STATEMENT

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Urgent advice on lumpy skin disease

EFSA Panel on Animal Health and Welfare

Abstract

In order to assess the effects on disease spread and persistence of partial stamping out of only clinically affected animals in holdings where the presence of lumpy skin disease has been confirmed, against total stamping-out policy of infected herds coupled with vaccination, a mathematical model for the transmission of LSDV between farms was developed and different scenarios explored. According to the model, vaccination has a greater impact in reducing LSDV spread than any culling policy, even when low vaccination effectiveness is considered. When vaccination is evenly applied so that 95% of the farms are vaccinated with 75% of vaccinated animals effectively protected, then total stamping out and partial stamping out result in a similar probability of eradicating the infection. When no vaccination is applied or when vaccination has a lower effectiveness (e.g. 40%), the probability of eradication is higher when total stamping out is performed as compared to partial stamping out. In general, partial stamping out results in limited increase of the number of farms affected as compared to total stamping out. Independently of the culling interventions applied in the model, vaccination was most effective in reducing LSDV spread if protection had already been developed at the time of virus entry, followed by protection of herds after virus entry. No vaccination is the least effective option in reducing LSDV spread. In order to reach the above described effects, it is necessary to implement vaccination of the entire susceptible population in regions at risk for LSDV introduction or affected by LSDV in order to minimise the number of outbreaks, and high animal- and farm-level vaccination coverage should be achieved. Farmers and veterinarians should be trained in the clinical identification of LSD in order to reduce underreporting, and the effectiveness of partial stamping out should be evaluated under field conditions.

Keywords: lumpy skin disease, spread, persistence, stamping out, vaccination, model

Requestor: European Commission

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Summary

Following a request from the European Commission, the EFSA Panel on Animal Health and Welfare (AHAW Panel) was asked to assess the implications in disease spread and persistence from the implementation of a partial stamping-out policy (killing and destruction of clinically affected animals only) in holdings where the presence of lumpy skin disease (LSD) has been confirmed, against the current EFSA's advice and policy in place for total stamping out of infected herds coupled with vaccination.

In the present statement, the effect of combinations of different stamping-out and vaccination options on LSDV spread is presented; in particular, insights are provided on the effect of vaccinating susceptible animals before the virus has been introduced in a region or country on the spread of LSDV.

The data used for this assessment included demographic and epidemiological data from Greece and Bulgaria provided by the respective competent authority, which are the two Member States currently affected by LSD, in particular data on cattle herds size and location, data on LSD outbreaks from the Animal Disease Notification System, data about vaccination (date and number of animals vaccinated per farm and at NUTS3 level), and data on clinical cases in vaccinated herds with dates of detection of symptoms and identification of type of virus (field or vaccine strain).

The assessment methodologies included a mathematical model similar to the one used in the previous opinion by EFSA (EFSA AHAW Panel, 2015) for simulating the between-farm LSDV spread according to different control measures applied, in particular different combinations of stamping out (no stamping out, partial stamping out of clinical cases, total stamping out of the affected herds) and vaccination (no vaccination, vaccination after detection of infection in a region, vaccination of the whole country or region leading to fully immunised population by the time of disease incursion). Furthermore, a survival analysis was conducted for the estimation of the effectiveness of vaccination as applied in Greece in 2016.

Since the model does not include within-herd dynamics, the effect of partial stamping out compared to no stamping out is incorporated in the model using alternative assumptions on the infectiousness and the duration of the outbreak on the farm under partial stamping out. These alternatives are (i) reduced infectiousness with the same outbreak duration as with no stamping out; (ii) reduced outbreak duration with the same infectiousness as with no stamping out; (iii) reduced infectiousness and prolonging the outbreak duration compared to no stamping out. Total stamping out is incorporated in the model by removing the farm at a certain time after reporting, with the delay between reporting and stamping out based on that observed in Bulgaria and Greece. The implementation of vaccination is modelled with different times of vaccination start, i.e. either all farms were vaccinated early enough to reach the maximum achievable protection before LSDV incursion, or vaccination was assumed to start after LSDV incursion with farms being vaccinated at a constant rate until all farms are vaccinated. The herd- and animal-level vaccination coverage is assumed to be 95% in all cases. The maximal protection is achieved 21 days after vaccination and the proportion of vaccinated animals protected (vaccination effectiveness) is either 75% or 40%, which is in line with the values from the literature and with the estimates resulting from the Greek data on the 2016 vaccination campaign (around 80%). The purpose of the present model is not to represent or predict how many farms will get infected under a specific control policy, but to compare the effect of different control measures on the spread of LSDV.

It can be concluded that, according to the model for the transmission of LSDV between farms, vaccination has a greater impact in reducing LSDV spread than any stamping-out policy, even when low vaccination effectiveness is considered (40%). When vaccination is evenly applied so that 95% of the farms are vaccinated with 75% of vaccinated animals effectively protected, then total stamping out and partial stamping out result in a similar probability of eradicating the infection. Nevertheless, when no vaccination is applied or when assuming a low vaccination effectiveness (e.g. 40%), the probability of eradication is higher when total stamping out is performed as compared to partial stamping out. Partial stamping out results in a limited increase of the number of farms affected as compared to total stamping out.

Independently of the stamping-out interventions applied in the model, vaccination measures were most effective in reducing LSDV spread if protection had already been developed at the time of virus entry, followed by increasing the number of protected herds through vaccination after virus entry. No vaccination is the least effective option in reducing LSDV spread.

According to this assessment, and in order to reach the above described effects, it is necessary to implement vaccination of the entire susceptible population in regions at risk for LSDV introduction or affected by LSDV in order to minimise the number of outbreaks, and high animal- and farm-level vaccination coverage should be achieved to increase the likelihood of extinction of outbreaks.

Farmers and veterinarians should be trained in the clinical identification of LSD in order to reduce underreporting and the effectiveness of partial stamping out should be evaluated under field conditions.

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1. Introduction

Lumpy skin disease (LSD) is a viral disease of cattle caused by a capripoxvirus (as sheep and goat pox viruses); it is characterised by fever, nodules on the skin, and it may lead to severe losses, especially in naive animals. Originally affecting cattle across Africa, the disease has spread outside the continent with outbreaks in Israel and Lebanon in 2012–2013 and currently (2013–2016) epizootics in Turkey, Cyprus,[1] Greece, Bulgaria, the former Yugoslav Republic of Macedonia, Serbia, Kosovo, Azerbaijan, Albania and the Russian Federation are reported.

To control the current LSD epidemic in the European Union (EU), the competent authorities of the affected Member States (MS) are currently implementing a total stamping-out policy of the affected holdings (stamping out the whole herd after detection of an infected case) coupled with vaccination using live homologous vaccines since there is consensus that stamping out alone does not seem sufficient to effectively control the disease, in line with the advice provided in the 2015 EFSA's scientific opinion. To this end, Commission Implementing Decisions (EU) 2015/2055, 2015/1500 and 2016/645 have been adopted to describe the vaccination programme for LSD in Greece and the safeguard measures for LSD in Greece and Bulgaria, respectively. Meanwhile, a specific question was raised by the Bulgarian authorities, regarding the implementation of stamping out in LSD-affected holdings, in accordance with Directive 92/119/EEC.

1.1. Background and Terms of Reference as provided by the requestor

By November 2014, shortly before the publication of EFSA's opinion on LSD (January 2015), the disease was confirmed in the island of Cyprus (in the areas not under the effective control of the Republic of Cyprus). In the months that followed, LSDV also gradually progressed from Anatolia (Turkey) where it is endemic, into the East Thrace area of Turkey (May 2015) and from there to Greece (Evros, August 2015) where it continued to spread westwards, producing new outbreaks as far as the regional units of Thessaloniki and Chalkidiki. By December 2015, spread of the disease came to a halt in Greece where stamping out of the affected holdings was implemented, coupled with mass vaccination, using a homologous, live attenuated vaccine, produced in South Africa. The disease however recurred in Greece in April 2016 in the regional unit of Serres and 1 week later, the disease was confirmed for the first time in Bulgaria too, and 2 weeks later in the former Yugoslav Republic of Macedonia. To control the current LSD epidemic, the competent authorities of the affected MS are implementing a stamping-out policy of the affected holdings coupled with vaccination using live homologous vaccines since there is a consensus that stamping out alone does not seem sufficient to effectively control the disease, bearing in mind its recent epidemiological progress, in line with the advice provided in the 2015 EFSA's scientific opinion. To this end, Commission Implementing Decisions (EU) 2015/2055, 2015/1500 and 2016/645 have been adopted to describe the vaccination programme for LSD in Greece and the safeguard measures for LSD in Greece and Bulgaria, respectively. Meanwhile, a specific question was raised by the Bulgarian authorities, regarding the implementation of stamping out in LSD-affected holdings, in accordance with Directive 92/119/EEC. In the light of the above, the Commission is in need of urgent scientific advice on the implementation of partial stamping out in confirmed LSD outbreaks.

1.1.1. Term of Reference

In view of the above, and in accordance with Article 29 of Regulation (EC) No 178/2002, the Commission asks the European Food Safety Authority (EFSA): to assess the implications in disease spread and persistence from the implementation of a partial stamping-out policy (killing and destruction of clinically affected animals only) in holdings where the presence of LSD has been confirmed, against the current EFSA's advice and policy in place for total stamping out of infected herds coupled with vaccination.

1.2. Interpretation of the Terms of Reference

The mandate requests to assess the disease spread and persistence under the implementation of a partial stamping-out policy (killing and destruction of clinically affected animals only) in LSD-affected holdings coupled with vaccination.

[1] In the areas not under the effective control of the Government of the Republic of Cyprus.

The effect of a partial stamping-out policy was already assessed for non-vaccinated herds in the EFSA scientific opinion on LSD (EFSA AHAW Panel, 2015), where stamping out of animals showing generalised clinical signs[2] in herds infected with LSD virus (LSDV) was considered. In that assessment, a simulation of a possible LSDV incursion in Greece showed that by applying a partial stamping-out policy, approximately 90% of outbreaks remained confined to the region around the initial site of incursion, but 10% of simulated outbreaks spread up to approximately 300–400 km from the site of introduction by 6 months after the incursion.

In the present statement, the effect of combinations of different stamping-out and vaccination options on LSDV spread is presented.

Due to the fast spread of LSDV throughout south-eastern Europe, it appears particularly important to provide insights into the effect of vaccinating susceptible animals before the virus has been introduced in a region or country on the spread of LSDV.

2. Data and methodologies

2.1. Epidemiological data

The following datasets were provided by the competent authorities from Greece and Bulgaria:

Data from Greece

- Cattle herd size and location per municipality and municipal department.
- Animal Disease Notification System (ADNS)[3] data of LSD outbreaks in Greece from August 2015 until June 2016.
- Data about date of vaccination and number of animals vaccinated per farm and per regional unit (NUTS3 level) since the beginning of the campaign.
- Clinical cases in vaccinated herds with dates of detection of symptoms and identification of type of virus (field or vaccine strain).

Data from Bulgaria

- Cattle herd size and location per municipality and municipal department.
- ADNS data from April 2016 until May 2016.
- Data on date of vaccination per farm, number of animals vaccinated at NUT3 level including municipality and settlement.

2.2. Methodologies

The methodologies included a mathematical model similar to the one used in the previous opinion by EFSA (EFSA AHAW Panel, 2015) for simulating LSDV spread according to different control measures applied and an estimation of the effectiveness of vaccination at the farm level using survival analysis in order to confirm the suitability of transmission parameters derived from published data from Israel (Ben-Gera et al., 2015) as used in the model.

