). One thousand synthetic maps were generated. Each map contained farms at the 19 known infected locations, as well as 695 farms randomly located within the state. The 30 sector 2 farms identified by Adene and Oguntade (2006) were assigned the flock sizes recorded by those authors. Following Bamiro et al. (2006), 89 of the remaining farms were assigned 4,000 birds, 253 farms were assigned 2,000 birds, and 342 farms were assigned 500 birds. We assumed that the village or traditional poultry production systems played a negligible role in the transmission of HPAI between the predominant sector 2 and 3 poultry premises in Ogun (Smith and Dunipace 2011). This did not mean that sector 4 flocks do not become infected, merely that the “spillover” infection to these flocks did not influence the rate of transmission between the larger commercial flocks.

The model—The architecture of the between-premises gravity model was identical to the between-state gravity model. The probability of spread was a function of the number of birds in the infected and susceptible premises and the distance between them.

We assumed that the interval between flock infection and infectiousness was 5 days (Rorres et al. 2011) and that quarantine and depopulation (the baseline strategy) occurred on the 15th day following infection (Stegeman et al. 2004). Having obtained the best-fit model, we used the estimated values of δ and p (and their corresponding synthetic maps) to simulate epidemics (1,000 simulations for each map and parameter pair). The map and parameter pair which most closely replicated the attack rate of Trop Anim Health Prod the observed epidemic was selected as the basis for comparing control measures.

Control measures—We evaluated the effect of adding ring culling, ring vaccination, countrywide vaccination, or increased biosecurity to the baseline control strategy. In preemptive ring culling a circular high-risk zone was established around each infected premises on the day of detection. Premises within the high-risk zone were depopulated at a rate of 10 farms each day. If, on a given day, more than one infected premise was detected, premises were depopulated starting with the premises closest to any known infected premises, and proceeding outward. We examined high-risk zone radii of 2, 4, or 6 mi.

In the countrywide vaccination protocols, 80 % of each flock was successfully protected against infection with H5N1, and vaccination began immediately after the first infected flock was detected. The vaccine failure rate mimicked observed vaccine inefficiencies (Kim et al. 2010). Premises were vaccinated in order of decreasing size, or in order of proximity to infected farms, or at random (to mimic regional variations in adherence and vaccine availability). Vaccination ceased when either all the premises in the region had been vaccinated or until 15 days after the last infected flock had been detected. Only 10 premises could be vaccinated each day. Countrywide vaccination has been more usual in Asia and

Africa (Vu 2009; Kim et al. 2010), but we also examined ring vaccination strategies using the same format as for ring culling and a vaccine efficacy of 80 %.

Biosecurity protocols were mimicked by reducing flock size. A biosecurity level of 5 % meant that the effective flock size of flocks with this level of biosecurity was deemed to be 5 % *less* than their *actual* size. We examined four scenarios (Fig. 2). Each scenario was implemented in two ways: first, the larger farms were assumed to have more effective biosecurity measures than the smaller farms (assignment by size), and second, the biosecurity levels were assigned to each farm at random (assignment at random).

Gravity model of transmission between poultry premises in Ghana

In May 2007, Ghana experienced an H5N1 avian influenza outbreak (Akunzule et al. 2009). However, being alerted by the earlier outbreaks in other countries, the Ghanaian authorities implemented surveillance and control measures in a timely and apparently effective manner (Aning et al. 2008). Nigeria is a close neighbor of Ghana, the two countries share the same latitude and a similar climate, and we posited that the parameters δ and ρ estimated for the Nigerian between premises model would generate the kinds of outbreaks Ghana could have experienced had the response to H5N1 been less robust. To test this, we generated a synthetic map for sector 2 and 3 farms in each of the Ghanaian administrative regions (1,371 farms in all—Aning 2006; Anon 2008). We introduced the infection into Accra (Akunzule et al. 2009). Our synthetic map contained 488 sector 2 and 3 farms in Accra. Taking each farm in Accra in turn as the site of first introduction, we carried out 1,000 simulations (488,000 simulations in all) and recorded the attack rate (infected farms expressed as a proportion of all 1,371 farms) for each simulation.

