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Vaccination of poultry against avian influenza: epidemiological rules of thumb and experimental quantification of the effectiveness of vaccination

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Abstract

In The Netherlands a large outbreak of highly pathogenic avian influenza in poultry occurred in 2003. The outbreak has had devastating consequences, from both economic and animal-health perspective. Vaccination of poultry offers a potentially attractive measure to control and prevent outbreaks of highly pathogenic avian influenza. In this paper we discuss, from an epidemiological perspective, the values and limitations of vaccination as a control measure during an outbreak and as a preventive measure in an area at risk. In particular, we will discuss (*i*) the epidemiological prerequisites that have to be met for a vaccine and vaccination campaign to be effective, and (*ii*) experimental data that have helped quantifying the effect of vaccination on the reduction of transmission levels. We also discuss (*iii*) how the theoretical insights and experimental results have assisted the Dutch authorities to decide on whether or not to implement vaccination as a control measure.
Keywords: outbreak; control; herd immunity; epidemic model; statistical analysis

Introduction

Low-pathogenicity avian influenza A (LPAI) viruses in poultry of the H5 and H7 subtypes are noted for their ability to transform into highly pathogenic counterparts (HPAI). Outbreaks of HPAI virus in poultry usually result in considerable damage, from both an economic and an animal-health perspective. At least 20 outbreaks of avian influenza have been recorded in poultry since 1959 (Alexander 2000; Alexander et al. 2000).

In this paper we will discuss the value of vaccination as a control measure during an outbreak and as a preventive measure in an area at risk. In particular, in the next section (*Characteristics of an effective vaccination campaign*) we will discuss the conditions that have to be met in order for a vaccination campaign to reduce transmission levels to such an extent that it can halt or prevent epidemic outbreaks of HPAI. In the following section (*Experimental quantification of transmission*) we will

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then examine the experimental evidence that has accumulated to quantify the effect of vaccination of the transmission dynamics of HPAI virus. In particular, we will show how the so-called basic reproduction number can be quantified to judge the effectiveness of a vaccine and vaccination campaign. Finally, in the last section (*Recommendations given during the Dutch outbreak*) we will indicate how the theoretical rules of thumb and experimental data may have helped policymakers to decide on whether or not to implement vaccination as a control measure.

Characteristics of an effective vaccination campaign

At first sight, vaccination seems an attractive option to prevent or control outbreaks of HPAI in poultry. Indeed, if a vaccine were available that could provide immediate and complete protection against infection, and if such a vaccine could be quickly administered to all animals in a certain area, a developing epidemic could certainly be halted by vaccination. It is, however, unlikely that a perfect vaccine will be available in the near future. Furthermore, there are considerable practical difficulties that need to be overcome before vaccination becomes a viable option (How can millions of animals be vaccinated in a fairly short time span? Which components should be included in the vaccine?).

In the next subsections we will lay bare, in the idealized context of a large unstructured population of hosts, what a vaccine and vaccination campaign should be able to achieve in order to control or prevent outbreaks of HPAI virus.

The reproduction number

Vaccination of poultry against infection with HPAI virus can have a number of objectives: (*i*) to reduce morbidity and/or mortality after infection with HPAI virus; (*ii*) to reduce transmission of HPAI virus within and between farms; and (*iii*) to reduce transmission within and between farms to an extent that it is sufficient to halt an epidemic.

From an epidemiological point of view, objective (*i*) has little value as it may do nothing to prevent the continuing spread of the virus from animal to animal, and from farm to farm. Objective (*ii*) may have some merits from an epidemiological perspective, as it may slow down the spread of the virus and may ultimately result in fewer animals and farms being affected. However, objective (*ii*) by no means guarantees that a vaccination campaign can prevent or effectively contain a major outbreak of HPAI virus. To prevent a large outbreak of HPAI or to fight off an outbreak once it has started, it is necessary to reduce transmission to such a level that, on average, each infected animal (or farm) infects less than *1* other animal (or farm). This quantity is commonly referred to as the (basic) reproduction number, or *R*.

Let us consider a simple model that contains several important features of HPAI-virus transmission in poultry. In the following we denote by g_1 and g_2 the susceptibility to infection of animals that are vaccinated and unvaccinated, respectively. Likewise, we denote by f_1 and f_2 the infectiousness of infected animals that are vaccinated and unvaccinated, respectively. Furthermore, we denote the relative frequency of infected vaccinated and unvaccinated animals by I_1 and I_2, respectively. Using the above notation the rates at which vaccinated animals are infected by vaccinated and unvaccinated animals are given by $g_1 f_1 I_1$ and $g_1 f_2 I_2$, respectively. Likewise, the rates at which unvaccinated animals are infected by vaccinated and unvaccinated animals are given by $g_2 f_1 I_1$ and $g_2 f_2 I_2$, respectively.

