MAJOR ARTICLE

Avian Influenza A Virus (H7N7) Epidemic in The Netherlands in 2003: Course of the Epidemic and Effectiveness of Control Measures

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An epidemic of high-pathogenicity avian influenza (HPAI) A virus subtype H7N7 occurred in The Netherlands in 2003 that affected 255 flocks and led to the culling of 30 million birds. To evaluate the effectiveness of the control measures, we quantified between-flock transmission characteristics of the virus in 2 affected areas, using the reproduction ratio R_h. The control measures markedly reduced the transmission of HPAI virus: R_h before detection of the outbreak in the first infected flock was 6.5 (95% confidence interval [CI], 3.1–9.9) in one area and 3.1 in another area, and it decreased to 1.2 (95% CI, 0.6–1.9) after detection of the first outbreak in both areas. The observation that R_h remained >1 suggests that the containment of the epidemic was probably due to the reduction in the number of susceptible flocks by complete depopulation of the infected areas rather than to the reduction of the transmission by the other control measures.

Influenza A viruses are common pathogens in various animal species, such as pigs, birds, horses, and humans [1]. Although only a few hemagglutinin (H) and neuraminidase (N) subtypes have been isolated from mammals, all subtypes have been isolated from birds [1]. High-pathogenicity avian influenza A (HPAI) virus strains can be devastating to poultry flocks because of their high transmissibility and high associated mortality rate [2]. HPAI is, therefore, categorized as an Office International des Epizooties list A disease [3]. Moreover, it is generally accepted that avian influenza (AI) viruses have played a crucial role in the start of human influenza pandemics [4, 5].

Outbreaks of HPAI most likely originate from wild waterfowl that are endemically infected with low-pathogenicity AI (LPAI) strains of the H5 and H7 subtypes. These LPAI strains can be transmitted directly from waterfowl to poultry and subsequently mutate into HPAI strains [2]. Outbreaks of HPAI among poultry are, therefore, difficult to prevent. Because of the potentially devastating effect on poultry and the possible public health risk, outbreaks of HPAI should be controlled as quickly as possible, to reduce virus output.

In the European Union (EU), the regulations for the control of HPAI strains are imposed by EU council directive 92/40/EEC [6]. Virus output is reduced by the killing and removal of infected poultry flocks (culling). This approach is followed in most countries—for instance, during outbreaks in Italy (1999–2000), the Netherlands (2003), most countries in Asia (2003–2004), and the United States (2003–2004). The culling of infected flocks is often accompanied by the depopulation (killing and removal) of uninfected flocks in the vicinity of the infected flock (preemptive culling) and other veterinary measures, such as a ban on the transport of poultry and poultry products and hygienic measures [6]. The question, however, is whether these measures are sufficient to stop the further spread of the virus

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Table 1. Control measures and their presumed effect on the spread of infection.

Control measures	Time of implementation	Presumed effect[a]
Ending transport of poultry and poultry products	28 February	Reduction of no. of contacts between flocks
Tracing dangerous contacts	1 March	Reduction of infectious period
Instituting hygienic measures	1 March	Reduction of transfer of infectious material when a contact is established
Culling infected flocks	4 March	Reduction of infectiousness (duration of infectious period)
Culling of contiguous flocks	2nd week of March onward	Reduction of infectiousness and of the density of susceptible flocks
Compartmentalizing of infected flocks	3rd week of March onward	Reduction of no. of contacts

NOTE. A chronology of main events during the epidemic and a list of decisions adopted by the standing Committee on the Food Chain and Animal Health of the European Commission can be found in reference [14].

[a] Contributions of individual measures to the overall reduction of virus transmission cannot be established [39]

during an outbreak. If not, additional measures, such as the vaccination or preemptive culling of flocks in large areas, may be necessary. Knowledge of the effectiveness of the control measures implemented during an epidemic [7] is important to determine how to control future outbreaks of HPAI strains.

The aim of the present study was to give a concise overview of the course of the Dutch epidemic and to quantify the effectiveness of the control measures implemented. To this end, we used an epidemiological model with the categories susceptible, latently infected, infectious, and recovered (SEIR) to estimate the reproduction ratio during various phases of the epidemic.

