Evaluating Progress towards the Elimination of Canine Rabies: a management tool and its application in Latin America

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Abstract

Background: A global target for the elimination of dog-mediated human rabies has been set for 2030, but guidance for managing rabies elimination programmes is limited. Countries across Latin America have progressed towards interruption of rabies transmission through a regional programme coordinated by the Pan American Health Organization (PAHO). Using surveillance data from the region, we investigated methods for evaluating the performance of rabies elimination programmes and guiding their management.

Methods: We developed a robust method to classify progress within administrative units using easily understood criteria applied to the PAHO rabies surveillance database SIRVERA. This algorithm combined criteria for case detection and logistic regression of time series.

Findings: Applying this tool sub-nationally across Mexico and Brazil demonstrated clear epidemiological transitions: most states progressed rapidly towards interruption of transmission but some regressed as a result of incursions and lapses in control. In 2015 foci remained in just 1 state of 32 in Mexico, and 2 of 27 in Brazil. Results highlight the importance of genomic surveillance to identify variants and sources of incursions as elimination is approached and intensified surveillance to verify freedom from disease.

Interpretation: Our tool provides guidance on how to progress efficiently towards control and elimination targets and tailor strategies to local epidemiological situations, while revealing insights into rabies dynamics and persistence. In Latin America, continued circulation in the poorest states puts neighbours at risk of re-emergence. Improved implementation and monitoring of mass dog vaccinations in these foci should minimize resurgence and catalyse progress towards elimination.

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Introduction

Rabies has been eliminated from domestic dog populations in high-income countries, but remains a major public health concern in low- and middle-income countries. Every year, thousands of people die and billions of dollars are lost due to rabies spread by domestic dogs[1]. Regional and national targets for the elimination of dog-mediated rabies have been set[2] and control programmes are now underway around the world[3-5]. Consequently there is an increasingly urgent need for scientific guidance to ensure progress towards these targets.

Most progress has been made towards the regional elimination of dog-mediated rabies in Latin America. Since 1983, national dog vaccination programmes coordinated by the Pan American Health Organisation (PAHO) have controlled canine rabies across much of the Western Hemisphere. Large parts of the continent have not experienced endemic circulation for years, but as the region approaches elimination, differences in progress have emerged[6]. Implementation of control measures, as well as geographic, population and socioeconomic differences likely underlie differential progress in rabies control, but observed patterns also reflect variation in the quality of surveillance. Clarifying the relationship between these influences and their effects on rabies dynamics is key to designing effective interventions during the endgame. For example, some areas have ostensibly achieved rabies freedom and competing priorities create pressure to reduce expenditure on rabies control. In contrast, other areas are struggling to control rabies, and continued circulation poses a risk for re-introduction into neighbouring areas, potentially threatening the success of the regional programme[7,8]. By tailoring efforts to local epidemiological situations, it should be possible to improve progress towards elimination and more sustainably maintain freedom.

We present a tool for programme managers and practitioners at regional, national and subnational levels to assess progress in their area and in neighbouring areas that may influence their situation, and to guide their programme management. The tool was designed using data from SIRVERA (http://sirvera.panaftosa.org.br/), a regional rabies surveillance database maintained by PAHO since the 1970s[3]. Our principles in developing this tool were that: (1) it should be possible to classify the epidemiological situation objectively in each area using routine surveillance; (2) categories and their criteria should be easy to understand; (3) classification should provide insight into the effectiveness of current management and guidance for further progression.

Here we describe the rationale for the tool, its methodological development and assessment of its robustness. By applying this tool sub-nationally across Mexico and Brazil, we reveal historical and current patterns of circulation, as well as providing guidance for surveillance and control strategies tailored to specific geographies and their progression towards elimination.

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Methods

Our aim was to develop a tool for understanding progress towards rabies elimination, distinguishing areas with ongoing transmission, from areas where efforts have controlled rabies, and ultimately interrupted transmission. Following development of a classification algorithm and its application to states (major administrative units) in Brazil and Mexico, we discussed classifications with state-level and national stakeholders to refine their interpretation and subjected our classifications to robustness testing and validation.

Data

We focused on the period January 2005 to December 2015, using data on laboratory confirmed rabies cases in dogs submitted to SIRVERA from Mexico and Brazil. State-level data on vaccination campaigns, dog and human population sizes and virus variants (i.e. canine vs. wildlife variants) were provided by government departments of Mexico. Information on socioeconomic indicators in Mexico was sourced from the United Nations Development Programme (http://hdr.undp.org/) and the National Institute of Statistics and Geography (www.inegi.org.mx/).

Classification criteria

We developed an algorithm to classify states into 5 categories: *Endemic*, *Declining*, *Intermittent*, *Absent-Vulnerable* and *Absent* (Box 1), based on characteristic patterns identified from SIRVERA via a set of objective criteria (Figure 1, Table 1).

I. Case detection

For each state, we calculated the time since the last detected case, and categorized case detection in the last 2 years as: present in consecutive months; present but not over consecutive months; and absent. If cases were detected over consecutive months in the past two years, we distinguished between *Endemic* and *Declining* classifications according to whether a declining trend in detection was identified (Criterion II). We classified states with cases detected in the past two years but not over consecutive months as *Intermittent* detection or *Declining*, again depending upon temporal trends in detection (Criterion II) or, if there was an absence of at least two years prior to the last detected case, as *Absent-Vulnerable*. Among areas with no case detection in the previous two years, we distinguished between two categories according to incursion risk (Criterion IV), classifying them as either *Absent* or *Absent–Vulnerable*.

The rationale for these criteria was based on the following arguments. Firstly, following an introduction, the serial interval for rabies means that ~28% of secondary cases would be expected to occur within one month, although cases in consecutive months could also result from independent introductions. A lack of detection over consecutive months therefore suggests secondary transmission is not sustained. Our decision to use a two-year window for the classification of *Absent* is based upon modelling showing that a two-year period without detection of rabies, while mass dog vaccinations are ongoing, should be sufficient to be confident of elimination from an isolated area, even at realistically low levels of surveillance[9].

II. Temporal trends in case detection

We used monthly state-level time series of laboratory confirmed cases to assess temporal trends. After converting these to presence/absence, we fitted a logistic regression to determine whether the monthly probability of case detection was increasing, decreasing or showed no trend. Although cases are only detected during the month when rabid animals become infectious, infection could be present prior to

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this due to latent infections. We accounted for this by including the month prior to case detection as presence. We classified states with time series exhibiting significant declines in the proportion of months with detected cases as *Declining*, versus those with no trend or an increasing frequency of months with detected cases as *Endemic*.

III. Variant identification

Cases detected in the previous two years were assessed to determine whether they were due to variants associated with dogs (V1 & V2) or with other species (e.g. bats, terrestrial wildlife). The classifications were then updated with wildlife-associated variants removed. A reclassification to *Absent* or *Absent-Vulnerable* could occur if all detected cases from the last two years were wildlife variants.