2.2.1. Mathematical model

The purpose of the modelling is to compare alternative control measures by their relative effect on the geographical between farm spread of LSDV and not to represent or predict the absolute number of farms that will get infected under a specific control policy.

The model was used to compare different scenarios for the spread and control of LSD in Bulgaria and Greece under different combinations of stamping out (no stamping out, partial stamping out of clinical cases, total stamping out of the affected herds) and vaccination (no vaccination, vaccination after detection of infection in a region, vaccination of the whole country or region leading to fully immunised population by the time of disease incursion). In each scenario, the initial incursion was assumed to result in the infection of the same three farms in the Evros region of Greece on 1 June. Model analyses are performed over 360 days with daily updating using 100 repetitions per scenario.

The geographical spread of LSDV was modelled at the farm level, since this is the smallest epidemiological unit with data being available. Transmission between farms was described using a

[2] Animals with at least five typical lesions of LSD, as in Ben-Gera et al. (2015).
[3] http://ec.europa.eu/food/animals/animal-diseases/not-system/index_en.htm

kernel-based approach (see Appendix A), as presented in detail in the EFSA opinion on LSD (EFSA AHAW Panel, 2015). The model was adapted to include vaccination by replacing herd sizes with the number of unprotected animals in each herd. With vaccination effectiveness being the proportion of vaccinated animals eventually protected from infection, herd size multiplied by 1 minus vaccination effectiveness gives the number of susceptible animals in a vaccinated herd (Anderson and May, 1983).[4]

The force of infection and outbreak duration were estimated from data on the location and time of infection for reported cases of LSD from the epidemic in Israel during 2012 and 2013, as in the previous opinion (EFSA AHAW Panel, 2015). These data were chosen to model the force of infection, because they are the only ones available for LSDV spread in a situation without vaccination and no stamping out of infected farms, this being the closest scenario to the 'natural' spread of the disease. The model assumes that seasonality in Bulgaria and Greece is the same as in Israel, because there are no data on vector abundance and the outbreaks occurred over a too short time period to provide data about seasonality in these MS. Considering the climatic conditions in Israel as compared to Greece and Bulgaria, the assumption might provide a worst-case scenario for LSDV spread in these MS.

The baseline parameter estimates of the model imply that similar control measures will be implemented, as applied in Israel. Under that situation, stamping out of generalised infections in dairy herds (but not in beef herds) and vaccination with a single sheep dose of RM-65 sheep pox vaccine was performed (Ben-Gera et al., 2015; EFSA AHAW Panel, 2015). There is no evidence indicating that the vaccination with single dose of RM-65 sheep pox vaccine in any way reduced transmission, thus these estimates are used for simulating LSDV spread without control.

In the model, reporting of clinical disease was assumed on 50% of the affected farms, irrespective of the stamping-out strategy, which can be considered a worst-case scenario for the level of under reporting. Changing the percentage of reporting, however, would not change the relative ranking of the scenarios, since there is no reason to assume different levels of reporting for partial and total stamping out. An outbreak on a farm is reported 1–2 weeks after infection (sampled from a gamma distribution with a mean of 10.5 days and shape parameter of 30[5]), thus reflecting the delay between the onset of infectivity and report of the outbreak (EFSA AHAW Panel, 2015).

In the model, all animals in a farm are assumed to be vaccinated at the same time, so that the number of immune animals is related to the time for the immunity to be established and to the vaccination effectiveness. The possibility that not all animals in a farm are vaccinated at the same time (because not all animals are present, or unvaccinated animals enter the farm because of new born animals, introduction of non-vaccinated animals, etc.) could not be considered explicitly due to lacking of a within-farm model. However, the scenarios assuming low vaccination effectiveness (lower than the one estimated from field data) provide worst-case insight into the importance of this possibility for the outcome of the compared strategies.

The implementation of vaccination is modelled with different times of vaccination start. On the one hand, vaccination is assumed to be implemented so that all farms are vaccinated and have reached maximal achievable protection before an LSDV incursion occurs, while on the other, vaccination is assumed to start 15 days after the LSDV incursion occurs, with farms being vaccinated at a constant rate until all farms are vaccinated 50 days later. In both cases, all farms in Bulgaria and Greece are assumed eligible for vaccination, with farms assigned a time of vaccination at random by NUTS2 region. The proportion of farms vaccinated (farm-level coverage) is assumed to be 95% in all cases, the vaccine effectiveness is either 75% or 40% and this level of protection is achieved 21 days after vaccination (reflecting the time for immunity development).

The two values of vaccination effectiveness are the estimate and lower 95% confidence limit, respectively, for the effectiveness of Neethling LSD vaccine estimated by Ben-Gera et al. (2015). The value of vaccination effectiveness as estimated from the data obtained from the regional unit of Serres in Greece is close to the upper limit used in the simulations (80%, see Section 3.3).

The implementation of the partial stamping out in the absence of a within-herd model was achieved via changing infectiousness and outbreak duration of reported farms under partial stamping out compared to farms without control. The implementation focuses on the fact that generalised cases are responsible for most of the virus transmission. The modelling approach is supported by the fact that skin lesions of clinical cases contain the highest level of virus as demonstrated in cattle experimentally infected with LSDV (Babiuk et al., 2008). In addition, outbreaks in Israel were fully

[4] The effectiveness of a vaccination programme is influenced by both vaccination effectiveness and vaccine coverage (see Glossary).
[5] The gamma distribution is a two-parameter continuous probability distribution. The shape parameter affects the shape of the curve.

controlled and the disease was completely eradicated using partial stamping out of generalised cases (Magori-Cohen et al., 2012; EFSA AHAW Panel, 2015).

Because the model does not include within herd dynamics, partial stamping out is incorporated in the model in one of three ways as follows:

1) by reducing the infectiousness by 50% compared with no stamping out, with the same outbreak duration as no stamping out;
2) by reducing the outbreak duration (assumed to be proportional to log herd size, see Appendix A) on reported farms (from a maximum of around 180 days with no stamping out to a maximum of 50 days with partial stamping out, for the largest herd in Bulgaria and Greece), with the same infectiousness as no stamping out;
3) by reducing the infectiousness by 50% compared with no stamping out and increasing the outbreak duration by 50% compared with no stamping out.

Total stamping out is incorporated in the model by removing the farm at a certain time after reporting (sampled from a gamma distribution with a mean of 7.6 days and shape parameter of 2.13), with the delay between reporting and stamping out based on that observed in Bulgaria and Greece.

2.2.2. Vaccination effectiveness

In order to estimate whether vaccination effectiveness in south-eastern Europe is similar to that in Israel, a survival analysis was performed comparing LSD incidence in vaccinated vs unvaccinated farms in the Greek region of Serres (Dohoo, 2004). This region was chosen because, by May 2016, in Serres the vaccination coverage was around 60%, so both vaccinated and unvaccinated farms were present, and the reoccurrence of LSD was registered in April 2016, after the apparent fade out of the outbreaks at the end of 2015.

In order to consider the delay for establishment of the protective immunity after vaccination, 0, 14 and 30 days were considered as lag period for herd immunity development. After vaccination herds moved from non-vaccinated to vaccinated status, according to the lag period of immunity development considered in each analysis.

The following approach was used to determine the vaccination status of each herd. The surveillance period for the study began on 4 April 2016 and ended on 25 June 2016 (a total period of 51 days). If vaccination date + lag period was before 4 April, the herd was considered to be vaccinated, and was followed for 51 days. If vaccination date + lag period was after 25 June or the herd was not vaccinated, the herd was considered to be non-vaccinated, and was followed for 51 days. A herd vaccinated during the outbreak period was considered non-vaccinated up to the date of vaccination + lag period, and followed from 4 April to that date, and thereafter was considered to be vaccinated and was followed from that date until 25 June. Farms that did not experience an outbreak were censored (removed from the dataset) at the end of each follow-up period for each herd status.

Kaplan–Meier survival curves were created considering lag periods of 0, 14 and 30 days, with the purpose of studying on herd-level the protective effect of vaccination of animal population in the EU. The herd was the unit of interest, and the outcome was 'a herd becoming infected (i.e. at least one infected animal was identified)'.

Incidence rate (IR) ratios and their 95% confidence intervals and vaccination effectiveness $(((IR_{unvaccinated} - IR_{vaccinated})/IR_{unvaccinated}) \times 100)$ were calculated for each lag period (Dohoo, 2004).

3. Assessment

LSDV is currently spreading rapidly through south-east Europe: the countries affected so far include Bulgaria, Greece, Kosovo, the former Yugoslav Republic of Macedonia, Serbia and Albania, with further outbreaks reported in Russia. In Greece, LSD was reported in August 2015 for the first time; 117 outbreaks have been reported in 2015, while up to 1 July nearly 70 outbreaks were reported in 2016, with within-herd morbidity of around 14%. In Bulgaria, there have been nearly 200 outbreaks notified between April and 1 July 2016, with around 10% within-herd morbidity. Up to 1 July the former Yugoslav Republic of Macedonia has reported 335 outbreaks, and around 5% within-herd morbidity, Kosovo has reported just a single outbreak, Russia has reported over 50 outbreaks in 2016 (10% within-herd morbidity), Serbia has reported over 80 outbreaks with low within-herd morbidity and Turkey has reported nearly 80 outbreaks in 2016. In Figures 1 and 2, respectively, the temporal dynamics and the morbidity (number of affected animals out of the susceptible in each outbreak) of LSD outbreaks as reported in Greece and Bulgaria are displayed.

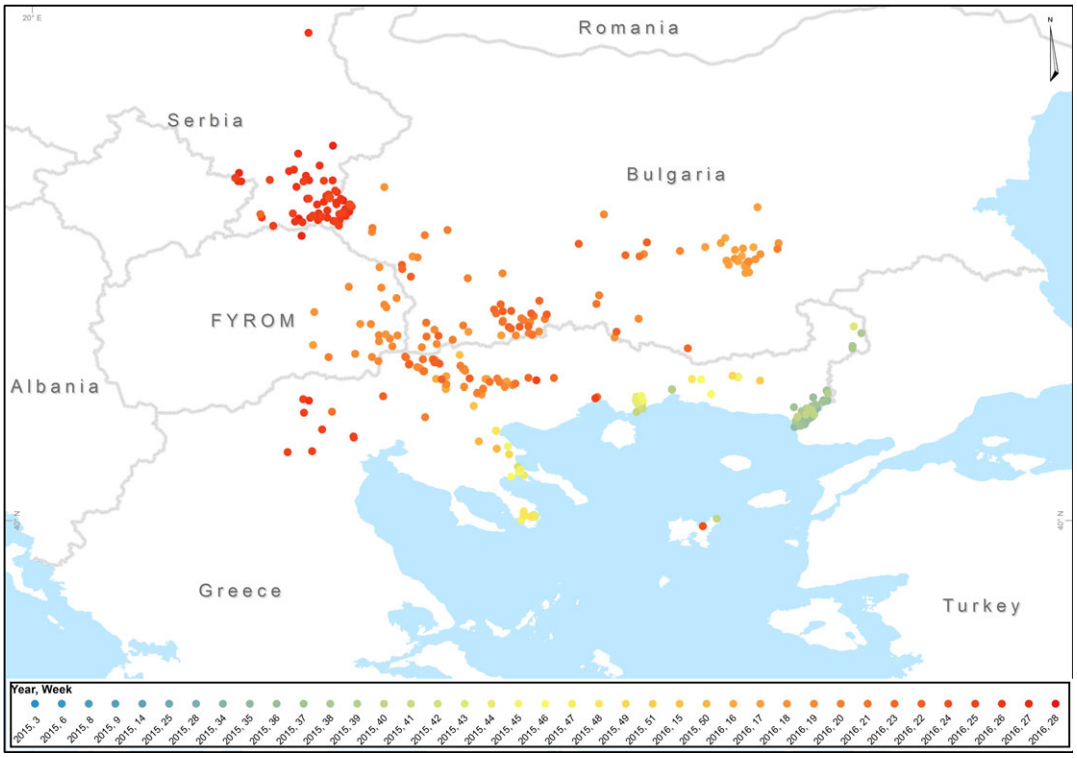

Figure 1: Map of lumpy skin disease outbreaks in Bulgaria and Greece according to the year and week of reporting up to July 2016

