Risk assessment of human exposure to Highly Pathogenic Avian Influenza after vaccination of poultry

Risicobeoordeling van humane blootstelling aan hoogpathogene aviaire influenza na vaccinatie van pluimvee

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Nederlandstalige samenvatting

Continue circulatie van hoogpathogene vogelgriep (HPAI) in Europese wilde-vogelpopulaties veroorzaakt introducties van HPAI in pluimvee gedurende het hele jaar. Aanvullende beschermingsmaatregelen zijn noodzakelijk en vaccinatie is een veelbelovende oplossing. Vaccinatie kan echter leiden tot verminderde zichtbaarheid van uitbraken bij pluimvee, waardoor de blootstelling van mensen aan zoönotische HPAI mogelijk toeneemt.

Hier rapporteren we een risicobeoordeling van menselijke blootstelling gebaseerd op een dynamisch simulatiemodel van HPAI in pluimvee. De beoordeling is gemaakt met een focus op leghennen en vleeskuikens. Deze modelleringsstudie bestaat uit een binnenbedrijfs- en een tussenbedrijfsevaluatie. Met het binnenbedrijfsmodel wordt de verandering in blootstelling relatief ten opzichte van de ongevaccineerde situatie berekend op basis van transmissiesnelheden verkregen uit vaccinatie-experimenten. Drie scenario's worden onderzocht: "*Partial high titre*", waarbij slechts een deel van een koppel beschermd is en blijft tegen klinische symptomen èn vooral transmissie ,"*Verminderde klinische symptomen*", waarbij vaccinatie leidt tot bescherming tegen klinische symptomen, maar er nog wel transmission plaatsvindt en "*Waning immunity*" waarbij de bescherming tegen transmissie en klinische symptomen door vaccinatie een tijdelijk karakter heeft. Voor "*Waning immunity*" is zowel naar een vaccin gebaseerd op de circulerende stam (homoloog) als een andere stam (heteroloog) gekeken.

Een bestaand tussenbedrijfstransmissiemodel, waarbij infectiekansen zijn gebaseerd op de afstand tussen bedrijven, is aangepast door de tijd tot detectie en de door vaccinatie verminderde kans op een grote uitbraak uit het binnenbedrijfsmodel te integreren. Voor het tussenbedrijfsmodel hebben we aangenomen dat alleen bedrijven met leghennen zullen worden gevaccineerd, omdat het huidige vaccin in Nederland in kippen wordt uitgetest en omdat vleeskuikens te kort leven om voldoende titre op te bouwen.

Resultaten van het binnenbedrijfsmodel geven aan dat er met vaccinatie een verminderde blootstelling van mensen is in alle scenario's, behalve in het scenario waarin bijna volledige klinische bescherming optreedt en er geen verandering is in de transmissie van HPAI binnen pluimveekoppels en tussen pluimvee en mensen. In de scenarios, waarbij vaccinatie leidt tot verminderde transmissie

van HPAIV, kan de detectietijd per bedrijf oplopen, maar de algehele blootstelling van mensen binnen een bedrijf neemt af. Dit komt door een vermindering van het aantal geïnfecteerde kippen op een bedrijf tijdens een uitbraak en een vermindering van de overdracht naar mensen door besmette gevaccineerde kippen.

Naast de effecten van bescherming tegen verspreiding binnen een bedrijf zal tussen-bedrijfstransmissie verminderen, doordat de kans op een grote uitbraak met als resultaat minder geïnfecteerde pluimveehouderijen. Hierdoor zal in het algemeen de blootstelling afnemen. Echter als er klinische bescherming is en maar 50% van de kippen is beschermd tegen transmissie, zal de blootstelling van mensen vergelijkbaar zijn met situatie zonder vaccinatie. De maximum blootstelling is 16 keer groter dan het gemiddelde wat iets groter is dan de maximale blootstelling in het scenario zonder vaccinatie, waarbij dit 14 keer groter kan zijn dan gemiddeld. Dus alhoewel het risico iets kan toenemen in dit uitzonderlijke scenario, dan zal de toename beperkt zijn.

Vaccinatie kan de detectietijd verlengen door verminderde spreiding of verminderde klinische symptomen. Actieve surveillance door 'bucket sampling' kan helpen om de detectietijd te verkorten en pluimveehouderijen die anders niet gedetecteerd worden te detecteren. Dit kan naast de vaccinatie leiden tot een verdere vermindering van menselijke blootstelling.

In de inschattingen van menselijke blootstelling zijn een aantal onzekerheden. Hiervoor is de volgende informatie, die deels uit de lopende veldproef zal komen, nodig.

- Het verloop van de HAR titres in de veldproef kan gebruikt worden om de risico-analyse up-to-date te brengen.

- Actieve surveillance kan worden ingezet om te monitoren op ongedetecteerde uitbraken. In eerste instantie kan hiermee worden vastgesteld of *silent spread* voorkomt in gevaccineerde koppels. Als dit het geval is, kan er een programma worden ontworpen om besmette bedrijven tijdig te detecteren. Economische berekeningen kunnen met behulp van de resultaten uit het hier gepresenteerde model worden gedaan om de kosten-effectiviteit van verschillende surveillance programma's door te rekenen.

Abstract

Continuous circulation of high pathogenic avian influenza virus (HPAIV) in European wild bird populations cause year round incursions of HPAIV in poultry. Prevention requires additional measures and vaccination is a promising solution. Vaccination can, however, result in reduced visibility of outbreaks in poultry, such that the exposure of humans to zoonotic HPAI might increase.
Here we report a risk assessment of human exposure based on a dynamic simulation model of HPAI in poultry. This modelling study exists of a within-farm and a between-farm part. With the within-farm model the relative change in exposure is calculated based on transmission rates obtained from vaccination experiments. Three scenarios are investigated: *'Partial high titre'*, in which a fraction of birds have a HI-high titre and is protected against clinical signs and have reduced infectivity if infected ; *'Waning of immunity'*, in which birds with a high H-titre loose their protection after a certain period, and *'Reduced clinical signs'* in which all birds (high or low) titre have reduced clinical signs, but only high titre birds will have reduced infectivity.
An existing between-farm transmission model based on farm distance was adapted to include the time until detection and the reduced chance of major outbreak from the within-farm model. For the between-farm model we assumed only layer farms will be vaccinated.

Within-farm model results indicate a reduced exposure of humans with vaccination in all scenarios except for the situation in which almost complete clinical protection occurs and no change in infectivity of HPAIV within poultry flocks and between poultry and humans. In other scenarios, where major outbreaks are possible and detection times might increase, the overall human exposure decreases due to a reduction of number of infected birds during an outbreak, reduction of transmission to humans and a reduction of the probability of a major outbreak. If vaccination only provides clinical protection, but no reduced transmission in all vaccinated flocks, the risk of a higher human exposure is present, but within the margins of the current situation.
Based on our model calculations and the assumptions on which it is based, vaccination is not expected to increase the exposure of humans to HPAIV. Increased detection times do not lead to higher exposure in most scenarios. Even if the length of exposure is longer due to a reduced infectivity, a lower number of infected birds and less infected farms results in an overall decrease in exposure.

Only under the specific conditions that transmission is not (or hardly) affected and clinical symptoms are absent in vaccinated animals, vaccination might increase human exposure. Based on transmission experiments, this particular situation seems unlikely[9, 19], but we have calculated this scenario in case, such a situation is observed in a field study or from observational data.
Vaccination results in a reduced speed of spread and reduced mortality of high HI titre birds. This will lead to longer detection times for passive surveillance, such that weekly active surveillance (bucket sampling) has an added value by reducing the time until detection and detecting otherwise undetected farms. This will result in less exposure to humans. For unvaccinated farms active surveillance has little added value, because outbreaks are readily detected by passive surveillance.

To accommodate for uncertainty around the risks of human exposure, the following recommendation can be made based on this modelling study:

- The HI titres dynamics in a real life circumstances during the entire life cycle of a flock will be found in the current field experiment. With these new figures this risk assessment should be updated.

- Active surveillance could monitor the occurrence of undetected outbreaks and the extend of clinical protection in flocks where the virus can spread. At first such surveillance can determine whether *silent spread* does occur, and if this is indeed the case a program can be designed to detect infected farms within a reasonable time. The results of the current model can be used to evaluate the benefit of active surveillance. The costs of such a program can be calculated to evaluate different surveillance strategies on feasibility and cost-effectiveness.

Chapter 1

Introduction

Since 2003 large epidemic originating from sporadic incursions of high pathogenic avian influenza (HPAI) have not occurred. Since 2003 risk have been mitigated by stamping-out, increased bio security, quarantine and movement restrictions. Since recent year, HPAI is present year round in wild birds in the Netherlands. This causes the frequent introductions of highly pathogenic avian influenza from wild birds into poultry farms. The costs (in terms of money and animal lives) of the eradication of HPAI in poultry are increasing.
Germeraad et al.. 2023 tested four vaccines in an experimental setting against HPAI H5N1 clade 2.3.4.4b. Vector-vaccines using Herpes virus (HVT) were found to significantly reduce the reproduction number ($R < 1$) in an experimental setting. The other two vaccines, one DNA vaccine and one inactivated virus vaccine, reduce transmission, but were not able to bring the reproduction number under the threshold value ($R > 1$). The reduction of transmission was found to be related to the Haemagglutination Inhibition test (HI)-titres [21].

Standardized small-scale vaccination-transmission experiments in a contained animal facility are an important first step for evaluating the potential effects of vaccines against HPAI. In a second step, the effect under field circumstances, as these likely differ from the experimental settings, needs to be investigated [22, 5]. The protection of vaccination against transmission might also reduce in time [22, 23, 16, 19]. Although this so-called immune waning has so far not been reported for vector vaccines against HPAI [9]. Even without immune waning, due to other factors in the field sub-optimal vaccination could occur. Sub-optimal vaccination might lead to silent spread of the infection, when clinical symptoms remain reduced in vaccinated birds. This has been predicted [20] and observed previously [15, 18].
Silent spread of the infection might prolong the time during which humans (in particular those working with poultry) are exposed to HPAI. HPAI is a potentially zoonotic infection [14] and a prolonged exposure increases the likelihood of an infection occurring. On the other hand, successful vaccination of a part of the flock increases the probability that the the introduction of the virus will

only lead to a minor outbreak [7]. Vaccinated birds were producing fewer virus particles [9], which is reflected in a decreased transmission towards birds and thus most likely to humans [12, 6]. It is thus not straightforward how these factors balance out and whether vaccination will increase or decrease human exposure.

Commissioned by the ministry of Agriculture, Nature and Food quality we conducted a risk assessment for the exposure of humans to HPAI when poultry is preventively vaccinated against avian influenza. The study uses an infectious disease simulation model based on the results of Germeraad et al. 2023 and extrapolates these to poultry farms in the Netherlands taking into account the possibility of sub-optimal vaccination.

1.1 Objectives

The aim of this study is to determine the change in human exposure to potentially zoonotic high pathogenic avian influenza under a vaccination strategy of poultry.

The exposure to HPAI is calculated cumulatively over a simulated outbreak in different scenarios and divided to the average cumulative exposure in a scenario without vaccination. This ratio will give an indication of an increased or decreased risk of exposure.