COURSE OF THE EPIDEMIC

On 28 February 2003, a suspected outbreak of AI in 1 flock of a commercial layer farm, consisting of 3 flocks, located in the most poultry-dense area of The Netherlands (Gelderse Vallei), was reported (figure 1). Mortality increased in 1 of 3 flocks from 1% on 22 February to ~90% on 28 February [8]. AI was diagnosed by the Dutch national reference laboratory (Central Institute for Animal Disease Control) by detection of HPAI type H7N7 [8–10]. The source was hypothesized to be an HPAI strain that emerged during an outbreak of an LPAI strain among poultry held in another shed. Antibodies against H7 were detected in 17 of 20 serum samples obtained from birds in that shed. Comparable routes of virus introduction were hypothesized for other outbreaks of AI [11–13].

This presumed index case was the start of a huge epidemic in The Netherlands. In accordance with Annex VI of Directive 92/40/EEC of the EU [6], control measures—such as culling and banning the movement of infected flocks and tracing and screening of the infection—were implemented, followed by preemptive culling of flocks in a 1-km zone around the infected flock (contiguous flocks) (table 1). A chronology of the main events and a list of decisions adopted by the standing Committee on the Food Chain and Animal Health of the European Commission is available [14].

The culling of infected flocks started on 4 March. At first, the killing was limited to 7000 birds/h, but this increased in the following weeks and reached 750,000 birds/day at the end of the epidemic in May [15]. The number of new outbreaks fluctuated between 2 and 11 cases/day until the end of March, without a clear trend up or down. By the start of April, the number of outbreaks per day had decreased markedly (figure 2). Almost all flocks in the infected area had been culled by that time. Virus transmission to another poultry-dense area (Limburg) caused infection in a further 43 flocks. This affected area was also cleared of all commercial flocks and those of hobbyists. Figure 1 shows the distribution of the infected flocks in The Netherlands.

The epidemic lasted 2 months—the last outbreak was detected on 7 May 2003. In total, 255 flocks became infected, and 1255 commercial flocks and 17,421 flocks of hobbyists, accounting for 30 million birds, were culled [10, 15]. HPAI H7N7 virus was isolated from 241 of the infected flocks [10], and seropositive animals were found in the other 14 flocks. The virus was transmitted to 89 people who had been in close contact with infected poultry [16], and 1 person died [17, 18].

MATERIALS AND METHODS

The between-flock transmission of HPAI virus was quantified by means of the reproduction ratio (R_h) [7], which is defined as the average number of secondary infections (i.e., infected flocks) caused by 1 infectious flock. If $R_h > 1$, each infected flock infects, on average, >1 susceptible flock, and a chain reaction of infections may occur. If $R_h < 1$, a prolonged chain reaction of infections is not possible, and the epidemic comes to a halt.

Data and reconstruction of the epidemic. For our purposes, R_h was calculated as the product of the infectious period at the flock level T (per time period) and the transmission rate at the flock level β (unit, time) [7]: $R_h = \beta T$. However, neither the infectious period T nor the transmission parameter β was measured directly. Instead, the infectious period was estimated for each flock as the period between the moment of detection