Finally, we denote by ρ_1 and ρ_2 the rates at which vaccinated and unvaccinated animals recover from the infection, and by μ_1 and μ_2 the rates at which animals die from the infection, respectively.

It is now standard practice to derive the reproduction number from the above model formulation (e.g. Diekmann and Heesterbeek 2000). The reproduction number R can be expressed in terms of the parameters as follows:

$$R = \frac{f_1 g_1}{\rho_1 + \mu_1} p + \frac{f_2 g_2}{\rho_2 + \mu_2}(1 - p)$$
$$= R_{vac} p + R_{unvac}(1 - p) , \quad (1)$$

where p denotes the fraction of the population that is vaccinated, $R_{unvac} = \frac{f_2 g_2}{\rho_2 + \mu_2}$ denotes the reproduction number in a population of susceptible animals, and $R_{vac} = \frac{f_1 g_1}{\rho_1 + \mu_1}$ represents the reproduction number in a population that consists entirely of vaccinated animals.

Minor versus major outbreaks

The reproduction number can be used to estimate the probability that an outbreak starting with one or a few infected animals will not by chance come to a standstill (a *minor outbreak*). In fact, under certain assumptions (Diekmann and Heesterbeek 2000), the probability f of a so-called *major outbreak* that affects a non-negligible fraction of the animals can be determined from the equation

$$1 - f = e^{-Rf} . \quad (2)$$

There is considerable scope for extension of the above result, but we will not dwell on this issue here.

Herd immunity and the critical vaccination effort

The fundamental property of a successful vaccination campaign is that it should provide *herd immunity* (Anderson and May 1991). The concept of herd immunity implies that vaccination does not only have a direct protective effect for those animals that are vaccinated, but also decreases the probability of infection for animals that are not vaccinated. In fact, in a population with herd immunity the transmission opportunities are decreased to such an extent that no long-lasting infection chain can be sustained.

For the model introduced above, the *critical vaccination fraction* at which herd immunity is achieved is found by putting $R=1$ in Equation (1), and solving the equation for $p=p_c$. The critical vaccination fraction is given by

$$p_c = \frac{1 - R_{unvac}}{R_{vac} - R_{unvac}} . \quad (3)$$

Notice that eradication of the pathogen is not possible whenever $R_{vac}>1$, i.e. when vaccination does not prevent the continued spread of the virus amongst vaccinated animals (of course assuming $R_{unvac}>R_{vac}$). In case that vaccination completely blocks transmission to or from vaccinated animals $R_{vac}=0$, and Equation (3) reduces to the familiar $p_c = 1 - \frac{1}{R_{unvac}}$ (Anderson and May 1991).

Experimental quantification of transmission

How can the above theoretical quantities be quantified, and how can the results be applied to real-world situations? Typically, it will be very difficult to obtain reliable indicators of pathogen and vaccine characteristics during the course of an outbreak, and one has to resort to *transmission experiments* to quantify the characteristics of certain pathogen–vaccine combinations (infectious period, virulence, infectiousness) (see De Jong and Kimman (1994) for an early application of these methods). In a transmission experiment a number of animals that are inoculated with the virus are put into a stable with a number of susceptible contact animals. The ensuing infection chain is monitored on a regular basis by taking swabs from the cloaca and trachea that are subject to virus-isolation techniques and PCR, and by collecting blood samples to determine antibody titres.

For practical reasons, the number of animals used in a transmission study is usually rather small (in the order of 10 to 20). Therefore the above theoretical results for large populations need to be adapted to small population sizes where several chance effects play an important role. In the next two subsections we will therefore shortly introduce the methods on which the statistical analysis of the experimental epidemics is based. The account in the next two subsections is based largely on the paper by Van der Goot et al. (2003a). In the last subsection we will give an overview of the experiments that have been carried out (see Van der Goot et al. 2003a; 2003b; in prep.-b; in prep.-a, for details).

Final size analysis

In first instance, the analysis of the experiments is based on the final size of the experiments, i.e. the number of contact animals that have been infected when the infection chain has ended. The final sizes are used to obtain estimates of the (basic) reproduction number, i.e. the number of infections that would be caused by a single infected animal in a large population of susceptible animals. A forte of final-size methods is that they are robust (e.g., inclusion of a latent period does not alter the results) and that different assumptions on the distribution of the infectious period are easily incorporated.