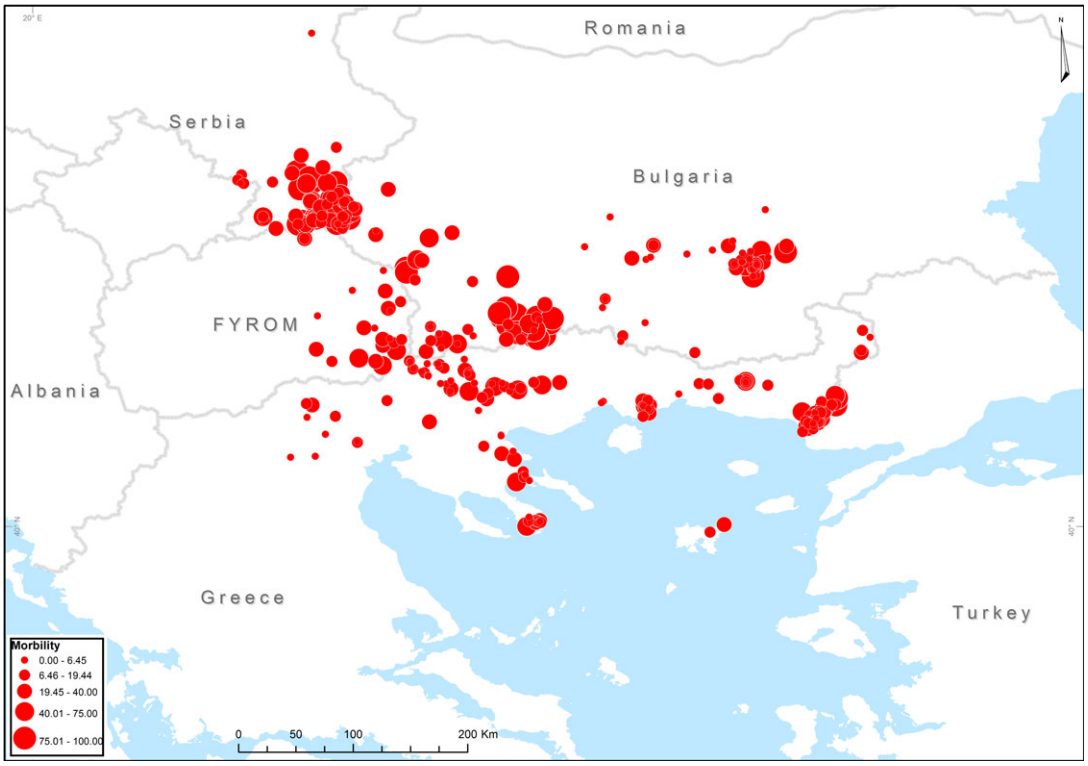

Figure 2: Morbidity (number of affected animals out of the susceptible in each outbreak) of lumpy skin disease outbreaks as reported in Greece and Bulgaria up to July 2016

In the EU, the outbreaks are currently managed according to the EU control measures based on Council Directive 92/119/EEC which foresees total stamping out of the affected holdings, destruction or appropriate treatment of substances that may be contaminated (e.g. animal feed, litter, manure, etc.), setting of surveillance and protection zone, cleaning and disinfection of facilities and epidemiological enquiry. Under Commission Implementing Decisions adopted in 2015 and 2016, emergency vaccination with homologous LSD vaccine and other emergency safeguard measures were implemented in Greece and Bulgaria.

3.1. Immune response and vaccines against LSD

Since vaccination is part of the eradication strategy, the main characteristics of the immune response and vaccination against LSD are reported below.

Immunity to capripoxvirus infections is predominantly cell mediated and requires a replicating agent to be effectively stimulated. Animals that have recovered from apparent or inapparent natural infection with LSDV develop antibodies capable of neutralising up to 3 logs of the virus, and are also resistant to reinfection. Animals that have been vaccinated or showed mild disease develop low levels of neutralising antibodies (EFSA AHAW Panel, 2015). Serological assays are not capable of distinguishing between neutralising antibodies of vaccination and infection origins.

Only live attenuated vaccines against LSD are currently commercially available, such as the attenuated Neethling strain (LSDV) vaccine. General requirements for LSDV vaccines are described in the European Pharmacopoeia and in the OIE Manual of Diagnostic Tests and Vaccines (OIE, 2014). It is widely agreed that vaccination using a homologous vaccine is the only effective way to control the spread of LSDV in endemic countries. In some contexts, the sheep pox/goat pox vaccine was used for cattle but cross-protection is poor. Neutralising antibodies to LSDV persist for at least 2–3 years after vaccination. Antibodies appear 10 days after vaccination and reach the highest level 30 days post inoculation. Calves born to immunised cows will have passive immunity that persists for about 6 months (EFSA AHAW Panel, 2015).

Currently, there are no inactivated or DIVA[6] vaccines of any kind (or associated tests) commercially available (EFSA AHAW Panel, 2015).

Literature review revealed only one randomised field study and two challenge studies on LSDV vaccines. The randomised field study, conducted on 5,000 cows in 15 dairy herds in Israel, compared an LSDV attenuated Neethling strain vaccine and a sheep pox attenuated RM-65 vaccine administered at 10 times the dose administered to sheep, both administered at $10^{3.5}$ TCID (Ben-Gera et al., 2015). The Neethling vaccine was 4.3 times more effective in preventing laboratory-diagnosed LSD than the 10x M-65 vaccine, and 11.2 times more effective in preventing severe LSD cases. This vaccine, however, caused adverse effects in 0.5% of the vaccinated cows, which was characterised by a very mild and transient LSD-like disease. A challenge study performed recently in Ethiopia showed that an attenuated Gorgon strain GTPV vaccine is effective in preventing LSD after challenge (Gari et al., 2015).

3.2. Scenarios of LSDV persistence and spread with different control measures

The implications of the implementation of the different control measures tested on the persistence of the infection are reported in Figure 3, where they are expressed in terms of the proportion of the epidemics which die out within one model year.

In scenarios without vaccination, the probability of extinction of the outbreaks predicted by the model is halfway between no stamping out and total stamping out strategy. Therefore, Figure 3 implies that in the model the application of any form of vaccination is prerequisite to the purposeful substitution of total stamping out by partial stamping out in terms of success of control.

Assuming a vaccination effectiveness of 75%, i.e. vaccinated animals that are protected, to be applied uniformly across the control area, the probability of extinction of the outbreaks predicted by the model is close to 100%, under both a partial stamping out and a total stamping-out policy. It is important to realise that this conclusion is based on either virus introduction in a region with 95% already vaccinated farms, or in a region where 95% of the farms are vaccinated between 15 and 65 days after introduction of the virus. When vaccination effectiveness is low (e.g. 40%), the difference between partial stamping out and total stamping out, in terms of the capacity to stop the outbreaks, becomes more evident – in particular, if partial stamping out is modelled while assuming a prolonged duration of infection (see Appendix B).

[6] Differentiating Infected from Vaccinated Animals.

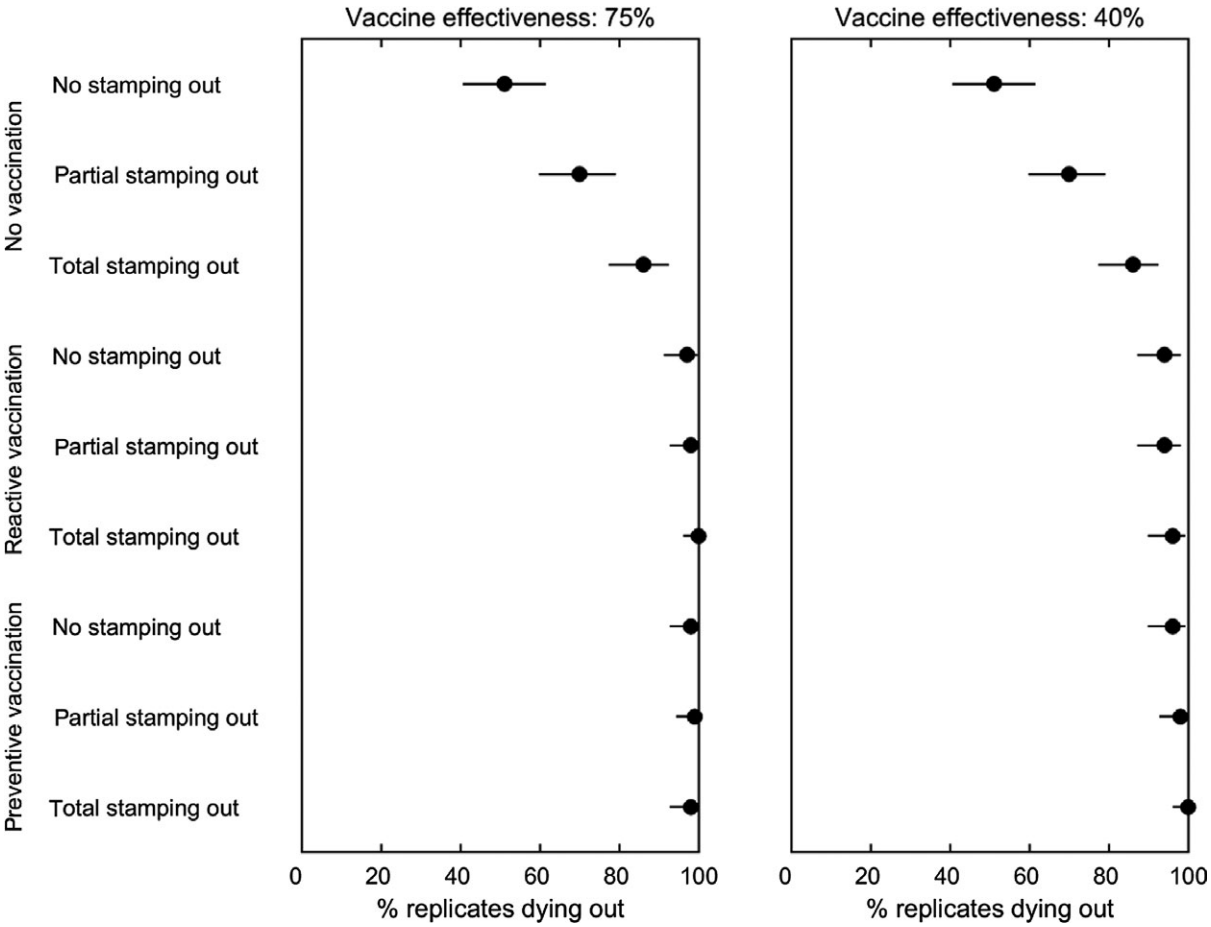

Figure 3: Proportion of epidemics which die out under the different scenarios of intervention. The dots represent the estimated proportion (i.e. no. of model replicates in which the epidemic dies out divided by the total number of model replicates) and the error bars are the 95% confidence intervals[7]

The results about the disease spread under the different control measures are presented in the form of maps (Figures 4 and 6), where the proportion (%) of simulations is shown for which at least one farm in a $0.1^\circ \times 0.1^\circ$ grid square becomes infected by the end of the year in which the incursion occurs. In addition, the number of newly LSDV-infected herds in Bulgaria and Greece is shown for the nine different scenarios for both values of vaccination effectiveness (75% and 40%) (Figures 5 and 7). Here the effect of partial stamping out is shown only considering halved infectiousness and unchanged outbreak duration compared to no stamping out (scenario i in 2.2.1), which was considered to be the most likely situation. The other two possible scenarios (i.e. reduction of the infectiousness with the same outbreak duration and reduction of the infectiousness with increase of the outbreak duration) are shown in Appendix B (Figures A.2 and A.4).