Exposure is calculated

1. based on an outbreak on a single farm
2. based on an epidemic of multiple farms

The simulations of outbreaks on a single farm gives more detailed insight in the risk of vaccination for human exposure in a single infected farms and the effect of factors, such as the size of the farm. Simulations over multiple farms investigate the effect of vaccination on human exposure on the national level.

1.1.1 Approach

This is a modelling study in which the knowledge on HPAI transmission and effect of vaccines is described in two mathematical models; one for an outbreak in a single farm and one for an epidemic among farms. The parameters of the models are obtained from literature and a report by WBVR, Utrecht University, Wageningen University and RoyalGD [9] (see Table 2.1). The first within-farm model used to calculate the probability of a minor outbreak within-farm, time until detection of farms, and human exposure to HPAI in a single farm. We used a stochastic event-based Susceptible-Infected-Recovered (SIR) model with two types of birds. Birds either with high titre due to vaccination, which reduces

the infectivity (rate of infecting other birds), lengthens the infectious period and protects against clinical signs. Birds with a low titre are assumed to have the same characteristics as unvaccinated birds.
Human exposure in the within-farm model is calculated based on the epidemic curve. Assuming that the rate of transmission from bird-to-human is proportional to bird-to-bird transmission. The absolute probability of infection depends on many more factors, such as being an employee or not, number of visits to a flock, compliance with bio-security measures, ventilation and the dose-response. Therefore, we could not calculate the absolute probability of infection with any accuracy. We determined the relative risk of vaccination on the exposure to HPAI by calculation of the total exposure during an outbreak (until detection) and dividing this by the mean exposure during an outbreak without vaccination.
The second between-farm model is an individual-based stochastic simulation model in which a farm is the epidemiological unit. The individual characteristics of a farm are size, type of farm, vaccination status and time until detection. Time until detection and human exposure are derived from the within-farm model. The human exposure of all infected farms is added and divided by the mean total human exposure in a scenario without vaccination.

Technical details of the model and methods are described in Appendix A. Short descriptions of the methods are included in separate sections within the results.

1.1.2 Scenarios

The effect of vaccination is compared to a baseline without vaccination. In the baseline, we assumed no vaccination and a 99% mortality of infected birds. Outbreaks were simulated for several scenarios (see Table 1.1).In all scenarios, birds with a high HI-titre will have clinical protection against severe disease and mortality, and will not be observed as being infected unless they die of other causes. The scenarios were *'Partial high titre'*, in which only a part of the population has a high HI-titre, *'Waning of immunity'*, in which the high HI-titre lasts for a specific period depending on the strain being heterologous or homologous to the circulating strain and *'Clinical protection'* in which low titre birds are partially protected against clinical symptoms. Within each scenario we simulated outbreaks for several parameter settings (Table 1.1). The simulated outbreaks are used to determine the time of detection by either passive surveillance, when a threshold of death birds is reached, or by active surveillance, when active monitoring of dead birds is implemented.

Scenario		**Values**		**Reference**
Partial high titre without immune waning				
Percentage high HI-titre	p_{high}	$50\% - 90\%$		[9]
Immune waning scenarios				
Immune waning [a]	T_{hl}	Homologous	Heterologous	
	Mean(days):	514	280	Estimated from
	Std.dev.(days):	86	140	[19]
Moment of introduction[b]	t_0	0,50, 100,200,300,400,500		
Reduced clinical signs				
Percentage high HI-titre	p_{high}	$0\%, 50\%$		[9]
Probability of dying				
after infectious period [a]	ϕ_l	0.50		
	ϕ_h	0.01		

Table 1.1: Parameter values for the scenarios.
[a]Subscripts h = high titre, l = low titre
[b] The moment of introduction t_0 and the waning rate ν_{hl} determine the initial percentage with a high HI titre: $\mathbf{e}^{-\nu_{hl}t_0}$

Chapter 2

Within-farm transmission

2.1 Short model description

A detailed description including parameterization of the model can be found in the appendix A.

Infection dynamics The within-farm model divides the population into two groups (high titre and low titre). High titre birds are expected to have the same susceptibility as low titre birds, but differ in the infectivity [21]. Whether a bird has a high or low titre birds can be due to biological factors (e.g. physiological differences between chickens), environmental factors (e.g. prior exposure to avian influenza), or human factors (e.g. incorrect application of the vaccine). In our model, the birds are randomly divided into high or low titre. In the scenarios with immune waning, high titre birds can become low titre birds. High titre birds can become infected and due to the vaccination will have a longer infectious period because these will not die. The infectious period of high titre birds is 4.0 days versus 3.0 days of low titre birds. At the end of the infectious period birds either die in 99% of the cases for low titre birds and 1% of the high titre birds. Birds that do not die will be considered immune. Low titre birds will transmit the infection with the same rate as non vaccinated birds and we used the value of 1.13 day^{-1} from the study by Germeraad et al.2023. For the high titre birds we used the value of 0.058 day^{-1} from Table 2 in Sitaras et al.2016. This choice was made, because no transmission was measured in the first study for high titre birds.

Parameter	Symbol	Value	Range	Reference
Flock size and production round				
Flock size broilers	N	38 000	20 000 - 73 000	
Duration production cycle broilers		42 days		
Flock size layers	N	32 000	15 000 - 64 000	
Duration production cycle layers		510 days		
Infectious, vaccination and mortality				
Initial infected birds	I_0	10		
Background mortality rate	μ	0.0005 day^{-}1		
Intra-type transmission coefficient	β_{ll}	1.31 day^{-1}		[9]
	β_{hh}	0.058 day^{-1}		[21]
Inter-type transmission coefficient	β_{lh}	1.31 day^{-1}		[9]
	β_{hl}	0.058 day^{-1}		[21]
Mean infectious period	α_l/ρ_l	3.0 day		[9, 13]
		($\alpha_l = 60$, $\rho_l = 20$)		
	α_h/ρ_h	4.0 day		[9, 13]
		$\alpha_h = 80$, $\rho_h = 20$		
Dying after infectious period	ϕ_l	0.99		
	ϕ_h	0.001		
Immune waning	ν_{hl}	0.0 day^{-1}		

Table 2.1: Parameters and initial values. l = low titre, h = high titre, α is shape parameter of a gamma distribution and ρ the rate parameter

Detection Detection is modelled by passive surveillance when the mortality on a farm is more than 0.5% of the flock during two consecutive days[1]. Alternatively, we studied the effect of active surveillance assuming that all birds dying during a 7-day interval are tested at the end of that interval. The time of the first test is assigned randomly between 0 days and 7 days since the start of the simulation. In the active surveillance scenario we simulate testing of pooled samples of carcasses collected for destruction (bucket sampling).

Parameter	**Value**	**Reference**
passive surveillance		
Detection threshold	0.5% of flock	[1]
Detection time frame	2 days	
active surveillance		
Time interval	7 days	
Probability farm in active surveillance	1.0	
Probability dead animal in active surveillance	1.0	
Test sensitivity per animal	0.99	[9]

Table 2.2: Parameters for detection module

Human exposure The main objective of this study is a comparison of the risk of human exposure when poultry is vaccinated with the current situation without vaccination. Human exposure is calculated as the cumulative force-of-infection during the whole period of an outbreak. The outbreak ends either at detection, or when the outbreak fades out before detection. The cumulative force-of-infection is divided by the cumulative force-of-infection of the baseline scenario to obtain a relative risk of exposure due to an outbreak. We do not calculate absolute values, because the actual exposure is determined by many unknown parameters, such as the amount of virus particles inhaled, the exact dose-response and the time during which air with virus particles is inhaled.

2.2 Results: $\mathcal{R}$ and probability of a minor outbreak

The stochastic model for within-farm transmission is used to calculate the probability of a minor outbreak[2] given that the infection is introduced on a farm. The probability of a minor outbreak after introduction does not depend on the size of the farm, because in the first phase of an outbreak the number of birds will not be limiting. Therefore, these results are applicable to all farm sizes.

[1] https://www.nvwa.nl/onderwerpen/vogelgriep-preventie-en-bestrijding/vraag-en-antwoord/mijn-vogels-hebben-vogelgriep.-waar-moet-ik-dit-melden

[2] A minor outbreak is defined as an outbreak that goes extinct by chance in a early stage of the outbreak, rather than fading out due to a lack of susceptible animals.

First the relationship between high titre and the probability of a minor outbreak is calculated assuming that 10 birds will initially be infected either all with a high titre, all with a low titre or that these are equally distributed over the high titre and low titre.

At around 75% of the population having a high titre against the introduced strain, the population is protected against a major outbreak ($\mathcal{R} < 1$), which is the same as reported in Germeraad et al.. 2023. Here we also calculated the probability of a minor outbreak for sub optimal protection, when not all birds have a high titre. The probability of a minor outbreak is negligible, when less than 50% of the birds has a high titre. Between 50 % and 75 % high titres, the probability of a minor outbreak rapidly increases (Figure 2.1).

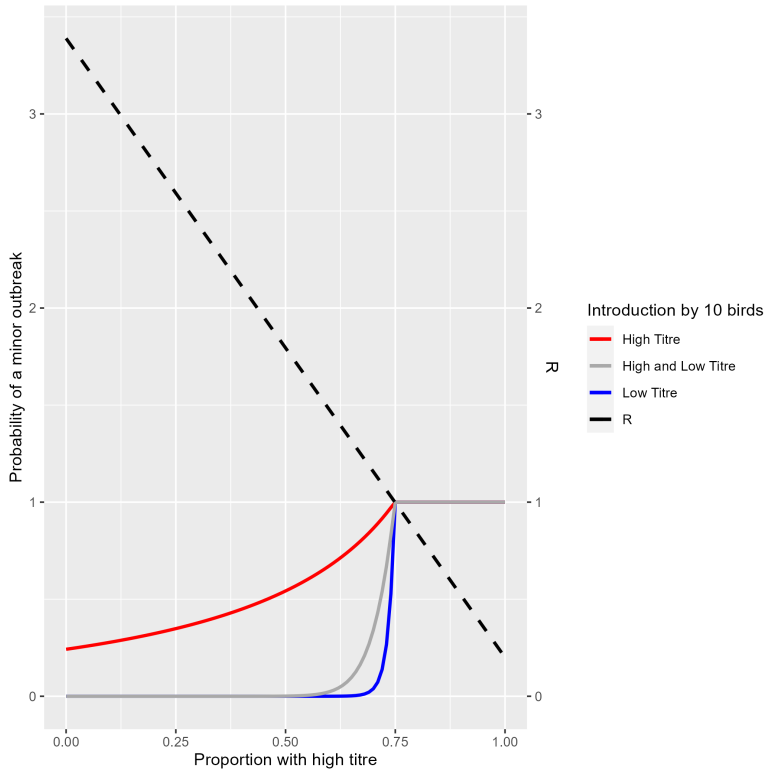


Figure 2.1: Probability of a minor outbreak in relation to $\mathcal{R}$ the proportion of birds with a high titre and initial infections occurring either all in high, all in low or proportionally distributed over high and low titre groups.

The calculation of the probability of a minor outbreak is used further on in the between-farm simulations. The probability of a major outbreak is used to determine if a farm will or will not experience an outbreak at introduction (Chapter 3). Technically we reduced the transmission rate between two farms by the probability of a major outbreak on that farm.

