Short Communication

CRITICAL RESPONSE TIME (TIME AVAILABLE TO IMPLEMENT EFFECTIVE MEASURES FOR EPIDEMIC CONTROL): MODEL BUILDING AND EVALUATION

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ABSTRACT

The time available to implement successful control measures against epidemics was estimated. Critical Response Time (CRT), defined as the time interval within which the number of epidemic cases remains stationary (so that interventions implemented within CRT may be the most effective or least costly), was assessed during the early epidemic phase (when the number of cases grows linearly over time). CRT was calculated from data of the 2001 Foot-and-Mouth Disease (FMD) epidemic that occurred in Uruguay. Significant regional CRT differences (ranging from 1.4 to 2.7 days) were observed.

The CRT may facilitate selection of control measures. For instance, a CRT equal to 3 days would support the selection of measures such as stamping-out (implementable within 3 days), but rule out measures such as post-outbreak vaccination (because intervention and immunity building require more than 3 days). Its use in rapidly disseminating diseases, such as FMD, may result in regionalized decision-making.

Selection of measures for control of diseases of rapid dissemination is a major problem affecting decision-making in epidemiology. The actual efficacy of a control campaign depends not only on the intrinsic efficacy of control instruments but also on the time required for their implementation (1). Regional (geographical) differences may also influence the selection process of a control measure (2).

The first parameter to be determined in an epidemic is the rate of epidemic growth (the number of new infected cases per unit of time). At the beginning of an outbreak of a rapidly disseminating disease, the cumulative number of cases usually follows an exponential growth

pattern with parameter β (Appendix), where β represents the number of new infections per unit of time per primary case. Therefore, in the early epidemic stage, the log number of cumulative cases typically follows a linear relationship with time, as shown by the 1967-1968 and the 2001 British FMD outbreaks during their first month (1-3). Consequently, β can be estimated from linear regression of data on cumulative cases.

The expected number of new infections generated by each primary case in a small time interval of length Δt can be estimated as $\beta\Delta t$. The inverse $1/\beta$ defines a critical time for responding to the epidemic, because if source cases (or their susceptible contacts) are removed within a time $1/\beta$, the epidemic cannot spread. For this reason, the Critical Response Time (or CRT) is defined as $1/\beta$. When an intervention is implemented in a period equal to or less than CRT, the number of secondary cases produced per source case will be less than 1 and the epidemic usually will die out.

These concepts can also be described by the Basic Reproduction Number (or R_0). R_0 is defined as the number of secondary cases per primary case when the infectious agent is introduced into a population of susceptible individuals (4-6). Therefore, $R_0 = \beta t$, where t is the mean infectious period. An epidemic can occur when $R_0 \geq 1$. Therefore, the goal of a control policy is to implement an intervention that leads to an effective Reproduction Number (R_{eff}) less than 1. If each infectious case is removed within an average time $T \leq$ CRT, then the maximum effective Reproduction Number ($R_{\text{eff}} = \beta T$) is less than 1 and the epidemic is expected to die out.

The association between Critical Response Time and early epidemic data is demonstrated here using the simple differential equation model for an epidemic outbreak (4-6). It is shown that, when there is a linear relationship between the log number of cumulative cases and time, CRT is equal to $1/\beta$ (Appendix). The most stringent epidemic scenario is when the number of

cases grows exponentially per unit of time. This results in CRT being a conservative measure, which implies that a policy completed within $1/\beta$ units of time is expected to be effective.

An evaluation of CRT may be facilitated by retrospective analysis of actual epidemic data. Such evaluation may give insight on: a) the time available to implement control measures, and b) whether epidemic regional differences (associated with different CRTs) may result in region-specific control measures.

Foot-and-Mouth-Disease (FMD) is a disease of rapid dissemination that causes major economic costs (1-3,7). While several reports have analyzed the 2001 British epidemic data (1,2,7,8), the 2001 Uruguayan epidemic has yet to be explored. Uruguay remained free of FMD (without vaccination) prior to April 23, 2001, when the first case of an epidemic affecting primarily bovines was reported. The purposes of this study were to determine: 1) the CRT(s) of the 2001 Uruguayan FMD epidemic, and 2) whether regional CRT differences were observed in that epidemic.