[7] The apparent difference between the two level of vaccination effectiveness under the scenario of total stamping out coupled with preventive vaccination is due to chance (98/100 died out at 75% effectiveness while 100/100 died out at 40% effectiveness, which is not significantly different ($p = 0.49$).

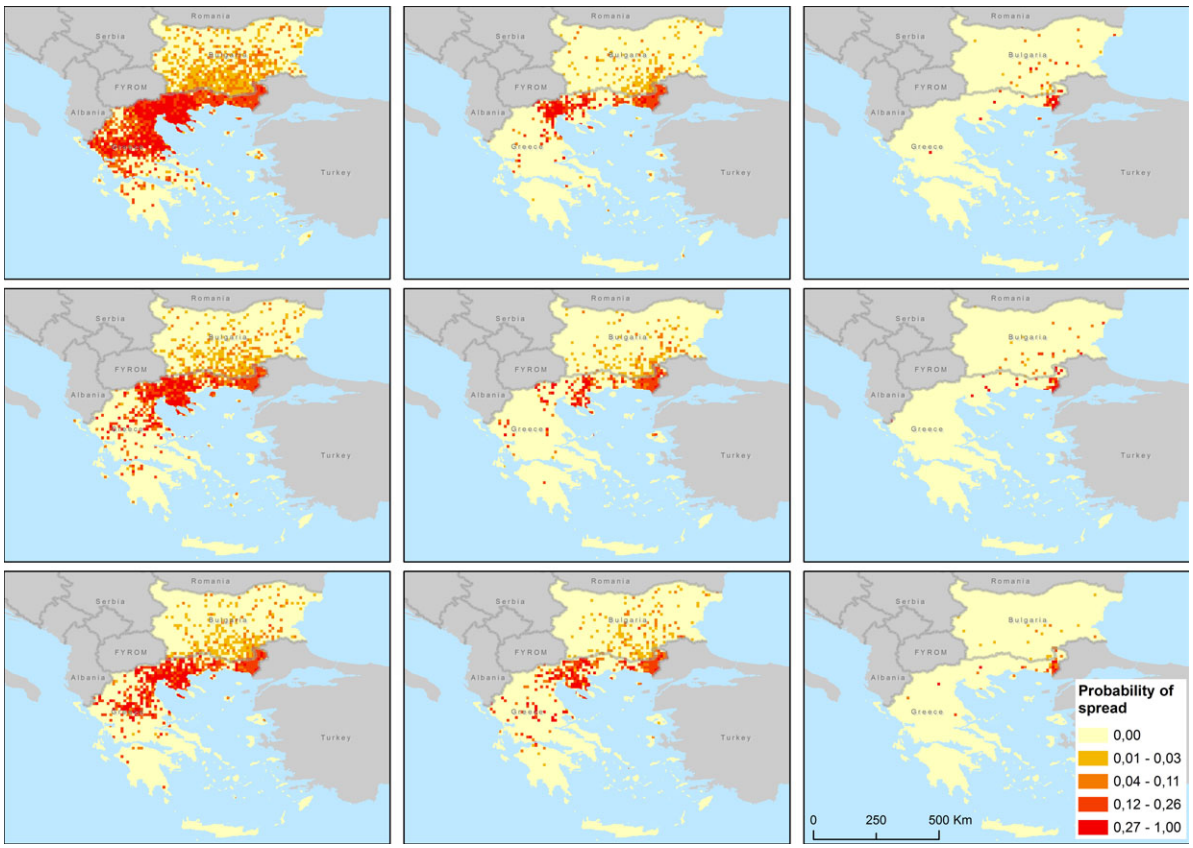

Figure 4: Predicted impact of different combinations of vaccination and stamping-out strategies on the geographical spread of LSDV in Bulgaria and Greece. The colour of the dots (and the related scale bar) show the proportion of simulations (%) for which at least one farm in a 0.1° × 0.1° grid square becomes infected by the end of the year in which the incursion occurs. Rows differ in the intensity of stamping out implemented: no stamping out (top row), partial stamping out of only animals showing clinical signs, assuming it reduces infectiousness (middle row) or total stamping out of all animals in an affected holding (bottom row). Columns differ in vaccination strategy: no vaccination (left-hand column), vaccination starting after the entry of the virus (middle column) or vaccination with animals fully immunised and protected at virus entry (right-hand column). Vaccination effectiveness is set at 75%

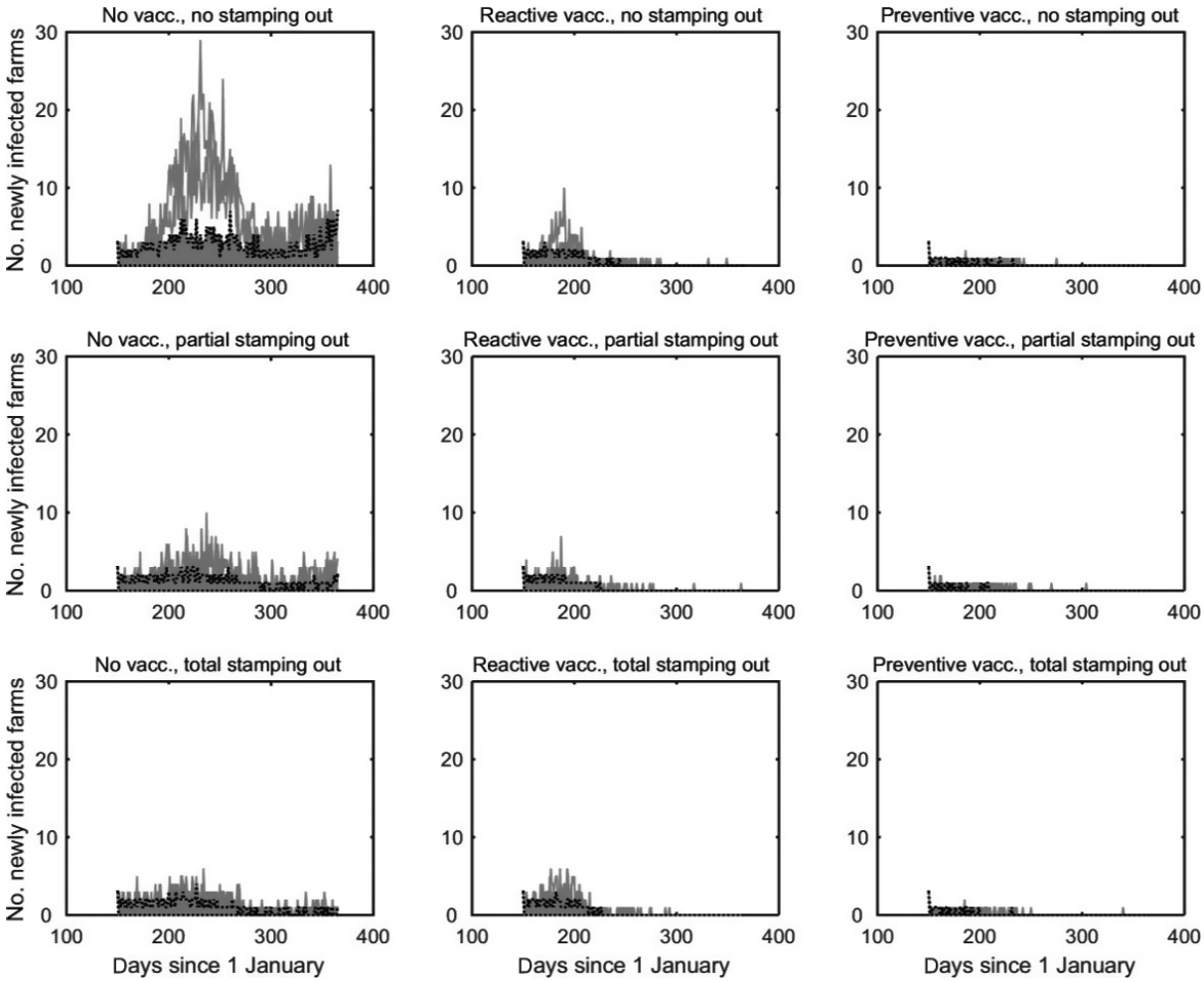

Figure 5: Predicted impact of different vaccination and stamping-out strategies on the number of newly infected herds in Bulgaria and Greece. Each plot shows the 2.5th and 97.5th percentiles (black dotted lines) and individual replicates (grey lines) for 100 simulated outbreaks. Rows differ in the intensity of stamping out implemented: no stamping out (top row), partial stamping out assuming it reduces infectiousness (middle row) or total stamping out (bottom row). Columns differ in vaccination strategy: no vaccination (left-hand column), vaccination starting after the entrance of the virus (middle column) or vaccination with animals fully immunised and protected at virus entry (right-hand column). Vaccination effectiveness is set at 75%

