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Evaluation of the control strategy for the 2010 foot-and-mouth disease outbreak in Japan using disease simulation

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[Running head]

Simulation of the 2010 FMD epidemic in Japan

[Summary]

In 2010, Japan experienced a foot-and-mouth disease (FMD) epidemic where 292 premises were infected over a period of 75 days. The epidemic was controlled by stamping-out and vaccination, applied 5 weeks after the first confirmation of disease within a 10 km radius of identified infected places. This study aimed at identifying the role of emergency vaccination to epidemic control while adjusting for the dynamic pattern of local spread, and assessing alternative vaccination strategies, using a disease simulation model. Our results indicate that the overall hazard of local spread remained high throughout the silent spread phase and the first two weeks post detection, with significant reduction occurring from week 3 onwards. The estimated effectiveness of emergency vaccination quantified as reduction in the hazard of infection was at most 81% and 44% for cattle and pig farms, respectively. The vaccination strategy reduced the simulated median number of IPs by 22%, epidemic duration by 64% and culling duration by 52%, but increased the total number of infected or vaccinated premises subject to culling by 144% compared with no vaccination. The simulation indicated that vaccination starting 2 weeks earlier (3 week post first detection) with a smaller vaccination radius (3 km) was more effective for eradication of the epidemic compared with the actually implemented strategy.

[Keywords]

Foot-and-mouth disease
Emergency vaccination
Local spread
Disease simulation model

[Introduction]

In 2010 Japan experienced its first outbreak of foot-and-mouth disease (FMD) in ten years. During 11 weeks (75 days) a total of 292 infected premises (IPs) were detected in Miyazaki Prefecture (Kyushu Island, in the southwest of Japan), a region in which around 10% of the total number of livestock premises in Japan are located (Anonymous 2007, 2008, 2009, 2010, 2011, 2012, 2013). The scale of this epidemic was different from the previous FMD epidemic that occurred in Miyazaki and Hokkaido Prefectures in 2000, which in total involved only four infected premises. The primary control strategy in earlier epidemics comprised a combination of depopulation of IPs, imposition of movement restrictions, and active surveillance in high-risk premises (Yamane 2006; Muroga *et al.* 2012). In the 2010 epidemic authorities resorted to a vaccinate-to-die policy at 5 weeks after

detection of the index case because of failure of the initial response strategy. Japan's OIE disease status, 'FMD-free where vaccination is not practised,' was suspended until February 2011, seven months after the last vaccinated animal was culled, that is, after the stipulated waiting period of three months, and an additional time lag of four months until the next OIE Scientific Commission meeting ratified the change in status.

The 2010 epidemic of FMD in Miyazaki caused significant economic damage to the local economy as livestock industries are a major source of income, with annual gross income from livestock products contributing 7% to the national income from livestock products (Anonymous 2014). Further, the culling of bulls of superior genetic merit was estimated to have a negative impact on the regional beef industry for at least five years (Nishiura and Omori 2010). The national livestock industry, particularly the beef sector, suffered losses due to trade restrictions on the export of wagyu beef. At the time of the outbreak, the cost incurred to the local economy and the livestock industry was estimated to be USD 2.0 billion (JPY 235 billion) over five years (Anonymous 2010a).

The epidemiological features of the 2010 epidemic of FMD in Miyazaki has been described in several studies (Nishiura and Omori 2010; Hayama *et al.* 2012; Muroga *et al.* 2012). The epidemic was caused by the serotype O virus, which was closely related to the strain that circulated in East Asian regions, such as Hong Kong SAR and The Republic of Korea in early 2010 (Muroga *et al.* 2012). Confirmation of disease occurred on 20 April 2010, which was thought to be at least 20 days after the onset of the clinical signs in the primary case (Muroga *et al.* 2012). During the period between first incursion and first recognition of disease (i.e. the silent spread phase), at least 10 premises were estimated to have been infected (Muroga *et al.* 2012). The daily number of detected IPs was relatively low at the early stage of an epidemic but rapidly increased from week three onwards. Due to a lack of burial sites and a shortage of veterinarians, the rate at which IPs were depopulated did not match the rate of detection for the first five weeks. This resulted in an accumulation of IPs waiting to be culled. During week five, as the spread of disease increasingly overwhelmed the resource capacity, two actions were notable: (1) local farmers and the general public were encouraged to refrain from unnecessary movements, as represented by the state of emergency declared by the Prefecture Governor (18 May 2010), and (2) the decision to apply emergency vaccination was made (22 May 2010). Specifically, animals on all susceptible premises within a 10 km radius of detected IPs (1,066 premises: 10% of susceptible livestock premises in the prefecture) were vaccinated to be subsequently culled. From week six onwards, the number of IPs waiting to be depopulated decreased and the epidemic ended with the final case of FMD detected on 4 July 2010.

A number of questions concerning preparedness and outbreak decision making were raised during and after the 2010 epidemic of FMD in Miyazaki. Firstly, the level of awareness by the authorities and stakeholders was not sufficient to manage an incursion of FMD, while there were repeated FMD outbreaks in neighbouring countries. For example, stringent and routine biosecurity measures were not consistently practised on farms (Anonymous 2010b). In addition, prefectural veterinarians were scarcely allocated in Miyazaki compared with the national average, even though the FMD susceptible population was relatively high. These factors contributed to delay in the confirmation of disease since the first suspicion of FMD, and failure in the initial response. Particularly, the cost of failing to promptly detect FMD would be substantial. It was illustrated by a simulation modelling study in the US, which predicted that every additional hour of delay in the onset of controls resulted in the national agriculture losses of USD 565 million (Carpenter *et al.* 2011). Secondly, the delay in making the decision to implement emergency vaccination was likely to play a role in increasing the size of the outbreak (Anonymous 2010b). This might be due to difficulty justifying the use of emergency vaccination in the absence of appropriate decision support tools and the absence of a vaccination plan with great uncertainty about the efficacy and benefit of emergency vaccination.

