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Modeling the Effects of Avian Flu (H5N1) Vaccination Strategies on Poultry

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Abstract: The work in this article addresses a problem posed by Dr. Maria Salvato to the CODEE community. The task was to model costs associated with varying vaccination strategies for the Avian Flu virus (H5N1) on chicken populations. The vaccination strategies proposed included vaccination varying proportions of the flock with live virus vaccine, dead virus vaccine, and no vaccination. This article encompasses the construction of a model for the problem using a modification to the SIER model and the subsequent analysis of that model. The analysis of the model revealed the most cost effective vaccination strategy to be vaccination of half the flock with dead virus vaccine.

1 Introduction

In the past month, March–April 2013, outbreaks of avian flu (H5N1) in humans have been reported in China, Egypt, Cambodia, Bhutan, Indonesia, Israel, Myanmar, Bangladesh, Vietnam, and India1. H5N1 virus has infected over 500 million poultry since 1997 leading to their obligatory extermination [9].

Despite the widespread awareness and impact of the virus, epidemiological models of the disease are lacking both due to scarce experimental data to support parameters and the difficulty in development of a conclusive model. One recent model that collected data on chickens vaccinated with a dead vaccine used a Susceptible-Infected-Recovered (SIR) based approach, which we shall similarly implement in our study [3].

There are two primary ways to vaccinate chickens against avian flu: 1) Using vaccinations comprised of dead virus particles that constitute a sufficient library to develop complete resistance to the infectious form of the virus, or 2) through exposure to a weakened but live sample of virus that is less harmful and will build some resistance so that when exposed to the virulent strain, the infection and death rate is less severe. The

cost and time required to manufacture dead H5N1 vaccines is greater than the cost for producing live-attenuated forms, making them expensive for use in developing countries.

Viral vaccines for poultry are commonly produced from eggs. It has been estimated that, since the ratio of virus produced per egg is the limiting cost in the production of dead vaccines [2] and production of live vaccines has been accelerated by a magnitude of over 10,000 for H1N1 vaccine production in eggs [5], the production of live attenuated vaccines can be estimated to cost 1/10,000th of that of dead vaccines. This makes the cost of producing a live attenuated vaccine nearly negligible. It was suspected that we would find that the cost of a treatment strategy for a flock of chickens would be lower with the live attenuated vaccine.

Through simulation with our modified SIR model we found that the most cost effective prevention strategy for a flock of 10,000 broiler chickens was, surprisingly, the use of dead vaccine on half of the chicken population. This was due to the high cost of higher death rates to the disparity in resistance from the different vaccine strategies and the fact that the majority of the cost of vaccination is, in fact, due to transport, labor, and other costs beyond production.

2 The Standard Incidence Model

The Standard Incidence Model is a basic form of horizontal incidence used in the classic SIR problem [7].

\[
\begin{align*}
S & \xrightarrow{\beta SI} I \\
I & \xrightarrow{\gamma I} R
\end{align*}
\]

In this model we let \( N \) be the total population size, which is fixed for all time (in our case we let \( N = 10,000 \) chickens). We define \( S(t) \) as the number of susceptible individuals at time \( t \), and further let \( s(t) = S(t)/N \), so \( s(t) \) is the susceptible fraction. Similarly, \( I(t) \) is the number of infected chickens at time \( t \) and \( i(t) = I(t)/N \) is the infectious fraction.

We now let \( \beta \) be the average number of contacts sufficient for transmission with units of chickens/(unit time). If we say that \( \beta I(t)/N = \beta i(t) \) is the average number of contacts with infectives of a susceptible per unit time, then we can let \( \beta IS/N = \beta N i(t) s(t) \) be the number of new cases per unit time due to the number of susceptibles.

Lastly, we let \( R(t) \) be the number of chickens in the Recovered/Removed compartment of our model at time \( t \). It is typical to make further assumptions to determine the movement from the I to R compartment with a term like \( \gamma I \) in an ordinary differential equation model. It has been shown [6] that these terms correspond to exponentially distributed wait times in each of the compartments, with recovery rate \( \gamma I \) (corresponding to \( P(t) = e^{-\gamma t} \)) being the fraction of infected chickens remaining after \( t \) amount of time has passed since they became infected. This makes \( 1/\gamma \) the mean infection period (from the definition of an exponential distribution).
Our model has been adapted from this basic model to best incorporate the experimental data available and to provide analysis that better helps solve the optimization problem of vaccination.

