Antiviral Research 99 (2013) 245–250

Contents lists available at SciVerse ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

The potential of antiviral agents to control classical swine fever: A modelling study

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ARTICLE INFO

Article history:
Received 7 April 2013
Revised 20 June 2013
Accepted 21 June 2013
Available online 1 July 2013

Keywords:
Classical swine fever
Pestivirus
Antiviral
Stochastic simulation model
Control strategy

ABSTRACT

Classical swine fever (CSF) represents a continuous threat to pig populations that are free of disease without vaccination. When CSF virus is introduced, the minimal control strategy imposed by the EU is often insufficient to mitigate the epidemic. Additional measures such as preemptive culling encounter ethical objections, whereas emergency vaccination leads to prolonged export restrictions. Antiviral agents, however, provide instantaneous protection without inducing an antibody response. The use of antiviral agents to contain CSF epidemics is studied with a model describing within- and between-herd virus transmission. Epidemics are simulated in a densely populated livestock area in The Netherlands, with farms of varying sizes and pig types (finishers, piglets and sows).

Our results show that vaccination and/or antiviral treatment in a 2 km radius around an infected herd is more effective than preemptive culling in a 1 km radius. However, the instantaneous but temporary protection provided by antiviral treatment is slightly less effective than the delayed but long-lasting protection offered by vaccination. Therefore, the most effective control strategy is to vaccinate animals when allowed (finishers and piglets) and to treat with antiviral agents when vaccination is prohibited (sows). As independent control measure, antiviral treatment in a 1 km radius presents an elevated risk of epidemics running out of control. A 2 km control radius largely eliminates this risk.

1. Introduction

Classical swine fever (CSF) is a viral disease that can cause major outbreaks in unvaccinated pigs. Outbreaks are detrimental to animal welfare, decrease economic revenues and unsettle society. Currently, Western Europe has a non-vaccination policy and is free of CSF in domestic pigs. Nevertheless, the pig population is continuously at risk for virus introduction from CSF-endemic countries or wildlife reservoirs. In case of an outbreak, the minimal measures imposed by the EU need to be applied (Council Directive 2001/89/EC, 2001): infected farms are completely culled upon detection, protective and surveillance zones are set up around detected farms where specific transport regulations apply, and dangerous contacts (from and to infected farms) are traced and screened. However, these measures are often insufficient to mitigate the epidemic (epizootic), especially in areas with a large pig population (densely populated livestock area or DPLA). Preemptive culling as an additional control measure encounters ethical objections and has been abandoned in the updated Dutch contingency plan (Contingency plan classical swine fever, 2007).

Currently, the preferred additional measure is emergency vaccination using the E2-subunit vaccine (Van Rijn et al., 1996). In a control radius of 2 km around infected premises all piglets (age 0–9 weeks) and finishers (age 9–26 weeks, i.e. slaughter age) are vaccinated. Sows are excluded from vaccination as infected vaccinated sows might give birth to persistently infected piglets (Contingency plan classical swine fever, 2007). However, several drawbacks have been identified for this approach. Firstly, vaccination needs time to take effect (Dewulf et al., 2004); during the period between vaccination and protection the animals can still be infected – just like the unvaccinated sows – possibly leading to a less effective control. Secondly, the accompanying marker test exhibits a relatively low sensitivity compared to conventional serological assays (Floegel-Niesmann, 2001), leading to large numbers of animals to be (re)tested during the final screening to regain the freedom-of-disease status. And thirdly, vaccination may have adverse economic consequences because of value loss of vaccinated pork products and trade restrictions that apply to vaccinated premises for a longer time (Council Directive 2001/89/EC, 2001).

