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EPIDEMIOLOGICAL CASE ANALYSIS OF NIPAH VIRUS: A META-ANALYSIS

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ABSTRACT

Nipah virus is the most common seen in forest area where bats can survive and the virus causes encephalitis in humans. On 19 May 2018, a Nipah virus disease (NiV) outbreak was reported from Kozhikode (Dist), Kerala, India. This is the first NiV outbreak in South India. There have been 17 deaths and 18 confirmed cases as of 1st June 2018. The two affected districts are Kozhikode and Mallapuram. A multi-disciplinary team led by the Indian Government's National Centre for Disease Control (NCDC) is in Kerala in response to the outbreak. WHO is providing technical support to the Government of India as needed. WHO does not recommend the application of any travel or trade restrictions or entry screening related to the NiV outbreak. The Nipah outbreak reported in Kozhikode and Malappuram districts of Kerala in May 2018 was the third of Nipah Virus Outbreaks in India, the earlier being in 2001 and 2007, both in West Bengal. A total of 23 cases were identified, including the index case with 18 laboratory-confirmed cases. The outbreak was managed by the state government and central government agencies and has been acknowledged as a success story. Recognizing the importance of documenting and sharing the Kerala experience, the Kerala government requested WHO to conduct an external review and documentation of the NVD response

INTRODUCTION

Nipah virus (NiV) has become one of the most recognized deadly viruses that we have observed, of late. The first 2 recorded NiV outbreaks reported in India, in 2001 [1] and 2007 [2], were from West Bengal. NiV was first discovered in Malaysia during a 1998 outbreak [4] and subsequently in Singapore (in 1999) [5], Bangladesh (in 2001) [6], and the Philippines (in 2014) [7]. NiV has 2 genetic lineages, known as NiV-Malaysian (NiV-M) and NiV Bangladesh (NiV-B) [8]. Considering its potential to cause public health emergencies, NiV infection was designated one of 10 priority diseases in the World Health Organization Research and Development Blueprint of 2018 [9]. On 17 May 2018, a 28-year-old man reported to a private hospital in the district of Kozhikode, State, India, with encephalitis. His father and aunt developed fever, body ache, and vomiting on the same day. 12 days earlier, his brother expired from a similar trend in illness. The family cluster of encephalitis cases among adults prompted the laboratory to test for NiV in addition to common causes of encephalitis [3]. Detailed microbiologic and virologic analysis at the Manipal Centre for Virus Research (MCVR), an Indian Council of Medical Research (ICMR) Virus Research and Diagnostic Laboratory (VRDL), resulted in the diagnosis of NiV infection late during the evening on 18 May. The ICMR National Institute of Virology–Pune reconfirmed the results on 20 May 2018 (Figure-1-See Appendix). In this report, we shall understand the characteristics of this outbreak, including case details, clinical features, laboratory and epidemiologic investigations, and human-to-human transmission dynamics.

EPIDEMIOLOGIC CASE HISTORY IN KERALA

Index case

The index case (case 1) was apparently healthy prior to this event. He reportedly had limited social contacts and was a nature and animal lover. At the time of his death, he owned pet rabbits and ducks. The broad timing of this outbreak coincided with the breeding

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season for bats, a known zoonotic reservoir of this disease. The index case may have come into contact with a NiV-infected baby bat.

Transmission dynamics

The outbreak had 3 clusters of cases, identified at hospitals, termed hospital 1, hospital 2, and hospital 3. Figure 4(See Appendix) depicts the transmission dynamics of this outbreak within the various hospital settings. Hospital 1, 4 May. The index case (case 1) was admitted to the male ward of hospital 1 on 4 May. There were at least 22 persons, including admitted patients, companions, housekeeping staff, and a staff nurse, in the ward during the night. Nine of 22 persons were infected with NiV. Case 2 (a brother of case 1) and case 5 (the father of case 1) pro- vided close care of case 1. Case 7 provided direct nursing care to case 1 and spent at least 10 hours with the patient while his symptoms worsened. Cases 3, 4, 8, 9, and 10 were either patients or companions in the ward who reportedly helped case 1 or came close to his bed, as his bed was next to the entrance of the ward (Figure 4- See Appendix). Case 6, an aunt of case 1, visited him at hospital 1 in the morning, before he was referred to hospital 2. The remaining 11 persons present in hospital 1 were not infected. The mother of case 1, present throughout his illness, did not become ill. She was observed to wear a long scarf on her head. She reported being uncomfortable with the indoor smell of hospitals and therefore covered her nose with the scarf while in the hospital. The brother and father had longer and more intimate contact with the index case, compared with the mother. Sick patients who were restricted to their beds were not infected. Hospital 2, 5 May. Case 1 was referred to hospital 2 on 5 May. The patient arrived at the emergency department of hospital 2 at around 10:00 am and was attended to by a junior physician. A trainee nurse (case 11) collected samples from case 1 before he was referred for CT. At 12:04 pm, the father (case 2) and brother (case 5) brought case 1 on a stretcher to the corridor, outside the CT room; the patient was restless and persistently coughing the patient spent approximately 3 hours in the corridor, during which 3 attempts were made before CT was successful. The initial attempt failed because the patient was persistently coughing; the patient was sent back to the emergency department. Fifteen minutes later, CT was attempted for a second time but again could not be performed. Case 1 was returned to the emergency department and brought back after 20 minutes, and CT was successful. He was then taken to the observation room near the emergency department, where he died of his illness at around 5:30 pm (Supplementary Materials). Based on the surveillance footage, at least 70–100 people potentially had contact with case 1 in the corridor, of whom 10 contracted the infection. Cases 12–18, and 20 were present in the corridor during the same period as case 1. They were either patients or companions of patients. Case 19 was an assistant in the radiology department.