3 Adaptation of the Standard Incidence Model

Adapting the general SIR model to better fit the case of the Avian Flu, we added a fourth compartment to our model, D(t), that contains those chickens that die due to infection. Separating the recovered chickens from the dead allowed us to better assess the success of different vaccination programs.

Second, when a susceptible bird comes into contact with an infected and receives the virus, it first becomes “exposed,” before becoming infected. Chickens in this stage are undergoing virus replication, in what is known as the incubation or latent period. These birds have the virus, but are not, yet, showing signs of the disease nor are they contagious. Once the virus has replicated to a sufficient level, the birds move to the infected compartment where they too can spread the virus. Since the latent period of the disease in chickens is roughly the same length of time as the period of infectiousness it must be accounted for. So we add a fifth compartment, E(t), for exposed chickens who are not yet infectious.

In this model, the definition of our $\beta$ parameter is the same. We added two additional parameters and similarly adjusted $\gamma$. First, we let $1/\epsilon$ be the average latent period, so that chickens move from the E to I compartment at a rate of $\epsilon E$. Next, once chickens are infected, we assume that they live in this state for a number of days based upon experimental data for the infectious period and then will either recover with probability $P(\text{recover})$, or die with probability $1 - P(\text{recover})$. Therefore, we let $\mu$ be the rate at which chickens die, which is equal to $(1 - P(\text{recover}))$ divided by the average length of infection. Similarly, we let $\gamma$ be the rate at which chickens recover, where $\gamma$ equals $P(\text{recover})$ divided by...

\textsuperscript{2}\url{http://www.oie.int/fileadmin/Home/fr/Health_standards/tahm/2.03.04_AI.pdf}
by the average length of infection. We can therefore establish the following dynamics:

\[
\begin{align*}
\frac{dS}{dt} &= -\beta IS/N \\
\frac{dE}{dt} &= \beta SI/N - \varepsilon E \\
\frac{dI}{dt} &= \varepsilon E - \mu I - \gamma I \\
\frac{dR}{dt} &= \gamma I \\
\frac{dD}{dt} &= \mu I
\end{align*}
\] (3.1a)

(3.1b)

(3.1c)

(3.1d)

(3.1e)

Since exposing chickens to live vaccines does not prevent them from becoming infected with the virulent strain, but rather lessens the intensity of infection (and in this way the value of the model parameters change), this SEIRD model is representative of both the unvaccinated and live attenuated vaccination cases we want to explore.

4 Incorporating the Dead Virus Vaccine

The previous model works well for estimating the effect of using live attenuated vaccines or simply leaving an entire flock unvaccinated. If dead virus vaccines were used within the flock, the chickens receiving the vaccine would become immune to the virulent strain of flu, moving them directly from the S to R category before an outbreak even occurs. We can choose and optimize the proportion of the flock to vaccinate, \( \rho \), leaving the unvaccinated birds as the new initial susceptible number to pass through the previous model, \( S_1 \). It is costly to vaccinate every bird and also unnecessary. Herd immunity occurs when enough of a population is vaccinated to stop the spread of disease by reducing the number of potential infectious carriers to a proportionally inconsequential number. Often, if only 80–90% of a population is immunized, the disease is halted despite the remaining susceptible individuals.
By adjusting our SEIRD model above to include direct passage from S to R compartments via dead virus vaccination prior to outbreak, we can adjust and optimize $\rho$ in order to identify herd immunity levels and seek cost optimal solutions. Since the unvaccinated birds are the only ones that will pass through the exposed, infected, and dead classes, we use the same dynamic equations and parameters as in the unvaccinated case, but start with different initial susceptible levels.

### 5 Determining Parameters

Three previous research studies had experimentally identified each of parameters we were seeking in our model using similar methods so that they could be compared \([3, 10, 11]\). These methods involved exposing over 10 chickens to different treatment conditions and housing them pair-wise in exposed cages, with each treatment group in different rooms.

In a study by van Boven et al, 8 experiments consisting of 11 trials each were carried out. In each trial an inoculated bird was placed in a cage with an uninfected contact bird, and the transmission chain was monitored daily by virus isolation performed on swabs taken from the trachea and cloaca \([3]\). Two experiments involved flocks of 22 unvaccinated chickens housed in paired cages, and the remaining 6 experiments used chickens given dead virus vaccinations. In this way, the experimenters were able to conclude that all unvaccinated birds who became infected died after an average of 2 days, and prior to death experienced a one day latent period. Additionally, they calculated that $\beta$ in this setting is 0.8. Furthermore, this research concluded that no transmission occurred among chickens vaccinated with dead virus vaccines.