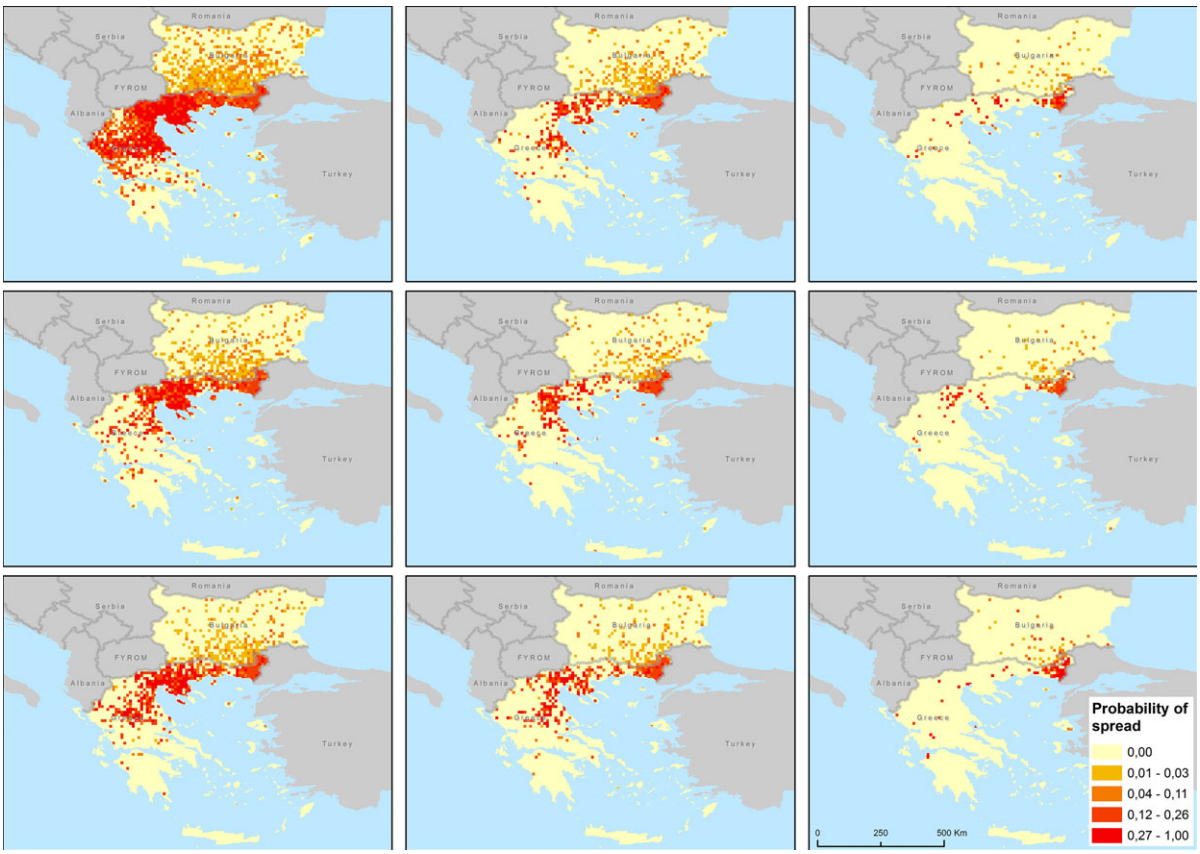

Figure 6: Predicted impact of different vaccination and stamping-out strategies on the geographical spread of LSDV in Bulgaria and Greece. Each map shows the proportion (%) of simulations (out of 100) for which at least one farm in a 0.1° × 0.1° grid square becomes infected by the end of the year in which the incursion occurs (indicated by the scale bar). Rows differ in the intensity of stamping out implemented: no stamping out (top row), partial stamping out assuming it reduces infectiousness (middle row) or total stamping out (bottom row). Columns differ in vaccination strategy: no vaccination (left-hand column), vaccination starting after the entrance of the virus (middle column) or vaccination with animals fully immunised and protected at virus entry (right-hand column). Vaccination effectiveness is set at 40%

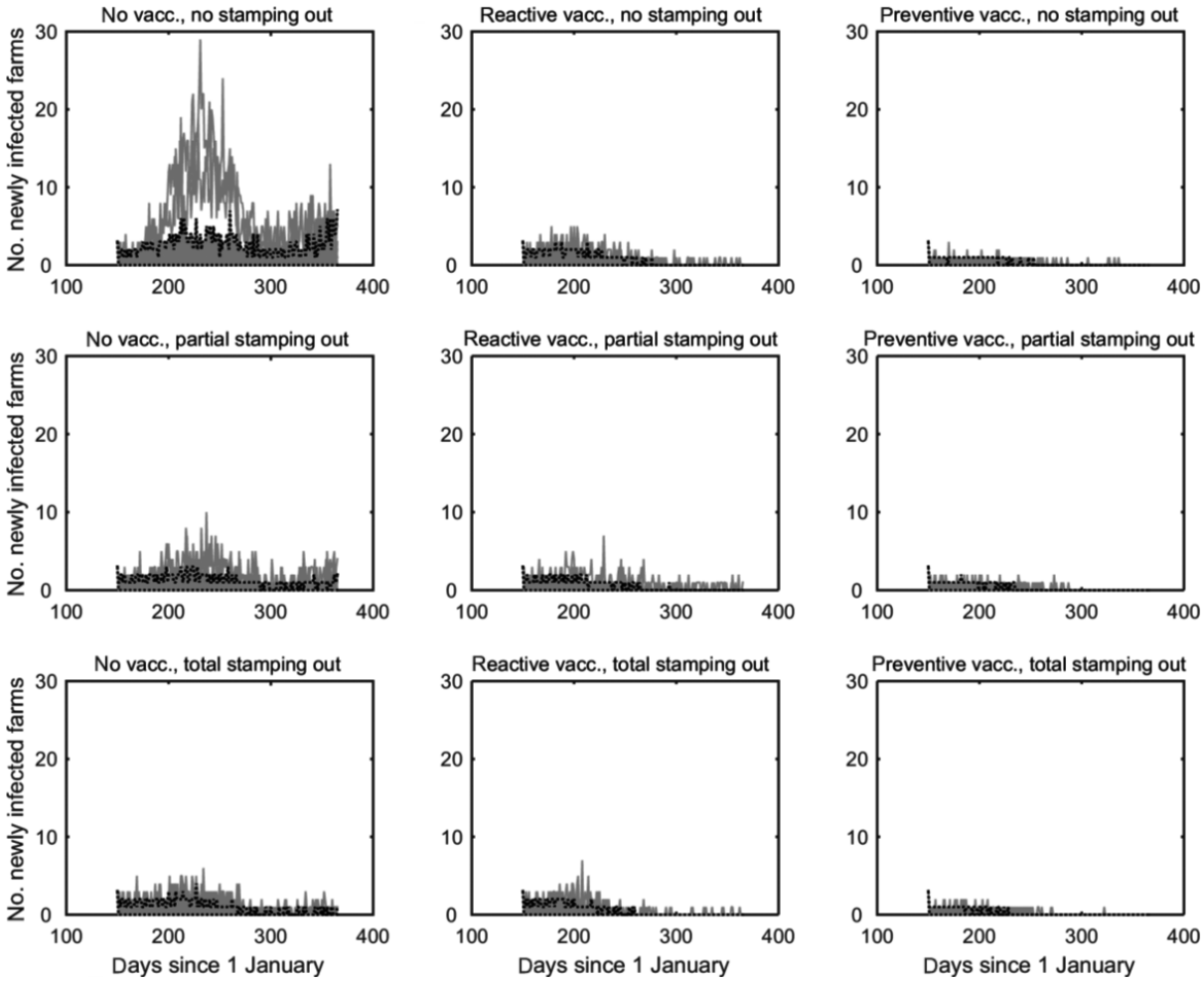

Figure 7: Predicted impact of different vaccination and stamping-out strategies on the number of newly infected herds in Bulgaria and Greece. Each plot shows the 2.5th and 97.5th percentiles (black dotted lines) and individual replicates (grey lines) for 100 simulated outbreaks. Rows differ in the intensity of stamping out implemented: no stamping out (top row), partial stamping out assuming it reduces infectiousness (middle row) or total stamping out (bottom row). Columns differ in vaccination strategy: no vaccination (left-hand column), vaccination starting after the entrance of the virus (middle column) or vaccination with animals fully immunised and protected at virus entry (right-hand column). Vaccination effectiveness is set at 40%

According to the model, partial stamping out results in limited increase of the number of farms affected when compared with total stamping out. In this respect, the three different ways to model partial stamping out lead to equivalent outcomes (see Appendix B).

3.3. Estimation of vaccination effectiveness

The Kaplan–Meier survival curves were created considering lag periods of 0, 14 and 30 days for establishment of full protection after vaccination (Figures 8, 9 and 10, respectively).

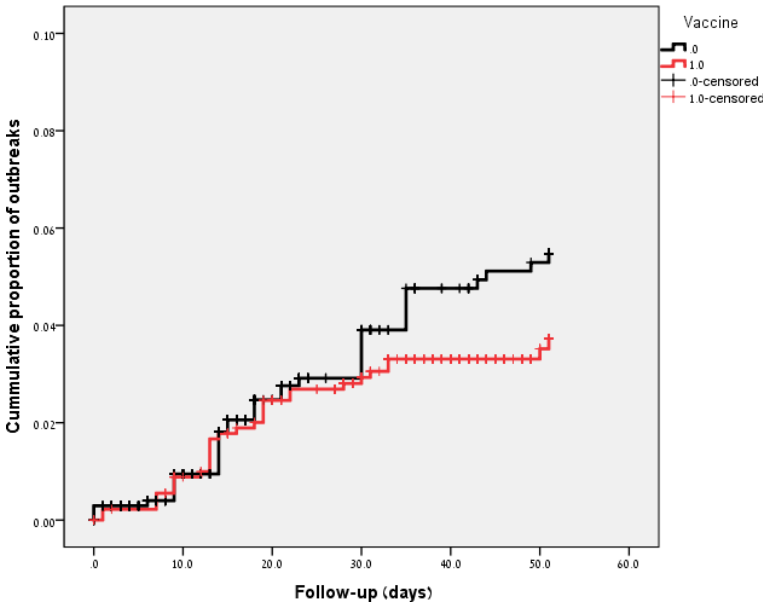

Figure 8: Kaplan–Meier curve showing the probability of infection in the vaccinated (red) and unvaccinated farms (black) in the region of Serres (Greece) All vaccinated farms were treated in the analysis as having reached maximum protection (i.e. no lag period between vaccination and immunity)

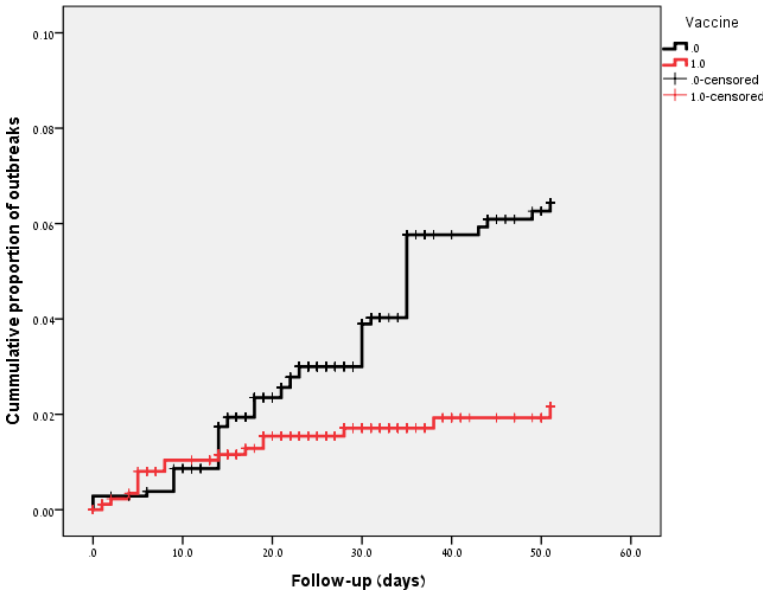

Figure 9: Kaplan–Meier curve showing the probability of infection in the vaccinated (red) and unvaccinated farms (black) in the region of Serres (Greece) Only farms vaccinated minimum 14 days prior to observation were treated in the analysis as having reached maximum protection (i.e. 14-day lag period between vaccination and immunity)

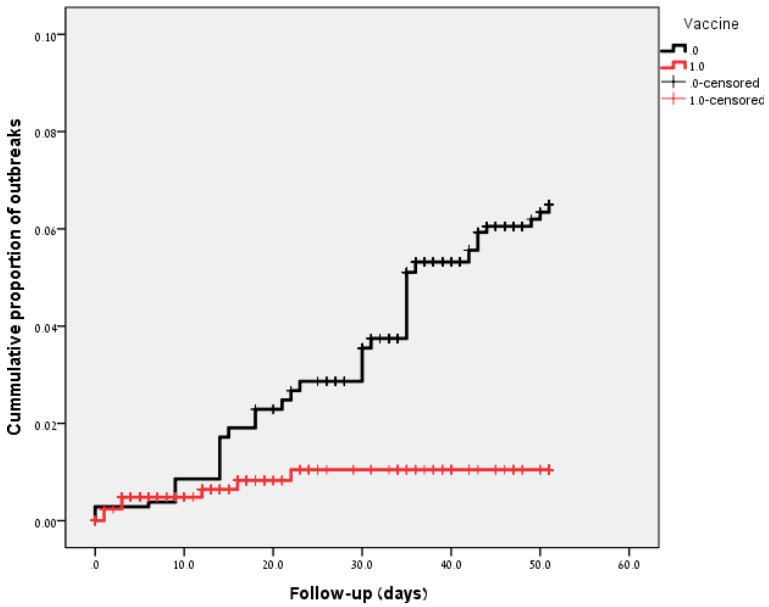

Figure 10: Kaplan–Meier curve showing the probability of infection in the vaccinated (red) and unvaccinated farms (black) in the region of Serres (Greece). Only farms vaccinated minimum 30 days prior to observation were treated in the analysis as having reached maximum protection (i.e. 30-day lag period between vaccination and immunity)

The estimated incidence rates, the incidence rate ratios and proportion of vaccinated herds protected from infection for each of the three lag periods (protective immunity assumed to develop after 0, 14 or 30 days) are shown in Table 1.