- **Hospital 2, 14 May.** Case 3, who was exposed at hospital 1 on 4 May, developed symptoms on 13 May and sought care at the emergency department of hospital 2 on 14 May. Case 22 was a companion of a patient in the emergency department during the same day**.**
- **Hospital 3, 19 May.** Case 10, who was present at hospital 1 on 4 May, developed symptoms on 17 May and was admitted to hospital 3 for treatment. Case 23 was in the bed across from case 10 during this period (Figure 4- See Appendix).
- Most of the transmissions from case 1 occurred during the 2 days preceding his death. Even though cases 1, 3, 4, 8, 12, and 16 died before the confirmation of the disease etiology, and their corpses were prepared for burial without any protective measures, including touching, bathing, and carrying the dead body, no disease transmission events were reported. We observed that the caregivers who contracted the disease had closer and longer contact, touched body fluids, or were coughed on.
- **Environmental Samples.** Of the 60 environmental samples, including partially eaten mangoes, guava, and areca nuts with bite marks of bats, collected from the surroundings of the residence and potential work places of the index case, none had evidence of NiV RNA detected by real-time RT-PCR. The pet rabbits and ducks of case 1 tested negative for NiV.

Public health response

The public health response by Kerala Health Services was launched on 18 May with the isolation of cases, contact tracing, enforcement of hospital infection control practices, and risk communication. The national team of experts deputed by the Ministry of Health and Family Welfare, Government of India, guided the response in close collaboration with the Kerala State health services. A total of 2642 contacts were identified and kept under surveillance. The antiviral ribavarin was imported by the Department of Health and Family Welfare, Government of Kerala. Fifty doses of an experimental monoclonal antibody against Hendra virus (M102.4) were provided by the Queensland Department of Health, Australia, at the request of the Indian Council of Medical Research, New Delhi, for compassionate use and stored at Government Medical

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College, Kozhikode. Since 30 May 2018, no new cases have been reported.

MATERIALS AND METHODS

Detection of nipah virus in bats

As part of a broader study on filoviruses and henipaviruses in wild bats, we systematically searched Web of Science, Centre for Agriculture and Biosciences International (CAB) Abstracts, and PubMed with the following terms: (bat OR Chiroptera) AND (filovirus OR henipavirus OR "Hendra virus" OR "Nipah virus" OR "Ebola virus" OR "Marburg virus" OR ebolavirus OR marburgvirus) NOT (human); we also performed a secondary search that included "human". We followed a systematic exclusion protocol [37] and, because the search was conducted during a study on viral detection or serological detection estimates, we only retained records from observational studies that measured the proportion of wild bats positive for each viral group as assessed by PCR (prevalence) or serology (seroprevalence). We supplemented these data with studies referenced in the systematically identified publications that report viral isolation but not prevalence or seroprevalence. For the generalized boosted regression analysis, we culled the global data by including only studies that reported Nipah virus (by serology or PCR). This search yielded 286 records from 25 papers. For each record, we classified the species, country of sampling, diagnostic method (PCR or serology), sample size, sampling and reporting method (single or multiple cross-sectional events, samples pooled to one estimate), and the proportion of PCR-positive or seropositive bats (Fig 1- See Appendix). We display these data in a phylogenetic context using the bat phylogeny derived from the Open Tree of Life and the rotl and ape packages (Fig 2) [38, 39].

