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Assessment of time available to implement measures for control of epidemics (Critical Response Time) in the context of the 2001 Uruguayan Foot-and-Mouth Disease outbreak

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Objective— To assess the critical response time (time available to implement an intervention such that an epidemic can be successfully controlled) in Foot-and-Mouth Disease (FMD) epidemics, and to explore the use of critical response time (CRT) in comparing and selecting interventions aimed at control of epidemics.

Animals and farms—The dataset of the first 60 days of the 2001 bovine FMD outbreak that took place in Uruguay.

Procedure— The *basic reproductive number* (number of secondary infections per primary infection, or R_0) was used to estimate the requirements of interventions expected to yield post-intervention $R_0 \leq 1$ (viral inability for transmission and thus, cessation of the epidemic). CRT was defined as the time available for an intervention to be implemented and achieve $R_0 \leq 1$. Cases observed in the first 7 days of the epidemic were regressed on time in order to estimate CRT according to an equation that also modelized case under-reporting and delayed reporting.

Results—The mean CRT for the whole country was 1.45 days (± 0.4). However, a fragmentation of the epidemic data into three non-overlapping geographic regions, showed individual CRTs ranging from 1.44 (± 0.3) in Region I (where, at 60 days into the epidemic, 60% of all national cases had been reported), to 3.02 days (± 2.3) in Region III (9.9% of all cases at 60 days). These estimates predicted that post-outbreak vaccination (intervention that requires several weeks to be implemented) would be unlikely to be successful. However, the Region III CRT estimate indicated that an intervention implementable within 3 days (such as stamping-out) was likely to be successful.

Conclusions— Findings supported the view that the basic reproductive number (R_0) facilitates epidemic control decision-making. The application of R_0–related concepts (such as CRT) based on data gathered within the first week of an epidemic, suggests that this

epidemiological approach could be applied in real time to inform epidemic control decision-making. However, additional variables are needed to obtain more elaborated models for R_0-related concepts. Data on farm geographical location, farm data on animal breed and age, and road networks could improve epidemiologic decision-making.

Epidemics can be perceived as natural experiments. Since experimental replication is not a tool available to those interested in the study of epidemic processes, epidemic data offer unique opportunities to test theoretical frameworks. One such case is provided by outbreaks of Foot-and-Mouth-Disease (FMD), disease causing major economic costs as recently observed in Great Britain.[1,2] Unfortunately, some FMD outbreaks go unrecorded. Thus, opportunities for testing epidemiological theories and potential control strategies are limited. Only a few (predominantly bovine) FMD epizootics have been recorded and their data are publicly accessible (i.e., those of 1967 and 2001 from England and the 2001 outbreak of Uruguay). While several reports have already utilized the 2001 British epidemic data[1,2], the dataset of the 2001 Uruguayan epidemic has yet to be explored.

The central concept on which most model-driven epidemic control programs are based is that of the **basic reproductive number** (or $\mathbf{R_0}$). $\mathbf{R_0}$ is a mathematical concept introduced first in human medicine by Sir Ronald Ross and Kermack and McKendrick between 1911 and 1927.[3] It is typically defined as the ratio of secondary cases/primary case when a virus is introduced into a fully susceptible population (i.e., virus-free and without prior history of anti-virus vaccination).[4] Epidemic theory shows that when $R_0 \leq 1$, the virus cannot invade hosts fast

enough and hence, the epidemic typically dies out. Consequently, for an intervention to be effective (i.e., to prevent further viral spread), post-intervention R_0 must be ≤ 1. R_0 appears to be the higher-order concept that links all other concepts associated with epidemic control (i.e., vaccine safety, logistics of vaccination campaigns). Interestingly, the use of the R_0 concept is not yet widely seen in the FMD-related veterinary literature. Until mid 2001, less than six articles had been published in the veterinary, FMD-related literature. In contrast, it is pervasive in the non-veterinary/non-FMD literature (**Fig 1**).[5,6]

The value of R_0 is a function of, at least: 1) the mean *incubation period*, 2) the mean *infectivity* period, 3) the *subclinical infection* ratio, and 4) the *effective contact rate.* The *mean incubation period* is negatively correlated with R_0 since for diseases with a relatively short incubation periods (< 7 days, such as FMD), there is a greater likelihood of achieving viral spread ($R_0>1$) than for diseases with longer incubation period. Hence, R_0 can be underestimated in subclinical outbreaks.[7,8] Diffusion of epidemic outbreaks is also dependent on the *infectious period* (i.e., the longer the virus can survive in animals or fomites, the easier the resurgence of epidemic/endemic episodes). In FMD, the infectious period for an individual animal may last up to three years.[9] However, for an infected premise (i.e., farm), the infective period may become much larger if the virus is not removed (the recovery period of an infected farm may exceed the mean lifetime of an individual animal).

In addition to outbreak-related factors, post-intervention R_0 may depend on intervention-related factors. Two distinct concepts refer to interventions: a) those related to the intrinsic efficacy of the tool under consideration (i.e., vaccine efficacy), and b) those related to the

efficacy of the implementation process (i.e., impact of the vaccination campaign). *Vaccine efficacy* may be influenced by several factors (i.e., *homology*, *safety* and *potency testing*). *Homology* (match between the vaccine strain and the strain actually infecting each animal) may change during the epidemic because of viral mutations.[10] *Safety* refers to protocols aimed at prevention of laboratory viral escapes.[11] *Potency testing* refers to independent vaccine production monitoring (regulatory practices).[12]

Vaccination impact is the fraction of *vaccine efficacy* which depends, at least, on: a) *coverage*, b) the initial *immune response* induced by the vaccine (or *vaccine take*), and c) duration of the protective immune response which diminishes over time (*antibody titer decay*). Vaccination programs require not only certain percentage of vaccinated animals (coverage compatible with post-vaccination $R_0 \leq 1$) but also that that level be evenly achieved, since pockets of unvaccinated animals within vaccinated farms may allow the virus to re-invade.[13] *Antibody titer decay* refers to the post-vaccination animal immune response, which decreases 7% or more after 4-6 weeks post-vaccination.[14, 15] *Mean duration of protective immunity* is not always synonymous with *antibody titer decay*. Protective immunity can also be lost, regardless of antibody titer decay, as a consequence of viral mutations, which are facilitated by high number of passages of the virus through the population, which may occur in an epidemic.[10] *Antibody titer decay* is also influenced by the age of the host. While age plays a minor effect in disease control of animals of relatively short life expectancy (thereby facilitating the success of vaccination as a disease control measure, as in foxes' rabies), it plays a major role in control of diseases of animals of greater mean age, such as cattle.[16] These concepts are not necessarily independent or non-overlapping. Some may be shared by

various conceptual clusters. For instance, *vaccine take* is shared by *vaccine efficacy* and *initial immune response.*

Thus, an epidemiologic decision-making model may be based on estimation of post-intervention R_0, which is dependent, at least, on three conceptual clusters: 1) epidemiologic (dependent on initial R_0), 2) intervention-related (i.e., vaccine efficacy, which is dependent on vaccine specificity, vaccine production safety and independent vaccine potency monitoring), and 3) logistics-related (i.e., vaccination impact, which is dependent on coverage, mean age of animals, initial immune response and post-vaccination antibody titer decay) (**Fig 2**).