Assuming 30 days is the true protection threshold for individuals, as suggested by animal experiments, the estimated proportion of vaccinated herds protected from infection in the data was 80%. It might even be higher as most observed infections under the 30-day lag period assumption occurred shortly after 30 days, but the study period was too short to examine that. The values of vaccination effectiveness estimated here for Greece corroborate those reported in Israeli studies (Ben-Gera et al., 2015).

Table 1: Incidence rate ratio and proportion of vaccinated herds protected from infection according to different lag periods between vaccination and onset of protection

	0 day	**14 days**	**30 days**
$IR_{Vaccinated}$	31 cases in 38,927 days of follow-up	16 cases in 32,481 days of follow-up	7 cases in 25,773 days of follow-up
$IR_{Non\text{-}Vaccinated}$	39 cases in 34,724 days of follow-up	54 cases in 41,170 days of follow-up	63 cases in 47,857 days of follow-up
IRR	1.410 (95% CI: 0.88–2.26)	2.663 (95% CI: 1.52–4.65)	4.847 (95 CI %: 2.22–10.58)
Proportion of vaccinated herds protected from infection (%)	29.1	62.5	79.4

IR: incidence rate; IRR: incidence rate ratio; CI: confidence interval.

4. Conclusions

- According to the model for the transmission of LSDV between farms, vaccination has a greater impact in reducing LSDV spread than any stamping-out policy, even when only 40% of vaccinated animals eventually is protected from infection (low vaccination effectiveness).
- According to the model for the transmission of LSDV between farms, when vaccination is applied assuming an effectiveness of 75% as reported from the literature, total stamping out results in similar probability of eradicating the infection than partial stamping out.
- When no vaccination is applied or when assuming a low vaccination effectiveness (e.g. 40%), the probability of eradication is higher when total stamping out is performed as compared to partial stamping out.

- According to the model for the transmission of LSDV between farms, partial stamping out results in limited increase in the number of farms affected as compared to total stamping out.
- Independent of the stamping-out interventions applied in the model, vaccination measures were most effective in reducing LSDV spread if protection had already been developed at the time of virus entry, followed by increasing the number of protected herds after virus entry. No vaccination is the least effective option in reducing LSDV spread.
- The proportion of vaccinated herds protected from infection as estimated using Greek data is in line with that previously reported in studies from Israel.

5. Recommendations

- If the objective is to minimise the number of outbreaks of LSD in regions at risk for LSDV introduction or where LSDV has been already introduced, it is recommended to implement vaccination.
- To increase the likelihood of extinction of outbreaks, high within- and between-farm vaccination coverage should be achieved.
- Vaccination needs to be applied as uniformly as possible across the population to avoid areas where there are high densities of unvaccinated farms.
- The implementation of vaccination could be accompanied with partial stamping out instead of total stamping out if a small increase in the number of affected farms and/or a reduction in the probability of extinction of the outbreaks are considered acceptable.
- Farmers and veterinarians should be trained in the clinical identification of LSD in order to reduce underreporting.
- The effectiveness of partial stamping out should be evaluated under field conditions.

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Abbreviations

ADNS	Animal Disease Notification System
IR	incidence rate
IRR	incidence rate ratio
LSD	lumpy skin disease
LSDV	LSD virus
MS	Member State
TCID	tissue culture infectious dose

Glossary

Partial stamping out	Killing and destruction of clinically affected animals only
Total stamping out	Killing and destruction of all animals in an affected farm
Generalised clinical signs	Animals with at least five typical lesions of LSD (Ben-Gera et al., 2015)
Vaccine efficacy	The proportion of vaccinated animals which are protected from infection under ideal conditions (experimental study), usually expressed as a percentage
Vaccination effectiveness	The proportion of vaccinated animals which are protected from infection under field conditions
Vaccination coverage	The proportion of animals that are vaccinated in a target population

Appendix A – Model structure

A.1. Demographic data

Farm-level location data could not be obtained for Bulgaria and Greece. Accordingly, regional-level (NUTS2) data were used to generate synthetic farm-level datasets for both countries (EFSA AHAW Panel, 2015).

A.2. Modelling approach

Spread between farms was modelled using a kernel-based approach and assumed a seasonally varying transmission rate. In this case, the force of infection, $\lambda_i(t)$, for farm i on day t is given by,

$$\lambda_i(t) = h_0\left(1 + \varepsilon\cos\left(\frac{2\pi(t-\phi)}{365}\right)\right) \times (1 - v_i(t))N_i \times \sum_{j\neq 1} K(d_{ij})(1 - v_j(t))(1 - r_j(t))N_j I_j(t), \quad (1)$$

where h_0 is the mean transmission parameter, ε is the seasonal amplitude, ϕ is the seasonal phase, v_i is the level of vaccine protection for farm i, N_i is the number of cattle on farm i, $K(d_{ij})$ is the distance kernel, d_{ij} is the distance between farms i and j, r_j is the reduction in infectiousness due to partial stamping out and $I_j(t)$ is a variable indicating whether farm j is uninfected (0) or infected (1) on day t. A density-dependent, fat-tailed distance kernel was used, so that,

$$K(d_{ij}) = \left(1 + \left(\frac{d_{ij}}{d_0}\right)^{\alpha}\right)^{-1}, \quad (2)$$

where α and d_0 are parameters which control the shape of the kernel. Once a farm became infected, the duration of the outbreak, T_E, was assumed to be proportional to the log number of cattle (Swinton, 1998), that is,

$$T_E = \mu_D \log_e(1 - v(t_I))N, \quad (3)$$

where μ_D is the constant of proportionality, $v(t_I)$ is the level of vaccine protection at the time of infection (t_I) and N is the number of cattle. Parameters for each replicate were sampled from the joint posterior distribution estimated from the Israeli outbreak data (EFSA AHAW Panel, 2015) and are summarised in Table A.1.

Table A.1: Estimates[(a)] for parameters in the model for the spread of lumpy skin disease between farms

Parameter	Symbol	Estimate	95% range	
			Lower	Upper
Transmission rate	h_0	2.65×10^{-6}	1.26×10^{-6}	6.08×10^{-6}
Seasonal amplitude	ε	0.87	0.79	0.93
Seasonal phase (days)	ϕ	105.75	95.16	116.27
Distance kernel power	α	2.06	1.80	2.38
Distance kernel scale (km)	d_0	1.01	0.52	1.77
Outbreak duration	μ_D			
No stamping out		16.81	12.02	28.09
Partial stamping out		7.95	–	–
Maximum vaccination effectiveness	v_{max}	0.75	–	–
Time to full protection (days)	t_{FP}	21	–	–

(a): Where a range is given, parameters are sampled from a joint posterior distribution (summarised by the range); where a single value is given, the parameter is fixed.

Three scenarios were considered when partial stamping out is implemented in a herd. In the first, partial stamping out was assumed to reduce the duration of an outbreak, which was incorporated in the model by reducing the constant of proportionality, μ_D. Specifically, μ_D was set to 7.95 with partial stamping out (cf. outbreak described in Magori-Cohen et al., 2012). In the second scenario, the

duration of an outbreak was assumed to be the same as for no stamping out, but the infectiousness of a herd was assumed to be reduced by 50% (i.e. r_j is set to 0.5 in equation (1) after the herd reports disease). Finally, in the third scenario, the duration of an outbreak was assumed to be increased by 50% compared with no stamping out, but the infectiousness of the herd was reduced by 50%.

The level of vaccine protection on a farm, v, was assumed to increase linearly from zero at (or before) vaccination to the maximal level of protection. That is,

$$v(t) = \begin{cases} 0 & t < t_{vacc} \\ v_{max}\left(\frac{t - t_{vacc}}{t_{FP}}\right) & t_{vacc} \leq t \leq t_{vacc} + t_{FP} \\ v_{max} & t > t_{FP} \end{cases} \quad (4)$$

where t_{vacc} is the time of vaccination, t_{FP} is the time at which full protection is reached and v_{max} is the maximum level of protection.

Table A.2: Assumptions underlying the model and relative explanation

Model assumptions	Explanation and values
Vaccination	Included in the model by replacing herd sizes with the number of unprotected animals in each herd (i.e. the herd size multiplied by 1 minus vaccination effectiveness)
Force of infection and outbreak duration	Estimated from data on the location and time of infection for reported cases of LSD from the epidemic in Israel during 2012 and 2013
Difference between preventive and reactive vaccination	Different time of vaccination commencement
Preventive vaccination	All vaccinated farms have reached maximal achievable protection before an incursion occurs
Reactive vaccination	Starts 15 days after the incursion occurs with farms vaccinated at a constant rate until all farms are vaccinated 50 days later
Eligibility of farms for vaccination	All farms in Bulgaria and Greece
Time of vaccination	Assigned at random by NUTS2 region
Proportion of farms vaccinated	95% in all cases
Vaccination effectiveness	75% and 40%
Maximal protection	Achieved 21 days after vaccination
Seasonality	Same as in Israel
Spread without intervention	Stamping out of generalised infections in dairy herds (but not in beef herds) and vaccination with a single sheep dose of RM-65 sheep pox vaccine
Underreporting	50% of the affected farms to report the occurrence of clinical disease
Delay between infection and outbreak report	1–2 weeks after infection (sampled from a gamma distribution with a mean of 10.5 days and shape parameter of 30)
Partial stamping out	• By reducing outbreak duration (assumed to be proportional to log herd size, see Appendix A) on reported farms (from a maximum of around 180 days with no stamping out to a maximum of 50 days with partial stamping out, for the largest herd in Bulgaria and Greece), with the same infectiousness as no stamping out; • By reducing the infectiousness by 50% compared with no stamping out, with the same outbreak duration as no stamping out; • By increasing the outbreak duration by 50% compared with no stamping out, and by reducing the infectiousness by 50% compared with no stamping out.
Total stamping out	Removing the farm at a certain time (sampled from a gamma distribution with a mean of 7.6 days and shape parameter of 2.13) after reporting)
Delay between reporting and stamping out	Values observed in Bulgaria and Greece in 2015 and 2016

Appendix B – Effects of partial stamping out

As explained in the body text, the partial stamping out is incorporated in the model in one of three ways as follows:

- by reducing outbreak duration (assumed to be proportional to log herd size, see Appendix A) on reported farms (from a maximum of around 180 days with no stamping out to a maximum of 50 days with partial stamping out, for the largest herd in Bulgaria and Greece), with the same infectiousness as no stamping out;
- by reducing the infectiousness by 50% compared with no stamping out, with the same outbreak duration as no stamping out;
- by reducing the infectiousness by 50% compared with no stamping out, by increasing the outbreak duration by 50% compared with no stamping out.