IV. Incursion risk

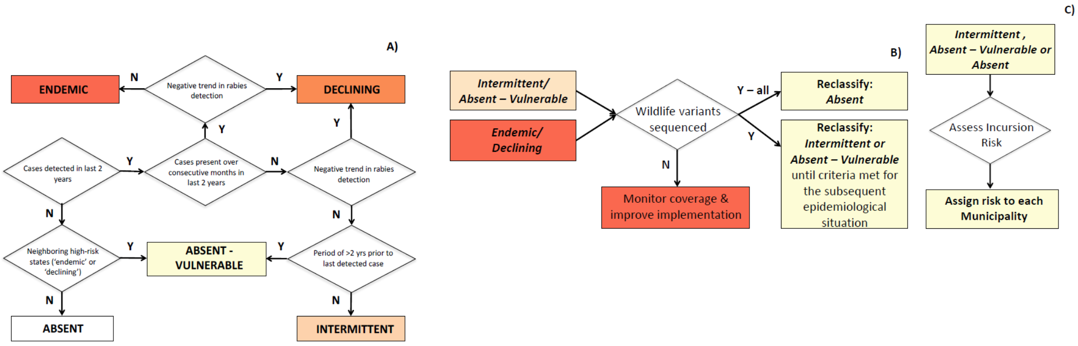
We assessed the risk of incursions into non-endemic states (*Intermittent*, *Absent* or *Absent-Vulnerable*) based on shared borders with high-risk states. We considered states neighbouring states classified as either *Endemic* or *Declining* to be *Vulnerable* (Table 1). We further examined every case in the time series and identified whether they could be recognized as incursions based on the following criteria applied to the two years preceding each case:

1) Less than 12 months with case detection
2) The average interval between months with detected cases (period of absence) exceeds 2.5 months
3) The time since the last detected case is at least 6 months, or is equal to or exceeds the mean period of absence

Robustness testing and validation

We applied our algorithm to SIRVERA data from 2005 to 2015 for Mexico and Brazil, classifying states in both countries retrospectively using a five-year time window. We compared classifications in 2005, 2010 and 2015, and assessed whether criteria enabled unambiguous classifications and epidemiological transitions. To explore how the time series length affected the sensitivity of the logistic regression approach to identifying trends, we refitted to incrementally truncated time series of presence/absence data, and compared classifications according to the years of data included. To assess how well our algorithm performed under different levels of surveillance and/or reporting quality, we simulated canine rabies dynamics, resampling simulated time series to mimic differing levels of surveillance (1%, 2.5%, 5%, 10%, 20%) and applied our algorithm (see supplementary information for further details).

Figure 1. Three-stage classification process: A) Algorithm for initial classification; B) reclassification based on variant assessment; C) incursion risk assessment.



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Classification	Cases in last 2 years	Trend (model coefficient)	Absence (>2 yrs with no V1 or V2)	Incursion risk
Endemic	Yes, V1 &/ V2, in consecutive months	None/ positive	NA	NA
Declining	Yes, V1 &/ V2	Negative	NA	NA
Intermittent	Yes, but not in consecutive months	None/ positive	NA	NA
Absent - Vulnerable (i) or (ii)	(i) No (ii) V1 &/V2 in 1 month only	(i & ii) NA	(i) At least last 2 years (ii) >2 yr absence prior to last detected case(s)	(i & ii) Adjacent to *Endemic* or *Declining* area(s)
Absent	No	NA	NA	Not adjacent to any *Endemic* or *Declining* areas

Table 1. Criteria for classification of epidemiological situations. NA - not applicable, V1 and V2 - canine rabies genetic variant of type 1 and 2 respectively.

BOX 1. Epidemiological classifications:

1) **ENDEMIC TRANSMISSION:** Canine rabies (genetic variant 1 & 2 in Latin America) detected over at least two consecutive months during the previous two years, indicating focal transmission. No significant increase in the frequency of disease-free months over the previous five years.
2) **DECLINING TRANSMISSION:** At least one case detected in the previous two years, but an increasing frequency of months with no detected rabies cases over the previous five years.
3) **INTERMITTENT DETECTION:** Cases detected during the past two years but not over consecutive months. No temporal trend in the proportion of months with detected cases during the previous five years.
4) **ABSENT-VULNERABLE:** Either: (i) canine rabies cases not detected in the previous 2 years, but neighbouring an area where rabies is *Endemic* or *Declining*, and therefore vulnerable to incursions; or (ii) a single month with cases detected during the previous two years, but no case detection prior to that month for at least 2 years (i.e. recently experienced an incursion that did not lead to further spread).
5) **ABSENT:** No cases of canine rabies cases detected during the last 2 years and minimal risk of incursion from neighbouring states (i.e. not neighbouring with any *Endemic* or *Declining* states).

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Results

Using our algorithm, we were able to unambiguously classify states in Mexico and Brazil based on 5 years of surveillance data, as shown in Figure 2 (and Table 2), comparing classifications in 2005, 2010 and 2015.

Over the last decade considerable progress was evident in both countries, with several *Endemic*, *Declining* or *Intermittent* states transitioning to *Absent* or *Absent-Vulnerable.* In 2015 most states in both countries were classified as either *Absent* or *Absent-Vulnerable*, with only limited focal circulation remaining in southern Mexico and northeast Brazil except for a 2015 outbreak in Mato Grosso do Sul.

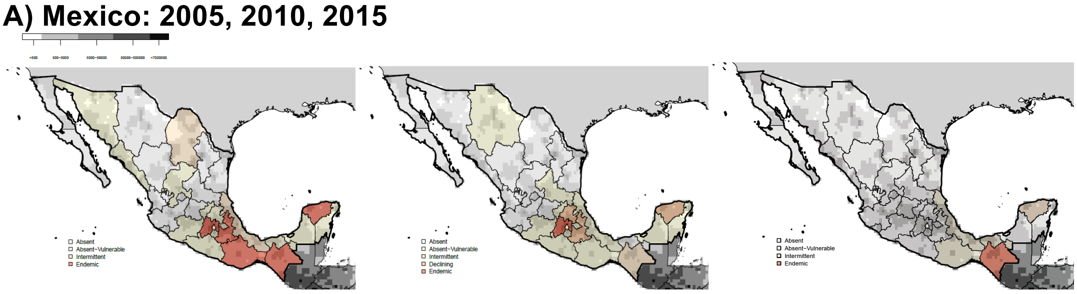
In Mexico, only Chiapas state was classified as *Endemic* and Yucatán state as *Intermittent.* Examination of variants in Yucatán revealed one of the two detected cases in the last two years (2014, 2015) as a wildlife variant. Given no further canine variant cases detected in Yucatán in 2016, the state would be reclassified to *Absent* or *Absent-Vulnerable*.

In Brazil, Mato Grosso do Sul were classified as *Endemic* as a consequence of the 2015 outbreak which has since been controlled. In Northeast Brazil Rio Grande do Norte was the only state classified as *Endemic*, whereas Ceará and Maranhão were *Declining.*

Five years was a sufficient time window to both detect consistent temporal trends, and be responsive to changing dynamics (Figure S3): shorter time windows magnified transient patterns, whereas dynamical transitions were less apparent with longer windows.