Alternatively, the use of antiviral agents has been proposed (Goris et al., 2008). An 'ideal' antiviral agent would have an instantaneous effect upon administration (akin to preemptive culling), rapidly clear from the body when administration stops,

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http://dx.doi.org/10.1016/j.antiviral.2013.06.013

and be suited for easy administration. Promising *in vitro* and *in vivo* results have been obtained with the early hit compound 5-[(4-bromophenyl)methyl]-2-phenyl-5H-imidazo[4,5-c]pyridine (BPIP) as antiviral agent against CSF virus (CSFV). BPIP, when mixed in pig feed for daily oral administration, significantly reduced viraemia and viral load in infected pigs (Vrancken et al., 2009b) and reduced transmission to untreated contact animals (Vrancken et al., 2009a). BPIP was cleared from the plasma of the treated animals within 24 hours after the last treatment (own data). BPIP thus fulfills the desired requirements. Antiviral agents could be used either to provide a control option for sows, to bridge the period between vaccination and full immunity (immunity-gap) or as an independent control measure.

However, an antiviral agent like BPIP – akin to the E2-subunit vaccine – has not been tested in a field situation. The effect of new control measures on the course of a CSF epidemic can be simulated using disease transmission models. Recently, Ribbens et al. (2012) performed an epidemiological evaluation of BPIP for the control of a CSF outbreak in a pig-dense area in Belgium. The antiviral strategy was found to be as effective as other "conventional" control strategies.

In this study, different scenarios were analysed on how antiviral agents can be deployed to rapidly and effectively control CSF epidemics. To this end, a previously developed model describing CSFV transmission between animals and between commercial pig farms (Backer et al., 2009) was improved and extended to include the effect of antiviral agents. This model was applied to the Dutch pig farm data (census year 2006). Ten strategies were evaluated with varying control measures (EU minimal measures, preemptive culling, E2-subunit emergency vaccination or antiviral treatment) for different herd types. In addition, a combination strategy of vaccination and antiviral treatment was evaluated. Furthermore, several model parameters for the antiviral agent were varied to assess their influence on the model outcome (sensitivity analysis). The effectiveness of any strategy was expressed by the (median) outbreak duration and the (median) number of infected farms.

2. Materials and methods

2.1. CSF transmission model

A stochastic individual-based model was previously developed describing CSFV transmission between animals, pens and farms (Backer et al., 2009). In the within-herd SEIR model, each pig is in a susceptible state (S) until it becomes infected, after which it is first latently infected (E) and then infectious (I) until removal or recovery (R) (top of Fig. 1). To include the effect of antiviral agents on transmission, the SEIR model was extended with four additional compartments for susceptible (S_{AV}), latently infected (E_{AV}), infectious (I_{AV}) and recovered (R_{AV}) animals in a treated state (bottom of Fig. 1). Parameters for finishers, piglets and sows (Table 1) were estimated from transmission experiments and from herds infected during the CSF epidemic in The Netherlands in 1997/1998 (Stegeman et al., 1999; Klinkenberg et al., 2003). The effects of antiviral agents and vaccination on the individual animal (Fig. 2 in Supplementary Material) were based on experimental results with the antiviral agent BPIP (Vrancken et al., 2009a,b) and with the E2-subunit vaccine (Backer et al., 2009). The transmission between herds was modelled as a function of the distance between source and destination herd. This distance-dependent infection probability was estimated from the 1997/1998 CSF epidemic in The Netherlands (Boender et al., 2008). A more detailed description of this model and the parameter estimation for the antiviral properties is given in the Supplementary Material.

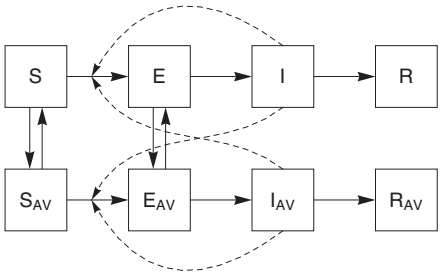

Fig. 1. Schematic overview of SEIR model with effect of antiviral agents. The pig population is divided in susceptible (S), latently infected (E), infectious (I) and recovered (R) animals, that can be treated with antiviral agents (subscript AV). Animals can transfer from one compartment to the other (solid lines); animals in the infectious compartments affect the infection events (dotted lines).