There have been two published studies using disease models for the 2010 FMD epidemic in Japan. Nishiura and Omori (2010) examined the temporal pattern of the outbreak reproduction number (R_0) and found fluctuations in R_0 remaining greater than 1 until the later stage of the epidemic, and species-specific risk over calendar time. Due to limited data and failure to account for the geographic location of IPs, the implications of their results are limited and questions regarding the effectiveness of control measures were not addressed. Hayama *et al* (2013) developed a microsimulation model incorporating the explicit spatial component and compared alternative control measures with actual outbreak data. However, the effect of emergency vaccination might be overestimated firstly because of their assumption of perfect effectiveness of vaccination. Secondly, by assuming a static pattern of disease spread (transmission kernel), a possible suppression of human contacts responsible for disease transmission might not be captured.

For FMD, short-distance disease spread without any identified movements ('local spread') has often been reported as an important mechanism of transmission in FMD (Sanson 1994; Donaldson *et al.* 2001; Gibbens *et al.* 2001; Sanson *et al.* 2006; Muroga *et al.* 2013). During the 2010 epidemic of FMD in Miyazaki human activities as well as environmental factors were found to be a key risk factor for such mechanism of spread (Muroga *et al.* 2013). In the 2001 epidemic of FMD in the UK, it was shown that local spread risk changed markedly throughout the course of the epidemic (Wilesmith *et al.* 2003).

In this study, our first aim was to identify the contribution of suppression in local spread and emergency vaccination to the containment of disease for the 2010 Japan epidemic of FMD, considering potential variation in the pattern of local spread over time. A simulation model for the 2010 epidemic of FMD in Japan was parameterised using InterSpread Plus (Stevenson *et al.* 2012), a spatially explicit stochastic simulation model platform. Our second aim was to assess the effect of alternative epidemic control measures (i.e. an earlier start of vaccination, use of a smaller vaccination radius, and no vaccination) on predicted numbers of IPs and predicted epidemic duration. Our intention here was to provide a more quantitative basis for decision making concerning the way FMD outbreaks in Miyazaki might be better handled in future.

[Materials and methods]

Data

The dataset for the FMD epidemic in Miyazaki (2010) was obtained from Japan Agricultural Cooperatives (JA) Koyu and Osuzu (Miyazaki Prefecture, Japan). The data were comprised of 880 livestock units (premises) with FMD susceptible species, located in five adjacent towns (Tsuno, Kawaminami, Shintomi, Takanabe, and Kijo). The data set included 272 IPs (93% of the total number of IPs in the 2010 outbreak). The other 20 IPs were located outside the area and not included in the analyses because the data for the susceptible population in these external areas were absent. Based on these data, a time-to-event (survival) dataset was constructed as described in another paper (Wada *et al.* in preparation). Briefly, the outcome was measured as time from the onset of infectiousness of a source IP until transmission of FMD to a neighbouring premises at risk of local spread from that source IP. Because the source of each infection is unknown, it was hypothesised by randomly selecting a source among all the temporally and spatially probable candidate sources, with the weight on spatial proximity. All other pairs of infectious and susceptible premises located within 10 km of each other were included as censored data. The data set comprised of (i) hypothesised occurrence of transmission of FMD from the potential source premises to the susceptible premises, (ii) the start date of infectiousness of the potential source premises (t_0) and (iii) the end date of infectiousness of the potential source, or the date of infection in the susceptible premises, whichever occurred first (t_1), (iv) the Euclidian distance (km) between the two premises, (v) dominant animal species on the infectious premises and (vi) dominant animal species on the susceptible premises, and (vii) herd/flock size of the infectious premises and (viii) herd/flock size of the susceptible premises (both presented as log of base 10 of the number of animals on the premises).

Epidemic phases

Table 1 shows the weekly counts and the mean daily rates of detected and depopulated premises by week from the first confirmation of disease (20 April 2010), based on the official report (Anonymous 2010c). Initially, the period between the onset of infectiousness in the primary case farm (~25 March 2010) and the start of culling of vaccinated animals (7 June 2010) was split into eight phases based on the calendar time, i.e. the silent spread phase (~25 March – 19 April 2010) and weeks 1 to 7, as defined in Table 1. To determine epidemiologically meaningful phases, a simple survival model was fitted using two variables, i.e. calendar-based phases and distance between a potential source and a susceptible premises, as described in the following section. Based on the estimated regression coefficients (β) and 95% confidence intervals of the fitted model, epidemiological phases were determined by merging adjoining periods if their regression coefficients were statistically similar.

For both calendar and epidemiological phases, the data were structured to allow for a piece-wise survival analysis. That is, any pair of infectious and susceptible premises whose observation period (between t_0 and t_1) extended over two or more phases was split into multiple phase-wise records. In the restructured data, the first follow-up period ran from the start of infectiousness to the end of the phase, and then the subsequent follow-up period(s) ran from the start of the next phase to the end of the phase or infectiousness.

Data analyses

The probability of occurrence of disease transmission on day t after the onset of infectiousness, given that the susceptible premises had been uninfected until day t, was represented using a hazard function $h(t)$. A Weibull regression model was fitted as:

$$h(t) = \lambda_0 s t^{(s-1)} \exp\left(\sum \beta_i x_i\right) \quad (1)$$

where s is a shape parameter, λ_0 is a scale parameter (i.e. the hazard when all the explanatory variables are 0), and β_i are the estimated regression coefficients for explanatory variable x_i. Candidate variables were: (i) phases of an epidemic defined in the previous section, (ii) distance between a potential source and a susceptible premises, (iii) species on a potential source premises, (iv) species on a susceptible premises, (v) herd/flock size on a potential source premises and (vi) herd/flock size on a susceptible premises. Any candidate variable was included in the baseline model if significance of the log likelihood ratio test statistic was less than 0.10. Based on the fitted multivariable model, inclusion or exclusion of any biologically plausible interaction term was determined based on a likelihood ratio test, with a significance level of $p < 0.05$. The final baseline

model was evaluated by whether removal of a single term would make a significant deterioration in fit by a level of $p > 0.05$.

Simulation model

InterSpread Plus version 6.01.6 (EpiSoft NZ) was used as a platform for building simulation models for the FMD epidemic in Japan in 2010.

As parameters for disease transmission, daily probabilities of local spread were predicted using the fitted survival model. The probabilities were estimated for up to 10 km from an infectious premises, counting from the onset of infectiousness which was assumed to be one day prior to the onset of clinical signs. Time from infection to the onset of clinical signs was parameterised as an empirical cumulative density distribution, based on the epidemic data, assuming clinical signs appeared on the date of detection. Variation in local spread patterns by phase, species and herd size were considered. We then examined whether predicted epidemics temporally and spatially matched that which actually occurred. If necessary, additional parameters for disease transmission by long-distance movements were considered.