This study estimated CRT values by analyzing data on cases (infected farms) observed in the first 60 days of the Uruguayan FMD outbreak beginning April 23, 2001, as reported by the Organization of International Epizootics (http://www.oie.int) and by the Uruguayan Ministry of Agriculture and Fisheries (http://www.mgap.gub.uy). Variables included the daily number of new cases and the fraction of daily case increase. Log-transformed cumulative cases were regressed on time (first 7 days from the first infected herd report in a given geo-epidemic region). Parameters of interest were the slope of the regression (β) and the Critical Response Time ($1/\beta$). Epidemiologic differences were assessed by testing the proportion of cases among geographic regions (χ^2 test). Significance was estimated at $P \leq 0.05$. Tests were conducted with the statistical package Minitab (v. 12.2; State College, Pennsylvania, USA).

Sixty days into the epidemic, 1736 infected farms had been reported. The proportion of cases across regions indicated that 60.1% of the total (1044/1736) were in Region I, 30.0% (520/1736) were in Region II, and 9.9% (172/1736) were in Region III (Fig. 1A). These proportions were significantly different across regions; a chi-square test of the null hypothesis that every observed case is equally likely to be in each of the three regions showed highly significant departure from this hypothesis (H_0: $p_1 = p_2 = p_3 = 1/3$), with test statistic $\chi^2 = 665.94$ (2 degrees of freedom), $P < 0.0001$. Epidemic data indicated linear relationships for the national (aggregated) number of cases and, at least, for those of Region I and Region II (Fig. 1B). Therefore, the requirement for estimation of CRT by regression analysis was met.

Four separate regression analyses were performed: all regions (national data), Region I, Region II, and Region III. The daily fraction of case increase (the slope β of the regression) and Critical Response Time (CRT = $1/\beta$) were estimated from these data, showing significant regional differences. The preliminary aggregated (national) $\hat{\beta}$ was 0.678, with regional $\hat{\beta}$ values of 0.692, 0.371, and 0.367 in Regions I, II, and III, respectively. Hence, the estimated CRT to conduct an intervention leading to $R_{\text{eff}} \leq 1$ was 1.475 days at the national (aggregated) level, with estimated regional CRT values of 1.444, 2.696, and 2.723 days in Regions I, II, and III, respectively (Table I and Fig 2).

Further analysis of the data indicated a high standardized residual (–2.11) for the first observation (day 1) in the national (aggregated) data (Table I), which suggested a possible outlier. After removal of that observation, no outliers were suggested, and the estimate of the national CRT increased to 1.805 days. Observation of an outlier at the very beginning of an epidemic may be the result of at least two factors, delayed reporting of the first case(s) and

exaggerated influence of errors when the number of cases is extremely low. Delayed reporting of the first case(s) is likely to occur due to human behavior (particularly at the very beginning of an epidemic caused by an exotic agent). Later, when there is public knowledge of the epidemic and the alert level increases, delayed reporting is likely to diminish. In addition, when the number of cases is low (in this epidemic only one case was reported on the first day), the effect of any error is the greatest.

In contrast, analysis of the Region III data did not reveal an obvious linear relationship. Thus, the validity of 2.723 days as the estimated CRT for Region III is uncertain. However, because CRT is, by definition, a very conservative estimate, the true CRT for Region III was very likely to be at least 2.723 days.

Estimation of CRT can suggest intervention- and region-specific control measures (as opposed to national campaigns in which relationships between specific interventions and regional conditions are not considered). In the scenario under analysis, almost twofold regional CRT differences (between 1.4 days in Region I and 2.7 days in Regions II and III) were observed, as well as non-overlapping 95% confidence interval for CRT (between Region I and Region II), which could result in different control measures (i.e., regionalization).