2.2. Pig farm data

The model was applied to commercial pig farms in The Netherlands, using the 2006 dataset containing information on location, size and type of all commercial pig farms. Although these data are not the most recent, the total number of pigs has not changed drastically (Land- en tuinbouwcijfers, 2011), and the data sufficiently reflect the relative farm densities in different areas. Only the numbers of finishers, sows, gilts and boars were recorded; the number of piglets was estimated as 4.3 times the number of sows (assuming 2.4 farrows a year per sow of 10.5 viable piglets each, that stay on the premises for 63 days (Klinkenberg et al., 2003)). The 8550 commercial farms with at least 200 finishers, 500 piglets and/or 100 sows, represented a total of 11 million pigs (Table 1). As pig farm densities vary across the country Fig. 2 virus introduction was assumed to occur in "De Peel" (in the south-eastern part of The Netherlands), one of Europe's most densely populated livestock areas and an intensive pig rearing region.

2.3. Initialization

A total of 473 farms were selected in "De Peel" (circle in Fig. 2) for random selection as source farm. Before first detection of a CSF infected farm, i.e. in the high risk period (HRP), little is known quantitatively about CSFV transmission. Hence, an artificial HRP of six weeks (Elbers et al., 1999) was constructed, by tripling the kernel height and demanding 10 infections to occur during the HRP (not necessarily by the source farm). Consequently, the source farm and 10 other farms were infected at the time of first detection. The likelihood of this scenario happening in practice is unknown, but it is probably not unrealistic, given the estimated 39 farms already infected at the time of the first CSFV-detection during the 1997/1998 epidemic in The Netherlands (Stegeman et al., 1999). In total, 1000 HRPs were generated as starting points for evaluation of the CSF control strategies.

2.4. Control strategies

For each control strategy, 1000 epidemics were simulated. As formulation of vaccines or obtaining permission to start antiviral treatment could delay the onset of additional control measures, all strategies initially applied preemptive culling in a 1 km radius around detected farms for a period of five days. The time between detection and culling of a detected herd was set at one day (Elbers et al., 1999). The time until additional measures were applied at neighboring farms was assumed to take another day, even though in the beginning of the 1997/1998 epidemic the delay between detection and preemptive culling exceeded two weeks due to the limited rendering capacity (Elbers et al., 1999). As culling and vaccination capacities are likely to be more limiting than antiviral

Table 1
Model parameters (top) and farm data (bottom) for different herd types. Farm data represent commercial pig farms in The Netherlands in census year 2006.

Parameter	Finishers	Piglets	Sows
Latent period T_{lat}	4 days	4 days	4 days
Infectious period T_{inf}	15 (7–25)[a] days	15 (7-25) days	15 (7–25) days
Reproduction number R_0	15.5	100	2.8
Transmission rate parameter β	1.03 day^{-1}	6.67 day^{-1}	0.187 day^{-1}
Number of animals per pen N_{pen}	10	10	1
Effective reproduction number R_{eff}	2.8	2.8	2.8
Reduction factor between pens $\epsilon = R_{eff}/(R_0 N_{pen})$	0.018	2.8 10^{-3}	1
Detection limit (# infectious animals)	12	23	26
Number of herds[b]	6429	3039	3331
Number of animals (x 1000)	5350	4181	1167
Herd size	596 (226–2323)[a]	1086 (559–3062)	254 (116–884)

[a] Between brackets the (5% – 95%) interval.
[b] The total number of farms is 8550, which include farms with multiple herd types (mixed farms).