Results

Gravity model of transmission between Nigerian states

State-level risk of involvement in an outbreak—Based upon the best-fit values for the transmission kernel parameters for the dry and wet seasons ($\delta_{\text{dry}} = 3.227 \times 10^{-10}$ km, $\rho_{\text{dry}} = 1.267$; $\delta_{\text{rainy}} = 7.317 \times 10^{-10}$ km, $\rho_{\text{rainy}} = 1.314$), the model-generated probability of any given state becoming involved in an outbreak that began in January as the result of two major introductions, one in Lagos and one in Kaduna, is shown in Table 1. Tables listing the probabilities of a state becoming involved in an outbreak following a single introduction in any given state in any given month can be downloaded from http://www.vet.upenn.edu/docs/SupplementaryMaterial_GarySmith_2011_12.pdf.

The validity of the model—An ROC curve is a graphical plot of the true positive rate (sensitivity) versus the false-positive rate (1–specificity) for an either/or classification system as its discrimination threshold is varied. A true positive occurs when there is a match between a model prediction that a state became involved in the outbreak and an actual report of a severe outbreak in that state. A false-positive occurs when the model prediction is not corroborated by an actual report of a severe outbreak in that state. The discrimination threshold is the value of the model-generated probability above which we decide that a state would be involved in the epidemic. In a completely successful predictive model, the area under the ROC curve would equal to 1. In a model in which the predictions of involvement were no better than tossing a coin, the area under the ROC curve would equal to 0.5. Hosmer and Lemeshow (2000) rate the success of a model in terms of the area TROP ANIM Health Prod under the curve as follows: 0.8 and above = excellent, 0.7–0.79 = good, and <0.7 = unacceptable. The area under the ROC curve in Fig. 1 is 0.79 (just short of “excellent discrimination”). When just the number of birds in each state was used to estimate the probability that a state would become involved in a national outbreak, the area under the

ROC curve (not shown) was 0.68 (“unacceptable”). Treating the model like a diagnostic test with a discrimination threshold of 0.5, the sensitivity and specificity of the model-generated probabilities of involvement are both 57%.

Gravity model of transmission between farms in Ogun, Nigeria

The best fit values of the transmission kernel parameters for the Ogun between premises model were $\delta = 5.8993 \times 10^{-5}$ km and $\rho = 2.0092$. The effectiveness of adding other control strategies to the baseline protocol was evaluated in terms of the likelihood of a major outbreak, the final size of the outbreak, the epidemic impact (number of depopulated premises), and the control effort (the number of premises visited to control the outbreak). In the absence of any additional strategies, the mean final size of the outbreak and the mean epidemic impact were identical (about 101 of 714 premises).

The likelihood of a major outbreak—Transmission being a stochastic process, not all introductions led to major epidemics. Some faded quickly; others resulted in extensive spatial spread and large numbers of infected flocks. With no ring culling, vaccination, or additional biosecurity, 15.4 % of simulations resulted in a major outbreak (Table 2). Adding ring culling or countrywide vaccination strategies to the default strategy reduced the likelihood of a major epidemic. Countrywide vaccination was the most effective strategy in this respect but at the cost of a greater control effort compared with the ring culling protocols (Table 2). Between 90 and 95 % of the premises had to be vaccinated to curtail the epidemic compared with only 17–27 % of the premises that had to be depopulated in a ring culling strategy. The differences between vaccinating and culling would be less given a lower rate of vaccine failure (i.e., <20 %) or if the feasible rate of vaccination was much higher than the feasible rate of preemptive ring culling. Furthermore, these results may not be generalizable to the other states in Nigeria because they depend upon the quantitative characteristics of transmission (i.e., the values of δ and ρ).

Final size of the outbreak and epidemic impact—Table 2 shows the final size of the outbreak and the epidemic impact for each of the control strategies calculated for the simulations that resulted in major outbreaks (>10 infected premises). The epidemic impact was always less for the countrywide vaccination protocols than for the ring culling protocols. The countrywide vaccination strategies where the vaccination sequence is determined by the risk factors for infection (flock size and proximity to an infected flock) were more effective in reducing the final size of the epidemic and the epidemic impact than vaccinating at random (Table 2). Ring vaccination was a generally ineffective strategy given the estimated values of δ and ρ . The infection almost always escaped the ring.