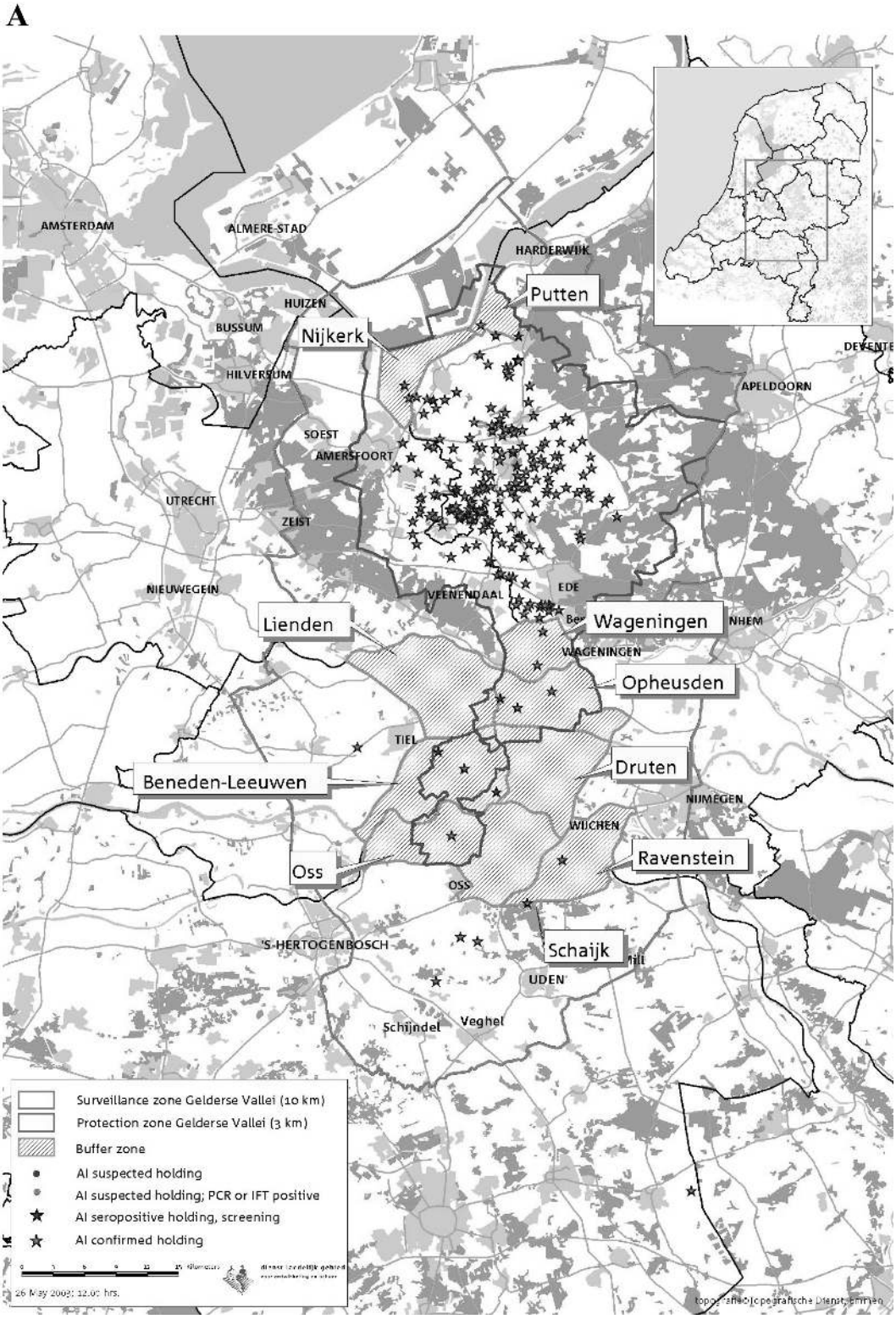

Figure 1. Distribution of the infected flocks during the 2003 epidemic of avian influenza (AI) in The Netherlands (*A,* Gelderse Vallei; *B,* Limburg)