One additional factor that influences logistics is the time available to implement efficacious interventions. Although the estimation and use of time available for interventions has not yet been explored in veterinary epidemiological theory, similar concepts have been used in the study of the impact of complex interventions against human diseases. For instance, the fact that HIV recovers at extremely fast pace has highlighted the importance of intervention timing.[17]

Due to the very protracted herd infective period, R_0 may become extremely large in FMD epidemics in which there is no precise information about the length of time and rate within which the virus is removed from the susceptible population (such as outbreaks in which stamping-out is not the adopted intervention). Consequently, rather than estimating the initial or pre-intervention R_0, the estimation of logistics requirements compatible with post-intervention $R_0 \leq$, such as the timing of the intervention, seems to be a more relevant piece of information. The **critical response time (CRT)** is here defined as the time available to

implement an intervention expected to result in post-intervention $R_0 \leq 1$ (i.e., a successful intervention). This information could be used to estimate the likelihood for success of various interventions. Only when CRT is equal or greater than the time required to implement an intervention, such intervention may achieve success.

Since the initial phase of an epidemic tends to show linear or exponential growth over a short period, the initial disease dynamics can be estimated from the linearization of the natural nonlinear epidemic model. In other words, the initial growth in the number of cases is modeled with an exponential. As a result, a simple regression analysis of observed cases over time can estimate the *effective contact rate* (number of new herds per infected herd per unit of time), parameter that then can lead to estimate CRT.

However, practice shows that there are always additional complications. For example, the number of observed cases (that is, cases that are actually reported) tends to be less than the actual number of cases. The number of observed (reported) cases is the result of three events: a) contracting the disease, b) becoming symptomatic (after contracting the disease), and c) being reported (after becoming symptomatic). Consequently, the estimation of effective CRT constructs need to include estimates of case under-reporting and delayed case reporting.

This study pursued two goals: 1) to develop and test a CRT construct which included estimates of the effective contact rate, case under-reporting and delayed case reporting, and 2) to assess whether estimated CRT can inform epidemiologic decision-making. These questions were investigated with data of the 2001 Uruguayan FMD outbreak.

Materials and Methods

Epidemic dataset— Cases (infected farms and infected bovines) of the first 60 days since April 23, of the 2001 Uruguayan FMD outbreak, as reported by the Organization of International Epizootics (http://www.oie.int) and, previously, by the Uruguayan Ministry of Agriculture and Fisheries (http://www.mgap.gub.uy). Epidemic data were clustered into three non-overlapping geographical regions based on a *post facto* analysis, according to time and density of case occurrence.

Indicators—Variables included: a) prevalence and incidence of reported cases before and after intervention, b) the effective contact rate, and c) the critical response time (time compatible with post-intervention $R_0 \leq 1$, when the influence of case under-reporting and delayed case reporting are considered).

Statistical analysis—Regression analysis of (log-transformed) observed daily cases on time (first 7 days of epidemic). Mann-Whitney tests of median beef/dairy farm ratio among geographical regions. Significance was estimated at $P \leq 0.05$. Tests were conducted with a commercial package.[a]

Results

Case prevalence— The number of FMD infected farms and infected bovines reported in Uruguay in 2001 and its temporo-geographical distribution is shown in Table 1 and **Fig 3.**

Animal prevalence per farm (number of new infected bovines /total number of bovines per infected farm, or *attack rate*) tripled within 2 months.

Epidemic curve— A linear (and, at times, exponential) cumulative prevalence growth pattern was observed before and after implementation of a nationwide vaccination campaign (**Fig 4**).

Regional distribution—Daily case prevalence (number of new infected farms) exhibited a rather uniform rate after the second week of the epidemic but showed a dissimilar regional distribution. Over 60% (1044/1736) of the incidence (old and new infected farms) occurred in Region I (which comprises approximately 15% of the national cattle herd) by the ninth week. In contrast, only 9.9% (172/1736) of all cases occurred in Region III, a region that comprises 50% of the national herd. At 60 days, the national incidence of infected farms (proportion of infected farms/all farms) was 5 %, and the national incidence of infected bovines (proportion of infected bovines/all bovines) was 3%. Region I showed the highest percent of infected farms in the country and the lowest ratio of beef/dairy farms. In contrast, Region III displayed the lowest percent of infected farms in the country and the highest rate of beef/dairy farms (Table 1 and **Fig 5** and **6**).

Determination of contact rate and critical response time estimates —The effective contact rate (β) and Critical Response Time (**CRT**) were estimated according to the model reported in Appendix I. The aggregated (national) β was estimated at 0.69. The β values varied from 0.331 (Region III) to 0.692 (Region I). The estimated CRT to conduct an intervention leading to $R_0 \leq 1$ was 1.45 days at national (aggregated) level. Estimated CRT values varied from 1.44

(Region I) to 3.02 (Region III). The 95% confidence intervals of these estimates are reported in Table 2.

Discussion

Until the early 1990, stamping-out was the choice strategy for FMD-free countries, whereas vaccination was only recommended for countries where the disease was endemic.[18-20] The 2001 English outbreak has highlighted the economic ramifications of such a choice. Doubts have been expressed about the convenience of slaughter over vaccination, and some have suggested vaccination as the choice control measure.[21] Since stamping-out has been analyzed recently[1, 22], this discussion focuses on other alternatives, such as vaccination and mixed regional policies (*regionalization*).

The estimation of the CRT facilitated the comparison of different control strategies aimed at reducing post-intervention R_0 below 1. Since post-outbreak vaccination is an intervention that usually requires several weeks to be implemented, the short CRT computed for each and all regions predicted that such intervention was unlikely to be successful. In agreement with this expectation, in the epidemic under study post-outbreak national vaccination was implemented and did not seem to be successful.