The effectiveness of emergency vaccines was determined based on the fitted survival model, assuming a decrease in the hazard in the post-vaccination phase from that of the previous phase was attributable to emergency vaccination. Vaccination was assumed to become effective at the earliest on the 4th day post vaccination and reach maximum effectiveness on the 7th days as reported from experimental studies (Doel *et al.* 1994; Salt *et al.* 1998; Barnett *et al.* 2004). Infectivity of vaccinated infected animals was assumed to be suppressed completely.

Control measures including depopulation of detected IPs, emergency vaccination, and surveillance were parameterised to follow what actually occurred during the epidemic. Depopulation was assumed to be conducted on detection of IPs but constrained by the resource capacity as follows: 1 IP per day (week 1 – 3), 5 IPs per day (week 4 – 5), 7 IPs per day (week 6) and 10 IPs per day (week 7 onwards) (see Table 1). Vaccination was assumed to be applied to apparently uninfected premises within 10 km of detected premises on the 32nd day after first confirmation of disease. The resource constraints for vaccination were set as 200 premises per day and premises were processed from outer to inner radius (Muroga *et al.* 2012). For surveillance, livestock owners were assumed to monitor their animals daily after initial confirmation, and 100% detection was assumed once clinical signs appeared.

The outcomes of an epidemic was measured as the number of IPs, number of culled premises, epidemic duration, culling duration and infected area. Epidemic duration was defined as the interval

from the date of first detection to the date of detection of the last case. Culling duration was defined as time from the first detection to completion of culling of all IPs and vaccinated animals, based on the last date of depopulation of IPs, and time to complete culling of vaccinated premises. We used the observed rate of culling of vaccinated premises, i.e. 26 premises per day. The criteria to start the activity of subsequent culling of vaccinated animals was assumed to be: (i) at least 17 days had elapsed since the onset of vaccination and (ii) the number of premises waiting to be depopulated was less than 60, as what actually occurred (Anonymous 2010d). Infected area was measured as the area enclosed by the convex hull of all simulated IPs within the investigated area.

Evaluation of alternative control scenarios

The outcomes of four alternative control scenarios were compared against that of the actual control strategy, i.e. 10 km ring vaccination five weeks after first confirmation of disease ('5w10k'), which took place during the epidemic. In the alternative scenarios emergency vaccination was: (i) applied within a 10 km radius 3 weeks (21 days) instead of 5 weeks (32 days: actual timing of vaccination) after first confirmation of disease ('3w10k'), (ii) applied within 3 km ring radius (instead of 10 km) 5 weeks after first confirmation of disease ('5w3k'), (iii) applied within 3 km ring radius 3 weeks after first confirmation of disease ('3w3k'), and (iv) never applied throughout the course of the epidemic.

[Results]

Epidemic phases

The hazard ratios for local spread and 95% confidence intervals for each of the calendar-based phases based on the initial survival model are shown in Figure 1. Four epidemiological phases were distinguished by a statistically significant difference in the estimated hazard: phase I (the silent spread phase, weeks 1 and 2), phase II (week 3), phase III (weeks 4 and 5), and phase IV (weeks 6 and 7). During the four epidemiological phases, there were 202,622 observations (phase I: 7%, phase II: 17%, phase III: 42%, and phase IV: 34%) of unique pairs of a susceptible premises and a potential source of local spread. The number of unique infectious premises for phases I, II, III, and IV were 25 (cattle: 13, pigs: 12), 66 (cattle: 36, pigs: 30), 194 (cattle: 133, small ruminants: 1, pigs: 60), and 186 (cattle: 138, small ruminants: 1, pigs: 47), respectively. It should be noted that a premises that was infectious during two or more phases was recorded as multiple observations. The estimated number of local spread transmissions (and all infections in parentheses) for phase I, II, III, and IV were 73 (74), 61 (63), 110 (110), and 27 (27), respectively.

Hazard of FMD transmission

A full model was fitted with five explanatory variables (phase, distance, source species, susceptible species, and herd size of susceptible premises) and three interaction terms (phase × distance, phase × susceptible species and distance × source species). The hazard ratios are shown in Table 2. Compared with phase III, the adjusted hazard of local spread for an adjacent susceptible cattle premises (i.e. 0 km distance) was 19.1 (95% CI: 13.7 to 26.6) and 3.3 (95% CI: 2.3 to 4.7) times greater in phases I and II, respectively. In phase IV, the adjusted hazard for an adjacent susceptible cattle premises decreased to 0.2 (95% CI: 0.1 to 0.3) times that of phase III. Factors associated with decrease in hazard were distance from infectious cattle premises (HR: 0.6 to 0.9, 95% CI: 0.6 to 1.0), susceptible pigs relative to cattle (HR: 0.4 to 0.5, 95% CI: 0.3 to 0.7) except for phase IV, and distance from infectious pig premises (HR: 0.5 to 0.7, 95% CI: 0.5 to 0.8). Factors associated with increase in hazard were infectious pigs relative to cattle (HR: 2.8, 95% CI: 2.2 to 3.7), and herd size of a susceptible premises (HR: 3.4, 95% CI: 3.1 to 3.8).

Simulation model

The epidemiological parameters for the simulation model were determined based on the modified survival model in which the interaction term between distance and source species was removed because multiple, simultaneous local spread patterns were not able to be modelled within the current InterSpread Plus. A subset of the local spread parameters used in the model is shown in Figure 2. For parsimony, small ruminant farms (n = 30) were classified as cattle primarily on account of their small numbers, and also their reported similarity in pathogenicity. The modified model did not include the term for source species since it was not significant after removing the above mentioned interaction term. The subsequent results from the modified model were slightly different from the full model, but the sign of the coefficients did not change. The estimated epidemiological parameters are shown in Table 3.

The performance of the model was assessed by the degree of agreement between the simulated and actual epidemics. Our assessment was that the simulated epidemics reasonably matched what was observed in terms of the cumulative epidemic curves (Figure 3), the pattern of the herd size and the species of the IPs (Figure 4), and the spatio-temporal pattern of the spread of IPs (Figure 5).