2.3 Results: Scenarios

2.3.1 No vaccination

The scenario without vaccination is used to investigate the effect of length of production cycle (layer vs. broiler) and the size of farms on the infection dynamics and the detection time. We used the sizes of 25% percentile, median, and 75% percentile of Dutch Layer and Broiler farms. In the further scenarios, broilers were no longer used as we assume that only layers will be vaccinated.

Outbreaks

Without vaccination introduction leads to an outbreak in all simulations with small fractions of susceptible and recovered animals at the end of the simulation (Figure 2.2). The outbreak peaks just around 10 days post introduction. This is similar for all farm sizes.

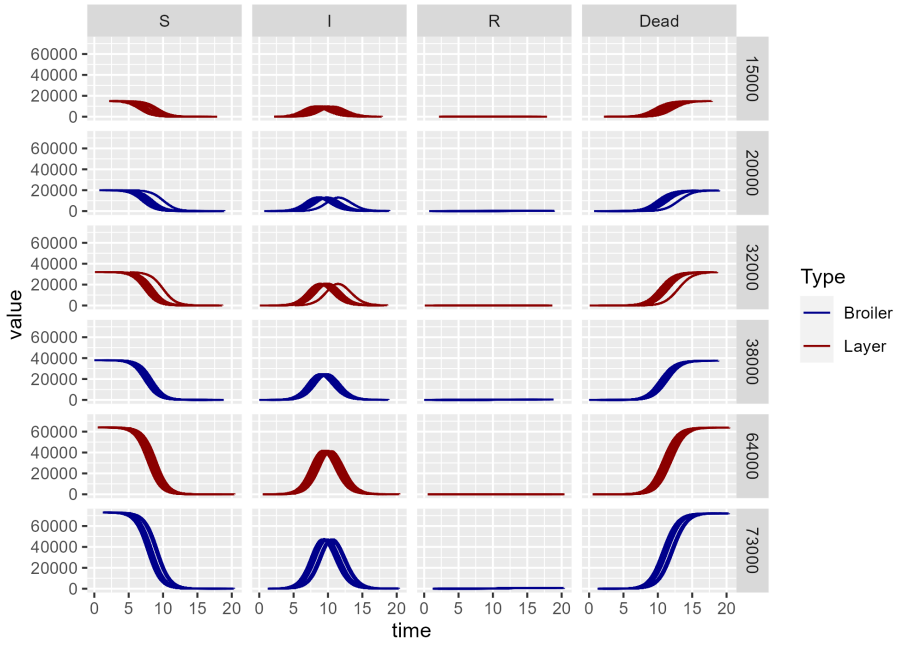


Figure 2.2: Baseline with no vaccination. Layer starts with 15 000, 32 000 or 64 000 birds, Broiler with 20 000, 38 000 or 73 000. Layers live for 510 days and Broilers for 46 days. S = susceptible, I = infectious, R = recovered.

Detection

In the scenarios without vaccination, the detection time for passive surveillance in layer and broiler is expected between 8 - 9 days after introduction (Figure 2.3),

which is similar to values estimated for outbreaks in the Netherlands previously [13]. The size of the flocks does not affect the time until detection, because the exponentially growing number of dead birds is not limited for the sizes of farms that we are interested in.

Active surveillance based on weekly sampling of dead birds is not likely to improve the detection time. With a 7 day interval of testing, the first sample will be between 0 to 7 days after the introduction of the disease, and on average birds will die 3 days after infection. The expected detection time is thus between 3 and 10 days, which is similar to the passive surveillance. Active surveillance will, however, always be accompanied by passive surveillance. Therefore, we also determined the earliest (minimum) detection time for each run. This is the time at which in the farm is detected by either the passive or active surveillance. The mean detection time does decrease in this scenario (Figure 2.3 .

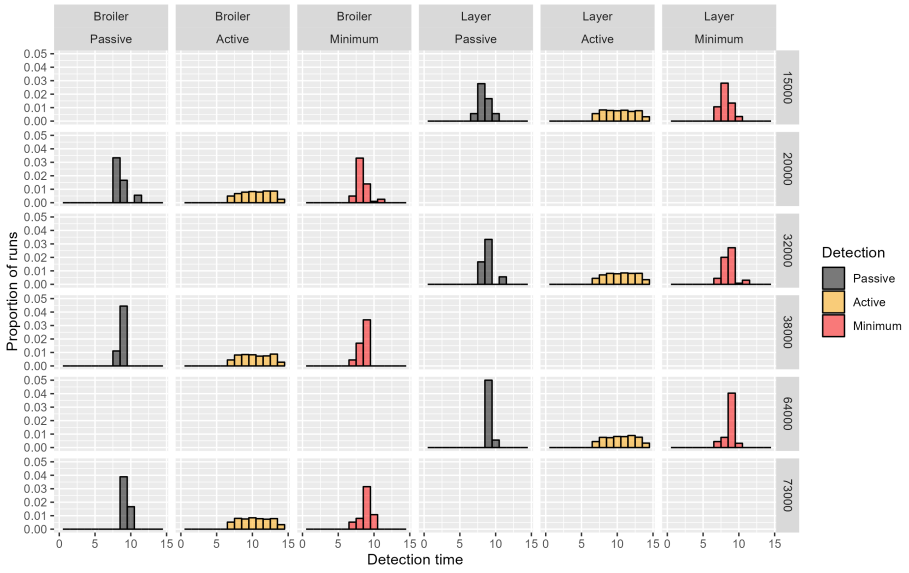


Figure 2.3: Detection times for passive (gray) and active (orange) surveillance and the minimum of these times(red) for the baseline scenarios.Each row represents a farms size as indicated on the right panel descriptions. The left three columns show broiler farms and the right three layer farms.

For broilers the probability of slaughter before detection is substantial due to the short production cycle.

2.3.2 Partial high titre

We studied the effect of Partial high titre, where due to a variety of causes not all chickens might obtain a high HI titre. We studied populations in which 50% to 90% of chickens have high HI titres and compared this to a population

without vaccination.

Outbreaks No major outbreaks should occur above 75% high titre birds (section 2.2 Figure 2.1). In our simulations, we see indeed no major outbreaks for values above this threshold (i.e. simulations with 80% or 90% high titre birds) Major outbreaks occur in 100% of the simulations, when the percentage of high titre birds is less than 75%. In these simulation, 95% of the low titre birds become infected and also a proportion of the high titre birds. (Figure 2.4).

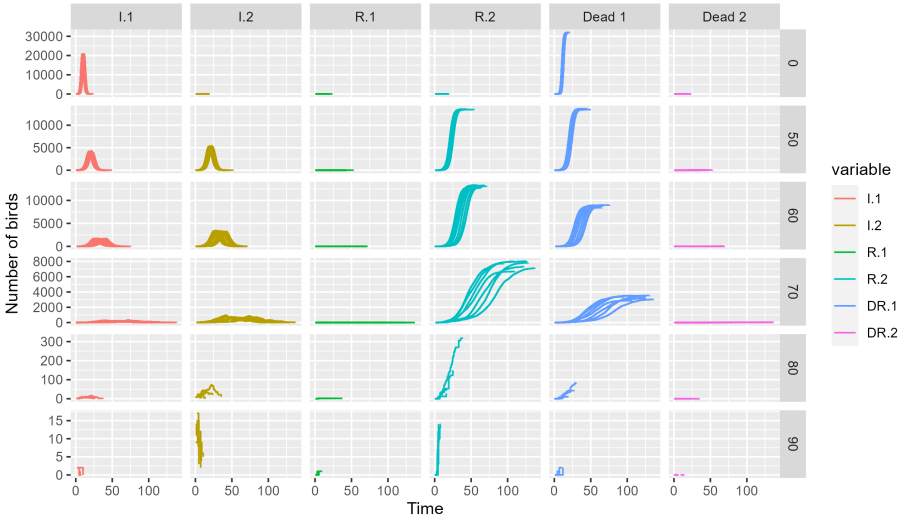


Figure 2.4: Infection dynamics for median size layer farm (32,000) with different fractions of birds with high titre. Each row are scenarios with a specific percentage of birds with a high titre as indicated in the panel labels at the right side.
I = infectious, R = recovered, 1 = low titre, 2= high titre.

Detection Detection times for passive surveillance (Figure 2.5) are not very sensitive to farm sizes although they might differ a few days between small (15,000 birds) and large farms (64,000 birds). Partial high titre will increase detection times for passive surveillance dramatically. For simulations with 70% high titre birds the threshold of 0.5% dead birds in two consecutive days will not be reached. For farms with more than 75% high titre, only minor outbreaks occur that will not be detected by passive surveillance.

Combined passive and active surveillance will always pick up the infection. The high sensitivity per animal to be detected, will result in detection of one of the original ten infected birds. The probability that these will not be detected is $(1 - 0.99)^{10} = 10^{-21} \approx 0$. The detection time for the simulations with 0%, 50% or 60% high titre birds is equal or longer than passive surveillance due to

the sampling frequency of 7 days in the unvaccinated populations(Figure 2.5) .

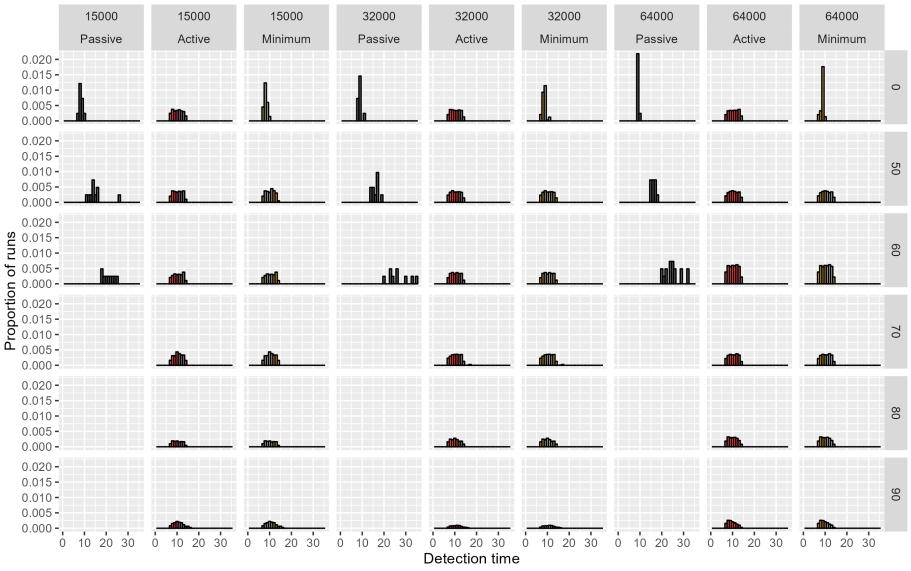


Figure 2.5: Partial high titre: Detection times different layer farms size (15 000 = 25% percentile, 32,000 = median and 64,000 is 75% percentile of Dutch farms) and different fractions of birds with high titres. I = infectious, R = recovered, 1 = low titre, 2= high titre.