Estimation of the specific spatial structure in which FMD spreads is essential for its control.[23] For example, it is known that s*mall world* structures, that is, structures that include clusters of

farms with long-distance contacts among them, disseminate diseases faster and farther than those on *square lattice* networks.[24-26] The 2001 Uruguayan epidemic data suggest that the contact network is well modeled by a *square lattice* but not by a small world network. It started on the southwest-most area of the country and although the epidemic reached distant areas later, even two months after the epidemic onset, 60% of all cases were among farms located within the original area of detection. Within 60 days of the epidemic, 1736 cases were observed in Uruguay while in England (a country with approximately the same number of heads of cattle) it took 122 days to reach 1773 cases in its 2001 outbreak (http://www.maff.gov.uk). Thus, the Uruguayan outbreak generated the same number of cases in half the time taken by the British epidemic in spite of the fact that the structure of the Uruguayan epidemic seemed compatible with a slower model of limited expansion (while the British resembled a model of faster and farther expansion).[27] It is suggested that the greater number of cases/unit of time observed in 2001 in Uruguay than in England was not associated with the epidemic contact structure, may have been the result of the use of vaccination. However, further explorations on the specific role of spatial structures on epidemic control measures are needed to substantiate this hypothesis.

Our CRT estimates indicated that interventions requiring shorter time frames than vaccination (such as stamping-out) might have been successful at least at the regional level. For example, in Region III, where CRT was 3.03 days and where the replacement cost of cattle was lower (because of predominance of beef farms), *regionalization* (stamping-out without vaccination) could have been considered.

The fact that FMD outbreaks have recently occurred even in countries with advanced scientific infrastructure and/or FMD-free status for many years suggests that no country can rely only on preventive measures. It is suggested that development of interdisciplinary teams and digital epidemiological databases including geographical data on farm location, animal age, animal movements and antibody titer decay may facilitate epidemic-specific decisions. Access to such data by scientists may facilitate further research.[2, 27] Decisions based only on *vaccine efficacy*-related considerations may lack validity whenever *intervention impact*-related factors (logistics) are not assessed. These findings highlight the informative potential of R_0–related concepts. It is concluded that CRT estimates can be calculated with data from only the first days of an outbreak and, although presumptive, can facilitate data-based epidemiologic decision-making

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Footnotes

[a] Minitab Inc., State College, PA.

Table 1— National and regional FMD cumulative and weekly prevalence in the first two months of the 2001 Uruguayan outbreak.

Date (week of the epidemic)	New & old cases	New cases	New & old infected Bovines	New infected bovines	Attack rate[a]	New & old cases Reg. I	New & old cases Reg. II	New & old Cases Reg. III	New cases Reg. I[b]	New cases Reg. II[b]	New cases Reg. III[b]
April 25 (1)	4	4	55	55	1.8	4	0	0	100.0	0.0	0.0
May 2 (2)	123	119	915	860	1.8	99	19	5	79.8	16.0	4.2
May 9 (3)	348	225	3604	2689	1.1	233	89	26	61.9	28.7	9.3
May 16 (4)	589	241	7421	3817	1.6	396	152	41	67.6	26.1	6.2
May 23 (5)	836	247	14031	6610	1.6	574	207	55	72.1	22.3	5.6
May 30 (6)	1158	322	25498	11467	2.3	787	296	75	66.1	27.6	6.2
June 6 (7)	1358	200	27308	1810	1.9	900	364	94	56.5	34.0	9.5
June 14 (8)	1596	238	31689	4381	3.1	995	480	121	39.9	39.9	20.1
June 21 (9)	1736	141	34127	2438	3.8	1044	520	172	34.7	44.7	20.6

Infected farms (cases) and infected bovines are reported in terms of new and old diagnoses (cumulative prevalence) and new diagnoses (weekly prevalence). Infected animals per farm are reported as number of infected/number of all animals (*attack rate*). Regions I-III correspond to those expressed in Fig 3. Source: http://www.oie.int.

[a] : percent of infected animals/all animals.

[b] : percent of all cases.

Table 2— Estimation of Critical Response Time.

A. Cases observed in the first 7 days of the 2001 Uruguayan FMD epidemic

Time[a]	Ln(All cases)[b]	Time[a]	Ln(Region I)[c]	Time[a]	Ln(Region II)[c]	Time[a]	Ln(Region III)[c]
1	0	1	0	2	0.693147	4	0
2	1.791759	2	1.386294	3	0.693147	5	0
3	2.079442	3	1.791759	4	1.098612	6	0
4	2.833213	4	2.564949	5	1.609438	7	0
5	3.465736	5	3.258097	6	1.94591	8	0.693147
6	4.077537	6	3.931826	7	2.564949	9	0.693147
7	4.454347	7	4.276666	8	2.772589	10	2.397895

[a] : number of day (days) cases were observed in relation to t = 1 (April 23, 2001).
[b] : cumulative number of cases (herds) reported in the whole country, as described in Table 1.
[c] : cumulative number of cases (herds) for region I, II or III, as described in Table 1.

B. Results of regression analysis of observed cases regressed on time.

All regions (whole country)

$\beta = 0.690 \pm 0.187$	$t_o(obs) = 0.128 \pm 1.187$	$t_o(exp) = -1.624 \pm 1.464$
CRT = 1.45 ± 0.393 days	$t_o(obs) - t_o(exp) = 1.753 \pm 0.864$	
Adj. $R^2 = 0.937$	Significance F = 0.0002	N = 7

Region I

$\beta = 0.692 \pm 0.127$	$t_o(obs) = 0.449 \pm 0.747$	$t_o(exp) = -1.301 \pm 1.051$
CRT = 1.44 ± 0.265 days	$t_o(obs) - t_o(exp) = 1.751 \pm 0.739$	
Adj. $R^2 = 0.970$	Significance F = 0.0000	N = 7

Region II

$\beta = 0.387 \pm 0.078$	$t_o(obs) = 0.797 \pm 0.940$	$t_o(exp) = -1.265 \pm 1.310$
CRT = 2.59 ± 0.522 days	$t_o(obs) - t_o(exp) = 2.062 \pm 0.913$	
Adj. $R^2 = 0.964$	Significance F = 0.0000	N = 7

Region III

$\beta = 0.331 \pm 0.274$	$t_o(obs) = 5.368 \pm 2.138$	$t_o(exp) = 3.230 \pm 2.551$
CRT = 3.02 ± 2.501 days	$t_o(obs) - t_o(exp) = 2.137 \pm 1.391$	
Adj. $R^2 = 0.590$	Significance F = 0.0267	N = 7

Values of β here reported where used to calculate a CRT such that would result in $R_o \leq 1$. For example in Region I, the time available to obtain a critical value of R_o ($R_o \leq 1$) (or CRT) would be about 1.4 days (since $R_o = \beta / \delta$ *or* $\delta_{(critical)} = 1/\beta$). No latency period for *herds* (i.e. the time between becoming infected and becoming infective) has been assumed. For individual animals this period (L) is about 2 days.[28] Based on the assumption that the primary mode of transmission between herds is delivery of non-symptomatic animals to uninfected farms, it has been hypothesised that infectiousness is immediate. If this is not the case, *CRT* should be reduced by a factor of $\exp(-L_H / CTR)$, where L_H is the latency period for *herds*.