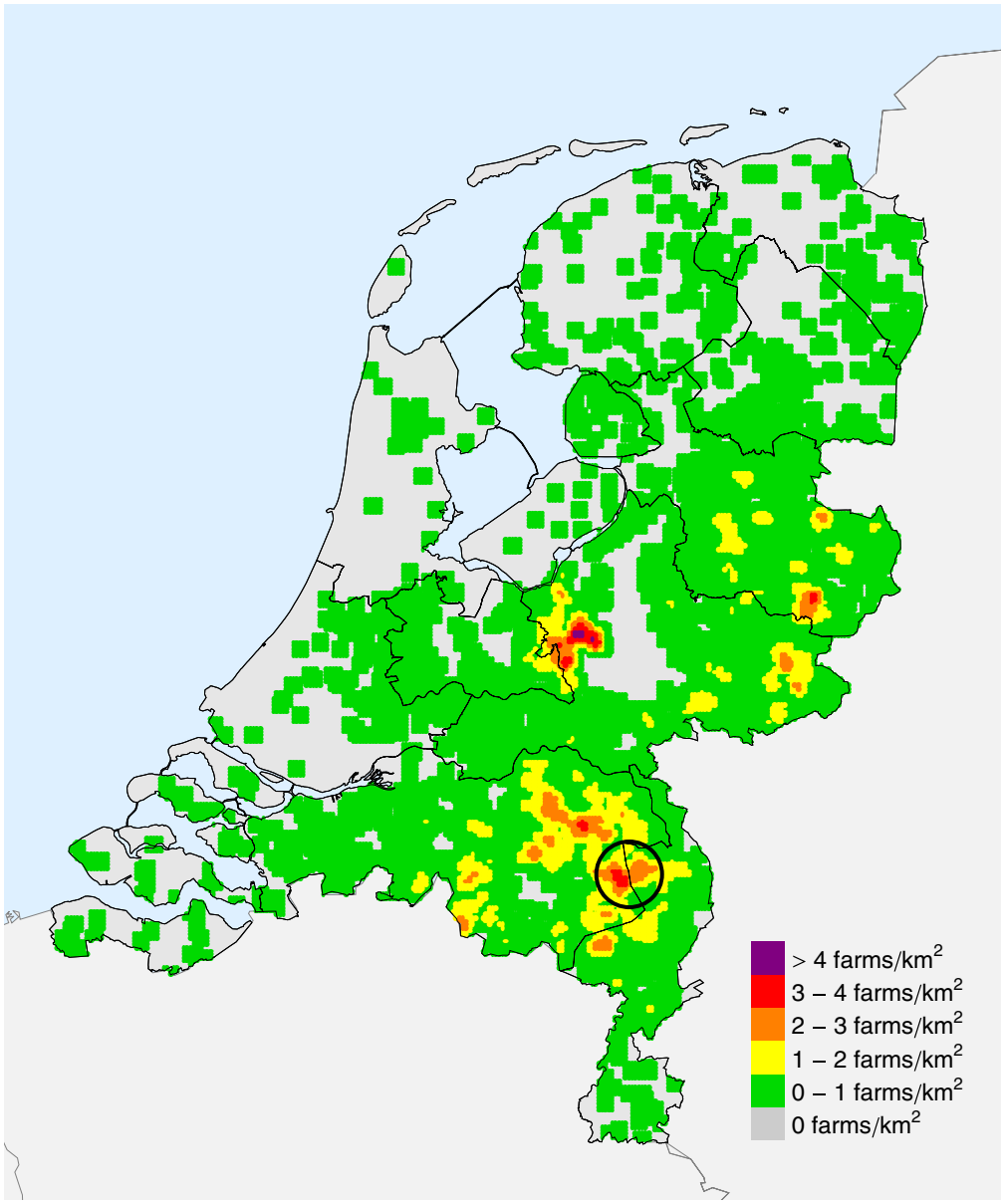

Fig. 2. Map of commercial pig farm densities in The Netherlands (census year 2006). The simulated epidemics will start in De Peel (black circle).

treatment capacities, the 2-day delay is a conservative choice for assessing antiviral treatment strategies.