Evaluation of alternative control scenarios

The predicted epidemic outcomes of the five control scenarios are shown in Figure 6 as ratios to the median predicted values of the reference model ('5w10k'). Vaccination with a smaller radius with the same onset ('5w3k') reduced the predicted number of culled premises and culling duration to a

median of 0.87 (5th to 95th percentiles: 0.78 to 0.94) and 0.93 (0.89 to 1.00), respectively. Earlier start vaccination with the same radius ('3w10k') reduced the predicted number of IPs, number of culled premises, epidemic duration, culling duration and infected area to a median of 0.74 (5th to 95th percentiles: 0.49 to 1.00), 0.99 (0.87 to 1.00), 0.84 (0.74 to 0.97), 0.89 (0.83 to 0.96) and 0.81 (0.60 to 0.99) of the reference, respectively. Earlier vaccination with a smaller vaccination radius ('3w3k') reduced the predicted number of IPs, number of culled premises, and culling duration to a median of 0.72 (5th to 95th percentiles: 0.49 to 0.97), 0.74 (0.64 and 0.81) and 0.80 (0.72 and 0.88) of the reference, respectively. Stamping-out alone ('novac') reduced the predicted number of culled premises to a median of 0.41 (5th to 95th percentiles: 0.23 to 0.59) and increased the predicted epidemic duration to a median of 2.79 (1.09 to 2.95) of the reference.

The density of IPs that were infected 3 weeks after first confirmation of disease using the reference and alternative control scenarios are shown in Figure 7. An early start 10 km radius vaccination ('3w10k') contained the simulated epidemic to the smallest area in northeast of the study area. Without vaccination, the infected area extended southwest of the study area around the border to an adjacent city.

[Discussion]

In this study, we developed a disease simulation model of the 2010 outbreak of FMD in Miyazaki, Japan using the disease simulation platform, InterSpread Plus (Stevenson *et al.* 2012). Alternative control scenarios, where vaccination was targeted to a smaller population (3 km vs 10 km) and/or applied earlier (week 3 vs week 5 post first confirmation), or never applied, were compared with the control scenario that was actually applied (10 km radius vaccination commencing in week 5). Our results showed that all four alternative vaccination strategies reduced the median predicted number of IPs (ratio range: 0.56 to 0.78), epidemic duration (0.30 to 0.37), culling duration (0.38 to 0.48) and infected area (0.70 to 0.90) relative to no vaccination, while the predicted median number of culled premises increased to 1.80 to 2.44 (Figure 6). Moreover, our findings indicated that without vaccination infection was more dispersed within the affected area and potentially spread to areas outside the investigated area (Figure 7), supporting the use of emergency vaccination as a means to assure containment of disease within an initial infection foci. A smaller vaccination radius (3 km) is likely to be less costly than larger radii (e.g. 10 km), as it contributed to a saving in the number of premises requiring culling and a shorter time to complete culling activities. The epidemiologically preferred vaccination radius is dependent on presence or absence of undetected IPs outside the vaccination radius, or local spread transmission occurring outside the immune belt. Based on our simulation model results, earlier vaccination with a smaller vaccination ring ('3w3k') provided the

most efficient approach of all the alternative vaccination scenarios tested. It should be noted, however, 27 out of 100 iterations for this strategy ('3w3k') resulted in an infected area larger than the reference, suggesting there is a risk of disease spread to the outside of immune belt by use of a small vaccination radius.

The hazard of local spread decreased significantly 3 weeks after the first confirmed case of FMD. In contrast, there was no significant change in hazard of local spread before and after first detection of disease. Moreover, there was a trend of increase in hazard in week 2 compared with other weeks of the epidemic. The change in hazard suggested that the majority of local spread during the early phase of the epidemic (week $\leq$ 2) was attributable to human interactions (which could change over time), rather than aerial dissemination of virus, or other environmental mechanisms of disease transmission (which would be constant over time). In other words, at the time of implementing emergency vaccination (week 5), the hazard of local spread was reduced to 5% of that during the early phase of the epidemic (week $\leq$ 2), with 95% of the initial hazard having been controlled by a combination of other factors. For example, enhanced biosecurity and an increased awareness of disease by livestock owners and the general public could have contributed to reduction in local spread. If the local spread probabilities of phase I were replaced with those of phase II, there was a marked reduction in the simulated number of infected places (median: 83 IPs, 5^{th} and 95^{th} percentile: 39 and 177 IPs, respectively).

The hazard of local spread post-vaccination was less than pre-vaccination. The estimated hazard post-vaccination was 0.19 times that of pre-vaccination for properties with cattle and 0.56 times for properties with pigs. The decrease in hazard could be partially attributable to emergency vaccination and other factors mentioned above. In addition, there may have been underreporting of IPs after vaccination, due to suppression of clinical signs (Nishiura and Omori 2010), which potentially could lead to an underestimation of post vaccination hazard. We conclude that the vaccination policy, as implemented, reduced the hazard of infection by at most 81% for cattle and 44% for pig enterprises. The efficacy of high potency emergency vaccine was reported to be consistent across species (cattle, sheep, goats and pigs) in experimental studies (Barnett *et al.* 2004), and variations in efficacy by species for emergency vaccine in the field are not clear.

In this study we used the previously described method (Wada *et al.* in preparation) for estimating local spread probabilities. We then used these estimates as input parameters for our simulation model. The temporal and spatial patterns of simulated IPs matched well with the actual epidemic, supporting the validity of our proposed method. Although long distance, high-risk movements are included in other FMD simulation modelling studies, these movements were not parameterised in

this modelling study because of absence of reliable movement data and the imposition of movement restrictions at the time disease was first detected which minimised the likelihood of such movements. As a result, local spread alone was sufficient to closely mimic the spread within the relatively small study area (median distance between two premises: 8.6 km, 10 – 90%: 2.8 – 19.1 km, data not shown). For an early vaccination scenario, we examined emergency vaccination three weeks after first confirmation of disease, allowing sufficient time for antigenic matching, manufacturing and transportation of vaccine. The implications for alternative vaccination strategies are the same as those of Hayama *et al* (2013), in that an earlier onset of vaccination (on day 7 or 21 post first confirmation of disease) using a 3 km vaccination radius was more effective in reducing the number of IPs than starting vaccination on day 32 (as actually occurred).