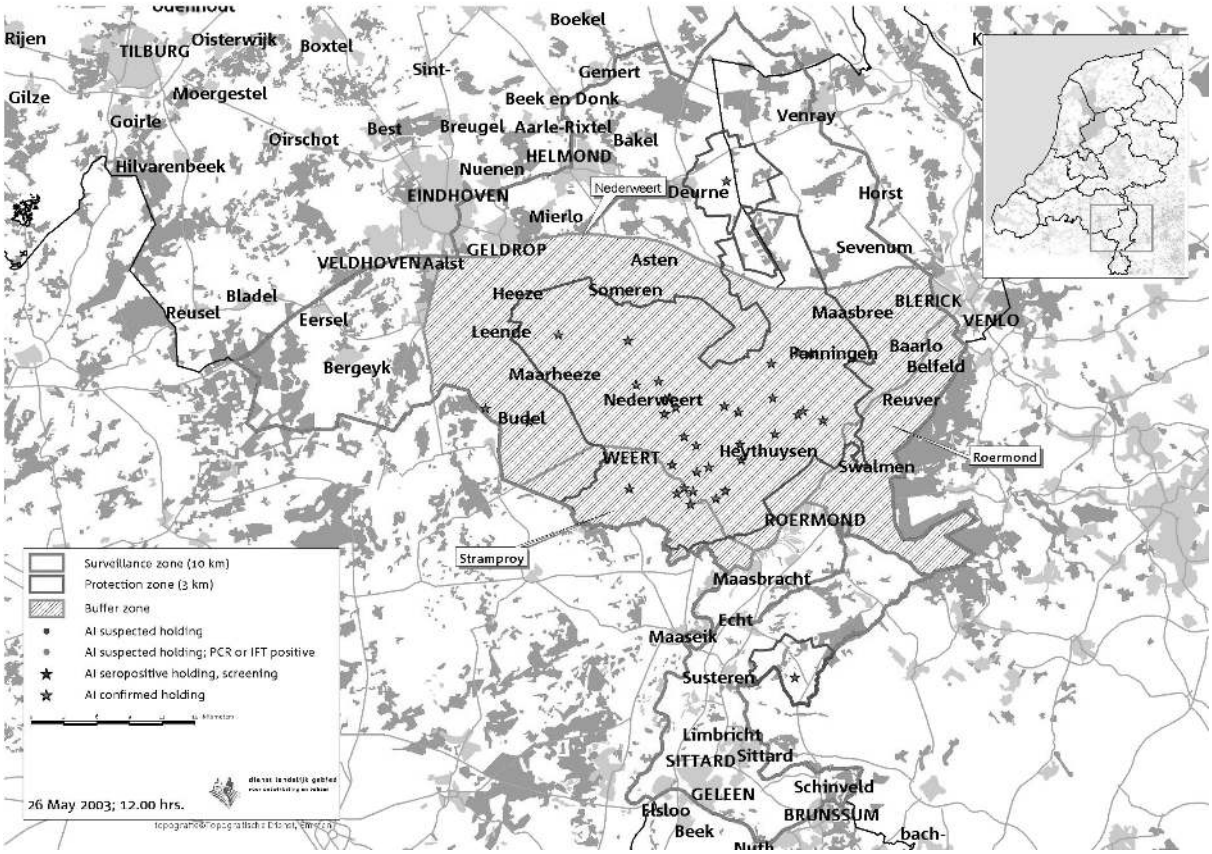

Figure 1. *(Continued.)*

(i.e., the day on which mortality was first noticed to have increased) and the moment of culling, plus an extra 4 days, to cover the time before the infection was detected but during which birds were infectious. This estimate was based on within-flock mortality, data feed-uptake data [10], and the infectious period of individual chickens, which was experimentally determined to be between 2 and 6 days [19].

Estimation of the transmission parameter requires knowledge of the number of susceptible and infectious flocks over time and the number of new cases (infected flocks) per period. We assumed that, from the moment of introduction of the virus, a flock would be latently infected for ~2 days [19] and would then become infectious (4 days in our default scenario; see above), after which time the infection would be detected. Figure 3 shows the reconstructed number of susceptible and infectious flocks as a function of time, together with the reconstructed number of cases.

The outbreak in The Netherlands took place in 2 clearly distinguishable areas and during 2 periods, with only limited overlap: the Gelderse Vallei in the central part of The Netherlands and Noord Brabant/Limburg in the southern part of The Netherlands (henceforth called Limburg; figures 1 and 3). For this reason, the data for each area were analyzed separately.

Analysis. The transmission parameter β (i.e., the average rate at which an infected flock infects susceptible flocks in a population consisting almost exclusively of susceptible flocks) of the stochastic SEIR model was estimated by means of a generalized linear model (GLM) [20]. Our implementation is a straightforward generalization of the GLMs described by Becker [21] that have been used previously in the context of the classic transmission of swine fever virus between pig farms [22] and the transmission of foot-and-mouth disease virus between cattle farms [23].