In the following figures all these effects are shown, compared to no stamping out and total stamping out and coupled with the different vaccination strategies (none, starting after disease incursion, completed before disease incursion) and effectiveness (75% and 40%).

The implications in disease persistence from the implementation of the different control measures tested are reported in Figure A.1, where they are expressed in terms of the proportion of the epidemics which die out.

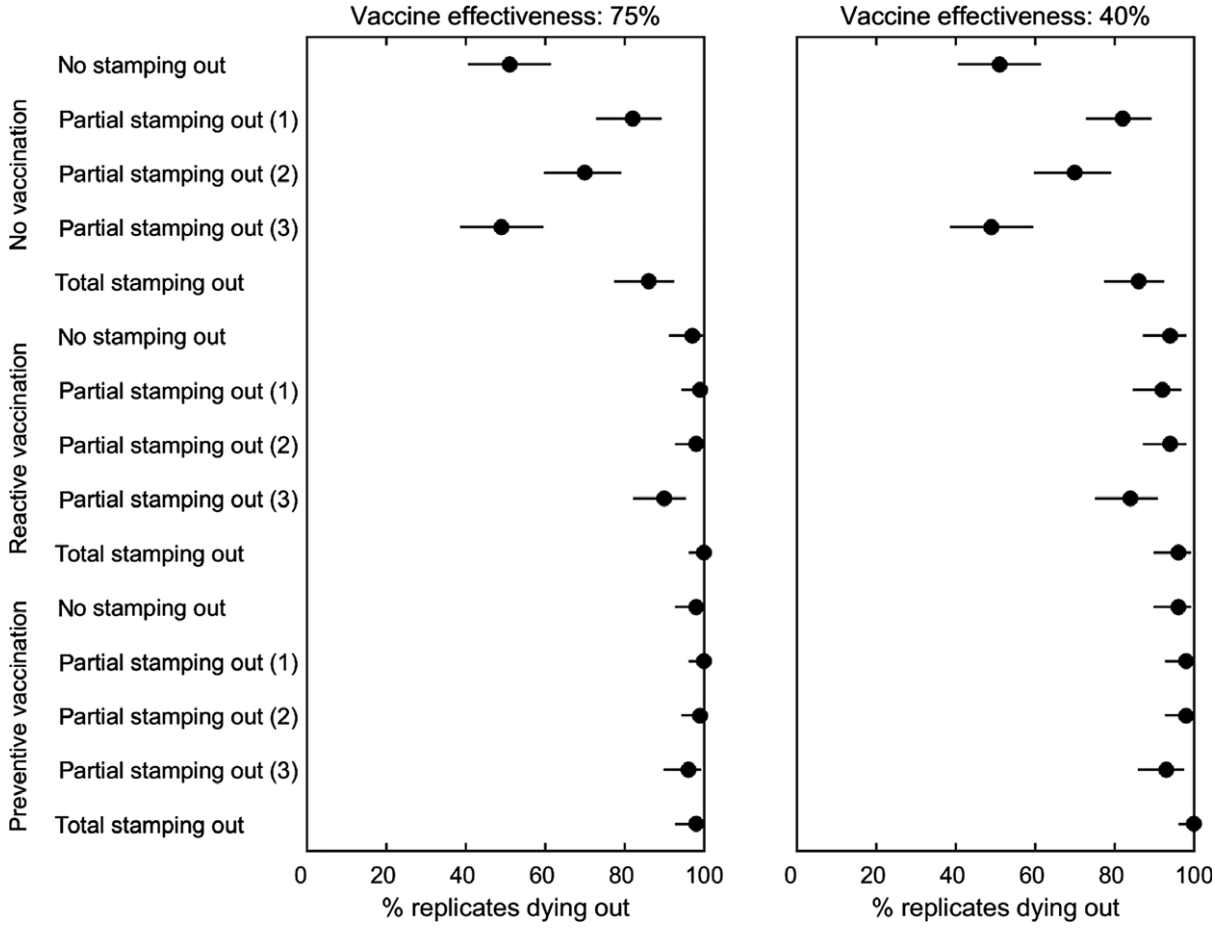

Figure A.1: Proportion of epidemics which die out under the different scenarios of intervention. Partial stamping out (1): assuming it reduces outbreak duration; partial stamping out (2): assuming it reduces infectiousness; partial stamping out (3): assuming it reduces the infectiousness and increases the outbreak duration

In Figures A.2 and A.4, the proportion (%) of simulations (see Section 2.2.1) (out of 100, which is considered to be enough given the differences amongst strategies observed) is shown for which at least one farm in a 0.1° × 0.1° grid square becomes infected by the end of the year in which the incursion occurs. In addition, in Figure A.3 and A.5, the number of newly LSDV-infected herds in

Bulgaria and Greece is shown for the different scenarios for both values of vaccination effectiveness (75% and 40%).

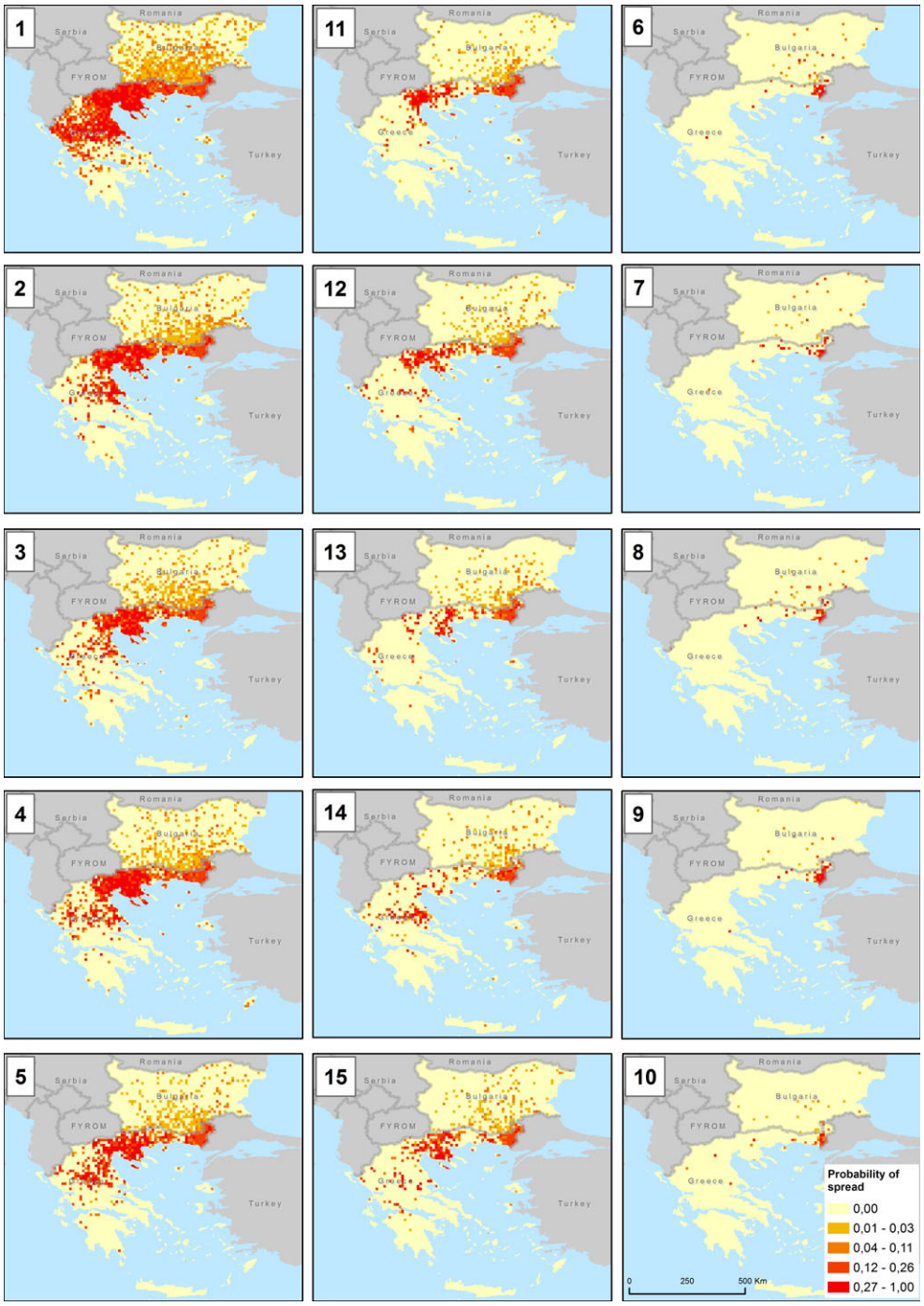

Figure A.2: Predicted impact of different vaccination and stamping-out strategies on the geographical spread of lumpy skin disease virus in Bulgaria and Greece. The colour of the dots (and the related scale bar) shows the proportion of simulations (%) for which at least one farm in a 0.1° × 0.1° grid square becomes infected by the end of the year in which the incursion occurs. Rows differ in the intensity of stamping out implemented: no stamping out (top row), partial stamping out assuming it reduces outbreak duration (1), or reduces infectiousness (2), or reducing the infectiousness and increases the outbreak duration (3) (three rows in the middle); or total stamping out (bottom row). Columns differ in vaccination strategy: no vaccination (left-hand column), reactive vaccination (middle column) or preventive vaccination (right-hand column). Vaccination effectiveness is set at 75%