Figure 2: Classification of states in A) Mexico and B) Brazil in 2015, 2010 and 2005. States are transparently shaded by their epidemiological situation. Grey shading shows human population density. Note that variant data was only used in the 2015 Mexico classification. *Absent-vulnerable* was mapped according to adjacency with high-risk states.

A) Mexico: 2005, 2010, 2015



B) Brazil: 2005, 2010, 2015

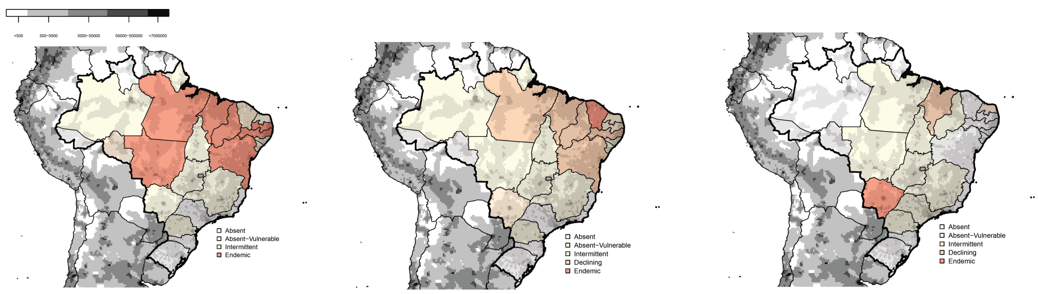


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Table 2. Classification of states in A) Mexico and B) Brazil in 2005, 2010 and 2015.

Mexico	epidemiological situation 2015	epidemiological situation 2010	epidemiological situation 2005
Aguascalientes	Absent	Absent	Absent
Baja California	Absent	Absent	Absent
Baja California Sur	Absent	Absent	Absent
Campeche	Absent	Absent-Vulnerable	Absent-Vulnerable
Coahuila de Zaragoza	Absent	Absent	Intermittent
Colima	Absent	Absent	Absent
Chiapas	Endemic	Intermittent	Endemic
Chihuahua	Absent	Absent-Vulnerable	Absent
Distrito Federal	Absent	Absent-Vulnerable	Intermittent
Durango	Absent	Absent	Absent
Guanajuato	Absent	Absent	Absent
Guerrero	Absent	Absent-Vulnerable	Absent-Vulnerable
Hidalgo	Absent	Declining	Absent-Vulnerable
Jalisco	Absent	Absent	Absent
Mexico	Absent	Endemic	Endemic
Michoacan de Ocampo	Absent	Absent-Vulnerable	Absent-Vulnerable
Morelos	Absent	Absent-Vulnerable	Absent-Vulnerable
Nayarit	Absent	Absent	Absent
Nuevo Leon	Absent	Absent	Absent
Oaxaca	Absent-Vulnerable	Absent-Vulnerable	Endemic
Puebla	Absent	Declining	Endemic
Queretaro Arteaga	Absent	Absent-Vulnerable	Absent-Vulnerable
Quintana Roo	Absent	Absent-Vulnerable	Absent-Vulnerable
San Luis Potosi	Absent	Absent-Vulnerable	Absent
Sinaloa	Absent	Absent	Absent-Vulnerable
Sonora	Absent	Absent	Absent-Vulnerable
Tabasco	Absent-Vulnerable	Absent	Absent-Vulnerable
Tamaulipas	Absent	Absent	Absent
Tlaxcala	Absent	Absent-Vulnerable	Intermittent
Veracruz de Ignacio de la Llave	Absent-Vulnerable	Absent-Vulnerable	Intermittent
Yucatan	Intermittent	Declining	Endemic
Zacatecas	Absent	Absent	Absent-Vulnerable

Brazil	epidemiological situation 2015	epidemiological situation 2010	epidemiological situation 2005
Acre	Absent	Absent	Absent
Alagoas	Absent	Absent-Vulnerable	Absent-Vulnerable
Amapa	Absent	Absent-Vulnerable	Absent-Vulnerable
Amazonas	Absent	Absent-Vulnerable	Absent-Vulnerable
Bahia	Absent	Declining	Endemic
Ceara	Absent	Endemic	Intermittent
Distrito Federal	Absent	Absent	Absent
Espirito Santo	Absent	Absent	Absent
Goias	Absent-Vulnerable	Absent-Vulnerable	Absent-Vulnerable
Maranhao	Declining	Declining	Endemic
Mato Grosso	Absent-Vulnerable	Absent-Vulnerable	Endemic
Mato Grosso do Sul	Endemic	Intermittent	Absent-Vulnerable
Minas Gerais	Absent-Vulnerable	Absent-Vulnerable	Absent-Vulnerable
Para	Absent-Vulnerable	Declining	Endemic
Paraiba	Absent	Intermittent	Endemic
Parana	Absent-Vulnerable	Absent-Vulnerable	Absent-Vulnerable
Pernambuco	Absent	Declining	Endemic
Piaui	Absent-Vulnerable	Declining	Endemic
Rio de Janeiro	Absent	Absent	Absent
Rio Grande do Norte	Intermittent	Intermittent	Absent-Vulnerable
Rio Grande do Sul	Absent	Absent	Absent
Rondonia	Absent	Absent	Intermittent
Roraima	Absent	Absent	Absent
Santa Catarina	Absent	Absent	Absent
Sao Paulo	Absent-Vulnerable	Absent	Absent
Sergipe	Absent	Absent-Vulnerable	Intermittent
Tocantins	Absent-Vulnerable	Absent-Vulnerable	Absent-Vulnerable