[Conclusion]

Emergency vaccination applied during the FMD epidemic in Japan in 2010 reduced the duration of an epidemic to less than 40% of what was simulated to have occurred without vaccination, but resulted in culling more than twice as many animals relative to no vaccination. Our results show that the epidemic could have been contained more effectively by starting vaccination 2 weeks earlier, with a smaller vaccination radius (3 km instead of 10 km). In addition, the hazard of local spread was remarkably high throughout the silent spread phase and the initial 2 weeks after the confirmation of disease. This reinforces the need for rapid deployment of effective control strategies (movement restrictions, enhanced premise-level biosecurity, rapid detection and quarantine of infected places) within the surrounding high risk areas immediately post detection.

[Acknowledgements]

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[Figure captions]

Figure 1 Estimated hazard ratio (HR) (points) and 95% confidence intervals (whiskers) of local spread of foot-and-mouth disease (FMD) for seven phases (silent spread phase, and week 1, 2, 3, 5, 6, and 7) relative to week 4, i.e. a week prior to application of vaccination (HR = 1: dashed line), for the FMD epidemic in Japan (2010).

Figure 2 Estimated probabilities of local spread for the foot-and-mouth disease (FMD) epidemic in Japan (2010), for four types of a susceptible premises (species: cattle/small ruminants or pigs and herd size: n = 10 or 100) on day 1 (straight line) and 7 (dotted line) of infectiousness for four phases (relative to the first confirmation of disease, phases I: week $\leq$ 2, II: week 3, III: week 4 – 5, and IV: week 6 – 7).

Figure 3 Evaluation of the reference simulation model (100 iterations) in terms of temporal patterns of infection for the foot-and-mouth disease (FMD) epidemic in Japan (2010). The red, black, and grey lines show the cumulative number of infected premises for estimated actual value, simulated median (black bold), and the 5^{th} and 95^{th} percentiles, respectively.

Figure 4 Evaluation of the reference simulation model (100 iterations) in terms of herd-specific risk factors for the foot-and-mouth disease (FMD) epidemic in Japan (2010). Distribution of herd size [A] and species [B] for the total population, and actual and simulated infected premises are shown.

Figure 5 Evaluation of the reference simulation model (100 iterations) in terms of spatial distribution of cases for the foot-and-mouth disease (FMD) epidemic in Japan (2010). Density of new cases by phase (relative to the first confirmation of disease, phases I: week $\leq$ 2, II: week 3, III: week 4 – 5, and IV: week 6 – 7) for the observed epidemic and simulated epidemic that produced a median number of cases. The asterisk (*) shows the primary case, and thin and bold contour lines show 0.6 and 1.2 cases/100km^2, respectively.

Figure 6 Box and whisker plots showing the ratios of the simulated outcomes of an epidemic for the number of infected premises (IPs, reference: 280 IPs), the number of culled (infected or vaccinated) premises (880 premises), epidemic duration (57 days), culling duration (76 days), and the size of the infected area (187 km^2) to the reference values (in parenthesis) for the five control strategies (5w10k, 5w3k, 3w10k, 3w3k, and novac: 10 km vaccination in week 5, 3 km vaccination in week 5, 10 km vaccination in week 3, 3 km vaccination in week 3, and no vaccination) for the foot-and-mouth disease (FMD) epidemic in Japan (2010). The box, whisker, and dot represent the interquartile range (IQR), 5^{th} and 95^{th} percentile, and outliers, respectively.

Figure 7 Density of simulated infected premises 3 weeks after the first confirmation of disease, controlled by the actual (5w10k: 10 km vaccination in week 5) and four alternative strategies (5w3k: 3 km vaccination in week 5, 3w10k: 10 km vaccination in week 3, 3w3k: 3 km vaccination in week 3, novac: no vaccination) for the foot-and-mouth disease (FMD) epidemic in Japan (2010) (n = 100 iterations). The thin and bold contour lines show 0.4 and 1.0 premises/100 km^2, respectively.

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Table 1 The weekly counts and daily rates of detected and depopulated premises during the course of a foot-and-mouth disease (FMD) epidemic in Miyazaki, Japan in 2010.

Week	Start date	Detected premises		Depopulated premises		Unprocessed IPs
		Weekly count (premises)	Rate (premises/day)	Weekly count (premises)	Rate (premises/day)	Cumulative count (premises)
1	20 April 2010	8	1.1	4	0.6	4
2	27 April 2010	9	1.3	6	0.9	7
3	4 May 2010	50	7.1	10	1.4	47
4	11 May 2010	59	8.4	29	4.1	77
5	18 May 2010	74	10.6	40	5.7	111
6	25 May 2010	47	6.7	47	6.7	111
7	1 June 2010	29	4.1	75	10.7	65
8	8 June 2010	13	1.9	50	7.1	28
9	15 June 2010	2	0.3	23	3.3	7
10	22 June 2010	0	0.0	7	1.0	0
11	29 June 2010	1	0.1	1	0.1	0

Table 2 Estimated hazard ratio and 95% condidence intervals (in parenthesis) for the full Weibull regression model for local spread infection for a foot-and-mouth disease (FMD) epidemic in Japan (2010) (n = 202,622).

Parameters	Phase I	Phase II	Phase III	Phase IV
Phase[*1]	19.07	3.27	1.00	0.19
	(13.68, 26.57)	(2.26, 4.74)	(reference)	(0.12, 0.32)
Distance (cattle source) [*2]	0.60	0.83	0.90	0.90
	(0.56, 0.64)	(0.78, 0.89)	(0.86, 0.94)	(0.83, 0.98)
Distance (pig source)	0.49	0.68	0.73	0.73
	(0.45, 0.52)	(0.63, 0.72)	(0.69, 0.78)	(0.67, 0.80)
Distance (small ruminant source)	0.32	0.43	0.53	0.49
	(0.00, ∞)	(0.00, ∞)	(0.00, ∞)	(0.00, ∞)
Source species				
- Cattle (reference)		1.00		
- Pigs		2.83		
		(2.19, 3.67)		
- Small ruminants		0.00		
		(0.00, ∞)		
Susceptible species				
- Cattle (reference)		1.00		
- Pigs	0.38	0.44	0.52	1.51
	(0.29, 0.51)	(0.32, 0.60)	(0.40, 0.67)	(1.00, 2.28)
- Small ruminants	0.00	0.00	0.82	0.00
	(0.00, ∞)	(0.00, ∞)	(0.30, 2.27)	(0.00, ∞)
Herd size of susceptible premises [*3]		3.42		
		(3.10, 3.77)		

Weibull shape parameter: 1.22 (95% CI: 1.16 to 1.29), baseline hazard: 2.66 (95% CI: 1.64, 4.33) $\times 10^{-5}$

*1 Relative to the first confirmation of disease, phases I (week $\leq$ 2), II (week 3), III (week 4 – 5), and IV (week 6 – 7) (see Table 1)

*2 Euclidian distance between a potential source and a susceptible premises (km). The hazard ratio for distance can be interpreted as every 1 km increase in distance from an infectious premises decreased hazard by 0.60 times for cattle source in phase I.

