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Molecular and mathematical modeling analyses of inter-island transmission of rabies into a previously rabies-free island in the Philippines

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ABSTRACT

Rabies is endemic in the Philippines and dog bites are a major cause of rabies cases in humans. The rabies control program has not been successful in eliminating rabies because of low vaccination coverage among dogs. Therefore, more effective and feasible strategies for rabies control are urgently required in the country. To control rabies, it is very important to know if inter-island transmission can occur because rabies can become endemic once the virus is introduced in areas that previously had no reported cases. Our molecular epidemiological study suggests that inter-island transmission events can occur; therefore, we further investigated these inter-island transmission using phylogenetic and modeling approaches.

We investigate inter-island transmission between Luzon and Tablas Islands in the Philippines. Phylogenetic analysis and mathematical modeling demonstrate that there was a time lag of several months to a year from rabies introduction to initial case detection, indicating the difficulties in recognizing the initial rabies introductory event. There had been no rabies cases reported in Tablas Island; however, transmission chain was sustained on this island after the introduction of rabies virus because of low vaccination coverage among dogs.

Across the islands, a rabies control program should include control of inter-island dog transportation and rabies vaccination to avoid viral introduction from the outside and to break transmission chains after viral introduction. However, this program has not yet been completely implemented and transmission chains following inter-island virus transmission are still observed. Local government units try to control dog transport; however, it should be more strictly controlled, and a continuous rabies control program should be implemented to prevent rabies spread even in rabies-free areas.

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1. Introduction

Rabies is a fatal viral disease caused by the rabies virus (RABV), and most countries in Africa and Asia are identified as high-risk areas for human rabies (World Health Organization, 2011). Similar to other Asian countries, rabies remains endemic in the Philippines and with approximately 200–300 human cases annually (Department of Health, 2009). Dog bites are a major cause of rabies cases in humans in the Philippines, and mass vaccination of dogs could be an effective control measure (Lembo, 2012; Tenzin and Ward, 2012). However, the rabies control program has not been successful in eliminating rabies because of low vaccination coverage among dogs, and more effective and feasible strategies for rabies control are urgently required. More data on dog populations and the transmission dynamics of RABVs should be obtained to understand how rabies spreads through the country. Previously, we conducted a molecular epidemiological study to define the spatiotemporal transmission patterns of RABVs in the Philippines. Our study revealed strong spatial effects on viral spread, indicating the potential effectiveness of rabies-control programs that targeted certain geographic areas (Saito et al., 2013; Tohma et al., 2014).

Previous viral phylogenetic analysis suggests that the sea is a strong barrier to viral transmission in the Philippines. However, it is very important for those implementing rabies control programs to know whether inter-island transmission can occur and how it can be detected early because rabies can become endemic once RABV is introduced in

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areas that previously had no reported cases. Our molecular epidemiological studies suggested that such transmission events were rare but could still occur; therefore, we investigated these inter-island transmissions using phylogenetic and modeling approaches.

The objectives of this study were as follows: 1) to define the spatiotemporal patterns of inter-island transmission of RABVs and 2) to simulate population dynamics after the introduction of new rabies cases to estimate the duration between introduction and the detection of the first case in the community. To achieve these objectives, we used recently developed phylogenetic analyses (Drummond et al., 2012; Lemey et al., 2009; Pybus and Rambaut, 2009) and mathematical modeling of the transmission of RABVs (Panjeti and Real, 2011). Our analyses focused on the recent inter-island transmission detected in Tablas Island, Romblon Province.

2. Material and methods

2.1. RABV sequence data set

The Philippines comprises three island groups (Luzon, Visayas, and Mindanao) and is administratively divided into regions, provinces, municipalities/cities, and barangays. Through passive surveillance of animal rabies, we collected samples of brain tissue from suspected rabid animals (mainly dogs) from all three island groups, as previously described (Saito et al., 2013). As of December 2014, we obtained 266 sequence data for the RABV glycoprotein (G) gene [1572 nucleotides (nt)] from animals in the Luzon island group. These samples were collected between 2004 and 2013, from eight regions in the Luzon island group, including Regions I, II, III, IV-A, IV-B, V, the Cordillera Administrative Region (CAR), and the National Capital Region (NCR) (Tables 1 and S1).

The study protocol was approved (No. 2008-01-1) by the Institutional Review Board of the Research Institute for Tropical Medicine (RITM), as required for all research projects conducted at the RITM.