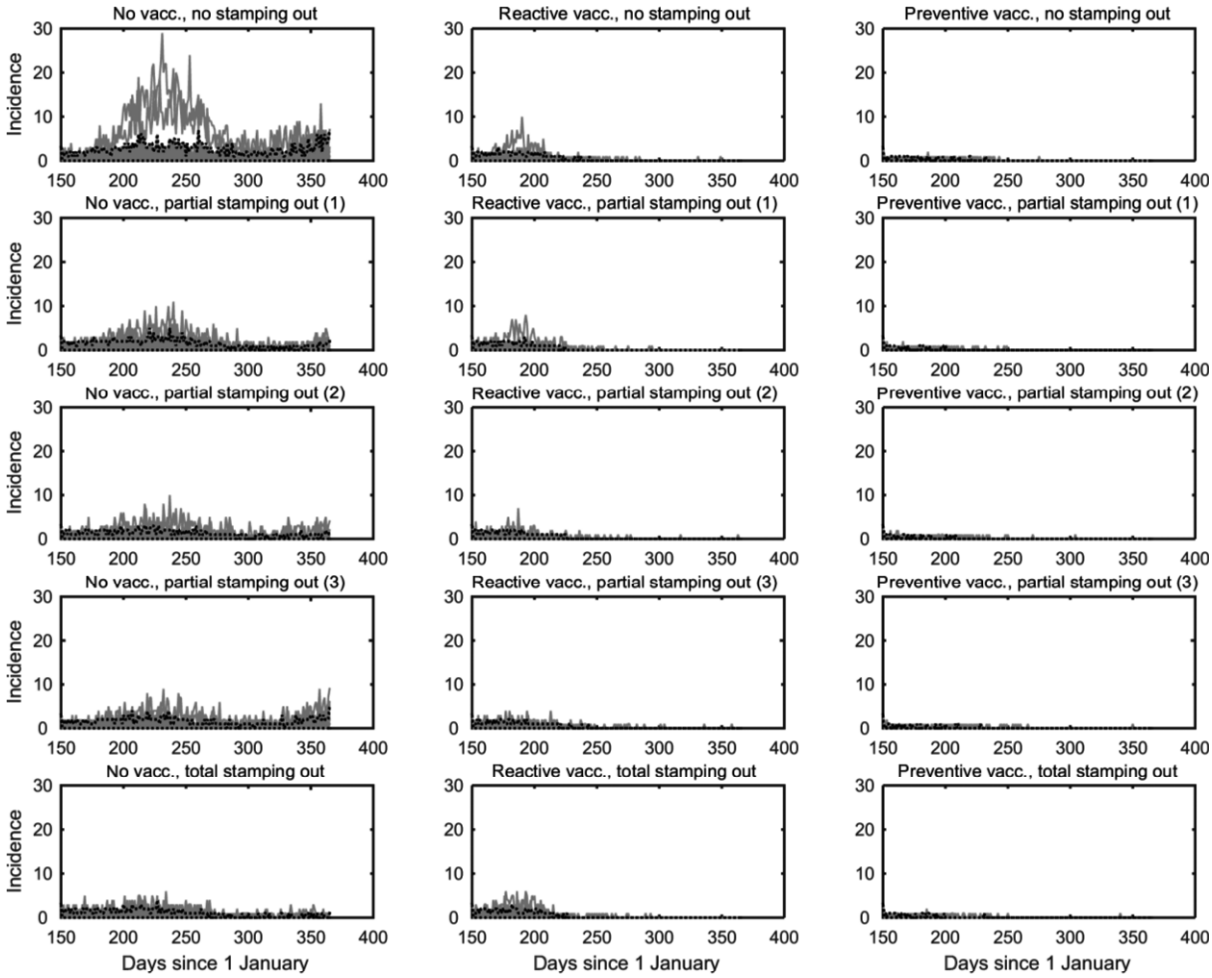

Figure A.3: Predicted impact of different vaccination and stamping-out strategies on the number of newly infected herds in Bulgaria and Greece. Each plot shows the 2.5th and 97.5th percentiles (black dotted lines) and individual replicates (grey lines) for 100 simulated outbreaks. Rows differ in the intensity of stamping out implemented: no stamping out (top row), partial stamping out assuming it reduces outbreak duration (1), or reduces infectiousness (2), or reducing the infectiousness and increases the outbreak duration (3) (three rows in the middle); or total stamping out (bottom row). Columns differ in vaccination strategy: no vaccination (left-hand column), reactive vaccination (middle column) or preventive vaccination (right-hand column). Vaccination effectiveness is set at 75%

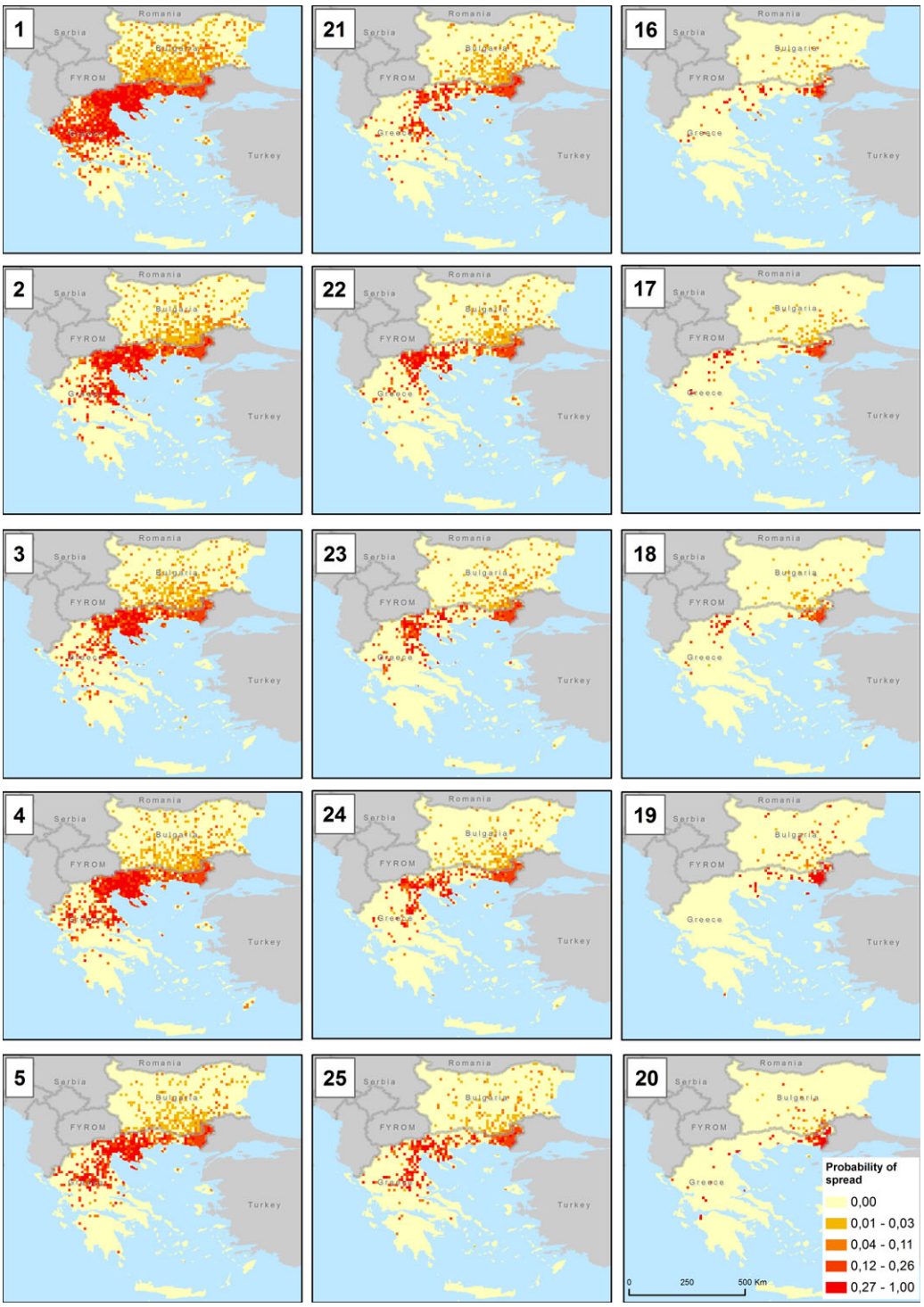

Figure A.4: Predicted impact of different vaccination and stamping-out strategies on the geographical spread of lumpy skin disease virus in Bulgaria and Greece. The colour of the dots (and the related scale bar) shows the proportion of simulations (%) for which at least one farm in a 0.1° × 0.1° grid square becomes infected by the end of the year in which the incursion occurs. Rows differ in the intensity of stamping out implemented: no stamping out (top row), partial stamping out assuming it reduces outbreak duration (1), or reduces infectiousness (2), or reducing the infectiousness and increases the outbreak duration (3) (three rows in the middle); or total stamping out (bottom row). Columns differ in vaccination strategy: no vaccination (left-hand column), reactive vaccination (middle column) or preventive vaccination (right-hand column). Vaccination effectiveness is set at 40%

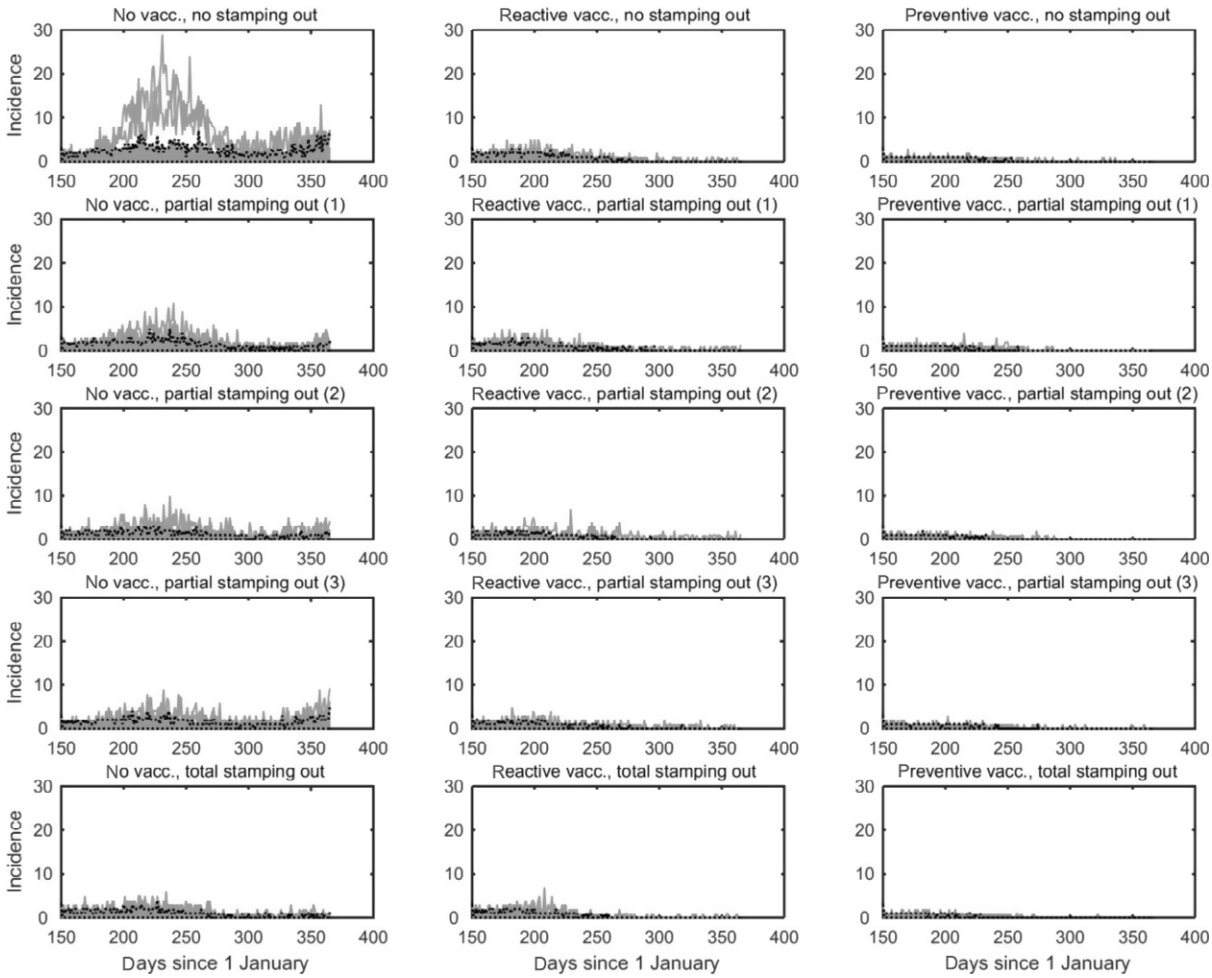

Figure A.5: Predicted impact of different vaccination and stamping-out strategies on the number of newly infected herds in Bulgaria and Greece. Each plot shows the 2.5th and 97.5th percentiles (black dotted lines) and individual replicates (grey lines) for 100 simulated outbreaks. Rows differ in the intensity of stamping out implemented: no stamping out (top row), partial stamping out assuming it reduces outbreak duration (1), or reduces infectiousness (2), or reducing the infectiousness and increases the outbreak duration (3) (three rows in the middle); or total stamping out (bottom row). Columns differ in vaccination strategy: no vaccination (left-hand column), reactive vaccination (middle column) or preventive vaccination (right-hand column). Vaccination effectiveness is set at 40%