To obtain estimates of the transmission parameter, data on the date of detection and on the number of susceptible and infectious flocks were transformed into the format *[S(t), I(t), C(t)]*, where *S(t)* is the deduced number of susceptible flocks present at time *t* (i.e., taking into account culling and infection), *I(t)* is the deduced number of infectious flocks at time *t*, and *C(t)* is the number of new cases (infected flocks) that have arisen between time *t* and time $t+1$. The total number of flocks

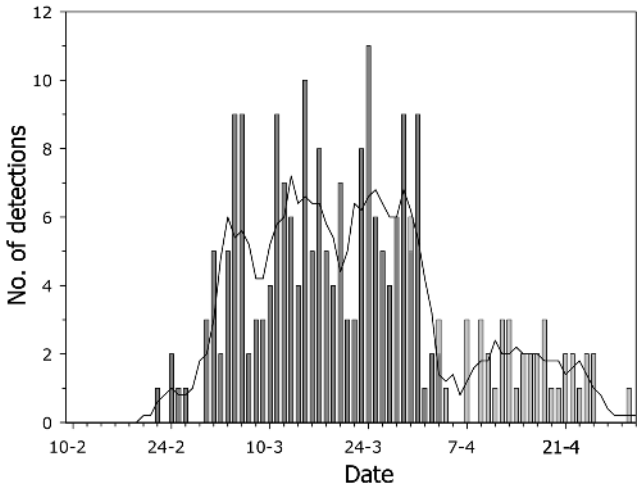

Figure 2. Course of the no. of detected outbreaks during the 2003 epidemic of avian influenza (AI) in The Netherlands. *Dark bars,* Gelderse Vallei; *light bars,* Limburg; *lines,* 5-day moving average.

before the start of culling is given by N. For the Gelderse Vallei, $N = 984$; for Limburg, $N = 378$.

By standard reasoning, we accept that the number of cases $C(t)$ arising in a fixed time period (1 day in the present study) is binomially distributed with the parameter [7]

$$p_{\text{inf}}(t) = 1 - e^{-\beta\frac{I(t)}{N}} \quad (1)$$

(the probability of infection) [21] and binomial totals S:

$$C(t) \sim \text{Bin}\left[\text{S(t)},\ 1 - e^{-\beta\frac{I(t)}{N}}\right] . \quad (2)$$

Notice that the above model entails the following implicit assumptions: (1) all susceptible flocks are equally susceptible, (2) all infected flocks are equally infectious, and (3) each infected flock poses an independent and identical risk of infection to each susceptible flock. These assumptions can be relaxed, but this seems wise only if a large amount of data is available or if the fit of the model is unsatisfactory.

In the above model, $\ln(\beta)$ was estimated by use of a complementary log-log link function (i.e., $\ln[\ln(1 - p_{\text{inf}})]$), with $\ln\{[I(t)]/N\}$ as an offset variable. The fit of the model was checked by inspection of the residual deviance, which, under standard assumptions [16], is approximately χ^2 distributed, with degrees of freedom given by the number of records minus the number of estimated parameters. All analyses were done by use of GenStat software (version 6; VSN).

The infectious periods of the flocks were calculated as described above, on the basis of the moment of detection and the moment of culling. R_h was calculated as the product of the estimates of the transmission parameter and the infectious period: $\hat{R}_h = \hat{\beta}\hat{T}$. The corresponding confidence interval (CI) was based on the identity (under the assumption that β and T were independent) $\text{Var}(\beta T) = (E\beta)^2\,\text{Var}(T) + ET^2\,\text{Var}(\beta)$ [24]. Substitution of the estimated means and variances of β and T into this formula yields an estimate of the variance of R_h, which can be used to calculate the CI. Because the model yields estimates of $\ln(\beta)$, we took into account that (asymptotically) $\hat{\beta}$ is log-normally distributed. Hence, $E\beta$ and $\text{Var}(\beta)$ were calculated as $E\beta = e^{\mu+\frac{1}{2}\sigma^2}$ and $\text{Var}(\beta) = (E\beta)^2(e^{\sigma^2} - 1)$, where μ and σ^2 denote the (estimated) mean and variance of $\ln(\beta)$, respectively.