2.2. Phylogenetic analysis

A Bayesian tree was constructed from G gene sequence data of 266 RABV samples using MrBayes software v3.2.3 (Ronquist et al., 2012). The phylogenetic relationship among RABV samples collected in the Luzon island group was inferred by summarizing 5e6 iterations (the first 10% was excluded as burn-in) in a Markov Chain Monte Carlo (MCMC) run. A general time-reversible model with gamma distribution was used for the G gene nucleotide substitution model, referring to the Akaike Information Criterion with a correction value (AICc) in the model selection procedure in MEGA 5.0 (Tamura et al., 2011). From this phylogenetic analysis, we detected phylogenetic clusters that suggested recently occurring inter-island transmissions (Fig. 1A and B). A subclade, comprising 39 samples (6 samples from Tablas Island in Romblon Province, Region IV-B and 33 samples collected in Pangasinan, Bulacan, and Pampanga provinces, Regions I and III on Luzon Island), was used for the molecular clock and phylogeographic analyses described below to investigate the details of possible inter-island transmission in Tablas Island, Romblon Province (Fig. 1 and Table S1).

Table 1
Temporal and regional summary of sequence data (n = 266).

Region	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
CAR	0	0	0	0	0	7	1	0	0	6
I	0	0	0	0	1	27	3	0	14	1
II	0	0	0	0	0	4	0	0	0	7
III	1	2	0	0	39	20	0	0	14	36
IVA	4	0	10	4	0	0	0	1	3	0
IVB	0	0	1	0	0	0	0	3	3	2
NCR	2	8	0	0	0	0	0	0	0	0
V	0	0	0	0	13	9	0	0	12	8
Total	7	10	11	4	53	67	4	4	46	60

CAR: the Cordillera Administrative Region, NCR: the National Capital Region.

In addition to the data described above, animal rabies case records for Tablas Island, Romblon Province were retrospectively collected from the Department of Agriculture (DA) to provide information on the situation regarding animal rabies in Tablas Island over the last 10 years.

Map data for the Philippines were obtained from the Global Administrative Areas website (http://www.gadm.org/country) and visualized with either ArcGIS 10 (ESRI Inc., Redlands, CA, USA) or the *sp*. and *maptools* package in R, version 3.1.0 (R Core Team, 2014, R Foundation for Statistical Computing, Vienna, Austria).

2.3. Molecular clock and phylogeographic analyses

To increase the phylogenetic information, the phosphoprotein (P) gene (891 nt) of the 39 subclade samples was obtained as follows: the viral RNA was amplified with a Superscript III One-Step RT-PCR System with Platinum Taq (Thermo Fisher Scientific, Waltham, MA, USA) and NPM1F and NPM1R primer sets (Campos et al., 2011) and then purified with a QIAquick PCR Purification Kit (Qiagen, Hilden, Germany). The purified PCR amplicon was sequenced using an ABI3730xl DNA Analyzer (Thermo Fisher Scientific), a BigDye Terminator v3.1 Sequencing Kit (Thermo Fisher Scientific), and a BigDye XTerminator Purification Kit (Thermo Fisher Scientific). The P gene obtained was concatenated to the G gene, which yielded 2463 nt sequence data for molecular clock and phylogeographic analyses.

Using the 39 samples of RABV P–G concatenated gene data, we conducted molecular clock and symmetric discrete phylogeographic analyses. Bayesian MCMC analyses were performed using BEAST v1.8.0 (Drummond et al., 2012). The viral divergence time and viral spatial spread were estimated by tracking viral RNA mutations and integrating the sampling date and sampling location (in provincial level) (Drummond et al., 2012; Lemey et al., 2009). A Tamura–Nei model with gamma distribution was used for the nucleotide substitution model, with reference to the AICc calculated with MEGA 5.0. In line with the AICM [AIC for MCMC samples (Baele et al., 2012; Raftery et al., 2007)], a strict clock was assumed in the model (although there was no difference in estimates between strict and relaxed clock models, with ΔAICM = 2.82) and 2e7 iterations were performed in the MCMC analysis to obtain an effective population size >200 and convergence of parameter estimation. Ten percent of the posterior tree sets were excluded as burn-in. The maximum clade credibility (MCC) tree was constructed using the TreeAnnotator program in the BEAST software package and visualized using FigTree (http://tree.bio.ed.ac.uk/software/figtree/). The posterior density of the estimates was summarized with Tracer v1.6 (http://tree.bio.ed.ac.uk/software/tracer/). Significant migrations were detected with the Bayes factor test using the Bayesian stochastic search variable selection procedure (Lemey et al., 2009). Migrations with a Bayes factor >3, as calculated in SPREAD (Bielejec et al., 2011), were accepted as well-supported migrations. The number of migrations between locations (Markov jump counts) was estimated along the branches of the posterior trees (Minin and Suchard, 2008; O'Brien et al., 2009). The migration history was inferred by summarizing the Markov jump density via kernel density estimation in R (Nunes et al., 2012).

2.4. Mathematical modeling

To assess the possible duration between the introduction of the RABVs and the detection of the first case on the island, we constructed a deterministic compartmental model and simulated the transmission dynamics of the virus in the dog population. (Hampson et al., 2007; Kitala et al., 2002; Panjeti and Real, 2011). An SEI (Susceptible-Exposed-Infectious) model, in which a V (vaccinated) compartment was also included, was constructed by assuming random

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