This study was conducted to evaluate the CRT construct in the context of an actual epidemic situation. The quality of the data set being analyzed was checked with two sources. Both provided identical information. Common limitations associated with an epidemic scenario (which may hamper data quality) include delayed reporting and the difference between the time an individual (animal or farm) becomes infective (i.e., capable of transmitting the disease to others) and the time it becomes symptomatic (i.e., showing symptoms and, therefore, observable or reportable). While delayed reporting is unlikely to be a significant source of error when there

is public knowledge on the epidemic (i.e., after its first case[s] is/are reported), the difference between the time becoming infectious vs. symptomatic is likely to be a systematic error. Although the pre-symptomatic period for herds (i.e., the time between becoming infected and showing signs) may be up to 2 days (9), this time interval may be ignored because in large populations it is expected to follow a normal distribution with very low variance (i.e., on average, the population will have very similar pre-symptomatic periods). Consequently, the gap between becoming infected and becoming symptomatic is expected to be nearly constant (the two slopes, except for the first day, are nearly parallel). If the data gathered on the first day of the epidemic are deleted, the values of the symptomatic (observable) cases provide an estimate of CRT very similar to that yielded by infected but not symptomatic cases (which cannot be observed).

CRT is assumed to be associated with most effective/least costly control measures because it is the time interval associated with a number of secondary cases less than or equal to the number of primary cases, the condition in which cessation of epidemic growth is expected. However, complete implementation of control measures within CRT is not always followed by cessation of new cases. An exponentially rapid decay of new cases is expected when $R_0 < 1$; however, when individuals can move between compartments (i.e., regions), an event likely to depend on the contact structure (e.g., road structure, animal trade structure, human movement patterns), new cases may occur even with $R_0 < 1$, as suggested in the 2001 British epidemic (2, 8). Consequently, estimation of CRT is more likely to be effective if conducted together with assessment of temporal-spatial (local or regional) contact rates. This could be facilitated by use of complementary technologies, such as Geographical Information Systems (1, 8).

CRT facilitates the comparison of different measures under conservative assumptions. Therefore, the true CRT is likely to be larger than estimated when only early epidemic data are considered. Consequently, great confidence can be placed in measures supported by the estimated CRT. For instance, consider a hypothetical situation in which the number of cases is growing linearly or exponentially over time, the epidemic is spreading at a 10-km radius per day, and there is a 100% effective vaccine that can be administered to all herds within 3 days. In that situation, a vaccination policy would require 3-4 additional days (a total of 7 days from the time the decision is made) to induce protective immunity (10). To achieve results, the area to be vaccinated should have at least a 70-km radius, comprising 15,394 square kilometers. This can be compared to a stamping-out policy (assumed to be 100% effective and implemented in 2 days), which would involve a 20-km radius area comprising 1,257 square kilometers. In this situation, if CRT were estimated at 3.0 days, the second measure could be adopted with a high degree of confidence in its success. Assuming a perfect linear relationship (with 1, 2, 4, 8, 16, 32, and 64 cases per day over a week), stamping-out would achieve $R_{\text{eff}} \leq 1$ by implementing a measure that would cover less than one-twelfth as much territory (1,257 sq km / 15,394 sq km), in which only one-sixteenth as many herds would be sacrificed (4 herds would be expected to be infected at day 3 day compared to 64 herds infected at day 7).

CRT may be useful if applied in the early epidemic phase. However, this implies a balance between data quality (which requires the longest possible interval) and intervention efficacy (which requires the shortest possible interval). Such a balance may be achieved: i) after one incubation period of the infective agent, and ii) as soon as a linear or exponential growth phase is documented. The same data allow for identification of regional epidemiological

differences (based on statistical analysis), so this simple model also facilitates region-specific epidemiological decision-making.

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TABLE I— ESTIMATION OF CRITICAL RESPONSE TIME.

i. Early national and regional cases observed in 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	0.6931	4	0
2	1.792	2	1.3863	3	0.6931	5	0
3	2.079	3	1.7918	4	1.0986	6	0
4	2.833	4	2.5649	5	1.6094	7	0
5	3.466	5	3.2581	6	1.9459	8	0.6931
6	4.078	6	3.9318	7	2.5649	9	0.6931
7	4.344	7	4.2767	8	2.7726	10	2.3978