Appendix I. Regression equation for estimates of effective contact rate and CRT.

The concept of R_o is derived from the following nonlinear differential equation that models epidemic outbreaks in a farm community.

$$\frac{d}{dt}I(t) = \beta\frac{I(t)S(t)}{N(t)} - \delta I(t)$$

N is the *number of herds in a neighbourhood* (where disease can be spread easily), such that $S+I = N$;

S is the *number of susceptible herds in the neighbourhood*;

I is the *number of diseased or infected herds in the neighbourhood*;

β is the *effective contact rate* (i.e. the number of new cases [infected herds] per infected herd per unit time);

δ is the *removal rate* (units of the fraction of infected herds removed per unit time), when removal can occur as a result of mortality, recovery, isolation or removal of infected animals from contact with susceptible population on other herds, or any combination;

$1/\gamma$ is the average time that a herd remains infectious or, alternatively, the average time that infected herds put susceptible herds at risk.

The initial disease dynamics can be estimated from the linearization of this equation around the disease-free equilibrium yielding

$$I(t) \approx I(t_o) \cdot e^{(\beta-\delta)\cdot(t-to)}$$

Defining t_o as the day when the first infection occurred $I(t_o) = 1$, and assuming the an average infectious period of a *herd* is very large (greater than 5 years, the average lifespan of cattle when there is no culling), then it can be assumed that δ is essentially zero for this dataset.

$$I(t) \approx e^{\beta\cdot(t-to)} \quad \text{or} \quad \ln[I(t)] = \beta\cdot t - (\beta\cdot t_o)$$

Therefore, a crude estimate of β can be obtained by a simple linear regression of the (log transformed) number of cases observed on time (days). This is based on the fact that the first few cases (those of the first 7 days of epidemic), showed an exponential growth over time (Fig 5).

Since it is expected that the observed number of infectious cases at any particular time is less than the actual number, it was assumed that under-reporting involves: a) infectious but non-symptomatic cases, and b) delays in reporting of symptomatic cases. It is hypothesised that both occur as a (exponential) random processes with mean time between becoming infectious and symptomatic = γ; and mean time to report = λ.

The number of observed cases at any particular time can then be formulated as the convolution of the three events: contracting the disease, becoming symptomatic, and being reported. We then have

(Appendix I, Cont'd)

$$J(t) = \int_{\omega=0}^{t} \int_{\xi=0}^{\omega} \int_{x=0}^{\infty} \frac{d}{d\omega} I(\omega - \xi - x) f(\xi|\lambda) f(x|\gamma) dx\, d\xi\, d\omega$$

where J is the number of observed (reported) cases and f is the probability density function for an exponential random variable. The solution to this equation is

$$J(t) = \frac{1 + \beta\lambda\, e^{-(1+\beta\lambda)t/\lambda}}{(1+\beta\lambda)(1+\beta\gamma)} I(t) \approx \frac{1}{(1+\beta\lambda)(1+\beta\gamma)} I(t) \quad \text{for } t > \lambda$$

Then, the regression equation becomes

$$\ln(J(t)) = \beta \cdot t - (\beta \cdot t_o) - \ln(1+\beta\lambda) - \ln(1+\beta\gamma)$$

letting $\alpha = -[(\beta \cdot t_o) + \ln(1+\beta\lambda) + \ln(1+\beta\gamma)]$ and $Y(t) = \ln(J(t))$ we have

$$Y(t) = \alpha + \beta t$$

The expected value of t_o can be obtained by the Delta method[28], which gives

$$\mathrm{E}(t_o) \approx \frac{1}{\beta}[\alpha + \ln(1+\beta\lambda) + \ln(1+\beta\gamma)]$$

The error on the estimate of t_o is also obtained by the Delta method[28], which gives

$$\begin{aligned}\mathrm{var}(t_o) &\approx \left(\frac{\partial t_o}{\partial \alpha}\right)^2 \mathrm{var}(\alpha) + \left(\frac{\partial t_o}{\partial \beta}\right)^2 \mathrm{var}(\beta) + \left(\frac{\partial t_o}{\partial \lambda}\right)^2 \mathrm{var}(\lambda) + \left(\frac{\partial t_o}{\partial \gamma}\right)^2 \mathrm{var}(\gamma) + \cdots \\ &\qquad + 2\left(\frac{\partial t_o}{\partial \alpha}\frac{\partial t_o}{\partial \beta}\right)\mathrm{cov}(\alpha,\beta) \\ &\approx \frac{\mathrm{var}(\alpha)}{\beta^2} + \left(\frac{\lambda}{1+\beta\lambda} + \frac{\gamma}{1+\beta\gamma} + t_o\right)^2 \frac{\mathrm{var}(\beta)}{\beta^2} + \frac{\mathrm{var}(\lambda)}{(1+\beta\lambda)^2} + \frac{\mathrm{var}(\gamma)}{(1+\beta\gamma)^2} + \cdots \\ &\qquad + 2\left(\frac{\lambda}{1+\beta\lambda} + \frac{\gamma}{1+\beta\gamma} + t_o\right)\frac{\mathrm{cov}(\alpha,\beta)}{\beta^2}\end{aligned}$$

(Appendix I, Cont'd)