Human exposure The longer detection times for passive surveillance in imperfectly vaccinated flocks will not lead to a higher exposure of humans (Figure 2.6). The explanation for this result is under this scenario the size of outbreak is smaller (fewer infected birds) than without vaccination. Additionally we assume that the exposure by high titre birds is proportional to the transmission rate, which is more than 20 times lower, while the duration of exposure by a single bird is on average 1 day longer (infectious period of 4 instead of 3 days). These assumptions are challenged in the scenarios with clinical protection (Section 2.3.4).

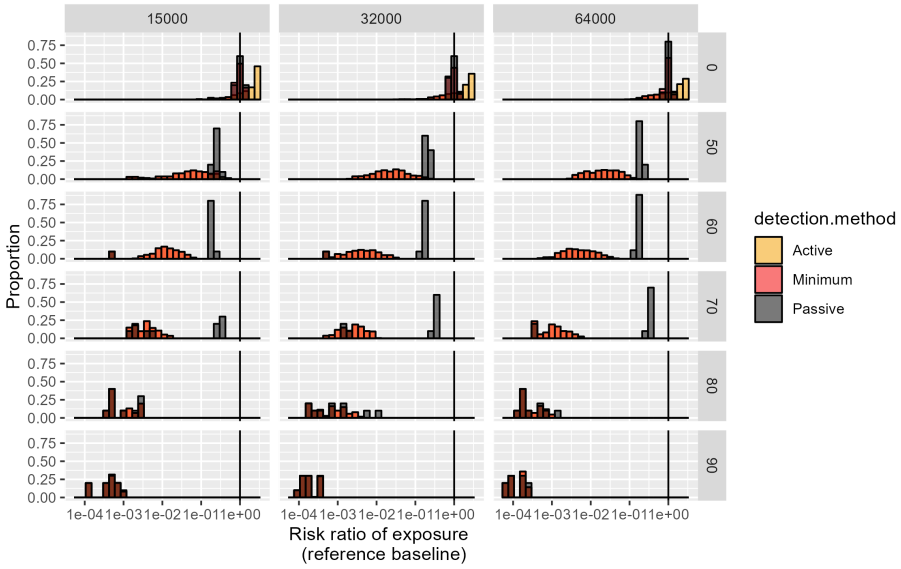


Figure 2.6: Partial high titre: Human exposure for an outbreak one farm relative to mean exposure without vaccination from introduction until either passive surveillance or fade-out of infection for different layer farms size (15 000 = 25% percentile, 32,000 = median and 64,000 is 75% percentile of Dutch farms) and different fractions of birds with high titres. Active is detection time by active surveillance only, Passive is detection time for passive surveillance only, and Minimum is the shortest detection time of either. I = infectious, R = recovered, 1 = low titre, 2= high titre.

2.3.3 Waning immunity

In this scenario we investigate waning of immunity in layers, when the vaccine is homologous or heterologous to the circulating HPAI strain. We consider introduction at 0, 50, 100, 200, 300, 400 or 500 days after protection has build. In reality it will take some weeks before vaccination can start and to build up a titre.

Homologous strain The animals have a gamma-distributed period between having a high titre, becoming low titre with average of 514 days (73 weeks) and a standard deviation of 85 days (12 weeks) [19] (see Appendix A.4and Figure A.1) . We consider the case when the infection is introduced 0, 50, 100, 200, 300, 400 or 500 days after (partial) protection of the vaccination occurs, which corresponds in this scenario to an initial fraction of high HI titre birds of 100.0%, 100.0% 100.0%, 99.9%, 99.8%, 91.8% and 54.5%.

Heterologous strain The animals have a gamma-distributed period between having a high titre, becoming low titre with average of 280 days (40 weeks) and a standard deviation of 140 days (20 weeks). Only 70% of the animals will build up a high titre for the circulating strain [19] (see Appendix A.4and Figure A.1). We consider the case when the infection is introduced 0, 50, 100, 200, 300, 400 or 500 days after (partial) protection of the vaccination occurs, which corresponds in this scenario to an initial fraction of high HI titre birds of 70.0%, 69.6%, 66.0%, 47.5%, 26.6% and 12.5% and 5.2%.

Outbreaks When introduced before 400 days after vaccination with a homologous strain, the percentage of birds with low titre is still below the threshold of a major outbreak and thus all outbreaks will be minor (Figure 2.7a). The minor outbreaks can be slightly bigger than in the scenario without waning of infection, although at the moment of introduction the same fraction of high HI titre occurs. Also waning of immunity can extend the length of an outbreak before fade-out occurs. When the threshold is passed, a major outbreak will occur similar to the *'Partial high titre'* scenarios (see section 2.3.2). When a heterologous strain is circulating, all introduction times will result in a major outbreaks. The size of the outbreaks depends on the time of introduction (Figure 2.7b).

Detection

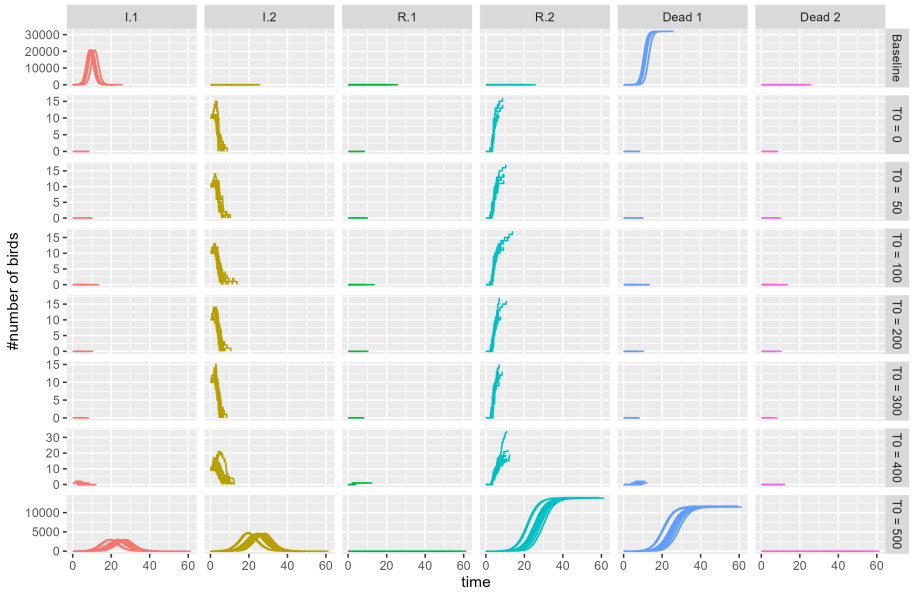
Introduction at time 0 after vaccination (this is the moment that vaccination is fully effective) with a homologous strain until 400 days after vaccination, the minor outbreaks will not be detected even if active surveillance is implemented. The number of infected birds that die will be too low for detection. This is because of almost 100% high titre bird, which differs from the *'Partial high titre'* scenario for which the highest coverage still had 10% with a low titre. Introductions 500 days will be detected, but for minor outbreaks only by active surveillance. Introduction at 500 days after vaccination will result in major outbreaks that will be detected by passive surveillance on average 10.5 days after introduction, which is later than the baseline scenario of 8.4 days.

When a heterologous strain is circulating, passive detection is not able to pick up the infection. Although a large number of birds do get infected (Figure 2.8b), the percentage of dead birds remains below 0.5% per day for any two consecutive days (in this case 160 dead birds per day).

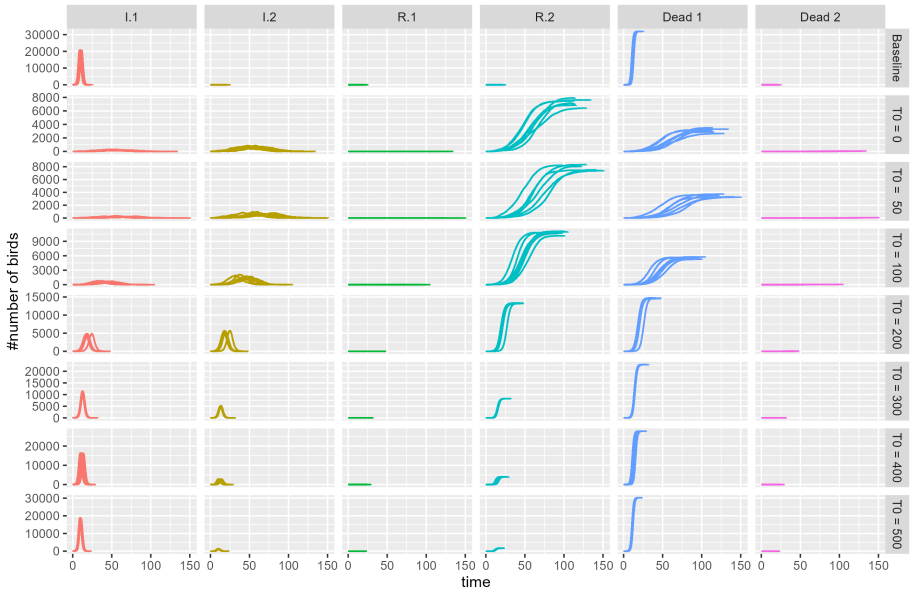
Human exposure

Human exposure will be lower than without vaccination even when the vaccine protection wanes in time. This will be the case for both the situation in which a homologous strain (Figure 2.9a) or a heterologous strain (Figure 2.9b) is circulating.

Similar to the scenario "*Partial high titre*", either a minor outbreak occurs or when a major outbreak is possible the detection times are close to the baseline,

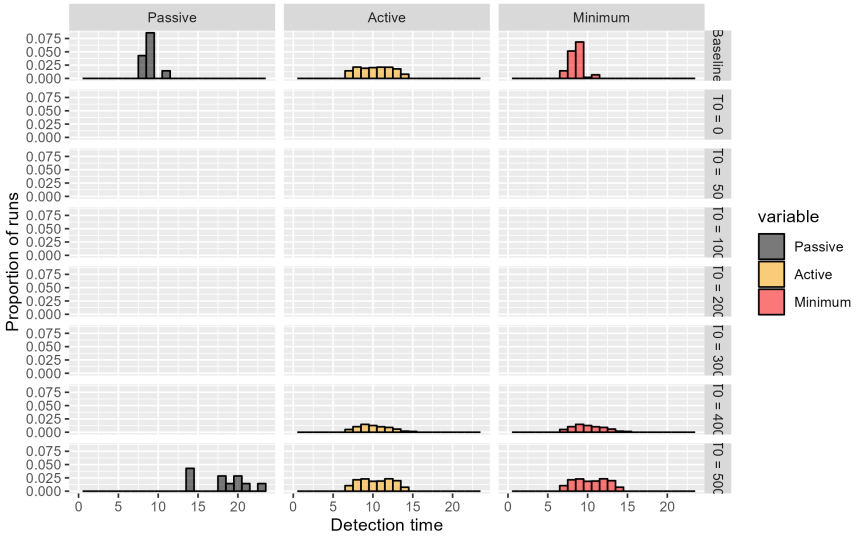


(a) Homologous strain

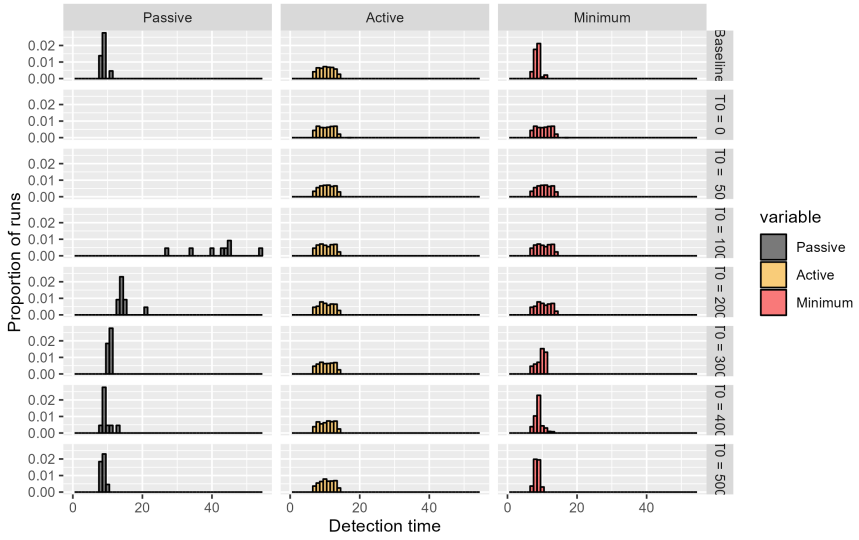


(b) Heterologous strain

Figure 2.7: Infection dynamics with waning immunity in a median size layer farm (32,000), when high HI titres wane and the infection is introduced at day 0, 50, 100, 200, 300, 4000 or 500 days after vaccination. I = infectious, R = recovered, 1 = low titre, 2= high titre.