Next, an experiment was designed by de Jong et al to determine the inoculation dose for live attenuated vaccination with H5N1 that involved vaccination of 4 groups of 22 chickens each with varying concentrations of viral particles in order to determine the lowest $\beta$ parameter achievable \([11]\). This was determined to be 0.9. We averaged survival data for the vaccination strategies closest to the lowest beta value in order to assume that 3 out of every 10 chickens die due to infection, and recorded that the latent period in this case doubled.

Multiple live attenuated vaccines have been suggested since the de Jong paper in 2011.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Vaccination</th>
<th>Live Attenuated Vaccine</th>
<th>Dead Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$</td>
<td>.8</td>
<td>.9</td>
<td>.8</td>
</tr>
<tr>
<td>Av. Latent Period</td>
<td>.25 days</td>
<td>.5 days</td>
<td>.25 days</td>
</tr>
<tr>
<td>Av. Infectious Period</td>
<td>2 days</td>
<td>2 days</td>
<td>2 days</td>
</tr>
<tr>
<td>Survival Rate</td>
<td>100%</td>
<td>30%</td>
<td>100%</td>
</tr>
<tr>
<td>Death Rate</td>
<td>.0%</td>
<td>.3 (1/2)</td>
<td>.7 (1/2)</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>1/1</td>
<td>1/2</td>
<td>1/1</td>
</tr>
<tr>
<td>$\mu$</td>
<td>1 (1/2)</td>
<td>.3 (1/2)</td>
<td>.7 (1/2)</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0</td>
<td>.7 (1/2)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1: Relevant parameters for our model. The first and last columns of values are from \([3]\). The middle column uses parameters from \([10, 11]\).
The paper we chose to base our assumptions/estimations of live attenuated virus parameters upon was a more recent paper which showed that H1N1 and H2N1 live attenuated virus can be used to vaccinate against H5N1 [10], but only with partial heterologous protection. Unvaccinated chickens that were exposed to H5N1 virus showed signs of disease in half the time it took for chickens that had been vaccinated with the live-attenuated virus. Consequently, we chose a latent period ($\beta$) that is twice as long for the live-attenuated vaccinated chickens as for the unvaccinated chickens. Identical to the de Jong paper, this vaccination strategy showed a 7/10 survival after exposure to H5N1 contacts and the chickens showed no signs of clinical disease due to the H1N1 or H2N1 viruses and shed no viral particles associated with H1N1 or H2N1 [11].

6 Survival Results

Using Mathematica to solve the system of differential equations and the parameters discussed above and values $S(0) = 9990$, $E(0) = 10$, and $I(0) = D(0) = R(0) = 0$, (corresponding to an initial population of 10,000 chickens with 10 newly infected individuals) we were able to generate the following results.

We saw that when our flock is left unvaccinated, the highest rate of death corresponds with the peak in infectious chickens (Figure 1). Eventually, the number of exposed and infected chickens decreases as the disease runs its course and more chickens die. As infected and exposed categories go to zero, we see that we are left with approximately 35% of our flock never exposed to the disease and 65% dead due to infection.

Figure 1: Equilibria for dead and surviving birds across one year post initial outbreak
When we simulated vaccinating the flock with live attenuated virus, we find that only 22% of the flock dies (Figure 2). We are left with 78% of the flock surviving at the end of the epidemic, 51% of which became infected but recovered, and 27% which escaped exposure entirely. Thus, by using live attenuated vaccination methods, the physical loss within the flock is about one-third of the physical loss experienced when the flock is left unvaccinated. When we examined the effects of the dead vaccine, we varied the proportion that we initially vaccinated, \( \rho \), giving us differing initial values of \( S \) when an outbreak occurs. For example if we first vaccinate 50% of our flock of 10,000 as a preventative measure, then these 5,000 vaccinated birds are moved directly to the recovered compartment. Thus, in the event that the flock is exposed to the virulent H5N1 virus, \( S \) within our SEIRD model is now 5,000, less the number of chickens that initially contract the virus. Given smaller initial susceptible populations after some proportion is removed through vaccination, the death rate among the unvaccinated significantly decreases. The corresponding losses for each vaccinated proportion are discussed in the next section.