It is assumed that symptoms occur at or about $\gamma = 2.5$ days[29], and that the mean time to report $\lambda = 1/3$ day (based, for dairy cattle, on 2 daily milkings, and on response time data observed in the 2001 British FMD epidemic[27]). The variance of these rates was estimated at about 0.27 (based on metanalysis of data published by Burrows[29]), and 0.037 (1/12 the range squared), respectively. The expected time of the first case observed is a slightly simpler calculation where expected value is $\mathrm{E}(t_o obs) \approx \alpha/\beta$ and the variance is

$$\mathrm{var}(t_o \mathrm{obs}) \approx \left(\frac{\partial t_o}{\partial \alpha}\right)^2 \mathrm{var}(\alpha) + \left(\frac{\partial t_o}{\partial \beta}\right)^2 \mathrm{var}(\beta) + 2\left(\frac{\partial t_o}{\partial \alpha}\frac{\partial t_o}{\partial \beta}\right)\mathrm{cov}(\alpha,\beta)$$

$$\approx \left(\frac{\alpha}{\beta}\right)^2 \left(\frac{\mathrm{var}(\alpha)}{\alpha^2} + \frac{\mathrm{var}(\beta)}{\beta^2}\right) - 2\frac{\mathrm{cov}(\alpha,\beta)}{\alpha\beta}$$

With this, β and CRT can then be estimated from a regression analysis of (log-transformed) observed *cases* regressed on *time* (7 first days of the epidemic), as reported in Table 2.

LEGENDS

Figure 1— Publications on the Basic Reprodctive Number (R_0). Source*: Science Citation Index.*

Figure 2— Concepts influencing R_0. Two opposing forces determine the result of post-intervention (post-vaccination) R_0: 1) the outbreak and 2) the intervention. The outbreak is composed of factors related to the virus (i.e., virus incubation period and the virus infectivity period) and factors related to the spatial farm contact network or structure which together result in pre-intervention R_0 .The intervention is composed of, at least, two subsets: a) vaccine efficacy and b) vaccination impact. Vaccine efficacy is, at least, composed of vaccine homology, vaccine production safety and vaccine potency testing. Vaccination impact is, at least, composed of coverage (including proportion of vaccinated farms or vaccination inter-herd coverage, and proportion of vaccinated animals or intra-herd coverage), initial immune response (proportion of vaccinated animals that develop antibodies), animal age, and proportion of animals with protective immunity after antibody titer decay.

Figure 3— National distribution of the 2001 Uruguayan FMD epizootic after two weeks into the outbreak. Three regions (I, II and III) are indicated based on case density. Each square represents 1-5 cases (infected farms). Closed squares: cases detected 1-7 days post-onset. Open squares: cases detected 8-14 days post-onset. Star: geographic location of first reported case. Sources: http://www.oie.int and http://www.mgap.gub.uy.

Figure 4— The 2001 FMD epizootic of Uruguay. Farm and animal cumulative prevalence in the first 9 weeks. Source: http://www.oie.int.

Figure 5—Regional daily farm prevalence in the first 30 days of the 2001 FMD epizootic of Uruguay. The parallelogram indicates the data points of the first 7 days which were analyzed to calculate Critical Response Time.

Figure 6— Relationships between regional outbreak prevalence, regional proportion of the national herd and regional predominance of beef farms. Regional FMD cases are expressed as percent of all cases at 60 days into the epidemic. Regional proportion of the national herd is expressed as percent of the national herd. Predominance of beef farms is expressed as the ratio of dairy/beef cattle (significantly higher median ratio in Region III than in remaining regions). Source: http://www.mgap.gub.uy.