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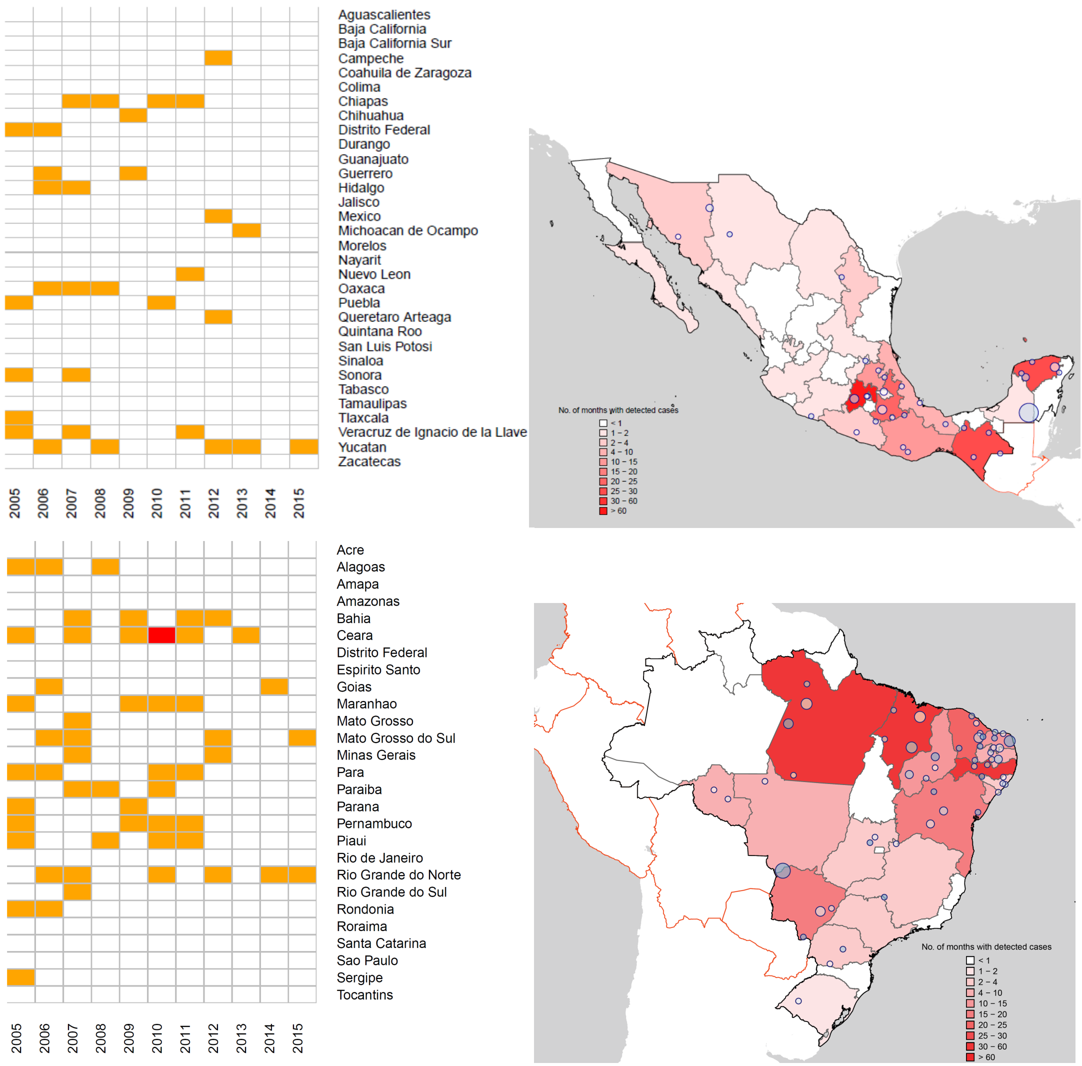
We identified 32 incursions in Mexico and 54 in Brazil between 2005 and 2015, with their frequency and distribution varying by state and over time (Figure 3). Potential sources of incursions declined substantially over this period as rabies was brought under control across many states.

In Mexico, incursion risks largely came from ongoing transmission in Chiapas and possibly Guatemala (Figure 3a,b). A prolonged absence led to reclassification of Chiapas from *Endemic* to *Absent-Vulnerable* in 2006-2007 prior to detection again in 2008 (Figure S3a). It is unclear whether the transition in Chiapas to *Endemic* was the result of improved surveillance or importations between Guatemala and Chiapas. States surrounding Mexico City, particularly Puebla and Veracruz, were until recently high-risk for incursions, but all transmission in that region has now apparently been interrupted (Figure 3).

Figure 3. Identified incursions by state in Mexico and Brazil (A, C heat maps; B, D static maps). Circles indicate the year of incursions, with more recent incursions larger in size. Current high-risk states (*Endemic* or *Declining*) are indicated by red text in the heat maps and the number of incursions coloured (1 = orange, 2 = red).



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In Brazil, incursion risks are driven by endemic circulation in Maranhão, and other Northeastern states including Rio Grande de Norte and Ceará, in addition to Mato Grosso do Sul in the South. The outbreak in Mato Grosso do Sul was detected in Corumba, a border town with Bolivia, and was restricted to the municipalities of Corumba and Ladario (Figure 2). Sao Paulo State was initially classified as *Intermittent* detection, but variant information indicated that recent cases were associated with wildlife rather than canine rabies (variant 1 or 2).

We examined whether cases without location data (major and minor administrative units corresponding to states and municipalities respectively) affected the classifications in Mexico (of 442 cases reported to SIRVERA between 2005 and 2015, 386 and 34 had no municipality or state information respectively) and Brazil (of 558 cases reported between 2005 and 2015, 326 and 14 had no municipality and state information respectively). However, from 2011 onwards, municipalities were reported for all cases (Figure S3), hence the few missing locations (even at major administrative level) from 2010 were unlikely to affect state-level classifications. However, inference from incursion analyses could have been further developed with complete municipality information.

More generally, through subsampling and classification of time series generated from an individual-based model, we were able to confirm that our classification tool was robust in determining the status of states. Surveillance has to reach extremely low levels (for example, detecting less than 2.5% of all circulating cases) or be very biased for states to be misclassified.

Based on our classifications we derived management guidance for the epidemiological situations across Mexico and Brazil, summarized in Figure 4 and detailed in Box 2. We also developed a tool to dynamically visualize progress towards elimination across the region, and to communicate tailored guidance on rabies management at the state-level: https://boydorr.shinyapps.io/paho/.

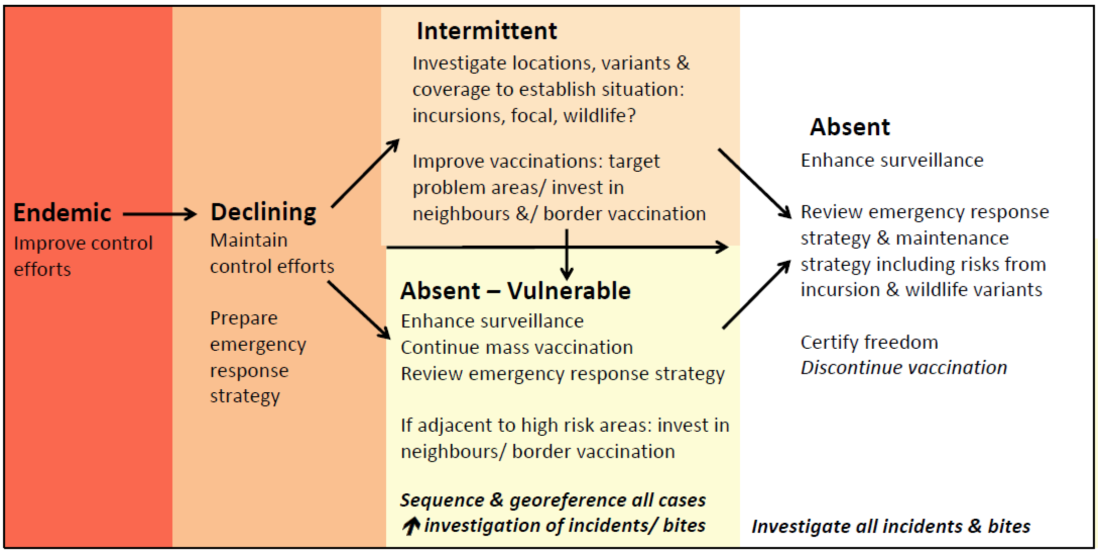

Figure 4. Epidemiological classifications and management actions indicating progression towards elimination

BOX 2. Management guidance based on classifications

1) **ENDEMIC TRANSMISSION:** control measures have not been implemented sufficiently to demonstrably reduce incidence. Mass vaccination campaigns should therefore be implemented within all administrative units, at least annually, using modern cell-culture vaccines of proven efficacy, aiming to reach >70% of dogs in all communities. Gaps in coverage can allow persistence, even when average coverage is high[10,11]. Therefore, if ongoing vaccination campaigns are not controlling rabies, their implementation and coverage at local levels should be monitored to identify areas for improvement.