For the 1997/1998 CSF epidemic, the distant-dependent kernel height was estimated for a situation with many relatively small farms. Since then, pig farm numbers have decreased, whereas the average herd size has increased (Land- en tuinbouwcijfers, 2011). To account for the larger herd sizes (involving more frequent contacts, more emissions, etc.), the kernel height was doubled. It

should be noted that this is only a scenario assumption to better distinguish between the modelled control strategies.

The following four control strategies served as benchmark strategies. The minimal control strategy (strategy *1*), imposed by the European Commission (Council Directive 2001/89/EC, 2001), implements culling of all infected farms, regulation of transport in protection and surveillance zones, and screening and tracing of dangerous contacts. Strategy *2*, the preferred EU-strategy for DPLA's adds preemptive culling in a 1 km radius around infected premises. Two strategies used emergency vaccination in a 1 km and 2 km radius around infected premises (strategy *3* and *7* respectively), the latter being the preferred strategy of The Netherlands (Contingency plan classical swine fever, 2007). Only finishers and piglets were vaccinated; sows were excluded.

Antiviral strategies were evaluated for a control radius of 1 km and 2 km. Antiviral agents were either used to treat only unvaccinated sows in a vaccination strategy (strategies *4* and *8*), to treat piglets and sows as they are usually held at the same premises (strategies *5* and *9*), or to treat all animals (strategies *6* and *10*). When sows were treated, suckling piglets were assumed to be protected via the milk (unpublished results). Based on Vrancken et al. (2009a,b), treatment duration was set at 15 days. This period however, was extended when a newly detected herd was located within the control radius of the former. The treatment duration was limited to maximally two treatment periods, i.e. 30 days. To evaluate the effect of the treatment duration on the effectiveness to control CSF epidemics, two variants of the treatment-only strategies were evaluated lifting the 30-day limitation (strategies *6a* and *10a*). To assess the effect of the variation of antiviral properties on the model outcomes, the 2 km treatment-only strategy was repeated with optimistic properties (strategy *10b*, using the upper bounds for the antiviral parameters), and with pessimistic properties (strategy *10c*, using the lower bounds for the antiviral parameters). Finally, a combined strategy was evaluated where finishers and piglets were vaccinated and treated simultaneously to bridge the immunity-gap (strategy *8a*).

3. Results

The effectiveness of any control strategy was measured by the time between first and last detection (epidemic duration) and the number of infected herds (epidemic size). These characteristics were compared by their median and 95th percentile value (Table 2).

The minimal control strategy imposed by the EU (strategy *1*) was insufficient to control the simulated epidemics (Table 2 and Fig. 3). With a median value of over 500 infected herds over the course of two years, it was clear that additional control measures are needed to bring a CSF epidemic under control in a DPLA. The 1 km preemptive culling strategy (strategy *2*) effectively reduced the epidemic size and duration. Compared to this strategy, 1 km vaccination (strategy *3*) was less effective since marker vaccination needs time to induce a protective immune response. Emergency vaccination in a 2 km radius (strategy *7*) however, was more effective than culling in a 1 km radius; the advantage of the larger control radius outweighed the disadvantage of the immunity-gap.

In The Netherlands, sows are left unvaccinated (Contingency plan classical swine fever, 2007), but they might be treated with antiviral agents as such inhibitors do not induce an anti-CSFV antibody response. Administering an antiviral treatment to sows in addition to vaccination of finishers and piglets (strategies *4* and *8*), increased the effectiveness by at least 10% compared the vaccination-only strategies. As piglets and sows are often farmed together, it would be practical to administer antiviral treatment not only to sows but also to piglets. Switching piglets from vaccination to antiviral treatment, slightly reduced the effectiveness of the control strategy (strategy *5* vs. *4* and strategy *9* vs. *8*). Apparently, the delayed but long-lasting protection offered by vaccination, was slightly more effective than the instantaneous but temporary protection provided by antiviral treatment. Applying antiviral treatment to all animals in the control radius reduced the effectiveness, making the treatment-only strategies (strategies *6* and *10*) comparable to or somewhat less effective than the vaccination-only strategies (strategies *3* and *7*).