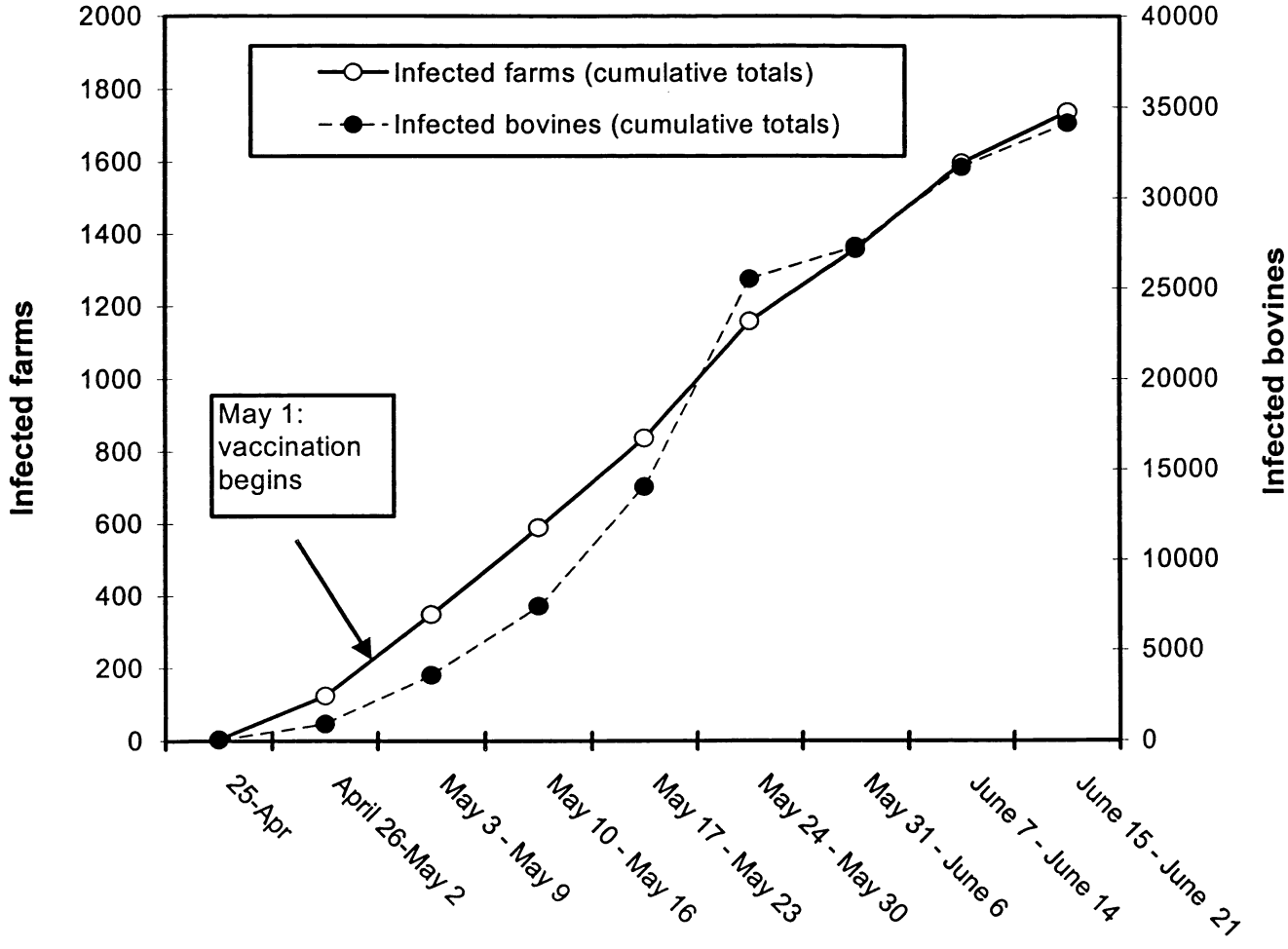

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FIG. 1

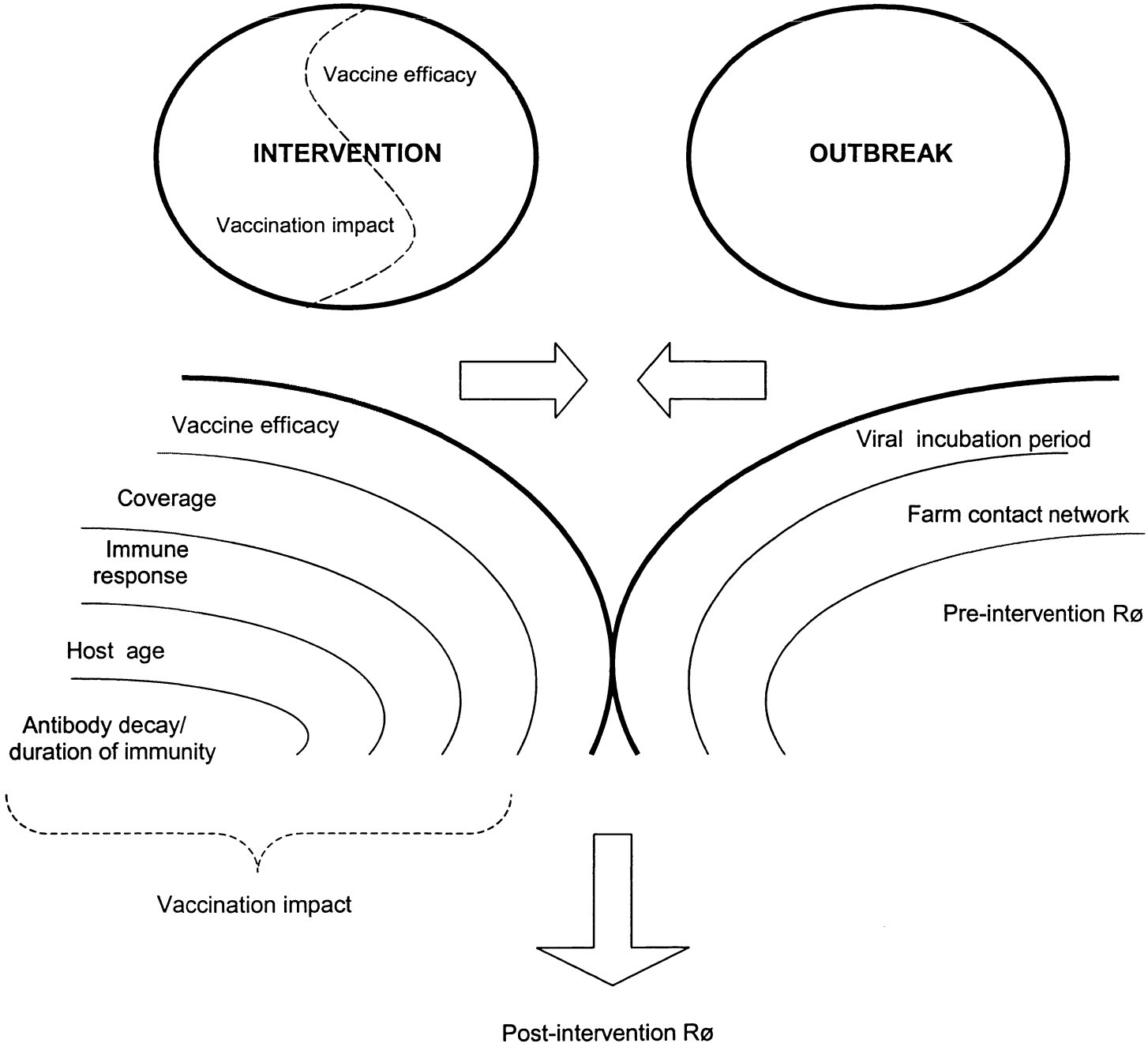

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FIG. 2