*3 Herd size was measured as $\log_{10}$ of the number of total animals. The hazard ratio for herd size can be

interpreted as every 10 fold increase in the size of a susceptible premises was associated with increase in hazard by 3.42 times.

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Table 3 Estimated epidemiological parameters for an InterSpread Plus simulation model for the foot-and-mouth disease (FMD) epidemic in Miyazaki, Japan, in 2010.

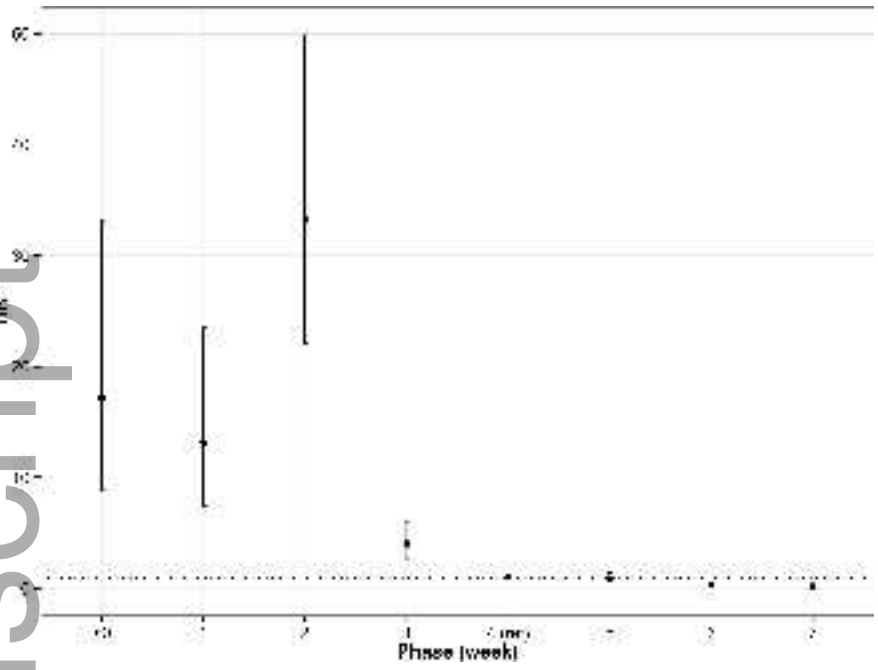
	Phase I[*1]	Phase II	Phase III & IV
Local spread		See Figure 2	
Susceptibility by species			
- Cattle or small ruminants (reference)		1.00	
- Pigs	0.38	0.44	0.51
Susceptibility by herd size[*2]		$32.5^{log_{10}(n)}$	
Incubation period (days)		0, 10, 20, 30, 40, 50 60, 70, 80, 90 and 100th percentiles: 2, 5, 5, 6, 7, 8, 8, 9, 10, 11 and 22	
Vaccination effectiveness			
- Cattle or small ruminants (reference)		NA	82%
- Pigs		NA	47%

*1 Relative to the first confirmation of disease, phases I (week $\leq$ 2), II (week 3), III (week 4 – 5), and IV (week 6 – 7) (see Table 1)

*2 Risk due to herd size was based on:

$$\exp(\beta \times log_{10}(n))$$

where β = 3.48 and n is the number of animals on a premises. Risk was calculated for all individual premises.



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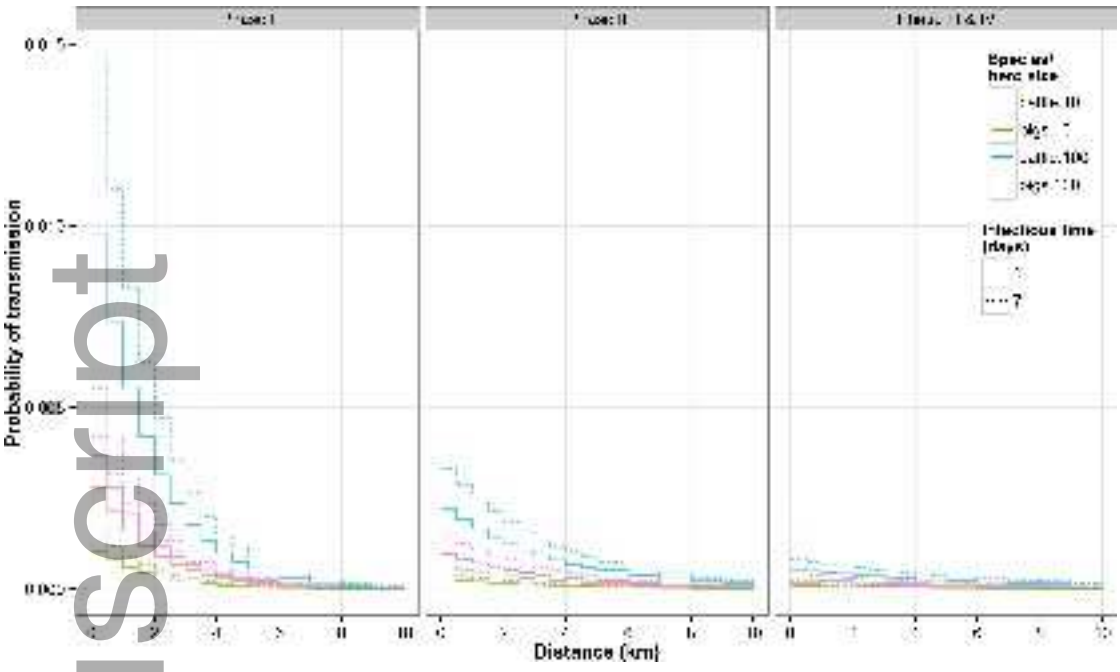