Scenarios. To investigate whether the transmission rate decreased after AI was detected, we distinguished 2 time periods in the analyses: before and after the detection of AI. Thus, separate analyses were performed for data for before and after 1 March in the Gelderse Vallei and before and after 3 April in Limburg. We performed an additional analysis for data for the Gelderse Vallei, before and after 14 March, when culling had reached its highest level.

To check the robustness of the results regarding the assumptions about the infectious period and the latent period

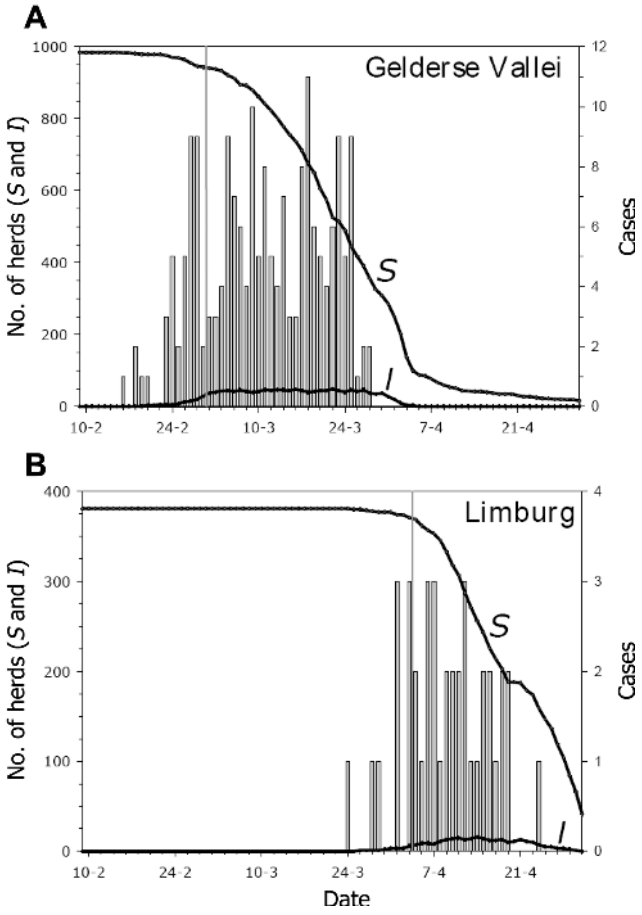

Figure 3. Reconstruction of the epidemic in the Gelderse Vallei *(top)* and Limburg *(bottom).* Shown are the reconstructed number of susceptible *(S)* and *(I)* infectious flocks *(lines; left),* and the daily no. of new cases *(bars; right).*

before detection (2-day latent period and 4-day infectious period in our default scenario), we also analyzed scenarios in which the latent period was 8 days and the infectious period before detection was 2 days.

To check the robustness of the model with respect to assumptions concerning the transmission term, we considered a model in which the transmission probability p_{inf} depended on the relative frequency of infected flocks rather than on the absolute number of infectious flocks:

$$p_{\text{inf}}(t) = 1 - e^{-\beta \frac{I(t)}{N(t)}} \quad . \tag{3}$$

In technical terms, the model specified by equations (1) and (2) is commonly called a "density-dependent" model, because the contact rate and infection probability depend on the (initial) density of infectious flocks. The model specified by equation (3) is referred to as the "frequency-dependent" model, because the overall contact rate, the effective contact rate (i.e., the rate at which contacts are made with infectious flocks), and the probability of infection depend on the fraction of flocks that are infectious but not on the density of infectious flocks. Hence, the density-dependent model assumes that the contact rate decreases if the number of flocks decreases, whereas the frequency-dependent model assumes that the contact rate is constant [25, 26].

RESULTS

Transmission parameter. The estimate of the transmission parameter β decreased significantly after the detection of AI in both areas (table 2). In fact, the between-flock transmission parameter decreased from $\beta_{\text{before}} = 0.47$/day before detection to $\beta_{\text{after}} = 0.17$/day after detection in the Gelderse Vallei and from $\beta_{\text{before}} = 0.39$/day to $\beta_{\text{after}} = 0.18$/day in Limburg. However, the mean deviance before and after notification of the circulation of HPAI virus was 1.6 and 1.5, respectively, in the Gelderse Vallei and 1.4 and 1.0, respectively, in Limburg, which indicates that there was some overdispersion with respect to the model.