The variation in outcomes was larger for the treatment-only strategies (strategies *6* and *10*) than for the other strategies, expressed as a disproportionally thick tail in the prevalence curves (Fig. 3). While this is clear for the av1_av1_av1-epidemics (disproportionally high 95th percentiles), this effect was less pronounced for the 2 km strategies. When the treatment limitation of maximal 30 days was lifted (strategies *6a* and *10a*) the herds were treated for a median duration of 15 (5% - 95% interval: 15 – 45) days in the 1 km strategy and 15 (15 – 48) days in the 2 km strategy. The 95th percentiles for both the 1 and 2 km strategies were effectively decreased, but the outcome variation for the 1 km strategy is still larger than for the other strategies. Additionally, vaccinated animals were also treated for 15 consecutive days to protect animals during the immunity-gap (strategy *8a*). Although more

Table 2
Results control strategies: median values of epidemic duration and the number of infected, preemptively culled, vaccinated and treated farms (between brackets the 5%-95% interval). The evaluated strategies comprise the control measures applied to finishers_piglets_sows: EU measures (EU) with additional preemptive culling (cul), vaccination (vac), antiviral treatment (av), or vaccination and antiviral treatment (vacav), in a control radius of 1 or 2 km. Antiviral treatment strategies are repeated without a maximal treatment duration (_inf), and with optimistic (_best) and pessimistic (_worst) properties for the antiviral agents.

	Control strategy	Duration (days)[a]		Number of infected farms		Number of culled farms		Number of vaccinated farms		Treated farms	
1	EU_EU_EU	724	(249–1227)	546	(79–1003)	0	(0–0)	0	(0–0)	0	(0–0)
2	cul1_cul1_cul1	162	(69–342)	48	(21–101)	212	(84–436)	0	(0–0)	0	(0-0)
3	vac1_vac1_EU	192	(85–383)	56	(24–113)	11	(2–27)	230	(84–470)	0	(0–0)
4	vac1_vac1_av1	166	(73–329)	48	(22–102)	11	(2–27)	200	(75–426)	95	(34–197)
5	vac1_av1_av1	175	(77–361)	51	(21–113)	11	(2–27)	163	(60–351)	99	(38-217)
6	av1_av1_av1	207	(85–549)	58	(21–181)	11	(2–27)	0	(0–0)	247	(78–657)
6a	av1_av1_av1_inf	201	(85–449)	57	(21–151)	11	(2–27)	0	(0–0)	241	(79–570)
7	vac2_vac2_EU	118	(56–234)	34	(18–63)	11	(2–27)	345	(154–631)	0	(0-0)
8	vac2_vac2_av2	100	(51–196)	30	(17–54)	11	(2–27)	304	(140–575)	144	(66–269)
8a	vacav2_vacav2_av2	101	(51–200)	31	(17–53)	11	(2–27)	299	(139–552)	305	(142–564)
9	vac2_av2_av2	104	(54–200)	30	(16–56)	11	(2–27)	237	(108–443)	148	(68–265)
10	av2_av2_av2	119	(67–283)	31	(17–69)	11	(2–27)	0	(0–0)	332	(156–700)
10a	av2_av2_av2_inf	118	(66–228)	32	(17–60)	11	(2–27)	0	(0–0)	326	(153–639)
10b	av2_av2_av2_best	117	(62–262)	32	(17–67)	11	(2–27)	0	(0–0)	329	(146-674)
10c	av2_av2_av2_worst	120	(64–291)	32	(17–71)	11	(2–27)	0	(0–0)	337	(158–722)

[a] Duration of the epidemic is defined as the period between the first and last detection.