[a] : Time (day) = day 1 was April 23, 2001.
[b] : cumulative number of cases (herds) reported in the whole country.
[c] : cumulative number of cases (herds) reported in Region I, II, or III.
: possible outlier (standardized residual < –2)

ii. Preliminary analysis of observed cases regressed on time

	95% CI for β			95% CI for CRT ($1/\beta$)		T	P
	$\hat{\beta}$	SE($\hat{\beta}$)	(β_{low}, β_{high})	$1/\hat{\beta}$	(CRT_{low}, CRT_{high})		
All regions (national)	0.678	0.0762	(0.482, 0.874)	1.475	(1.144, 2.073)	8.91	<0.001
Region I	0.692	0.0494	(0.565, 0.819)	1.444	(1.220, 1.769)	14.02	<0.001
Region II	0.371	0.0317	(0.283, 0.459)	2.696	(2.179, 3.536)	11.69	<0.001
Region III	0.367	0.1680		2.723		2.19	0.273

iii. Final analysis of observed cases regressed on time (national), after removal of first-day case

	95% CI for β			95% CI for CRT ($1/\beta$)		T	P
	$\hat{\beta}$	SE($\hat{\beta}$)	(β_{low} , β_{high})	$1/\hat{\beta}$	(CRT_{low}, CRT_{high})		
All regions (national)	0.554	0.0361	(0.454, 0.654)	1.805	(1.529, 2.204)	15.35	<0.001

A regression of the log of the cumulative number of cases over time provides the coefficient of the regression slope (β). The lower and upper limits of a 95% confidence interval (CI) for β are indicated within parentheses. Results also include the t-value ($T = \hat{\beta}/SE$) of the regression slope and the corresponding P value (P). Confidence intervals for β and CRT were not calculated in Region III because no linear relationship was observed ($P > 0.05$).

LEGENDS

Figure 1. Regional distribution of the 2001 Uruguayan FMD epizootic outbreak. A: Three regions (I, II, and III) are indicated according to percentage of all cases reported within the first 60 days of the outbreak (1736 cases), of which 60.1% were observed in Region I, 30.0% in Region II, and 9.9% in Region III ($P < 0.0001$, χ^2 test). Star indicates the site of the first reported case. Sources: http://www.oie.int and http://www.mgap.gub.uy. B: Log-transformed regional daily cases in the first 30 days of the epidemic in Regions I, II, and III.

Figure 2. Relationships between early cases and time. The log of the cumulative number of cases was regressed on time (the first 7 days from the first reported case). Plots show the observations (dots), the regression line (solid line), and the 95% confidence interval (broken lines). A-D: National, Region I, Region II, and Region III, respectively.

APPENDIX

Critical Response Time: conceptualization and operationalization

For a highly infectious disease, let the number of infected cases at time t be denoted by $I(t)$. At the beginning of an outbreak (when it is plausible to assume that all contacts are susceptible), the time evolution of the infected population $I(t)$ can be modeled by

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

where β is the transmission parameter and δ is the removal rate. Therefore, in the early epidemic phase, the infected population grows exponentially as described by

$$I(t) = I(t_0) e^{(\beta - \delta)(t - to)}$$

or

$$ln[I(t)] = (\beta - \delta)(t - t_0),$$

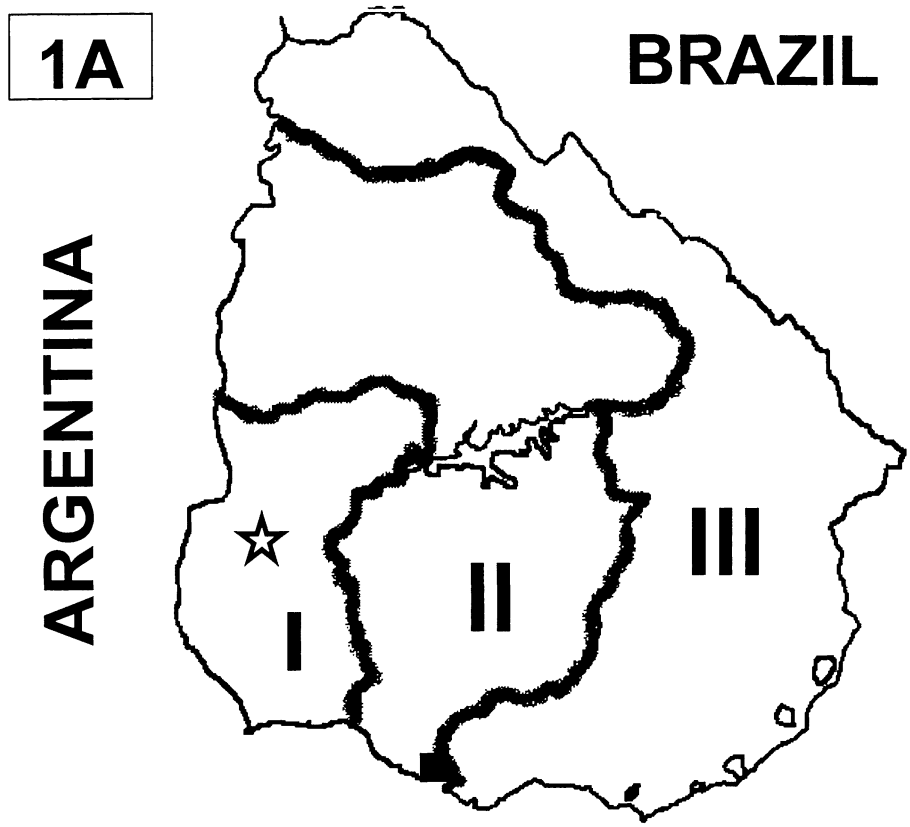
where t is the time a case is clinically observable, t_0 is the time when the first case was reported, and $ln[I(t_0)] = 0$ because $I(t_0) = 1$. In highly infectious diseases, β is much greater than δ, so