We also performed analyses in which the latent period was increased stepwise from 2 to 8 days. The assumption of a latent period of 8 days resulted in $\beta_{\text{before}} = 0.80$/day and $\beta_{\text{after}} = 0.10$/day for the Gelderse Vallei and $\beta_{\text{before}} = 0.90$/day and $\beta_{\text{after}} = 0.11$/day, respectively, for Limburg. The assumption of a longer latent period invariably resulted in an increase in the estimate of the transmission parameter before detection and an exacerbation of the differences between the estimates of the transmission parameter before and after detection.

The assumption of a longer infectious period before detection resulted in (1) lower estimates of the transmission parameter both before and after detection and (2) higher estimates of the prevalence of infection but also did not qualitatively alter the results. The assumption of a shorter infectious period was shorter resulted in an increase in the estimates of the transmission parameter for both periods.

To investigate the robustness of the above results with respect to transmission, we considered a scenario in which transmission was frequency dependent instead of density dependent (see the Analysis subsection above). The frequency-dependent model consistently produced lower estimates of the transmission parameter after detection than did the density-dependent model, whereas the estimate of the transmission parameter before detection was not affected. Specifically, in the frequency-dependent model, the estimates of the transmission parameter were $\beta_{\text{before}} = 0.47$/day and $\beta_{\text{after}} = 0.12$/day in the Gelderse Vallei and $\beta_{\text{before}} = 0.39$/day and $\beta_{\text{after}} = 0.12$/day in Limburg. In other words, the differences in the estimates of the transmission parameter before and after detection were consistently stronger in the frequency-dependent model than in the density-dependent model. This could be explained as follows: as long as the number of flocks remained constant, the 2 approaches gave identical results, because the infection probabilities in equations (1) and (3) were equal. If the number of flocks decreased, then, for a fixed number of infectious flocks, the prevalence of infection *[I(t)]/[N(t)]* in equation (3) was higher than in equation (1). Because of this, a lower transmission-rate parameter would be needed to explain the new cases.

Finally, we studied the consequences of analyzing the data in 2 separate analyses. The data for the period after AI detection in the Gelderse Vallei (28 February) were divided into a period from 28 February through 13 March and a period from 14 March onward, and the reproduction ratio was $\beta_{\text{up to 14-3}} = 0.15$/day (95% CI, 0.12–0.18) and $\beta_{\text{after 14-3}} = 0.19$/day (95% CI, 0.14–0.26), respectively. Thus, splitting the data set did not significantly alter the estimates of the transmission parameter.

Table 2. The transmission parameter (β), infectious period *(T),* and corresponding reproduction ratio *(R_h)* in the Gelderse Vallei and Limburg, before and after notification of the circulation of high-pathogenicity avian influenza A virus.

	Before notification			After notification		
Area	β /day	*T,* day	R_h	β /day	*T,* day	R_h
Gelderse Vallei	0.47 (0.3–0.7) [11]	13.8 (9.9–17.6) [5]	6.5 (3.1–9.9)	0.17 (0.1–0.2) [35]	7.3 (3.4–11.1) [185]	1.2 (0.6–1.9)
Limburg	0.39 (0.2–0.9) [9]	8.0 [2]	3.1	0.18 (0.1–0.2) [27]	6.9 (3.9–9.9) [38]	1.2 (0.6–1.9)

NOTE. Data are given as parameter (95% confidence interval) [no.].

For the other periods, the relatively small number of records ($n < 30$) made this type of analysis inappropriate.

Infectious period. In the Gelderse Vallei, the infectious period decreased from 13.8 days (95% CI, 9.9–17.6 days), for the 5 flocks suspected to have AI on the first day of detection, to 7.3 days (95% CI, 3.4–11.1 days), for the period after detection. In Limburg, the infectious period for the first 2 affected flocks was 7 and 9 days. During the period after detection, the average infectious period was 6.9 days (95% CI, 3.9–9.9 days).