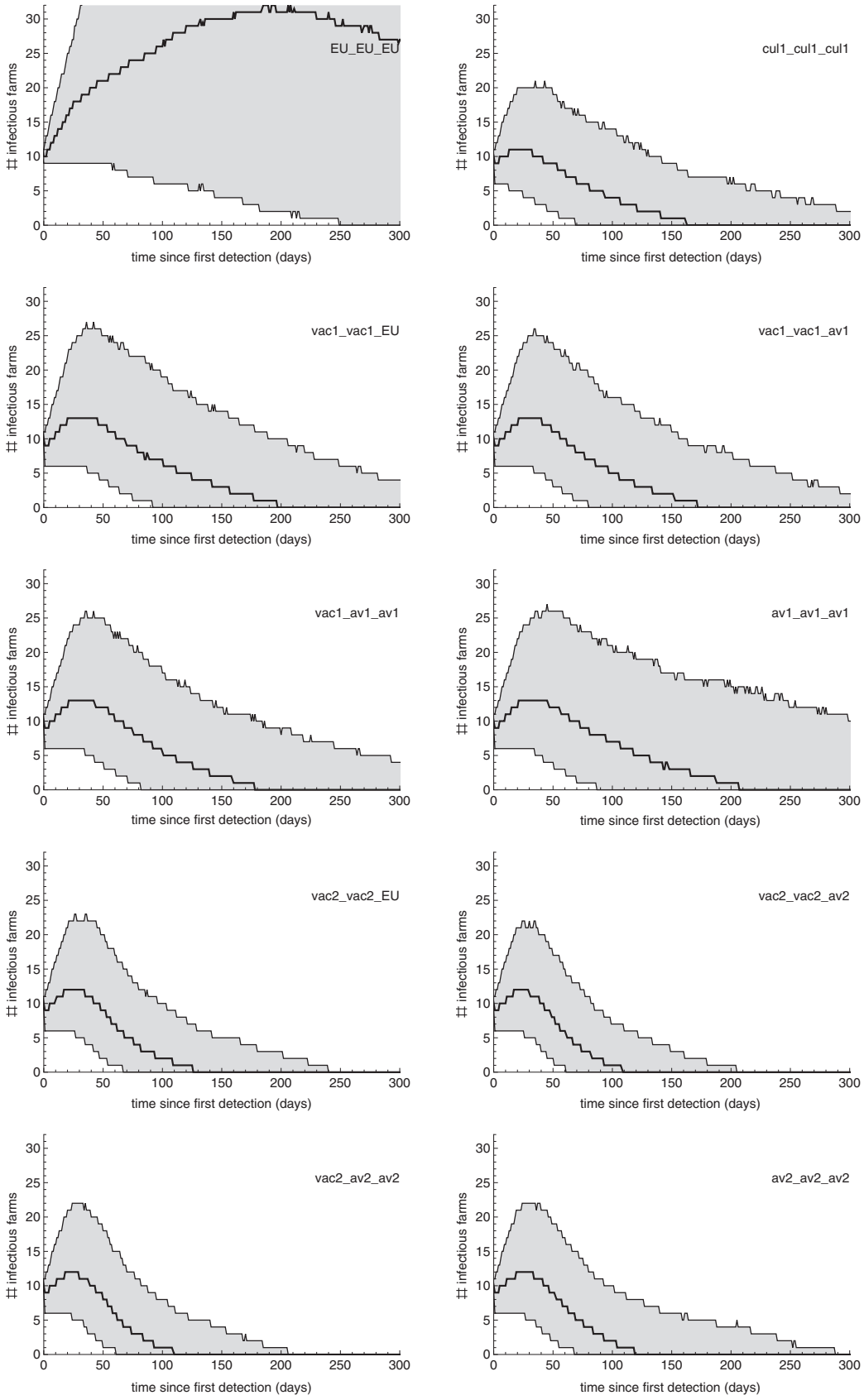

Fig. 3. Prevalence curves of simulated epidemics: median values (thick line) and 5% – 95% interval (shaded area). The evaluated strategies comprise the control measures applied to finishers_piglets_sows: EU measures (EU) with additional preemptive culling (cul), vaccination (vac) or antiviral treatment (av), in a control radius of 1 or 2 km.

effective than only vaccinating finishers and piglets (strategy *7*), the gain is not large. When implementing optimistic (strategy *10b*) or pessimistic (strategy *10c*) properties of the antiviral agent in the model, the epidemic size and duration changed accordingly. However, the differences did not affect the ranking of the simulated control strategies based on the default antiviral properties.