2) **DECLINING TRANSMISSION:** Control measures are demonstrably effective. Current mass dog vaccinations should be sustained. Plans for maintaining rabies freedom should be developed, including emergency response strategies and preparation for enhanced surveillance needed to verify freedom from disease[12].

3) **INTERMITTENT DETECTION**: Criteria indicate that either: i) transmission is endemic but surveillance is poor; ii) transmission has been interrupted but incursions are frequent; or iii) other circulating variants are causing cases in dogs. Assume surveillance information is available, updating the classification with removal of wildlife variants could resolve scenario *iii* and case locations may allow incursions to be distinguished from local transmission, otherwise surveillance needs enhancing to distinguish these scenarios. Management recommendations are either for improved high coverage comprehensive vaccination campaigns to interrupt transmission (scenario i); or investment in rabies control in source populations and in populations at risk from incursions (scenario ii); or maintained dog vaccination to prevent further spread of these spillover variants (scenario iii).

4) **ABSENT-VULNERABLE:** Control efforts should be maintained while incursion risks remain high. Enhanced surveillance should be implemented for early detection of incursions and a detailed emergency response strategy prepared to ensure rapid response capacity[9]. In light of any incursions this emergency response strategy should be reviewed. All cases should be sequenced to identify variants and sources of incursions. Evidence should be compiled to verify freedom from rabies, including the absence of case detection under 2 years of enhanced surveillance[12].

5) **ABSENT:** Although no cases have been detected for extended periods, enhanced surveillance should be maintained and evidence compiled to verify rabies freedom.

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Discussion

Despite country and state differences in progress towards elimination in Latin America, guidance for canine rabies control and elimination programmes is limited and not geographically specific[13,14]. The management tool that we developed enables identification of mutually exclusive epidemiological situations using a simple algorithm, without the need for extensive statistical expertise. By classifying states in Mexico and Brazil, we determined urgent priorities for surveillance and control measures locally, nationally and regionally. Furthermore, we derived accordingly tailored guidance on how to progress efficiently towards rabies control and elimination targets, while revealing critical insights into the dynamics of rabies (Figures 2 and 3, Box 2).

For our analysis, we assumed that surveillance quality was sufficient throughout Mexico and Brazil to enable classification of all states. However, an absence of detected cases could reflect weak surveillance and would need to be identified a priori. For example, detection of locally-acquired human rabies cases in the absence of confirmed canine cases would be a clear indication of inadequate surveillance. Proficiency testing can also be used to ensure adequate laboratory surveillance[15]. Nonetheless, using sub-sampled simulated data, we demonstrated that our tool was relatively robust to surveillance quality.

Overall, we recommend applying this tool to five years of surveillance data. Shorter periods tends to magnify transient patterns, whereas longer periods do not provide any further advantage, and are potentially less responsive to epidemiological transitions. We recommend that case location data be reported by state and municipality, as this also provides a simple criteria for assessing surveillance quality. In Mexico and Brazil, cases locations were almost complete at state-level and did not affect classifications, but missing locations might be problematic for other countries. Moreover, municipality locations could be incorporated into inference approaches to generate a better understanding of incursion risks and more tailored management recommendations to reduce them.

Progress towards elimination is evident in both Mexico and Brazil; however focal transmission remains a threat for re-emergence in ostensibly rabies-free states. Spatial connectivity has been demonstrated to play a critical role in rabies persistence with infection maintained across, and driven by, large interconnected metapopulations (rather than dense conurbations)[16,17]. Our classification identifies metapopulations that support focal transmission, like previously in central Mexico, and now in Southern Mexico and Northeast Brazil. Dog rabies has likely been eliminated elsewhere in these countries apart from outbreaks sparked by incursions, highlighting the urgent need to improve rabies surveillance and control in remaining foci. For example, in Bolivia, though no cases have been reported to SIRVERA in over three years, local reports indicate ongoing transmission seeded the outbreak in the municipality of Corumba, Mato Grosso do Sol, on the Brazil/Boliva border. Similar incursions with long-lasting consequences have been reported in other parts of Latin America[18], and more globally[9,19].

Despite evident progress, rabies persists in some states where control programmes have been ongoing for decades. We suggest that in *Endemic* states, post-vaccination monitoring is needed to identify the causes of slow progress, which likely relate to the implementation of dog vaccinations. Coverage in Latin America has generally been estimated retrospectively from comparisons of vaccine doses delivered with dog population estimates derived from human:dog ratios (HDR).

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However, HDR tend to be spatially heterogenous and can change considerably over time with population growth. Moreover, it is difficult to reliably estimate numbers of distinct dogs vaccinated during campaigns, with some dogs likely repeatedly vaccinated during outbreak responses, unless concerted efforts are made to target areas missed by campaigns. Gaps in coverage tend to be the most important factor prolonging progress towards elimination[11,20]. If coverage estimates are not accurate, locally tailored post-vaccination evaluations are needed, to both identify and remedy problematic areas[21]. Strengthening the monitoring and delivery of vaccination campaigns in areas with focal transmission, including neighbouring endemic states, is likely to be the single most important programmatic change for improving prospects of regional rabies elimination given the risk that endemic areas pose to seeding outbreaks that can re-establish transmission.

With the progressive control and elimination of domestic dog rabies, other circulating variants have become increasingly apparent[22-24]. Variant identification plays an important discriminatory role for our classification and should inform management. While circulating wildlife variants are not an obstacle to elimination of dog rabies variants, they pose risks of emergence into the dog population and for public health. Strategies for maintaining rabies freedom and for judicious use of post-exposure prophylaxis need to account for these complex situations, which may affect the scaling back of dog vaccinations and protocols for ensuring potential exposures are identified and treated.

Sequencing of viruses can resolve key questions about viral circulation, discriminating wildlife variants from dog variants[22], identifying sources of incursions[25], and detecting persistent lineages[26]. Genomic surveillance is an important epidemiological tool[27] that could be extremely useful in guiding the rabies endgame. Variant information played an important role in distinguishing the epidemiological status of states in both Mexico and Brazil in our classification. Further sequence analysis could provide key insights about the diversity and persistence of lineages in remaining foci, such as those circulating in both Chiapas state, Mexico and Guatemala. All detected cases in states classified from *Intermittent* to *Absent* should be sequenced. Since so few cases are detected in these situations, this should not be cost prohibitive. Moreover, additional functionality within SIRVERA for mapping georeferenced virus sequences could facilitate rapid assessment of the genomic landscape of circulating viruses and potential incursion threats.