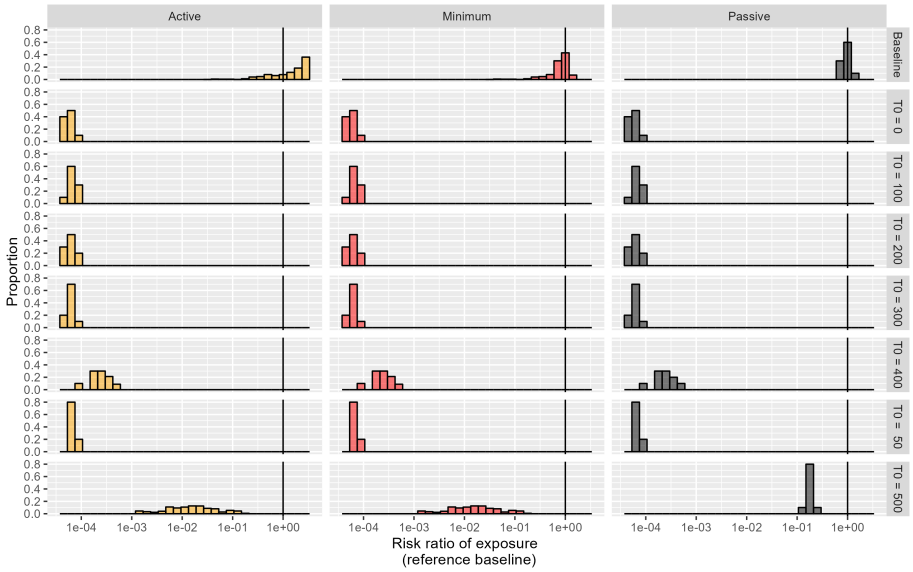
(a) Homologous strain..



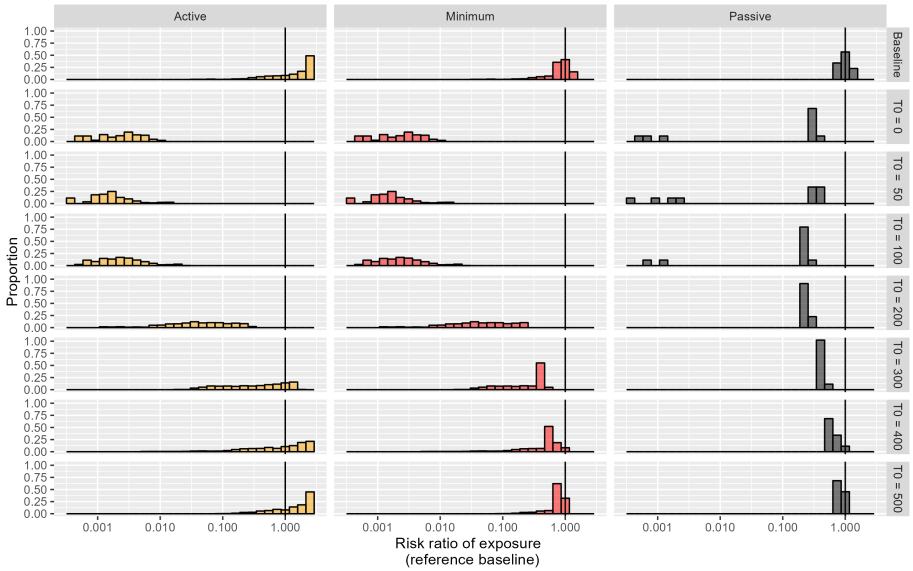
(b) Heterologous strain.

Figure 2.8: Immune waning: Detection times median sized layer farm (32,000) and different introduction times (right panel labels). If no bars are plotted, the introduction will not be detected. Active is detection time by active surveillance only, Passive is detection time for passive surveillance only, and Minimum is the shortest detection time of either. I = infectious, R = recovered, 1 = low titre, 2= high titre.

while the exposure to humans is reduced due to a smaller number of infected birds and reduction of transmission in high HI titre birds.



(a) Homologous strain.



(b) Heterologous strain.

Figure 2.9: Immune waning: Human exposure relative to that of the median human exposure in the baseline for a median sized layer farm (32,000) and different introduction times (right panel labels). For those simulations in which no detection takes place the exposure until fade-out of the outbreak are used. Active is detection time by active surveillance only, Passive is detection time for passive surveillance only, and Minimum is the shortest detection time of either.

2.3.4 Clinical protection

We investigated the effect on human exposure, when vaccination protects against clinical symptoms by reducing the mortality at the end of the infectious period for birds both with a high or a low titre. The clinical protection for low titre birds was modeled as 0.1% or 50% mortality at the end of the infectious period. High titre birds will have a mortality rate of 0.1% in all scenarios. Simulations were done for 0% and 50% high titre birds meaning that the transmission rate was reduced for either none or 50% of the animals (Table 1.1).

Detection

If the vaccination will not protect against transmission, but does protect against clinical disease, the detection times for passive surveillance will increase substantially (Figure 2.10. When only 0.1% of birds die of the infection, passive surveillance is no longer able to detect an outbreak. If only 50% of the birds are protected against death, but all transmit at the same rate as unvaccinated birds, the detection times for passive surveillance increase with only one or two days on average compared to the baseline scenario.

Active surveillance will effectively find the first dead infectious birds even when almost no birds will show clinical signs or have excess mortality. This is due to infected birds dying with the same background mortality as non-infected birds and are thus sampled, and the assumed high sensitivity of active sampling.

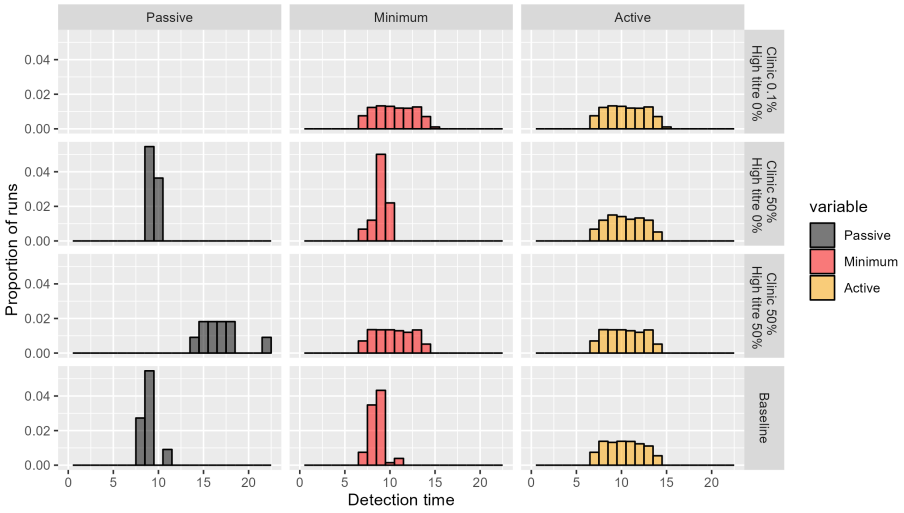


Figure 2.10: Clinical protection: Detection times for surveillance for the scenarios with clinical protection. Active is detection time by active surveillance only, Passive is detection time for passive surveillance only, and Minimum is the shortest detection time of either. When no bars are shown, none of the simulated outbreaks was detected by this surveillance method.

Human exposure

The longer detection times for passive surveillance in clinical protected flocks can lead to a higher exposure of humans (Figure 2.11). In both scenarios where transmission is not affected by vaccination, the exposure will increase with 50% to 300%. Especially when clinical protection is high (0.1% deaths), but no effect on transmission occurs the exposure can be very high. Active surveillance can mitigate this but not in all cases. If no clinical symptoms are present in 50% of the birds and no reduction of transmission occurs the overall exposure will be only slightly higher. When 50% of the flock has a high titre that will reduce transmission and the low titre birds have a 50% chance of dying (a more likely scenario [9]), the human exposure will be lower than that in the baseline scenario.

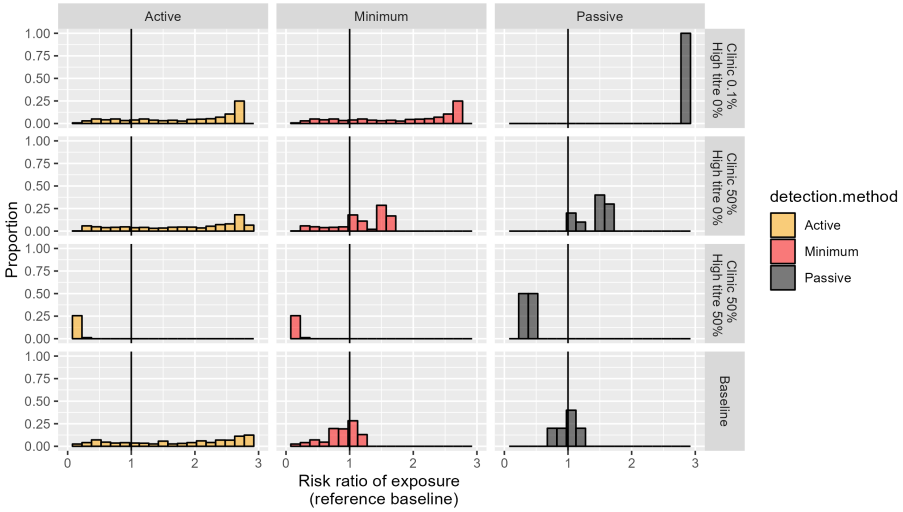


Figure 2.11: Clinical protection: Human exposure of an outbreak until detection relative to mean exposure without vaccination for the clinical protection scenarios. Percentage high titre indicates scenarios with reduced transmission. Active is detection time by active surveillance only, Passive is detection time for passive surveillance only, and Minimum is the shortest detection time of either.