R_h Although, in both areas, between-flock transmission decreased significantly after virus detection, R_h was still >1 ($R_h = 1.2$ for both areas) (table 2). This suggests that the control measures (table 1) were inadequate to interrupt the chain of infection. The containment of the epidemic was, therefore, probably due to the reduction in the number of susceptible flocks caused by depopulation of the infected areas rather than to the reduction of the transmission level by the other control measures (table 1).

DISCUSSION

Implications. We quantified the between-flock transmission characteristics (infectious period and transmissibility) of the HPAI H7N7 strain before and after detection of the first outbreak of AI in The Netherlands in 2003. Virus transmission apparently decreased considerably after the outbreak was first detected, and there is a strong indication that the infectious period decreased after the culling of infected flocks. As a consequence, R_h decreased quite strongly during the period after detection of AI, compared with that during the period before detection. This decrease is probably a consequence of the control measures implemented. Unfortunately, it was not possible to establish the contribution of individual measures to the overall reduction of virus transmission.

Although the control measures were effective in reducing transmission, the estimates of the reproduction ratio were still >1. This suggests that the control measures were probably not sufficient to halt the epidemic. In fact, containment of the epidemic may have been due to the depletion of susceptible flocks as a result of culling rather than to a decrease in the transmission rate. Therefore, the main value of the control measures may be in preventing the spread of virus to unaffected areas rather than in preventing the spread of virus within an area. This may be especially significant for areas with a high flock density, such as the Gelderse Vallei (mean flock density, >4 flocks/km^2), where an epidemic may be impossible to stop once it has taken off. This is in line with the findings in 1999 in Italy, where an outbreak of HPAI H7N1 virus spread quickly and extensively and could be controlled only by the depopulation of nearly all flocks in the affected area of 5500 km^2 [27].

Limitations and perspectives. We made a number of assumptions that could limit the scope and validity of the results. Apart from the assumptions about equal susceptibility and infectivity of flocks and the assumptions about the independence of transmission events (mentioned earlier), 2 other issues are important.

First, our analyses were based on rather simple and rigid assumptions about the relationships during the moment of detection, the latent period, and the infectious period before detection. Ideally, one would like to obtain more precise estimates of the (distribution of the) moment of virus introduction in a flock, as well as the viral output of infected flocks as a function of time. This would require data on the within-flock spread of the virus or within-flock mortality data in conjunction with within-flock transmission models. Nevertheless, in view of the qualitative robustness of the results with respect to assumptions about the infectious period and the latent period, we consider it to be highly unlikely that more refined analyses would yield qualitatively different results and conclusions.

Second, we ignored spatial considerations in our analyses, even though the vicinity of infected flocks substantially increases the risk of infection in susceptible flocks. We do not know to what extent the results of our study would be affected by the introduction of a spatial component (e.g., Keeling et al. [28]), but we are currently extending our analyses by including an estimate of a spatial "infection kernel." More detailed analyses into the local causes and risk factors of transmission of the HPAI virus from flock to flock would improve our understanding of the effectiveness of control measures.

Our results indicate that outbreaks of HPAI viruses are difficult—if not impossible—to control with usual measures in poultry-dense areas [6], and effective control could be achieved only by depopulation of the whole affected area. Moreover, new outbreaks can be expected, because AI virus strains are endemic in the wild waterfowl population [2]. It might be worthwhile to consider reducing the flock density of commercial flocks, to reduce the probability of another epidemic of this size, or to consider vaccinating poultry, as an additional control measure. Vaccination was used in outbreaks of LPAI in Italy in 2000–2002 [29, 30] and in Utah in 1995 [31, 32] and in an outbreak of HPAI in Mexico in 1994 [33]. Vaccination significantly reduces the excretion of virus [34–38], which may reduce virus spread in an infected area, thereby reducing the risk of human exposure. The risk of the introduction of AI virus into poultry from wild waterfowl might be reduced by keeping poultry indoors. However, this might be unacceptable to the general public, which prefers the idea of free-range poultry for (presumed) welfare reasons.

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