The methods are based on maximum-likelihood estimation (MLE). MLE can be used because final-size distributions can be determined under a wide range of assumptions. We refer to Ball (1995) for a fairly accessible introduction in final-size methods.

Generalized Linear Model

Final-size methods are flexible but do not make full use of the available information. To take the time course of the experimental epidemics into account, we estimate the transmission parameter β of the stochastic SIR model by means of a Generalized Linear Model (GLM). We refer to Becker (1989) for an introduction of GLMs in the context of epidemic models.

To apply a GLM the data of the experiments are first rendered into the format (S, i, C). Here S is the number of susceptible animals in a certain time period, i is the prevalence of infection (i.e. the average number of infectious animals divided by the total number of animals), and C represents the number of new infections that have appeared at the end of the time period. By standard reasoning we assume that the

number of cases C arising in a day is binomially distributed with parameter $p_{\text{inf}} = 1 - e^{-\beta i}$ (the probability of infection) and binomial totals S:

$$C \sim Bin(S, 1 - e^{-\beta i}) . \quad (4)$$

Experiments

Several experiments have been carried out with LPAI and HPAI viruses of the H5 and H7 subtypes. Table 1 gives an overview of the experiments. The first three sets of experiments involved LPAI and HPAI strains of the H5N2 subtype that were isolated during a large outbreak of HPAI in Pennsylvania in 1983. The results of these experiments are published in Van der Goot et al. (2003a; 2003b).

The next two sets of experiments were done using LPAI and HPAI strains of the H7N1 subtype, isolated during the outbreak of avian influenza in Italy in 1999. These experiments form part of the EU project AVIFLU on avian influenza. The last three sets of experiments were carried out using an HPAI strain of the H7N7 subtype that was isolated in The Netherlands during the outbreak of 2003. These experiments were also carried out as part of the EU project AVIFLU.

The analysis of the experiments with the H5N2 strains and the implications of the results are described in Van der Goot et al. (2003a; 2003b). The results of the experiments with H7N1 and H7N7 will be published by Van der Goot (in prep.-b; in prep.-a).

subtype and strain	control measure	no. replicates	remarks
A/chicken/Pennsylvania/83 H5N2 (LPAI)	none	4	Van der Goot et al. (2003a; 2003b); financed by Dutch government
A/chicken/Pennsylvania/83 H5N2 (HPAI)	none	2	Van der Goot et al. (2003a; 2003b); financed by Dutch government
A/chicken/Pennsylvania/83 H5N2 (HPAI)	previous infection with H5N2 (LPAI)	2	Van der Goot et al, (2003a; 2003b); financed by Dutch government
A/chicken/Italy/99 H7N1 (LPAI)	none	2	part of EU project AVIFLU/ financed by Dutch government
A/chicken/Italy/99 H7N1 (HPAI)	none	2	Van der Goot et al. (in prep.-a); part of EU project AVIFLU/ financed by Dutch government
A/chicken/Netherlands/03 H7N7 (HPAI)	none	2	Van der Goot (in prep.-b; -a); part of EU project AVIFLU/ financed by Dutch government
A/chicken/Netherlands/03 H7N7 (HPAI)	heterologous vaccination (H7N1)	4	Van der Goot et al. (in prep.-b); part of EU project AVIFLU/ financed by Dutch government
A/chicken/Netherlands/03 H7N7 (HPAI)	heterologous vaccination (H7N3)	4	Van der Goot et al. (in prep.-b); part of EU project AVIFLU/ financed by Dutch government

Table 1. Transmission experiments carried out with avian influenza A viruses of the H5 and H7 subtypes

Recommendations given during the Dutch outbreak

The above theoretical rules of thumb and experimental evidence on the transmission characteristics formed the basis on which the Dutch authorities were

advised on vaccination as a pre-emptive measure to prevent outbreaks of HPAI or as a control measure during an outbreak of HPAI (Van Boven et al. 2003). Shortly, the questions posed were the following:

1. Could **vaccination of a ring** around an infected farm be an effective control measure? If so, what would be the ideal 'vaccination radius' and how many farms would have to be vaccinated?
2. Would **vaccination of a compartment** (e.g., a province) once an infected farm has been detected in a compartment be effective to prevent the spread of the virus to other compartments? How large should the compartments be (in terms of area and number of farms)?
3. Is **preventive vaccination** of an area at risk a viable option? In particular, how does vaccine efficacy depend on vaccine composition? What is the maximal allowable rate of (primary) vaccine failure? Is it necessary to vaccinate all farms and animals in an area?
4. How should **repopulation** of an area in which HPAI has circulated before be carried out? Which farms should be repopulated first, and at what density? Should a repopulation programme be accompanied by a vaccination and/or surveillance programme?
5. What properties should a **surveillance programme** have in order to make sure that there is no transmission of influenza virus and that introductions of virus are noticed sufficiently quickly?