Preemptive ring culling always reduced the final size of the outbreak but increased the epidemic impact. Furthermore, the epidemic impact changed in a complicated manner as the radius of the high-risk zone was increased. This result has been noted by others (e.g., Tildesley et al. 2011) and serves to emphasize that there is no straightforward way of deciding in advance on an optimum preemptive ring culling strategy. For example, in our simulations of major outbreaks in Ogun, culling within a 4-mi radius high-risk zone resulted in the lowest attack rate (number of infected farms, 39.37 farms), but the epidemic impact (the total number of farms culled, 119.28 farms) was greater than resulted from the less onerous default strategy (100.97 farms, Table 2). If the focus was on reducing the risk of a major outbreak, or reducing the likelihood of human infection with HPAI (H1N1), then the preemptive ring culling strategy would be preferred. On the other hand, if the goal was to minimize the epidemic impact as well as the number of uninfected farms culled, then, in this specific case, the default strategy would be preferred. However, it should be emphasized that this outcome could not have been predicted in advance. Given different values for the

transmission kernel parameters δ and ρ , quite different results could have been obtained (e.g., Tildesley et al. 2011).

The effect of increasing levels of biosecurity on the epidemic impact of major epidemics is shown in Fig. 2. The figure shows that it is better to preferentially increase the biosecurity of the large flocks (solid line in Fig. 2) than to attempt to generally increase the overall biosecurity of all flocks without regard to flock size (dashed line in Fig. 2). The greatest disparity between biosecurity levels was in scenario 1 (5 to 75 %), the least was in scenario 4 (5 to 20 %). In Fig. 2, these disparities are reflected in the different epidemic impacts resulting from a biosecurity policy that focuses on the largest flocks or from a more general policy of trying to increase biosecurity overall.

Gravity model of transmission between farms in Ghana

A large majority (84 %) of all simulations seeded in Accra resulted in a major outbreak (Fig. 3). The mean proportion of premises infected during major outbreaks was 0.52 (range 0.47–0.56). These results represent what was likely to have happened had the Ghana authorities not been able to act as promptly as they did to control the outbreak. Given that our model suggests that there was a very high probability of major outbreak in Ghana, it seems likely that the smaller outbreak that actually happened was most probably a result of the very swift Ghanaian response to news of the first introductions.

Discussion

The between state model provides a means of estimating the probability that states would become involved in a future outbreak, given that the season and location of the introductions were known. The model predicted whether a state would experience a severe outbreak with a sensitivity and specificity of both 57%. One limitation of the between-state model is that the model parameters reflect the effects of the control strategies implemented by the Nigerian authorities and producers during the 2006–2007 outbreaks. This means that the model will be useful in creating risk maps for the occurrence of future outbreaks of H5N1 in Nigeria only if the efficacy of the control strategies for preventing long-distance transmission in future outbreaks remains as it was in 2006–2007.

The between premises model was used to evaluate control strategies. The results of adding ring culling or countrywide vaccination to the baseline culling strategy were similar to those reported in models of foot-and-mouth disease (Tildesley et al. 2006, 2011). Reactive countrywide vaccination strategies where the order in which premises are vaccinated is determined by known risk factors for infection (in our case, flock size and proximity to an infected flock) are more effective in reducing the final size of the epidemic and the epidemic impact than vaccinating at random.

All of the additional strategies examined (except ring vaccination) reduced the probability of a major outbreak, but always at some cost. Preemptive ring culling, which works by removing undetected infectious flocks and reducing the density of susceptible flocks nearest to known infected flocks, reduced the probability of a major outbreak by half but by depopulating many more flocks than were actually infected. Reactive countrywide vaccination had the most effect on the probability of a major outbreak, but at very considerable cost in terms of control effort. Almost all the flocks had to be vaccinated to achieve this result. Because we assumed that resources were sufficient to vaccinate or depopulate only 10 flocks each day, it is clear that all the ring culling strategies terminated major epidemics much faster than any of the reactive vaccination strategies.

Finally, in the between premises model for Ghana, 84 % of all simulations resulted in a major outbreak. This was not what actually happened, and it seems reasonable to conclude that the early implementation of control was crucial to the Ghanaian success.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

The area under the ROC curve (0.79) is a direct measure of the validity of the model in terms of its ability to discriminate between the states that will become involved in a national epidemic and those that will not as measured by an ROC curve

Fig. 2.

The effect of increasing levels of biosecurity on the epidemic impact (number of flocks culled) of major epidemics. In the assignment-by-size implementation (*solid line*), the larger farms were assigned the highest levels of biosecurity. In the assignment-at-random implementation (*dashed line*), the biosecurity levels in each scenario were assigned to farms randomly irrespective of their size (scenario 1—5, 20, 50, and 75 %; scenario 2—0, 5, 25, and 50 %; scenario 3—10, 20, 30, and 40 %; scenario 4—5, 10, 15, and 20 %)

Fig. 3.