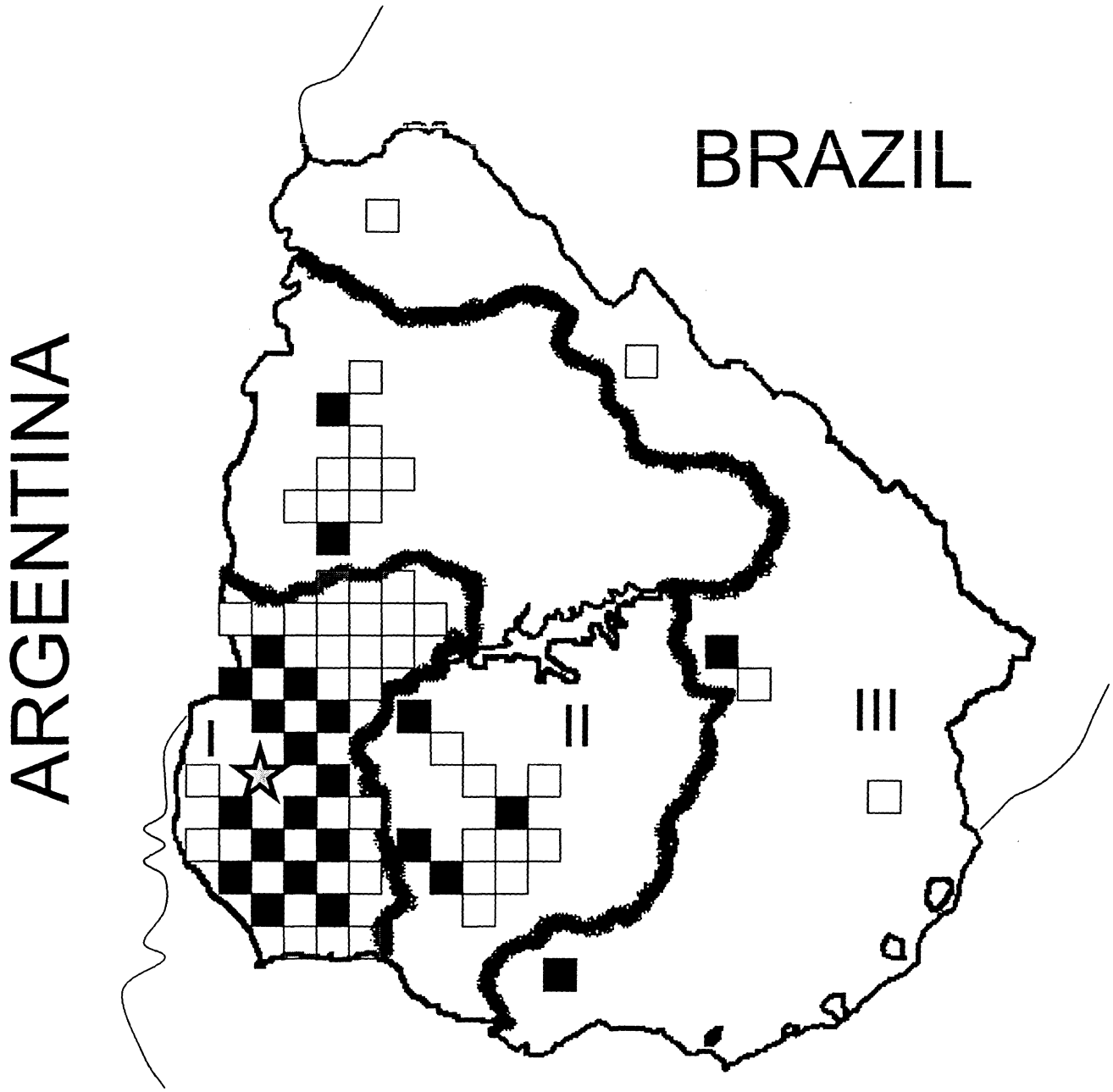

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FIG. 3

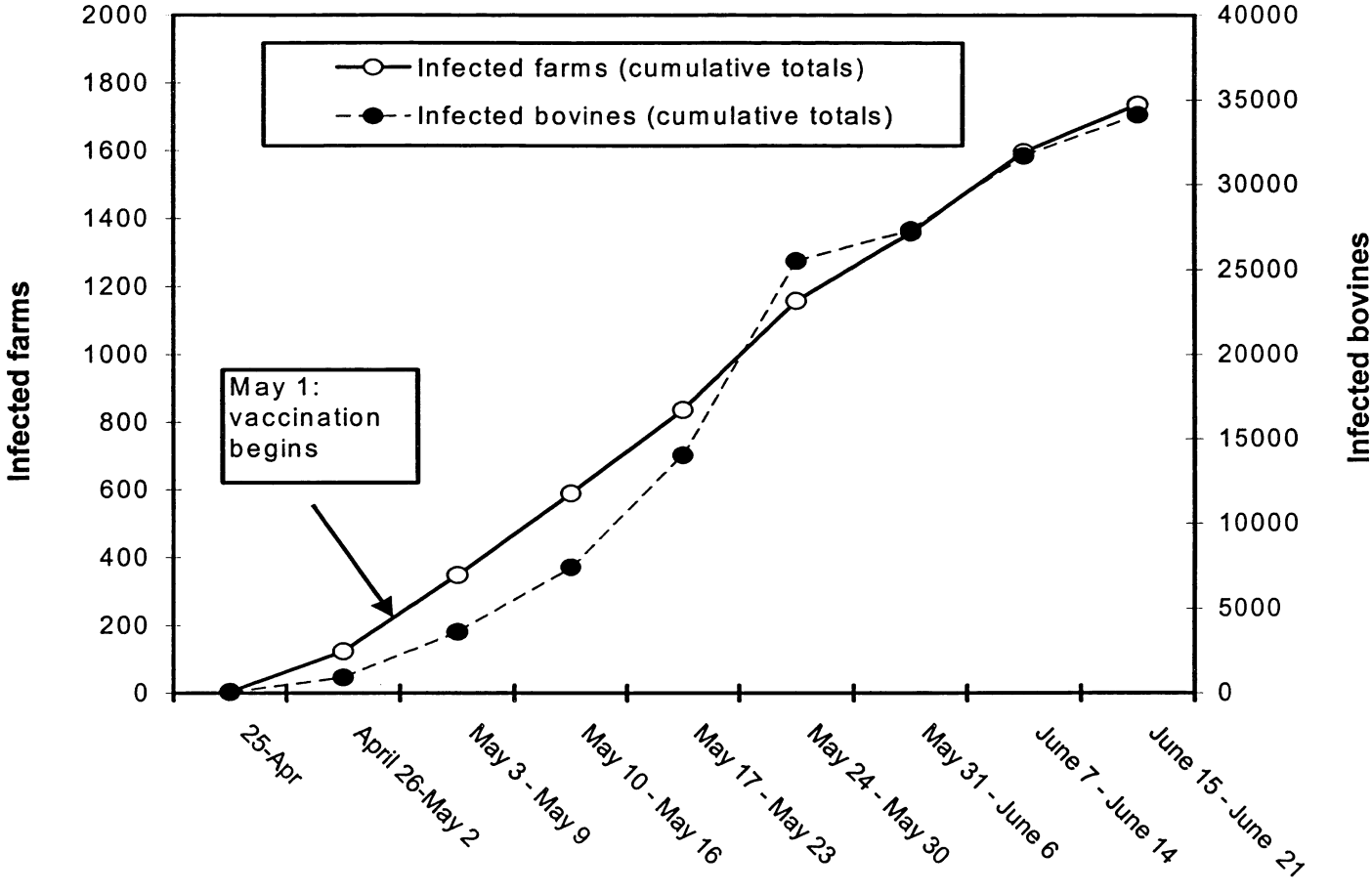

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FIG. 4