Chapter 3

Between-farm transmission

3.1 Model description

Between-farm transmission was modelled assuming that the transmission between farms depends on the distance r_{ij}between farms (Eq. 3.1). This is a well established method of modelling the transmission dynamics between farms [3, 1, 2]. We used the parameterization by Boender et al. 2007.

$$h(r_{ij}) = \frac{h_0}{1 + \left(\frac{r_{ij}}{r_0}\right)^{\alpha}} \tag{3.1}$$

We adapted the code by Beninca et al. 2020 to accommodate for vaccination. Vaccination was modelled by a reduced susceptibility of vaccinated farms. The susceptibility was equal to the probability of a major outbreak given a certain amount of high titre animals. We considered vaccination of layers and no vaccination of broilers, ducks or turkey. For each infected farm the total human exposure is randomly drawn from the within-farm simulations based on vaccination status.

Detection and human exposure

Based on the vaccination status of infected farms we drew a random detection and human exposure value from the outcomes of the within-farm model (e.g.

Parameter	description	value
h_0	Infection rate at distance 0	0.002 day^{-1}
α	Kernel shape	2.1
r_0	Spatial scaling	1.9 km

Table 3.1: Parameters of the spatial kernel [4]

Figure 2.3 for detection). We report the ratio between the exposure summed over all infected farms in the baseline and the vaccination scenarios. In this part of the report we will thus increase the scope from the effects on a single farm to the national level.

3.2 Scenarios

To assess the risk we formulate a few possible scenarios based on the within-farm simulations. In the '*Partial high titre* ' scenario we consider that 50% of the birds are protected against clinical signs and no effect of transmission. In this scenario major outbreaks are possible, the detection times were longer, but the exposure of an outbreak on a single farm was less. The second scenario is '*Waning of immunity*' in this scenario the immunity wanes after on average 514 days (for a homologous strain) or 280 days (for a heterologous strain) rendering the farm partially protected against a major outbreak. The amount of waning is determined by drawing random times since vaccination between 0 and 540 days for the flocks. The last scenario is '*Clinical protection*' in which we assume again 50% protection against death, but not protection against transmission. We studied both introduction in Densely populated poultry areas (DPPA) and in sparsely populated poultry areas (SPPA). For each farm we calculated the density of farms within 1 km of that farm (i.e. the point density). For DPPA areas we selected from the 5% farms with the highest point density and for SPPA we selected from the 25% farms with the lowest point density.

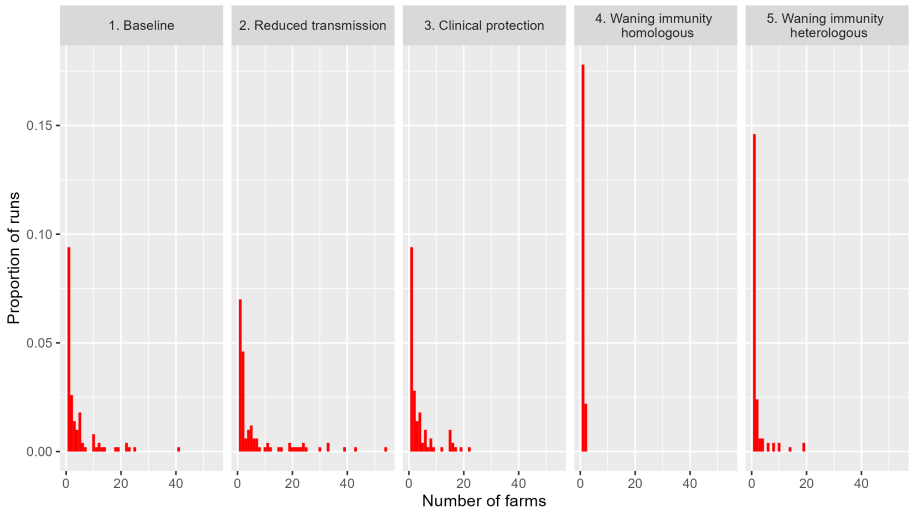
3.2.1 Passive surveillance

Number of infected and culled farms

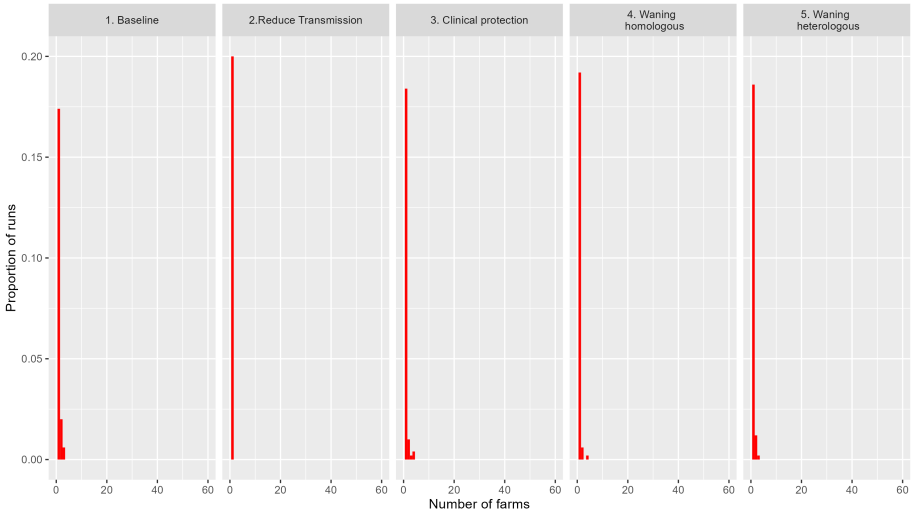
The effect of vaccination is largest in the immune waning scenario with a homologous strain (Figure 3.1). In this scenario, a vaccinated farm is protected against a major outbreak up to 400 days due to almost 100% high titre birds. Therefore, the majority of farms will have protection against a major outbreak resulting in just a few runs with additional infected farms. Please note that the scenario without waning assume that only 50% of a flock has a reduced transmission due to a high titre, the number of infected farms will decrease. Clinical protection will slightly increase the chance of major outbreaks with in one run even almost 40 infected farms.

Human exposure

The variation of human exposure without vaccination ranges in our simulations between 0.01 and 10 times the mean exposure. When clinical protection occurs together with 50% birds with reduced transmission the exposure will increase to a range of 1 to 100 times the mean exposure. Reduced transmission will decrease the mean exposure and the range is narrower. Waning immunity causes a distinct difference between small outbreaks in farms with partially high titre



(a) Densely Populated Poultry Area

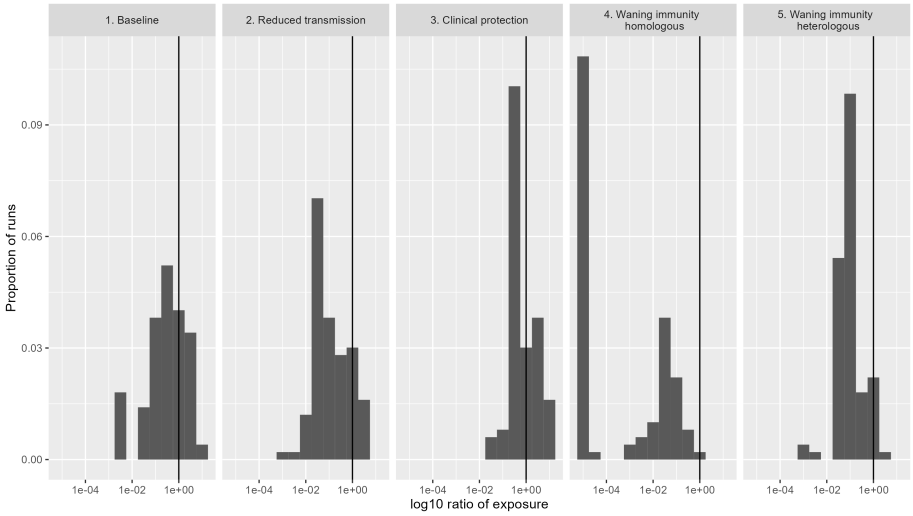


(b) Sparsely Populated Poultry Area

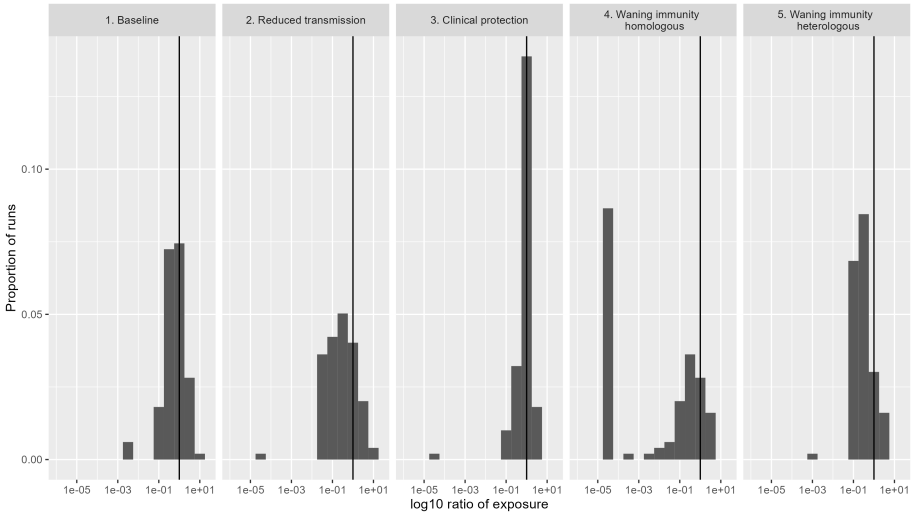
Figure 3.1: Histogram of number of infected farms for an epidemic starting in a high density poultry area or a low density poultry area.

but very low exposure, and larger outbreaks with multiple infected farms with on the same mean exposure as in the unvaccinated case.

When the infection starts in SPPA the outbreaks in terms of number of farms will be smaller and the human exposure will also be smaller. The clinical protection and waning protection scenarios have a few larger outbreaks due to



(a) Densely Populated Poultry Area



(b) Sparsely Populated Poultry Area

Figure 3.2: Exposure as sum of all infected farms in an epidemic relative to baseline scenario in the same area.

undetected infected farms. Comparing outbreaks starting in an SPPA, the ratio of exposure between the baseline without vaccination and the other scenarios is similar to that of the DPPA (see Figure 3.2).

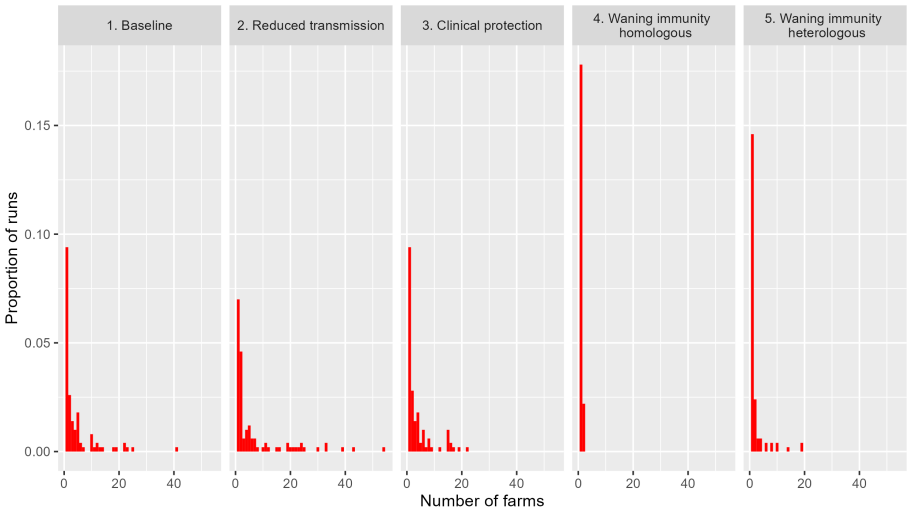


Figure 3.3: Histogram of number of infected farms for an epidemic starting in a high density poultry area and in which active and passive surveillance occur.