4. Discussion

In the present paper, a multi-level transmission model for CSF was developed including the effect of vaccination and antiviral treatment. Using data on pig farm structures in one of Europe's most densely populated livestock area, in casu De Peel (The Netherlands), this model was used to evaluate and compare the effectiveness of several CSF control strategies based on preemptive culling, emergency vaccination and/or antiviral treatment.

Unlike for vaccination, not all model parameters were available for the antiviral treatment strategies and several assumptions had to be made. To compensate for the current lack of information, these assumptions were kept rather conservative. For instance, a non-perfect coverage and only a moderate effect on susceptibility were assumed. In contrast, for other control measures, optimistic assumptions were made (e.g. rapid onset of preemptive culling and vaccination). In addition, the model allowed for outbreak re-emergence when antiviral administration was stopped, as the period between infection and detection of an infected herd often exceeded the treatment duration of 15 days.

In spite of the above restraints for the antiviral strategy, our findings indicate that antiviral agents can be deployed effectively to control a CSF epidemic. The robustness of the ranking of the antiviral strategies relative to preemptive culling and vaccination strategies is substantiated by sensitivity analyses on parameter uncertainty. These analyses (using both optimistic and pessimistic properties of antiviral agents) led to the same conclusions, giving confidence in the capability of antiviral agents to control CSF epidemics, even if their anti-CSFV effect has currently only been demonstrated under experimental conditions.

Applying solely antiviral treatment does not always prevent epidemics from running out of control, based on the large variation in the outcomes for these strategies. The imposed maximal treatment duration of 30 days (i.e. two treatment periods) might explain these observations, as farms are not protected beyond this period and regain their susceptible status. This argument is only partly confirmed by the two strategies where the treatment limitation was lifted. The assumed conservative, 'non-perfect' antiviral properties could possibly also contribute to run-away epidemics. With an assumed 95% coverage and a susceptibility reduction of 50%, less than half of the pigs are effectively protected against infection. These assumptions explain the difference between the antiviral treatment without limitation and preemptive culling strategies in a 1 km radius (strategies *2* and *6a*). Using antiviral treatment to bridge the immunity-gap did not provide much additional gain. Apparently, CSFV spread through a pig herd is sufficiently slow for the immune response to develop and reach herd immunity within the allocated time span.

The large variation in the epidemic size and duration represents the uncertainty in the outcomes due to stochasticity. Nevertheless, since the hypothetical epidemics were initiated using the same starting situations, the absolute differences between control strategies can be meaningful, despite the large overlap in outcomes. For instance, when vaccination was combined with antiviral treatment of sows, the median epidemic duration decreased by 25 days (1 km radius) and 16 days (2 km radius). These improvements can be important when economic consequences are considered.

In conclusion, this research indicates the potential value of antiviral treatment to control CSF epidemics. When antiviral agents are used to protect sows while finishers and piglets are vaccinated, the CSF free status will be regained only as early as six months following the last vaccination. This period can be shortened when antiviral treatment is applied as independent control measure. In a 1 km radius, antiviral treatment will most likely present a higher risk of epidemics running out of control, compared to preemptive culling and emergency vaccination in 1 km radius. However, antiviral treatment in a 2 km radius not only limits this risk but is also more effective than preemptive culling in a 1 km radius and equally effective as emergency vaccination in a 2 km radius.

Acknowledgments

This research was funded by Okapi Sciences NV. The funding source had no involvement in the study design, collection, analysis and interpretation of data, but assisted in the writing and in the decision to submit the article for publication.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.antiviral.2013.06.013.

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