Simulations for Accra in Ghana have been ordered according to the proportion of farms infected in each simulation (the attack rate). Eighty-four percent of all simulations resulted in a major outbreak (the mean proportion of premises infected during major outbreaks was 0.52, range 0.47–0.56)

Table 1

The model-generated probability that any given Nigerian state will become involved in a national outbreak

State	State(s) into which H5N1 was introduced		
	Kaduna	Lagos	Kaduna+Lagos
Abia	0.23	0.24	0.36 (0.35–0.37)
Adamawa	0.37	0.39	0.57 (0.56–0.58)
Akwa_Ibom	0.27	0.29	0.44 (0.43–0.45)
Anambra	0.35	0.38	0.55 (0.54–0.56)
Bauchi	0.45	0.41	0.65 (0.64–0.66)
Bayelsa	0.11	0.12	0.18 (0.18–0.19)
Benue	0.40	0.40	0.61 (0.60–0.62)
Borno	0.25	0.22	0.37 (0.36–0.38)
Cross_River	0.18	0.20	0.29 (0.28–0.30)
Delta	0.25	0.28	0.42 (0.41–0.43)
Ebonyi	0.39	0.41	0.61 (0.60–0.62)
Edo	0.16	0.18	0.27 (0.27–0.28)
Ekiti	0.29	0.34	0.48 (0.47–0.49)
Enugu	0.35	0.37	0.55 (0.54–0.56)
FCT(Abuja)	0.33	0.33	0.50 (0.49–0.51)
Gombe	0.07	0.06	0.10 (0.09–0.10)
Imo	0.41	0.45	0.65 (0.64–0.66)
Jigawa	0.35	0.31	0.50 (0.49–0.51)
Kaduna	1.00	0.25	1.00
Kano	0.34	0.30	0.48 (0.47–0.49)
Katsina	0.32	0.29	0.48 (0.47–0.48)
Kebbi	0.32	0.32	0.50 (0.49–0.50)
Kogi	0.33	0.34	0.51 (0.50–0.52)
Kwara	0.25	0.29	0.42 (0.41–0.43)
Lagos	0.26	1.00	1.00
Nasarawa	0.09	0.08	0.13 (0.12–0.14)
Niger	0.24	0.24	0.39 (0.38–0.39)
Ogun	0.27	0.50	0.58 (0.57–0.59)
Ondo	0.30	0.36	0.50 (0.49–0.51)
Osun	0.29	0.38	0.52 (0.51–0.53)
Oyo	0.25	0.33	0.45 (0.44–0.46)
Plateau	0.32	0.30	0.48 (0.47–0.49)
Rivers	0.32	0.35	0.51 (0.50–0.52)
Sokoto	0.11	0.10	0.16 (0.15–0.17)
Taraba	0.21	0.19	0.30 (0.29–0.31)
Yobe	0.23	0.20	0.33 (0.32–0.33)
Zamfara	0.32	0.31	0.48 (0.47–0.49)

The table compares the probabilities of involvement following a single introduction in Kaduna (second column), a single introduction in Lagos (third column), and a simultaneous introduction in both states (fourth column, with 95 % confidence limits). All introductions are assumed to have occurred in January. The 2006–2007 Nigerian outbreak is believed to have resulted from two introductions in January into Kaduna and Lagos

Table 2

The effect of adding ring culling strategies or general vaccination protocols to the default control strategy (movement ban and depopulation of detected infected farms)

Strategy	Epidemic final size	Epidemic impact	Mean number of uninfected premises depopulated	Mean number of undetected infected premises depopulated	Mean number of premises vaccinated	Percent of severe outbreaks
Default	100.97	100.97	0	0	0	15.4
Ring cull						
2-mi radius	91.58	163.50	71.92	27.38	0	5.2
4-mi radius	39.37	119.28	79.91	17.91	0	8.6
6-mi radius	43.35	194.70	151.35	22.98	0	8.0
Ring vaccination						
2-mi radius	101.08	101.08	0	0	84.25	15.2
4-mi radius	101.35	101.35	0	0	29.30	14.2
6-mi radius	96.25	96.25	0	0	309.49	13.8
Vaccination by size	42.50	42.50	0	0	691.00	0.4
Vaccination by proximity	50.10	50.10	0	0	686.85	4.0
Vaccination at random	84.00	84.00	0	0	655.50	0.4

The depopulation and vaccination results were averaged over only those simulations that resulted in a major outbreak among the 714 at risk premises in Ogun state. Epidemic final size is the total number of predicted infected premises in Ogun state, and epidemic impact is the predicted number of premises that were depopulated during the course of the epidemic