3.2.2 Active and passive surveillance

Number of infected and culled farms

The combination of active and passive surveillance changes the number of infected farms from the scenario with only passive surveillance towards less infected farms (Figure 3.3).

Human exposure

Active surveillance added to passive surveillance decreases the risk of outbreaks with higher human exposure than in the median of baseline outbreaks 3.4. Especially for the scenario with clinical protection, the human exposure is less when active surveillance is added to passive surveillance.

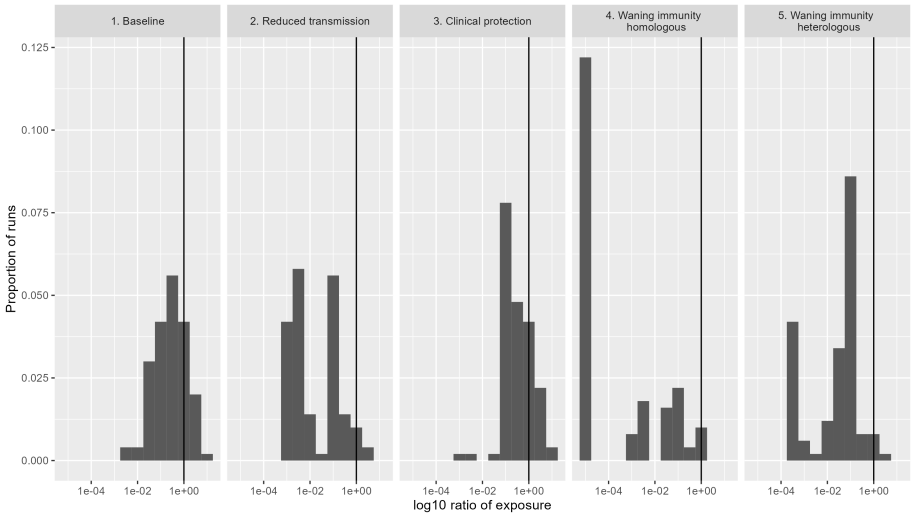


Figure 3.4: Exposure as sum of all infected farms in an outbreak with active and passive surveillance relative to baseline scenario with only passive surveillance

Chapter 4

Conclusions, discussion, and recommendations

4.1 Conclusions

Based on our model calculations, vaccination is not expected to increase the exposure of humans to HPAIV. Increased detection times do not lead to higher exposure in most scenarios, because an outbreak in a farm has a lower number of infected birds and there is reduced transmission from birds-to-humans reduce exposure. Also less farms will be infected given vaccination due to a smaller probability of a major outbreak, further reducing exposure on a national level. Only under the specific conditions that transmission is not (or hardly) reduced and clinical symptoms are absent in vaccinated animals, vaccination might increase human exposure. This particular situation seems unlikely for (vector) vaccines [9], but cannot be excluded such that monitoring is required.

Vaccination results in a reduced speed of spread and reduced mortality of high HI titre birds resulting in longer detection times for passive surveillance, such that weekly active surveillance (bucket sampling) has an added value by reducing the time until detection and detecting otherwise undetected farms. This will result in less exposure to humans. For unvaccinated farms active surveillance implemented as *weekly* bucket sampling will have some but limited added value, because outbreaks are readily detected by passive surveillance. More frequent bucket sampling can reduce the detection time as was shown previously [11].

4.2 Discussion

This report uses a simulation model to investigate the risk of a situation that is not present in reality. This means that the results are a structured summary of current knowledge and certain simplifications were required to keep the model

tractable and outcomes interpretable. An important assumption underlying our calculations is that the human exposure can readily be calculated from the exposure to birds accumulated over time. We refrained from calculating an absolute probability of infection of humans (e.g. 10% versus 20% chance of contracting the infection during an outbreak). To do this one would at first require a dose-response of avian influenza to humans. Such studies have been conducted for human adapted influenza viruses [6, 12], but this cannot directly be translated to poultry adapted strains. Secondly, this would require a proper quantification of the number of virus particles a human is exposed to in an outbreak. This varies between different people, stables, weather conditions etc. Therefore, this is unfeasible and for the purpose of this study not necessary.

Our outcome quantifies the cumulative exposure towards humans in a more abstract way. The question is not *how much* vaccination will change the risk of humans, but *if* it will increase or decrease compared to the situation without vaccination. Therefore, we report the ratio of exposure of humans between the scenario with and without vaccination. This ratio cannot directly be interpreted as a relative risk (ratio between probability of being infected for the vaccinated scenarios and unvaccinated scenarios). If the exposure is low and the probability of infection increases (almost) linearly with exposure, the ratio between exposure will be close to the relative risk, but if exposure is high and the probability of infection approximates 1 in both the scenarios with and without vaccination the relative risk is 1. Therefore, the actual relative risk is between the reported ratio and 1. In this study we therefore present visualisations rather than numbers, because the interest lies in a qualitative result, whether vaccination increases or decreases the risk of human infections.

Four assumptions in the between-farm model might influence results on the effectiveness of vaccination. The first assumption is that vaccines are protective from the moment of the start of a production cycle. This will overestimate the effectiveness of vaccines. This is a simplification of the reality, that effects the total number of infected farms in the simulations. The second assumption is that farms with a minor outbreak do not contribute to exposure to humans. This will slightly underestimate the exposure in simulations with vaccination, but the impact is negligible due to the short infectious period and extremely low number of infected birds. Thirdly, we have also assumed that all layers receive the vaccine. There is no differentiation between farms or birds. This might overestimate the effect of vaccination, but will not increase the exposure of humans above that of a situation without vaccination. Lastly, we assume infection dynamics and related detection times to be similar for layers, broilers, ducks and turkey. Silent spread among other types and species of poultry than layer might occur [10]. Again this will not affect the conclusion in an change of risk between a situation with or without vaccination in a qualitative way. The only concern would be when new variants are able to evolve, but that is outside the scope of this assessment.

Clinical protection might increase human exposure due to the handling of

infected birds. Although professionals in the poultry sector are aware of the zoonotic potential of HPAIV, absence of clinical symptoms could lead to more contact between humans and infected birds, if these birds are not recognized as being infected. The risk for humans could then increase when the vaccines are protecting against clinical symptoms but not or inefficiently against transmission. The change in human behaviour is, however, not part of this assessment.

Clinical protection by vaccination has been observed with other vaccines, but then also seems to reduce transmission [20, 15, 18]. Our simulations show that reduced transmission in a part of the layers in a flock can reduce exposure to humans. This might be the reason that vaccination campaigns although with variable effectiveness [22] in endemic countries can result in less human cases [1]. Vaccination might have played a role, but of course other factors such as increased awareness, improved bio-security and other control measures could have played a role.

4.3 Recommendations

To accommodate for uncertainty around the risks of human exposure, the following recommendation can be made based on this modelling study:

- The HI titres dynamics in a real life circumstances during the entire life cycle of a flock will be found in the current field experiment. With these new figures this risk assessment should be updated.
- Active surveillance could monitor the occurrence of undetected outbreaks and the extend of clinical protection in flocks where the virus can spread. At first such surveillance can determine whether *silent spread* does occur, and if this is indeed the case a program can be designed to detect infected farms within a reasonable time. The results of the current model can be used to evaluate the benefit of active surveillance. The costs of such a program can be calculated to evaluate different surveillance strategies on feasibility and cost-effectiveness.

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Appendix A

Technical description of the models

A.1 Overall approach

The modelling approach is two-fold. First we determine the effect of vaccination on within-farm spread with a stochastic individual-based model for different production types. This model will be used to determine key-parameters such as detection time, exposure of humans and probability of a major within-farm outbreak. These key-parameters are used in the stochastic individual-based spatial explicit between-farm model in which the farm is the epidemiological unit.

A.2 Within-farm model

The within-farm models is a two-type stochastic SIR model. The individuals can move from one type to another type as long as they are susceptible. The deterministic version of the model is

$$\frac{dS_i}{dt} = -\left(\beta_{ii} I_i + \beta_{ji} I_j\right) \frac{S_i}{N} - \mu S_i - \nu_{ij} S_i + \nu_{ji} S_j \tag{A.1}$$

$$\frac{dI_i}{dt} = \left(\beta_{ii} I_i + \beta_{ji} I_j\right) \frac{S_i}{N} - (\mu + \gamma_i) I_i \tag{A.2}$$

$$\frac{dR_i}{dt} = (1 - \phi_i)\gamma_i I_i - \mu_i R_i \tag{A.3}$$

$$\frac{dDS_i}{dt} = \mu S_i \tag{A.4}$$

$$\frac{dDI_i}{dt} = (\phi_i \gamma_i + \mu) I_i \tag{A.5}$$

$$\frac{dDR_i}{dt} = \mu R_i \tag{A.6}$$

The model describes susceptible animals that are either of one of two types (subscripts i or j). From next section on-wards, we define two classes high titre (h) and low titre (l) after vaccination. Transition between these types occurs at rate ν_{ij}. Transmission of the infection occurs with transmission parameters specific for transmitting and receiving animal β_{ij}. Infectious birds loose the infection at a type specify rate γ_i. All animals experience a background mortality μ, but infectious animals additionally die at recovery with probability ϕ_i.

In the continuous time Markov chain model (CTMC) the continuous flows are replaced by stochastic discrete changes in variables with specific rates (Table A.1) at which these 'jumps' occur or probabilities at infection age. The latter is

Jump	Rate
$S_i \to S_j$	ν_{ij}
$S_i \to I_i$	$\left(\beta_{ii} \frac{I_i}{N} + \beta_{ji} \frac{I_j}{N}\right)$
$I_i \to R_i$	$(1 - \phi_i)\gamma$
$S_i \to DS_i$	μ
$I_i \to DI_i$	$\mu + \phi\gamma$
$R_i \to DR_i$	μ

Table A.1: Transitions of the stochastic model: Either rate or probability at time at infection age a

Reproduction number $\mathcal{R}$ and probability of a minor outbreak

The reproduction number for the model is the average of infections caused by both types.

$$\mathcal{R} = \frac{1}{2}\left(\frac{\frac{N_l}{N}\beta_{ll}}{\gamma_l} + \frac{\frac{N_h}{N}\beta_{hh}}{\gamma_h} + \sqrt{\left(\frac{\frac{N_h}{N}\beta_{hh}}{\gamma_h} - \frac{\frac{N_l}{N}\beta_{ll}}{\gamma_l}\right)^2 + \frac{4\frac{N_h}{N}\beta_{lh}\frac{N_l}{N}\beta_{hl}}{\gamma_l\gamma_h}}\right) \quad \text{(A.7)}$$

To estimate the probability of a minor or major outbreak, the CTMC model is approximated by the Galton–Watson two-type branching process near the disease-free equilibrium [17]. Specifically the derivation[17] for a model with differences in host infectivity is used. In short a two-type branching process near the disease-free equilibrium is a stochastic process that describes the"offspring" generated by a case in the next time. This model is based on the assumptions that the number of infecteds is much smaller than the total population size, and thus depletion of susceptibles can be neglected. Furthermore each 'branch' is considered to be independent.