It is clear that, given the limited amount of information on the transmission dynamics of HPAI between flocks and given the very limited experience with vaccination applied as a systematic control measure (see Capua and Marangon (2003) for an exception), no definitive answers can be given to the above questions. Therefore, our advice was based on (1) the general epidemiological principles mentioned above, and (2) the developing experience with transmission experiments in a small population of poultry. The text below is translated from the Dutch report of Van Boven et al. (2003). We refer to Van der Goot et al. (in prep.-b) for an up-to-date account of transmission experiments in vaccinated poultry.

1. With a view to the very fast dynamics of AI in poultry flocks and the fact that it takes some weeks before a vaccination programme offers protection, **ring vaccination** is useless from an epidemiological point of view, unless the ring is quite large (a radius of >50 km). Moreover, in practice there will be an extra delay because it takes a while before all the farms in the area have been vaccinated, which only enlarges the area and the number of farms to be vaccinated.
2. It is extremely doubtful whether **a vaccination campaign in a large area/compartment** is at all useful. As it takes a relatively long time before the vaccine offers effective protection (2 to 4 weeks), and extra time to vaccinate all the farms (>1 week), it is quite unlikely that a vaccination programme that is started at the moment when an infection has been found will be effective.
3. The epidemiological analysis of the outbreaks in the 'Gelderse Vallei' and the province of Limburg indicate that there are **two risk areas in The Netherlands**: the 'Gelderse Vallei' and the area around the town of Weert in Limburg. As the density of poultry farms in these areas is very high, a chain reaction of new infections may arise after the introduction of the virus. The rest of The Netherlands does not seem to be an epidemiological risk area: an introduction of the virus is likely to result in few additional infected farms if the virus is detected in time and if effective measures are taken fast (closing down the farm and strict transport restrictions in an area around the focus of infection).

4. **Preventive vaccination** of an area/compartment before an outbreak has been spotted could be useful from an epidemiological point of view. Whether such a preventive vaccination is actually effective depends on 1) the effectivity of the vaccine in decreasing or blocking the transmission of avian influenza virus to and from vaccinated farms, and 2) the fraction of farms in the area that is vaccinated. General epidemiological principles say that the number of infected farms during an outbreak can only be kept small if the between-farm reproduction number R_h is brought below 1. The estimates of R_h during the outbreaks varied from 4 to 6. This means that if the vaccine blocks farm-to-farm transmission completely at least 75 to 84 % of the farms must be vaccinated. If the vaccine does not completely block the transmission between farms, then a higher percentage of the farms must be vaccinated.
5. **Repopulation** of farms in previously poultry-dense areas constitutes a high risk for the re-occurrence of the virus in poultry. In Italy repopulation programmes after a primary outbreak have repeatedly led to new outbreaks. Should this happen in The Netherlands in poultry-dense areas, then this could lead to a chain reaction of new infections. Therefore, from an epidemiological point of view it is advisable to re-populate the 'Gelderse Vallei' and Limburg in phases. As long as the density of farms remains lower than a certain critical density a reintroduction on a farm will in all probability not lead to an explosive wave of newly infected farms. Vaccination in the case of repopulation could be a useful additional measure besides better surveillance, improved hygiene and transport restrictions because it can reduce the effective density of farms that are at risk. To detect the possibly still present virus as soon as possible and with minimal cost farms that have been infected during the outbreak must be re-populated first.
6. Detecting new introductions of avian influenza virus fast is a crucial part of fighting the virus effectively. It is therefore advisable to launch a large-scale **surveillance programme** when repopulating areas at risk. Also, a surveillance programme can help monitoring the areas at risk for introduction along the border.
7. If it is decided to carry out a large-scale surveillance programme an effective test (i.e. a test with sufficiently high sensitivity) should be available that can distinguish between animals that have been vaccinated and animals that have suffered a natural infection. Such a test that can distinguish infection from vaccination plays an important part in a surveillance programme in a vaccinated area to detect infected farms as quickly as possible.
8. Since vaccination probably does not completely block transmission of the virus a vaccination programme can be useful only as an additional measure. The **real danger** is that because of vaccination a misplaced sense of security is created and that the necessary basic measures such as hygiene, transport restrictions and surveillance are no longer observed ("after all, we are vaccinating"). For that reason it is of the greatest importance to make sure that any possible vaccination campaigns are always accompanied by the necessary flow of information.

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