### 7 Cost Analysis and Conclusions

Direct costs of vaccination of poultry have been accounted for in previous studies. The average cost of a broiler chicken was taken to be 1.98858USD \([1]\). The fact that 3.8% annual mortality is expected in broiler chicken flocks was also accounted for within the surviving...
The cost of dead vaccine per chicken has been reported to be 0.10 USD for transportation, supplies, and personnel, and 0.04 USD for the cost of the vaccine, totaling to 0.14 USD. The cost of the live attenuated vaccine was considered to be negligible compared to the dead vaccine and so the total cost per chicken for live attenuated vaccine was assumed to be 0.10 USD for similar transportation and personnel reasons.

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Chicken deaths (natural+flu)</th>
<th>Price per chicken (USD)</th>
<th>Vaccinations provided</th>
<th>Price per vaccination (USD)</th>
<th>Total cost (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Vaccination</td>
<td>6564</td>
<td>1.98888</td>
<td>0</td>
<td>0</td>
<td>13053</td>
</tr>
<tr>
<td>100% live vac.</td>
<td>2495</td>
<td>1.98888</td>
<td>10000</td>
<td>0.1</td>
<td>5962</td>
</tr>
<tr>
<td>100% dead vac.</td>
<td>380</td>
<td>1.98888</td>
<td>10000</td>
<td>0.14</td>
<td>2156</td>
</tr>
<tr>
<td>80% dead vac.</td>
<td>381</td>
<td>1.98888</td>
<td>8000</td>
<td>0.14</td>
<td>1877</td>
</tr>
<tr>
<td>70% dead vac.</td>
<td>383</td>
<td>1.98888</td>
<td>7000</td>
<td>0.14</td>
<td>1741</td>
</tr>
<tr>
<td>60% dead vac.</td>
<td>387</td>
<td>1.98888</td>
<td>6000</td>
<td>0.14</td>
<td>1609</td>
</tr>
<tr>
<td>50% dead vac.</td>
<td>399</td>
<td>1.98888</td>
<td>6000</td>
<td>0.14</td>
<td>1493</td>
</tr>
<tr>
<td>40% dead vac.</td>
<td>490</td>
<td>1.98888</td>
<td>4000</td>
<td>0.14</td>
<td>1304</td>
</tr>
<tr>
<td>35% dead vac.</td>
<td>989</td>
<td>1.98888</td>
<td>3800</td>
<td>0.14</td>
<td>2416</td>
</tr>
</tbody>
</table>

Figure 3: Direct and predicted costs associated with preventative care strategies for H5N1 in a population of 10,000 chickens

We saw that both vaccination strategies are less expensive than no vaccination due to the cost of the majority of the unvaccinated flock dying due to outbreak (Figure 3). We saw the total costs of live vaccination of the entire population to be less than half of that without vaccination. Surprisingly, the dead vaccine, which is more expensive to produce, was roughly three times more cost effective than the live vaccine due to its superior efficacy in saving chicken lives (a major expense).

Varying distribution proportions of the dead vaccine, we saw that the range of 40–60% vaccination lead to a sufficiently small susceptible population so that few of the chickens died since the initial infection could not spread far due to a low number of potential disease carriers. We also saw that herd immunity was reached at roughly 80% vaccination of the whole chicken population with dead virus, at which point it was predicted that no chickens beyond the initial infection were to become infected. This value for herd immunity was in perfect agreement with the experimental outbreak performed by Bauma et al. These findings indicate that there may be an optimal economic vaccination window below 80%, which also attenuates spread of the disease and possibility of human infection.
Our model first serves to describe those parameters that most affect the prevention and transmission of Avian Flu. Simultaneously, our model allows for some recommendation as to current practice, but with severe hesitation due to the limitations of the model. Our model looks at isolated flocks and an unchanging virus, but one of the greatest threats of the Avian flu is its ability to mutate and defy vaccination attempts. A recent study examined the evolution within clades of H1N1, and suggested that rates of virus evolution increase in populations with higher vaccination rates [4]. A further model that would help to inform the application of our flock-based model would be one that looks at the effect of vaccinating portions of the country and incorporates the mutating nature of the disease.

8 Acknowledgment

This article is dedicated to the memory of Professor Robert Borrelli, who passed away on September 11, 2013. Professor Borrelli was enthusiastic from the start about the project that led to this article. He was instrumental in ensuring that the bird flu epidemiological questions be submitted to CODEE. He was also encouraging of the students from a Mathematical Modeling course at Pomona College taking on the challenge. Although he did not get to see the final article, he was aware that the modeling team had successfully addressed the problem.

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