The target for both Mexico and Brazil is now nationwide interruption of transmission and certification of disease freedom. For diseases that have been eradicated or regionally eliminated, intensified surveillance approaches with high levels of case detection have been employed[28-30]. Such approaches are now urgently required for areas classified as *Absent* or *Absent-Vulnerable*, or with *Intermittent* detection, to resolve uncertainties regarding viral circulation, initiate early outbreak responses and verify freedom (Box 2). We suggest that surveillance targeted through integrated bite case management programmes[31], with epidemiological investigations triggered by bites from suspicious animals, should enable verification of rabies freedom and guide scaling back of mass vaccination programmes[12]. This would help to identify transmission of other rabies variants, ensure appropriate treatment for exposed persons[32], and result in sample submissions, as well as observation or quarantining of biting animals[33]. More generally, contingency plans are needed for states approaching elimination, and these should be reviewed to ensure capacity in case of an incursion.

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The management tool we have developed can support rabies programme managers and practitioners to determine their progress towards elimination and provides tailored guidance for different epidemiological situations. We identified the main remaining challenges to rabies elimination from Mexico and Brazil as: 1) interruption of transmission from focally persistent states which pose wider incursion risks; and 2) establishment of enhanced surveillance to distinguish variants, respond to and minimize incursion risks and verify freedom from disease, that will allow relaxation of control measures without risking re-emergence. Application of this tool in Latin America could be used to prioritize efforts to accelerate progress towards regional elimination. Incorporation of this tool as additional functionality within the SIRVERA web interface would encourage further engagement and use by programme managers. More broadly, we suggest this tool could be adapted and used effectively in other parts of the world to guide progress towards the global elimination of canine rabies.

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Supplementary Information:

Robustness testing

We undertook rigorous testing of our classification algorithm using a variety of approaches. For temporal trends, we explored the possibility of using incidence (Figure S1) rather than presence/absence timeseries. However, incidence time series were highly variable (Table S1). We therefore used presence/absence trends which were more informative.

To assess how well our classification algorithm performed under different levels of surveillance sensitivity and/or reporting, we simulated canine rabies dynamics, adapting a previous model[20] after further validation that appropriate dynamics were captured (incidence patterns and persistence). Dog populations were modelled explicitly, tracking the number of dogs in each spatially-defined area, so that we could simulate vaccination coverage and its waning with population turnover.

We simulated dynamics for populations equivalent in size to the average dog population of states in Mexico (mean 634,361, median 409,877, simulated population 505,341), to represent states of sufficient size and configuration to support long-term persistence of rabies without incursions. We created heterogeneously distributed dog populations across 1km^2 grid cells by scaling up georeferenced dog population data from Tanzania. We assumed high dog population turnover (average lifespan of 2.5 years). For an endemic scenario, with an average incidence of around 1% of the dog population per annum[12]; given an incubation period of approximately one month, simulations were initiated with 450 cases, distributed randomly across the landscape with probability proportional to dog density.

We generated 50 stochastic realizations of 10 years of simulated cases for the following scenarios: with and without (a) realistic vaccination coverage and (b) incursions occurring on average at six-monthly intervals. This set of 50x4 simulation runs captured the full spectrum of classifications (box 1). We resampled the resulting simulated time series to mimic differing levels of surveillance (1%, 2.5%, 5%, 10%, 20%) and applied our classification algorithm, to assess its robustness to surveillance quality.

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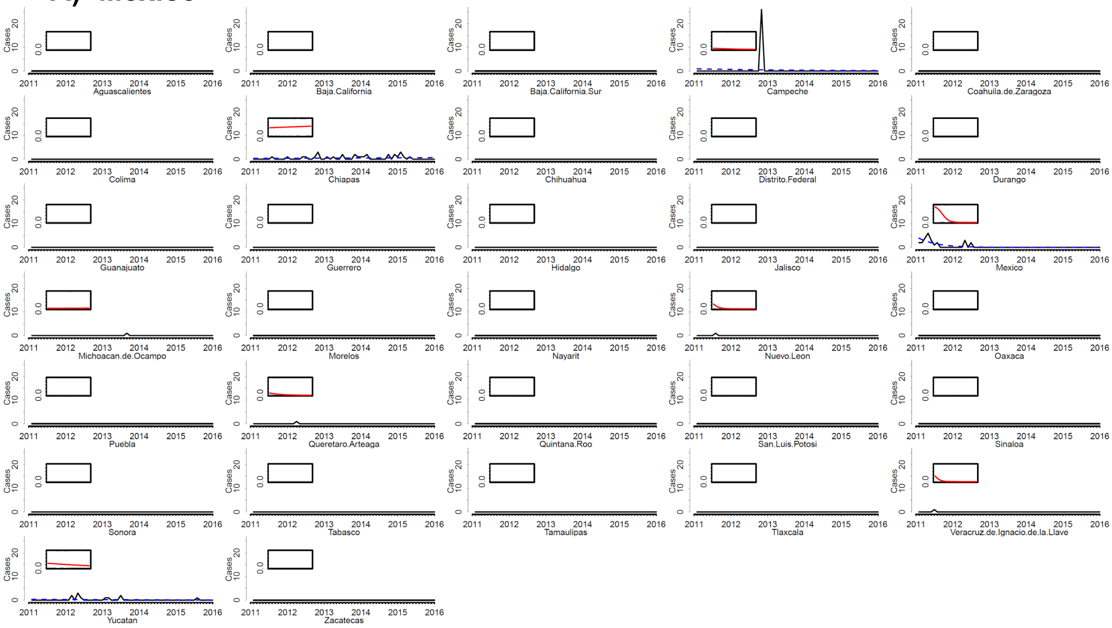
SUPPLEMENTARY MATERIAL

Figure S1. Confirmed rabies cases between January 2011 and December 2015 for A) Mexico and B) Brazil. Best fitting poisson regression model shown by dashed blue line and logistic regression models shown by red solid line (insets).