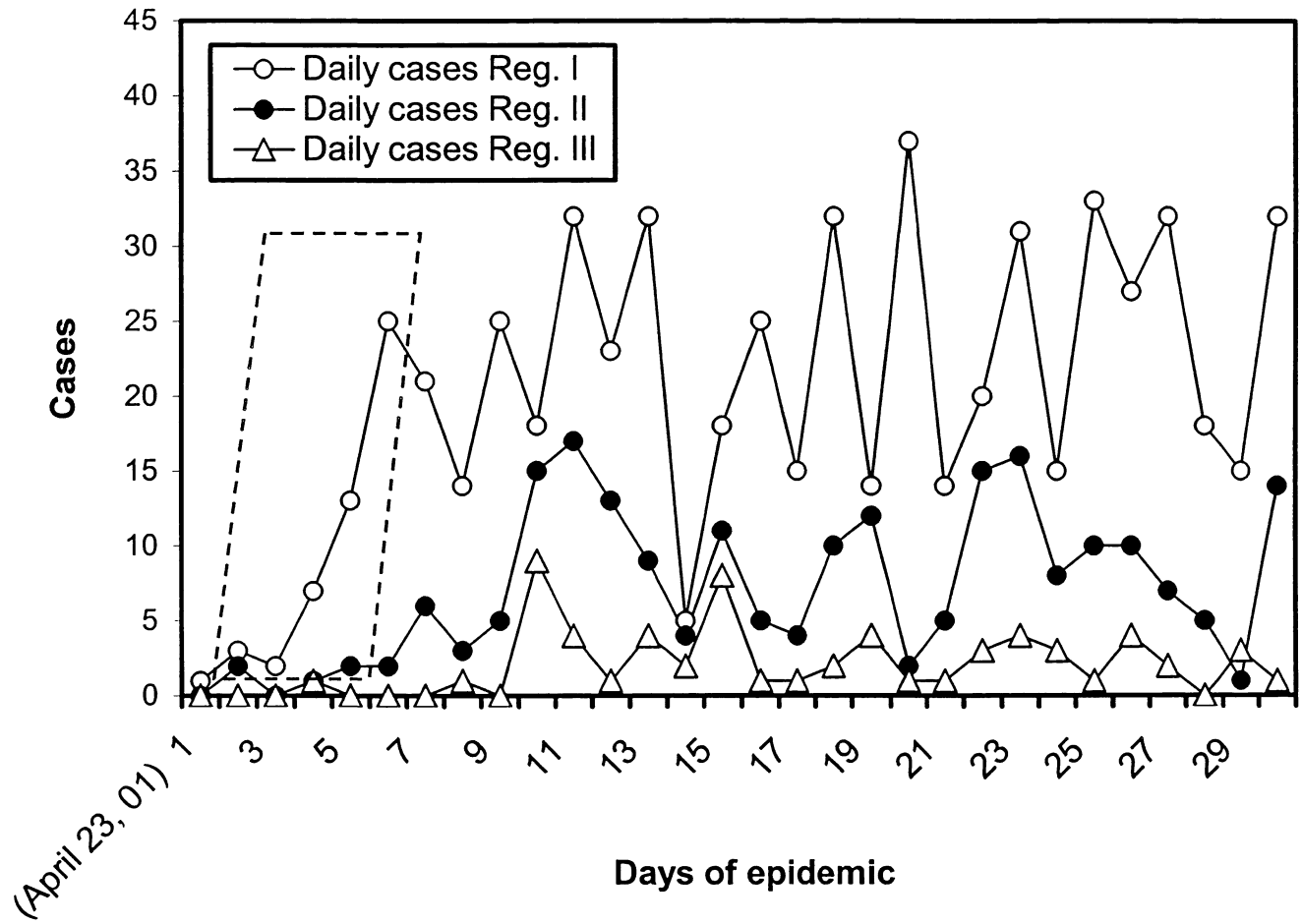

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FIG. 5

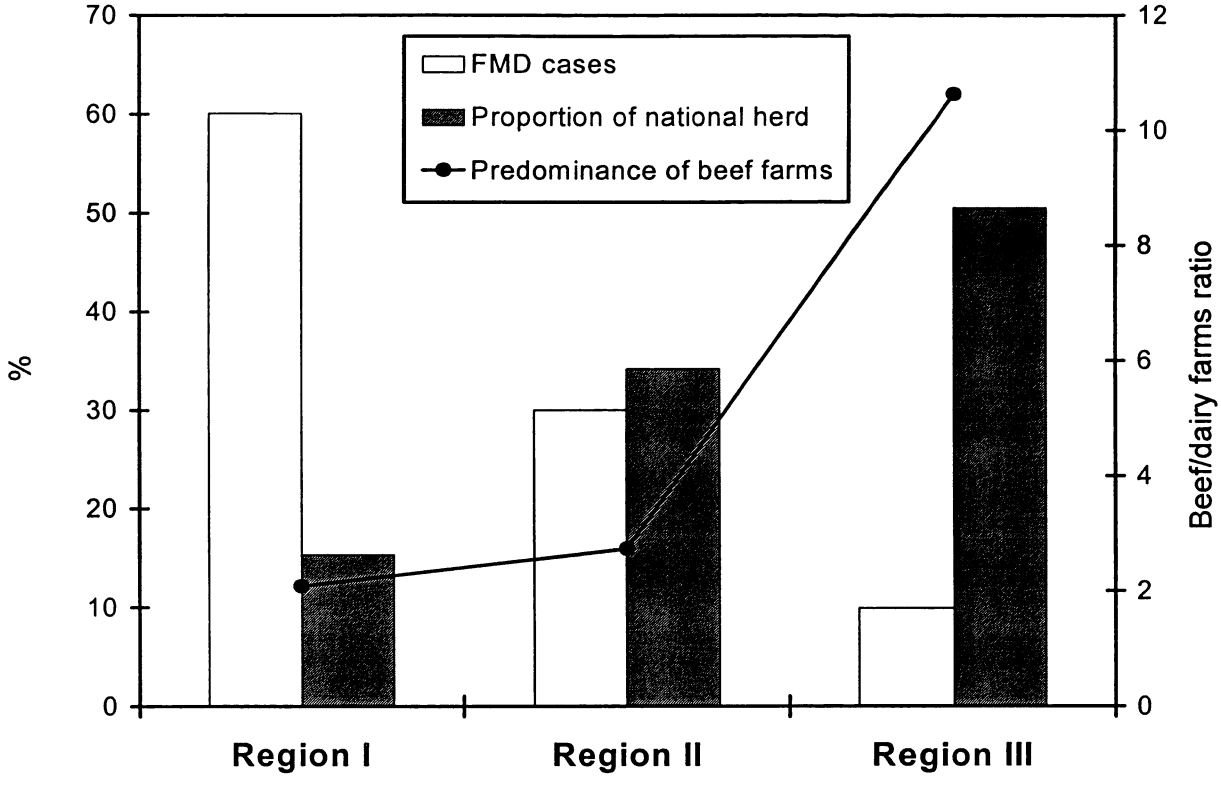

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FIG. 6