$$ln[I(t)] \approx \beta(t - t_0),$$

which coincides with the log of the cumulative number of cases at time t. The slope obtained from linear regression of $ln[I(t)]$ vs. time provides an estimate of the transmission parameter β. Therefore, an estimate of the Critical Response Time $1/\beta$ is given by $1/\hat{\beta}$.

Operationally, CRT is estimated as follows. The cumulative, natural log-transformed data on number of cases are regressed on time for at least 3-4 consecutive days from the time of the first case reported in a given territory, and for an interval not less than the mean incubation time of the infective agent (which, in the case of FMD, is approximately 3-4 days) (9). If a linear relationship is documented, CRT is estimated by the reciprocal of the estimated slope ($\hat{\beta}$) of the

regression. The lower and upper 95% confidence limits for β are calculated by subtracting from and adding to the estimated regression coefficient ($\hat{\beta}$) the product of the standard error SE($\hat{\beta}$) and the upper 0.025 critical value of the Student's t-distribution with n–2 degrees of freedom, where n is the number of observations (days). This gives the 95% confidence interval ($1/\hat{\beta}_{\text{high}}$, $1/\hat{\beta}_{\text{low}}$) for CRT.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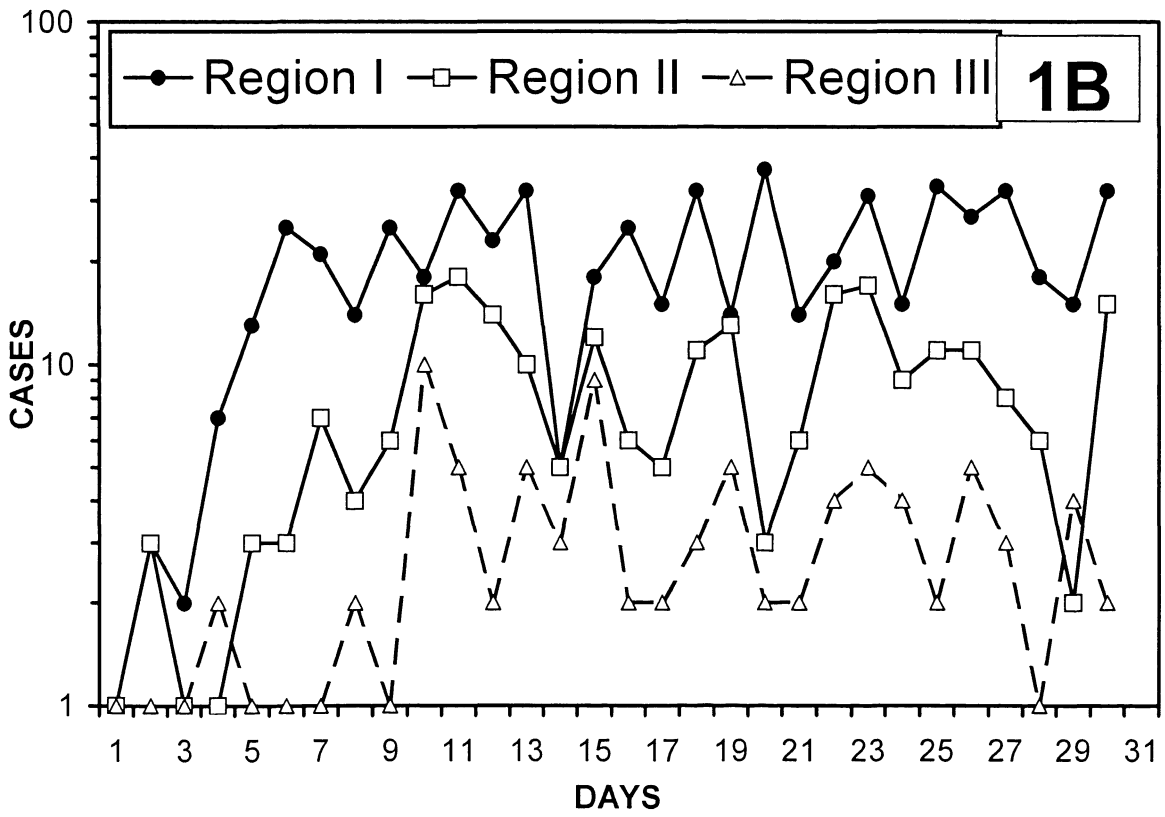
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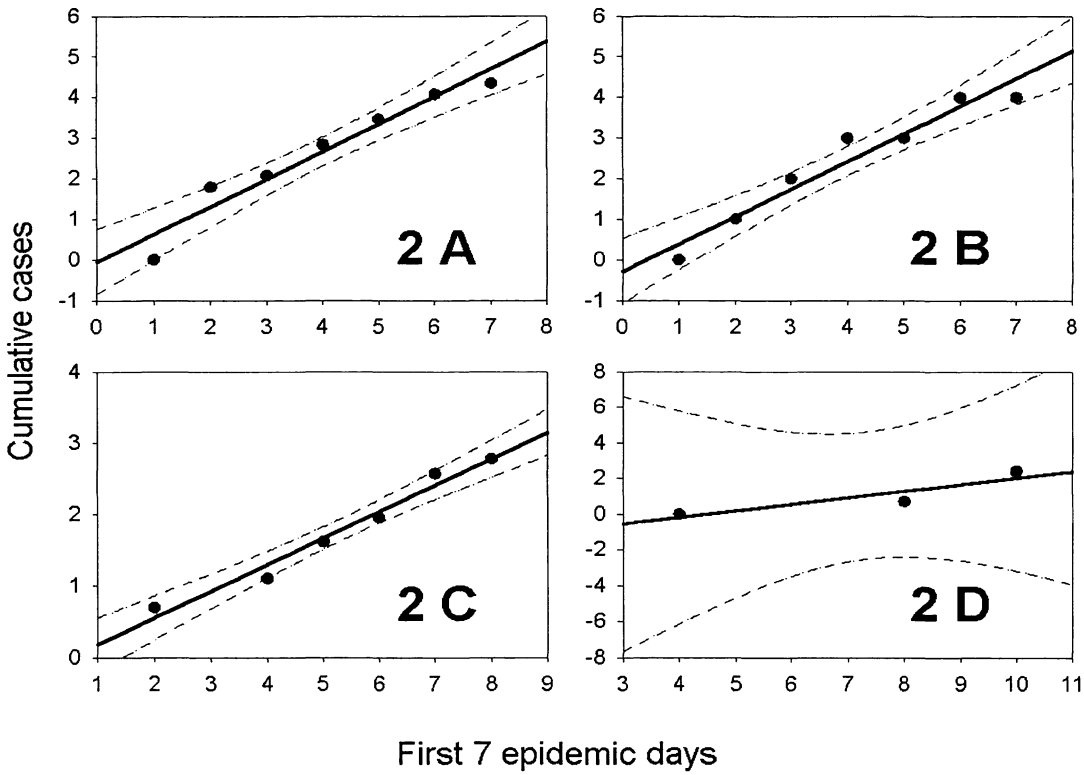
Cumulative cases
2 A
2 B
2 C
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First 7 epidemic days