A) Mexico



B) Brazil

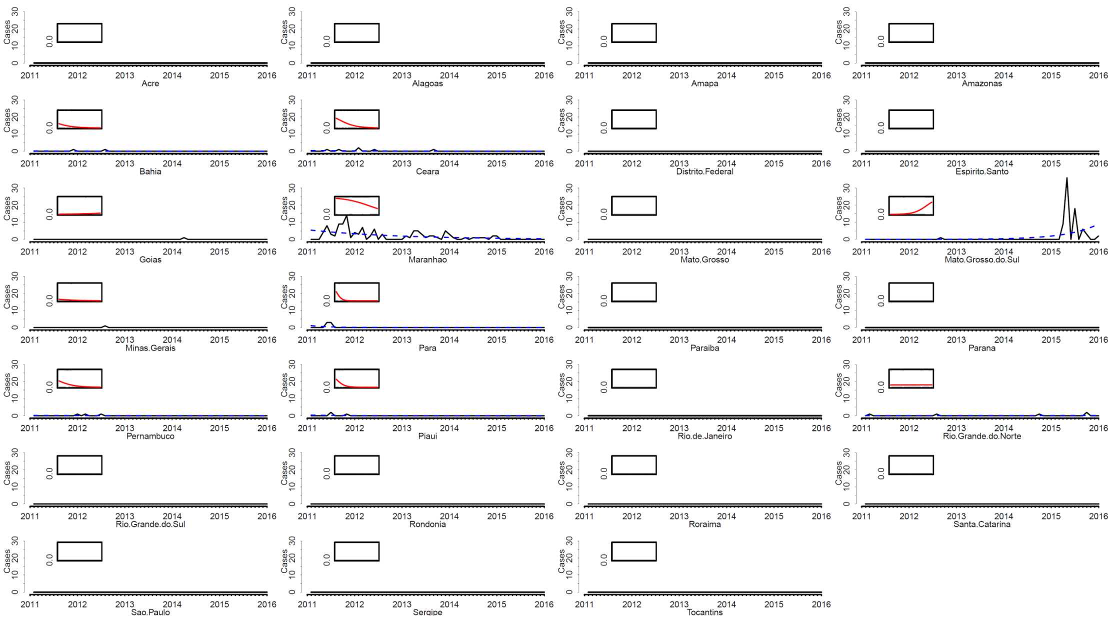


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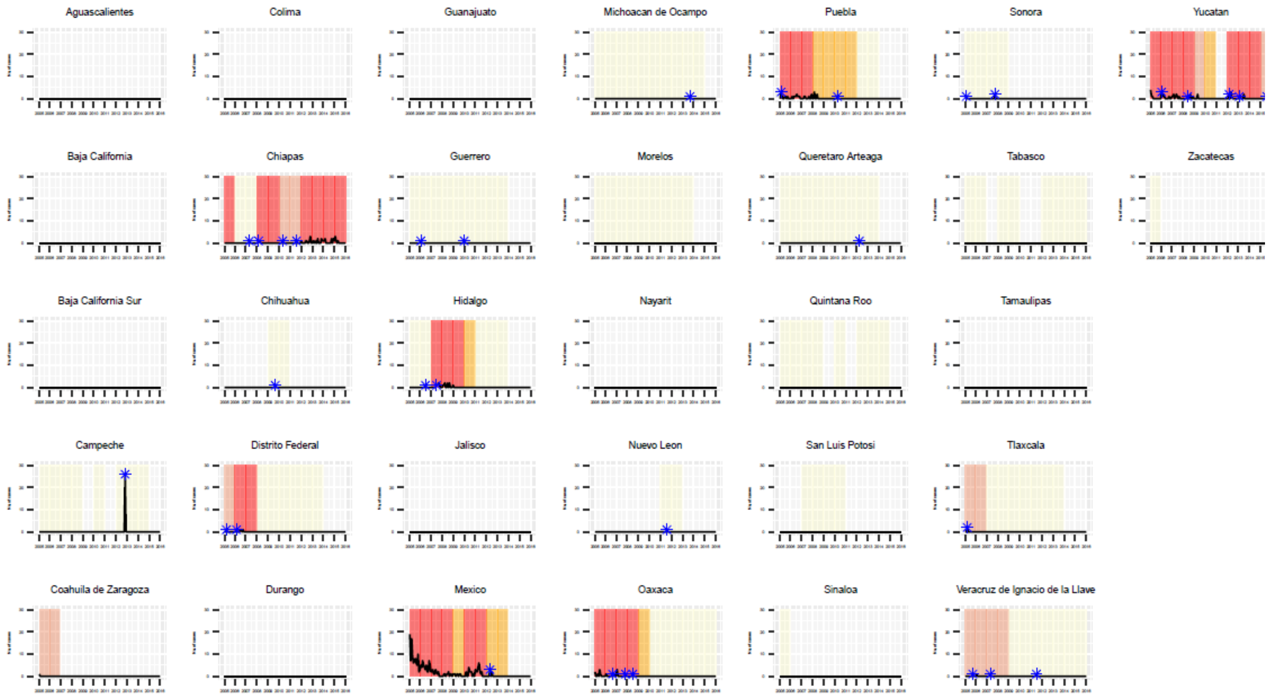
Figure S2: Confirmed rabies cases between January 2005 and December 2015 for A) Mexico and B) Brazil. Background shading is by the epidemiological situation in each state classified every year, blue stars indicate incursions.

A) Mexico



B) Brazil

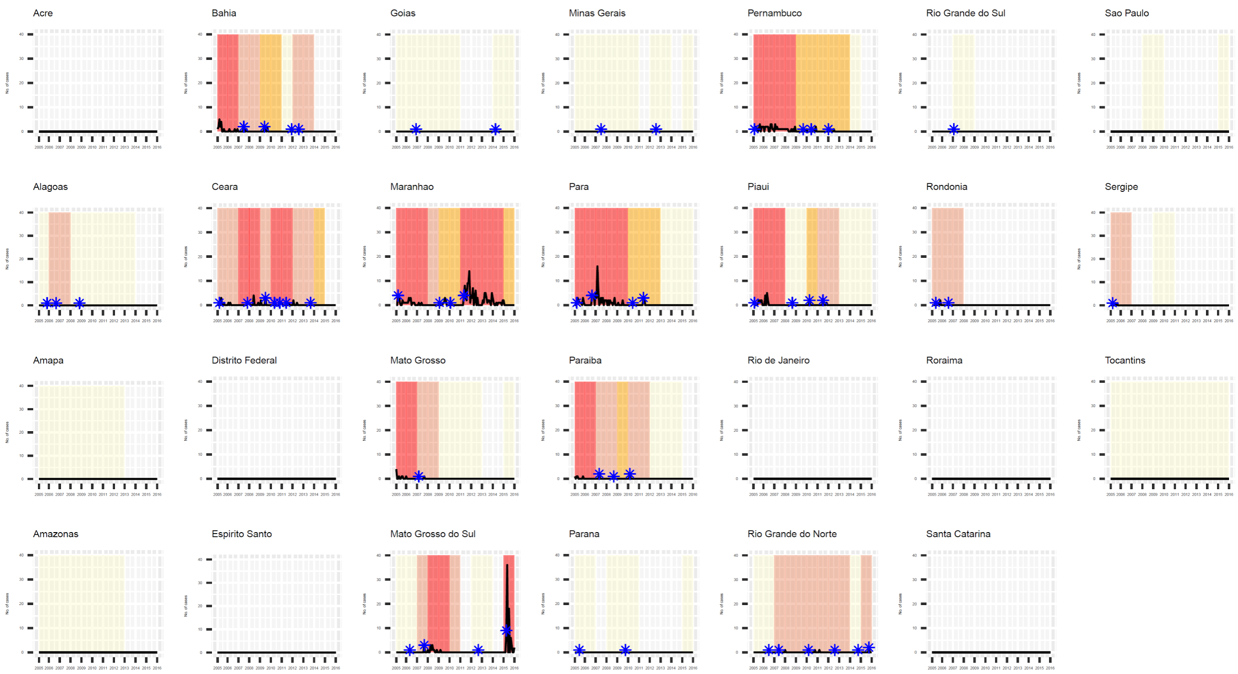


Figure S3. Completeness of location data for major and minor administrative units (states and municipalities respectively) in A) Mexico and B) Brazil.