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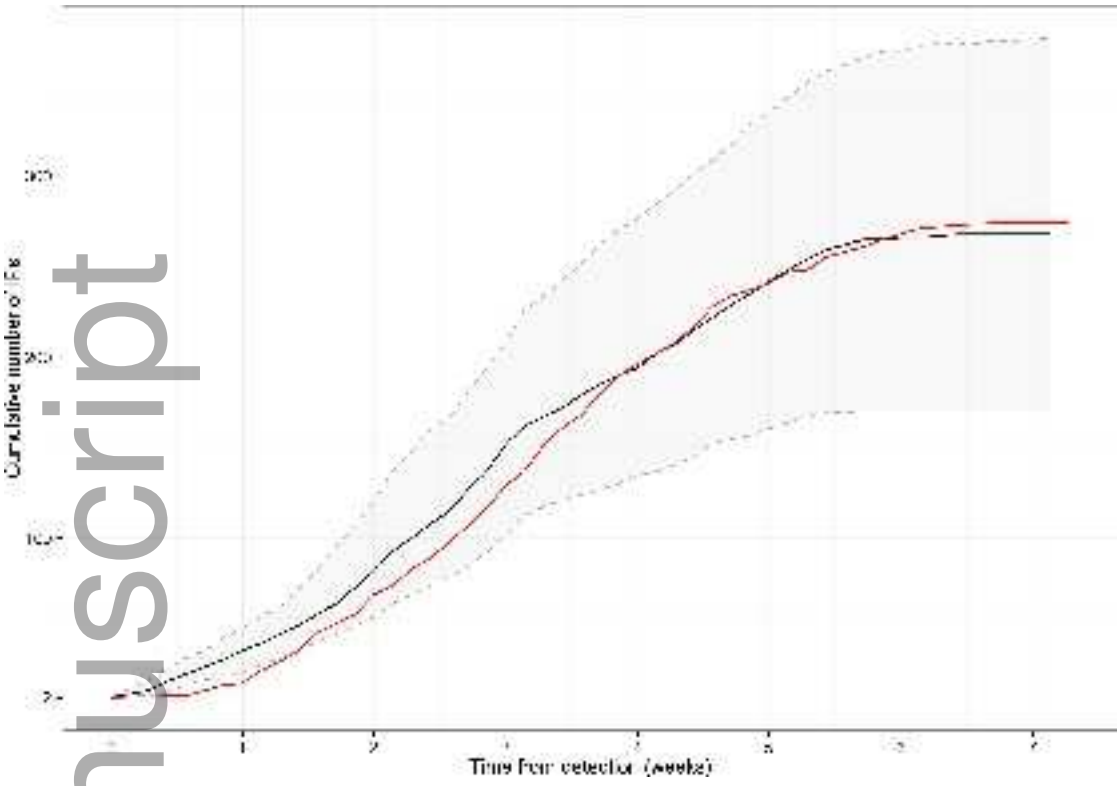

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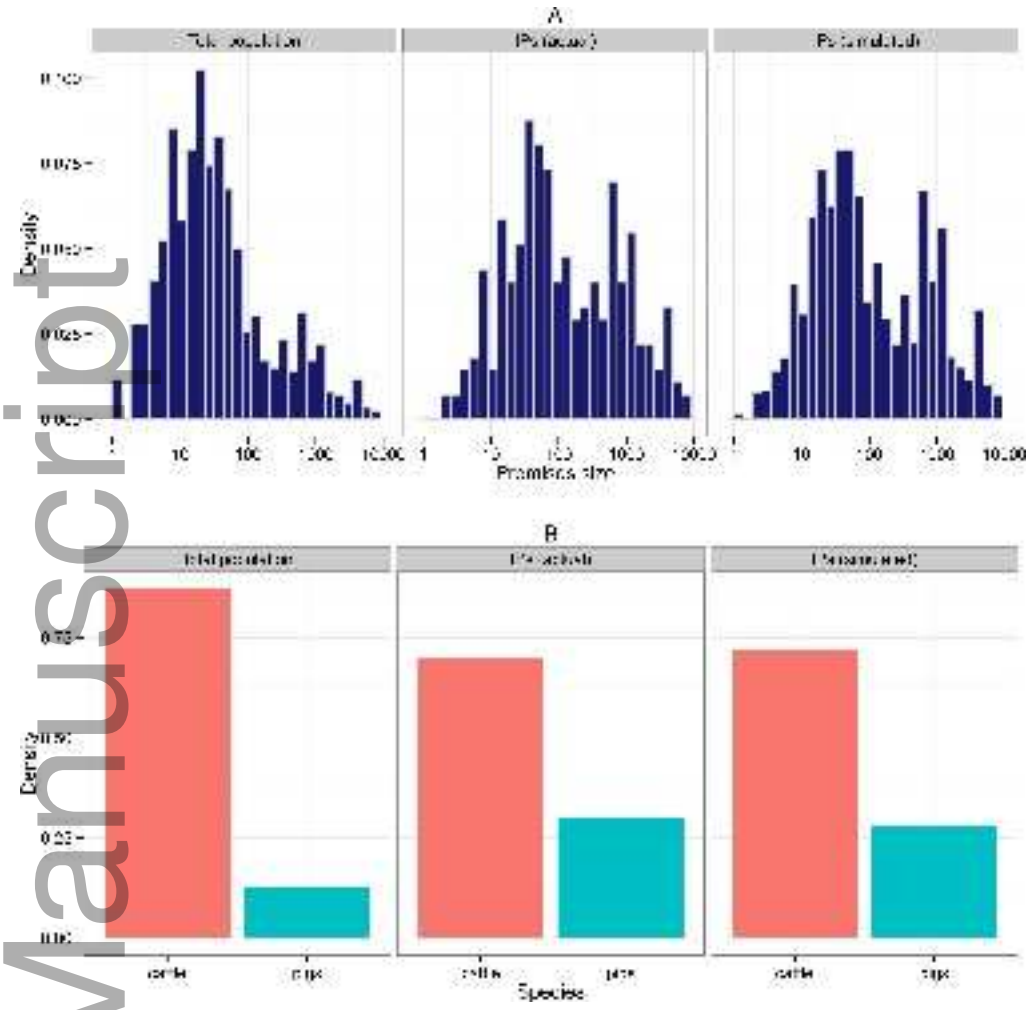