The probability of a minor outbreak calculated initialized by i_l and i_h birds with low or high titres [17]:

$$\mathbb{P}_{minor} = q_l^{i_l} q_h^{i_h} \Rightarrow \mathbb{P}_{major} = 1 - \mathbb{P}_{minor} \quad \text{(A.8)}$$

The q_l and q_h are interpreted as the independent probabilities of extinction, when the infection is introduced by on animal of low or high titre respectively. These values are obtained by solving the following system:

$$q_h = f_h(q_h, q_l) \quad \text{(A.9)}$$

$$q_l = f_l(q_h, q_l) \quad \text{(A.10)}$$

In which f_l and f_h of offspring probability generating functions (pgf's) from one low l or one high titre h animals:

$$f_h(u_h, u_l) = \left(1 + \frac{(1-u_h)\frac{N_h}{N_h+N_l}R_{hh} + (1-u_l)\frac{N_l}{N_h+N_l}R_{hl})}{a_h}\right)^{a_h} \quad \text{(A.11)}$$

$$f_l(u_h, u_l) = \left(1 + \frac{(1-u_h)\frac{N_h}{N_h+N_l}R_{lh} + (1-u_l)\frac{N_l}{N_h+N_l}R_{ll})}{a_l}\right)^{a_l} \quad \text{(A.12)}$$

$$\text{(A.13)}$$

This system was solved numerically by function `multiroot` in R-package `rootSolve`.

Outbreak simulations

The model as described in section A.2 (Table A.1) is simulated using R in which we implemented the Sellke construction [8]. The code of the model can be found on GitHub (https://github.com/EgilFischer/HPAIVaccination.git). For each scenario (Table 1.1) the model was run 10 times. Each run represents an outbreak and was later used to determine the detection time and human exposure. This allows for comparison of different detection methods and parameter settings for the detection model for the same outbreaks.

Detection model

The detection model has two different types of detection methods 1. passive surveillance and 2. active surveillance. The minimum detection time was determined as the minimum time of either of these two for an outbreak. The active surveillance model is stochastic and will be run on the same outbreak for several times. The passive surveillance model is deterministic and will only provide one detection time per outbreak. Parameters of the detection model can be found in Table 2.1.

passive surveillance passive surveillance is based on a simple principle of reaching a specific number of dead birds during a given interval or during subsequent intervals. This includes all dead birds including non-infected or recovered birds. Here we use the protocol in which a farmer is obliged to report death above 0.5% of the flock during two consecutive days. The passive surveillance time will thus be the second day in which the number of deaths is 0.5% of the flock.

active surveillance active surveillance is based on screening at the end of a given interval of a certain number of animals with a given test sensitivity. For each interval the number of dead animals is added, and each infected or recovered animal has a probability of being sampled and to test positive (sensitivity). The probability of a farm being detected is the probability of a farm being inspected multiplied by the probability that at least one animal in the sample tests positive. This can be done on dead animals or on living animals. Here we considered the protocol in which dead birds are screened for avian influenza in all farms at a weekly interval with a per infected bird sensitivity of 0.99 (Table 2.1).

A.2.1 Human exposure

A first approach would be to attempt to quantify the amount of viable virus particles in the stable, to calculate the number of viable virus particles inhaled by a human and subsequently calculating the probability of being infected. To our knowledge only experimental data is available for human adapted influenza viruses [12, 6]. This approach would, however, introduce several parameters with high uncertainty. Therefore we approach the matter by comparing the exposure of humans relative to the baseline based on two simple assumptions:

1. The decrease in virus shedding in high titre birds is completely reflected by a decrease in transmission rate.

2. The transmission rates of birds to humans is proportionate to the transmission rate of birds to birds

With β_{ii} being the transmission rate from type i to animals of the same type and α a scaling factor for susceptibility if humans to this strain. The exposure

of a human being infected at a certain time t is thus:

$$H(t) = \int_0^t -\alpha \frac{\beta_{ll} Y_l(\tau) + \beta_{hh} Y_h(\tau)}{N} d\tau \tag{A.14}$$

The number of infectious birds (Y_l and Y_h) are obtained from the simulation of the stochastic model. From this model we define the course of outbreaks and the moment of detection based on the number of dead birds in a given interval. We simulate both unvaccinated and vaccinated situations and report the ratio of the total exposure until the detection time of an outbreak over the average of the unvaccinated (baseline) simulations.

A.3 Between-farm model

The between-farm model is an individual based model in which the individual farm is the epidemiological unit. Each farm has three fixed characteristics: location, size and species. The vaccination status is the fourth characteristic is drawn for each run of the model.

Infection events

The infection events are determined by the between-farms transmission kernel ($h(r_{ij})$) and the probability of a major outbreak on the receiving susceptible farm based on the vaccination status (π_{major}). The Sellke algorithm enables an efficient simulation process [2, 8]. For each individual farm a random threshold is determined, and the farm is infected at the moment that the cumulative force-of-infection ξ exceeds this threshold. The cumulative force-of-infection is the force-of-infection exerted at this farm by all infected farms while these are infectious.

$$\xi(i) = \pi_{major}(i) \int_0^t \sum_{j \in J} I_j(\tau) h(r_{ij}) d\tau \tag{A.15}$$

$$I_j(t) = \begin{cases} 1, & \text{if } t \geq t_0 \ \ \& \ \ t \leq t_0 + T_j \\ 0 & \text{otherwise} \end{cases} \tag{A.16}$$

Infectious period T

The infectious period of a farm is determined by the detection time. We assume that the infectious period ends at the moment of detection. The moment of detection is determined by the vaccination status as described in the within-farm model. To obtain an estimate for the distribution of detection time, a gamma-distribution was fitted on the results of the within-farm model using R-package `fitdistrplus` version 1.1.8.

The function between the mean and variance (or standard deviation) of detection time T_d are functions of farm size, vaccination status and type of farm (layer yes/no).

Human exposure

Human exposure per farm is derived from the within-farm model assuming the full potential of exposure until detection or fade-out. To obtain an estimate for the distribution of human exposure, a gamma-distribution was fitted on the results of the within-farm model using R-package `fitdistrplus` version 1.1.8. We defined a function for the mean and variance of the distribution for the size, type and vaccination status of the farm. Detection time was not considered as a factor because the variation in the human exposure was already determined (mainly) by these three factors.
The function between the mean and variance (or standard deviation) of human exposure H were based on farm size, vaccination status and introduction time.

Initialization

Index farms were selected randomly in a high density poultry area (HDPA) or a low density poultry area (LDPA). DPPA farms were random selected from those farms with the 5% percentile highest point density within 1 km from a farm. SPPA were randomly selected among the 75% percentile lowest point density within 1 km.

A.4 Parameterization

Parameters of the baseline model are given in Table 2.1 and those of the scenarios in Table 1.1.

Farms The size of farms in 2022 were obtained from the *Rijksdienst voor Ondernemend Nederland* (RVO) via Wageningen Bioveterinary Research. For the within-farm scenarios, the 25%-percentile, median and 75%-percentile of layer and broiler farms were used. The length of a production round (42 days for broilers and 540 days for layers) and background mortality (0.0005 day^{-1}) was obtained by expert elicitation (pers. comm. Dr. Mieke Matthijs).

Transmission The within farm model was parameterized on the experiments done at WBVR and other literature. In the study by WBVR [9], the average infectious period was 3 for the control group and 4 for the vaccinated group. The infectious period was modelled as a gamma distribution with these values as mean and a rate parameter of 20 [13]. The transmission coefficient of low titre birds was obtained from [9]. In this study the transmission coefficient of high titre birds was 0, but using the final size method an upper limit of 0.7

of the reproduction number could be obtained. The transmission coefficient can be calculated by dividing the reproduction number by the infectious period resulting in 0.175 for the WBVR study [9]. Here we chose to take a lower value (0.058 day^{-1}) obtained from a previous study in which it could be estimated [21] .

Clinical protection Unvaccinated infected chickens do not survive the infection [9]. For vaccinated chickens 0.1% was expected to die of the infection.

Waning of high titre For the duration of a high titre (Figure A.1, the parameters of a gamma distribution were calibrated on the data of Table 1 of Rudolf et al. 2010. High titres were titre $\geq 5log_2$ against challenge strain antigen (H5N2) and challenge strain antigen (H5N1) after basic immunization. Basic immunization was vaccination at age 20 weeks and 4 weeks later.

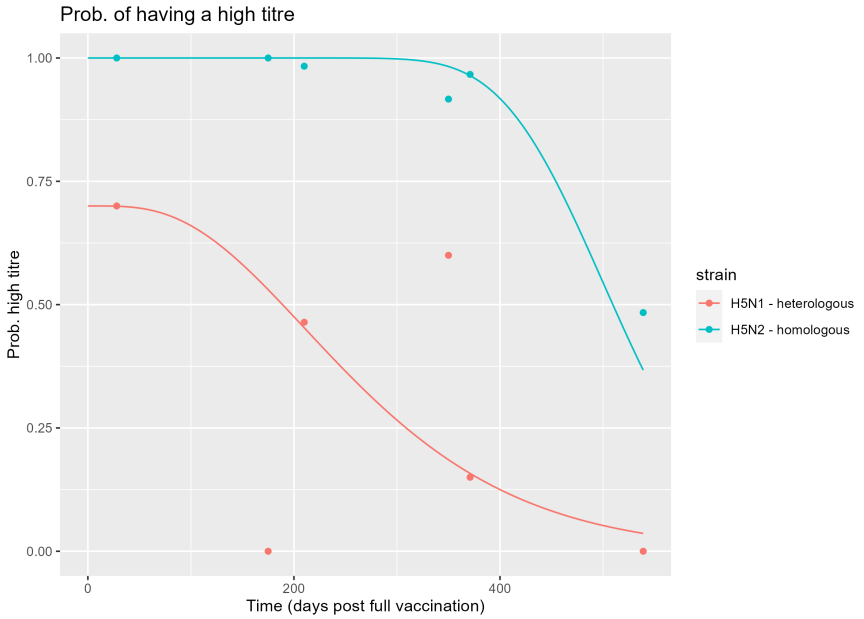

Figure A.1: Duration of high titre. Dots are fraction of vaccinated birds with high titre $\geq$ 5 $\log_2$ against the heterologous H5N1 strain antigen and the homologous H5N2 strain after basic immunization. Table 1 in Rudolf et al. 2010. Solid line is probability of having a high titre based on calibrated gamma distribution.

Between farm transmission The between-farm model uses the transmission kernel for HPAI in the Netherlands from the outbreak of 2003 [4, 2]. The

locations, size and type of farms in 2022 were obtained from the *Rijksdienst voor Ondernemend Nederland* (RVO) via Wageningen Bioveterinary Research.