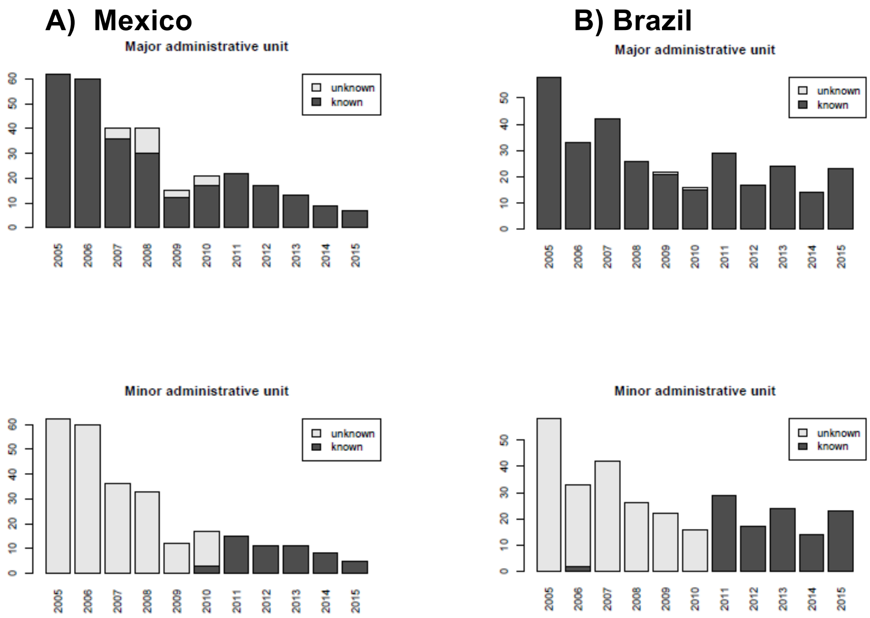


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Table S1. Trends in case detection in Mexico and Brazil for 2005-2010 and 2010-2015. Effect estimates, p-values and chi-square probability statistics (aka likelihood ratio p-value; <0.05 indicates the model performs better than chance at predicting the outcome, reject the null hypothesis) from Poisson regression (PR) and logistic regression (LR) models fitted to time series of detected cases and presence/absence data respectively. Effect estimates represent the multiplicative change in the odds of detection (for LR models) or incidence (for PR models) associated with the passing of one month. States absent from the table had no cases detected.

Mexico 2015		p-value LR	p-value PR	chi-sq probability LR	chi-sq probability PR	coeff LR	coeff PR
	Campeche	0.4848	0.0147	0.4667	0.0113	0.9685	0.9706
	Chiapas	0.6908	0.2784	0.6905	0.2755	1.0061	1.0118
	Mexico	0.0021	0.0000	0.0000	0.0000	0.8046	0.8448
	Michoacan de Ocampo	0.8992	NA	0.8991	NA	1.0054	NA
	Nuevo Leon	0.1590	NA	0.0197	NA	0.8329	NA
	Queretaro Arteaga	0.2399	NA	0.1684	NA	0.9338	NA
	Veracruz de Ignacio de la Llave	0.1590	NA	0.0125	NA	0.7992	NA
	Yucatan	0.4277	0.1903	0.4237	0.1793	0.9848	0.9763
Mexico 2010							
	Chiapas	0.9722	0.9770	0.9722	0.9770	0.9992	0.9992
	Chihuahua	0.3131	NA	0.2647	NA	1.0526	NA
	Distrito Federal	0.0150	0.0460	0.0000	0.0009	0.6903	0.8334
	Guerrero	0.8778	0.6284	0.8776	0.6220	1.0053	0.9797
	Hidalgo	0.0583	0.1625	0.0490	0.1545	0.9667	0.9793
	Mexico	0.2798	0.0000	0.2697	0.0000	0.9767	0.9634
	Oaxaca	0.0039	0.0092	0.0004	0.0017	0.9191	0.9296
	Puebla	0.0001	0.0013	0.0000	0.0003	0.9031	0.9500
	Sonora	0.4237	0.4527	0.3976	0.4306	0.9635	0.9668
	Veracruz de Ignacio de la Llave	0.0974	0.1642	0.0256	0.0438	0.9002	0.8828
	Yucatan	0.0002	0.0003	0.0000	0.0000	0.9194	0.9456
Brazil 2015							
	Bahia	0.0924	0.2517	0.0469	0.1849	0.9308	0.9391
	Ceara	0.0060	0.0437	0.0008	0.0187	0.9190	0.9372
	Goias	0.4848	NA	0.4667	NA	1.0326	NA
	Maranhao	0.0049	0.0000	0.0019	0.0000	0.9447	0.9561
	Mato Grosso do Sul	0.0019	0.0000	0.0000	0.0000	1.1224	1.1358
	Minas Gerais	0.3570	NA	0.3188	NA	0.9554	NA
	Para	0.0864	0.0145	0.0012	0.0000	0.7615	0.8182
	Pernambuco	0.0344	0.1538	0.0108	0.0964	0.9249	0.9372
	Piaui	0.0477	0.0853	0.0015	0.0080	0.8446	0.8638
	Rio Grande do Norte	0.9644	0.4822	0.9644	0.4754	1.0010	1.0189
Brazil 2010							
	Alagoas	0.2504	0.4527	0.2231	0.4306	0.9621	0.9668
	Bahia	0.0286	0.5719	0.0200	0.5704	0.9583	0.9905
	Ceara	0.1466	0.2235	0.1393	0.2182	1.0236	1.0162
	Goias	0.1758	NA	0.0686	NA	0.9012	NA
	Maranhao	0.0140	0.0082	0.0093	0.0055	0.9586	0.9669
	Mato Grosso	0.1242	0.3046	0.0816	0.2541	0.9426	0.9495
	Mato Grosso do Sul	0.1727	0.3086	0.1640	0.3038	0.9763	0.9851
	Minas Gerais	0.3131	NA	0.2647	NA	0.9500	NA
	Para	0.0036	0.0000	0.0016	0.0000	0.9499	0.9555
	Paraiba	0.8040	0.7669	0.8037	0.7663	1.0062	1.0077
	Parana	0.2836	NA	0.2270	NA	1.0583	NA
	Pernambuco	0.0042	0.0003	0.0014	0.0001	0.9427	0.9661
	Piaui	0.0581	0.0007	0.0410	0.0000	0.9550	0.9215
	Rio Grande do Norte	0.9681	0.9691	0.9681	0.9691	0.9992	1.0010
	Rio Grande do Sul	0.1993	NA	0.1090	NA	0.9194	NA
	Rondonia	0.1589	NA	0.0190	NA	0.8329	NA