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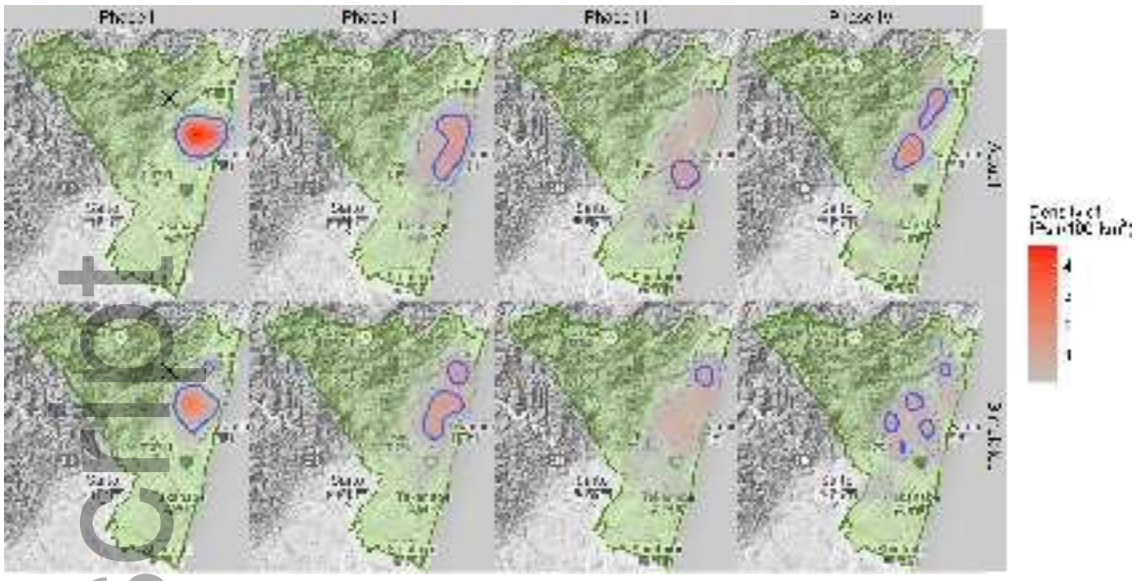

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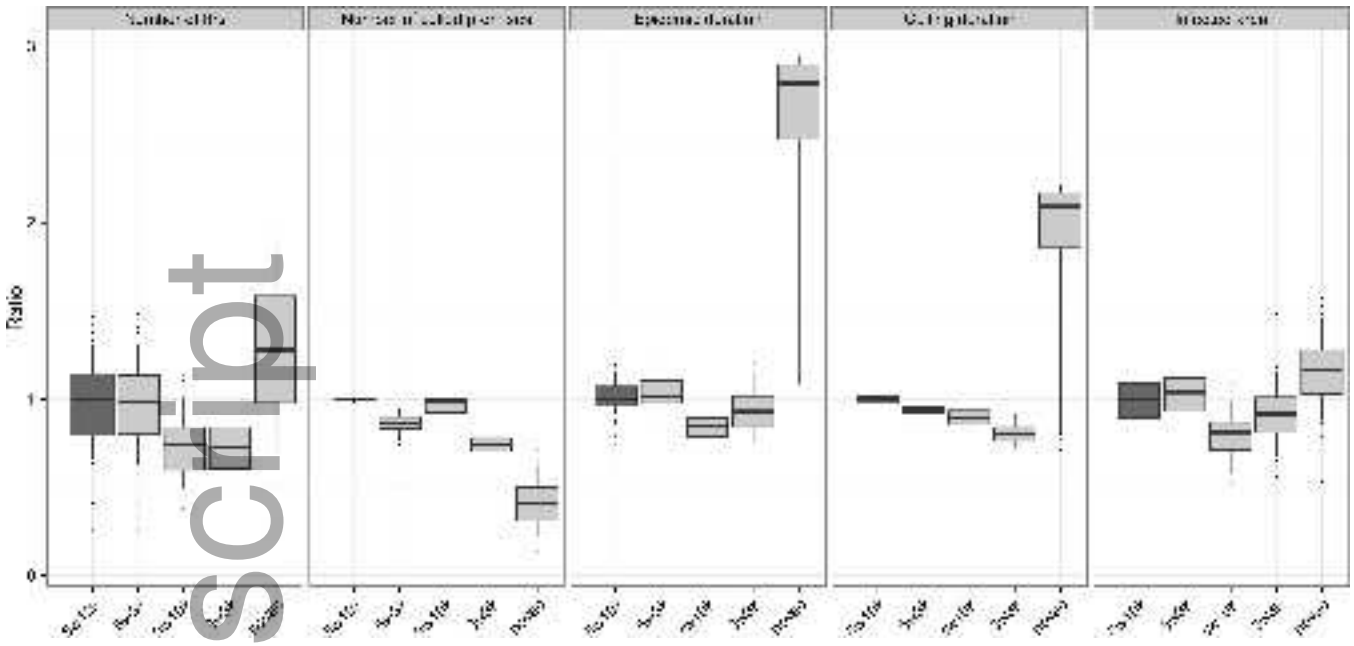

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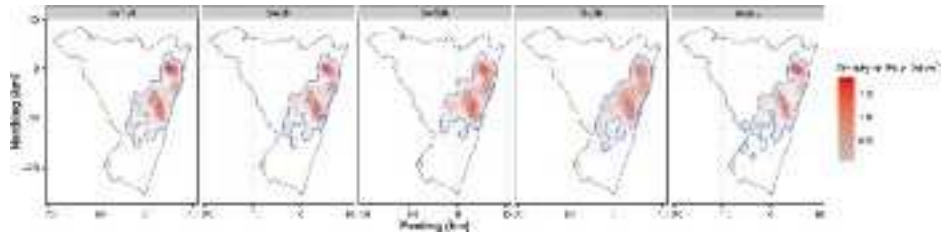

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