Machine learning analyses

To make predictions of bat species that may carry Nipah virus in India and the surrounding region, we trained a generalized boosted regression model on data that characterized 48 traits of 523 extant bat species with geographic ranges in Asia, Australia, and Oceana. By learning the intrinsic features of species that have previously been found to have evidence of Nipah virus- infection (in this study, either through serology or PCR), the objective is to identify additional bat species whose trait profiles suggest a high probability of being Nipah virus-positive. In addition, by examining those traits that are most predictive of Nipah virus-positive species, we may also glean ecological insights about why some bats are found to be Nipah virus- positive compared to others in this region. While examination of these suites of shared traits can be insightful, it is important to note that these methods are designed for pattern recognition rather than to identify mechanisms; however, in some cases, mechanisms may be suggested [42]). We acquired range maps from the International Union for Conservation of Nature (IUCN) [43]. We obtained data on foraging method and diet composition from EltonTraits [44]. We derived data on biological and ecological attributes from PanTHERIA [45]. We took data on torpor and migration behaviors from Luis et al. [46], and data on production (a measure of fit- ness output) from Hamilton et al. [47]. All variables, their definitions, coverage, and data source citations are reported in S1 Table. Models were trained on 80% of this full data set and comprised of 50,000 trees specifying a Bernoulli error distribution and built with 10-folcross-validation to prevent overfitting. In addition, we weighted each species by its sample size ("sum.sample. size") to account for the fact that some species are more frequently sampled for henipaviruses compared to others. We also applied target shuffling methods to calculate the corrected area under the curve (AUC) [48]. We conducted a second generalized boosted regression analysis to diagnose whether greater data availability for better-studied species leads to trait profiles that describe well studied bat species rather than species where evidence of Nipah virus infection has been reported. In this model, we used the number of citations in Web of Science for each species' scientific name as a proxy for study effort at the time this study was conducted. As before, models were trained on 80% of the full data set and were comprised of 30,000 trees specifying a Poisson error distribution and built with 10-fold cross-validation to prevent overfitting. Hyperparameter values and outputs for generalized boosted regression models can be found in S2 Table.

RESULTS

One hundred twelve species of bats have been detected in India, of which 39 have been detected within the state of Kerala [43, 49, 50]. Thirty-one bat species that occur in India (and 18 that occur in Kerala) have been sampled for Nipah virus and 11 of these species have been identified as having antibodies that react to Nipah virus serological tests. However, almost all sampling of these species occurred outside of India. The 11 positive species include seven species that reside in Kerala, including five Pteropodidae (Cynopterus brachyotis, C. sphinx, Eonycteris spelaea, Rousettus leschenaultii, and P. medius [formerly P. giganteus]) and two non- Pteropodidae (Scotophilus kuhlii and Hipposideros Pomona. Although all of these species had serological evidence of Nipah virus (or

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cross-reacting Nipah- like viruses), P. medius was the only species with virological evidence of Nipah virus (1 out of 31 individuals tested with PCR [3%]) [40, 41]. Seroprevalence in sampled species ranged from 0–83% and prevalence from 0–3% (Table 1). P. medius [41] and R. leschenaultia [56, 57] were the only species with seroprevalence >30%. However, most studies reported seroprevalence as pooled detection over time (i.e. samples from multiple time points were included in a single seroprevalence estimate). Only three species (P. medius, Cynopterus sphinx, and Megaderma lyra) were sampled within India, and one of these species (P. medius) had evidence of viral shedding within India [40, 41] (Table 1 and Fig 2). Recent media reports suggest that additional cross-sectional surveys of bats have been conducted in response to the outbreak in Ker- ala and that P. medius tested positive by PCR [14]. In Fig 2- (See Appendix), we map detections of Nipah virus by serology or PCR onto the phylogeny of bat species found in India. Our qualitative assessment of Nipah virus detections among these species, within a phylogenetic context, suggested clustering of Nipah virus positivity within Pteropodidae, consistent with the ongoing focus of research efforts on this family. However, Nipah virus reactivity was also detected in other bat families. Moreover, some clades that contain Nipah virus-seropositive bats also contain species that occur in Kerala but have not been sampled. For example, a number of unsampled Hipposideros and Rhinolophus that occur in Kerala are members of clades that include Nipah-virus seropositive bats (Figure-2- See Appendix). Phylogeny of Indian bats and Nipah virus detections (Figure-3 See Appendix).

Likely Reservoirs

The generalized boosted regression model that we applied to species-level trait data identified Nipah virus-positive bat species with ~83% accuracy (Fig 3; corrected AUC = 0.83; complete model outputs and hyperparameters are reported in S2 and S3 Tables). In addition to Nipah virus-positive bat species, we identified six species with geographic ranges overlapping Asia, Australia, and Oceana that are not currently identified as Nipah reservoirs but, on the basis of trait similarity with known Nipah virus-seropositive or virological-positive bat species, have high likelihood of exposure to Nipah virus: Rousettus aegyptiacus, Taphozous longimanus, Taphozous melanopogon, Rhinolophus luctus, Chaerophon plicatus, and Macroglossus minimus. The geographic ranges of four of these species overlap with India: C. plicatus, R. luctus, T. longimanus, and T. melanopogon. The latter two species overlap with Kerala, with probabilities of Nipah virus-positivity ~80%. (S3 Table and Fig 4- (See Appendix); note that IUCN distribution maps erroneously include R. luctus, Murina cyclotis, Taphozous theobaldi, and Pipistrellus pipistrelles in Kerala; however, these species are not found in Kerala [58, PO Nameer personal communication, 59]). Study effort was not predictable on the basis of traits, suggesting that the trait profile of bat species that are Nipah virus-positive are not confounded by traits simply associated with well-studied species. Model hyperparameters, performance metrics, and relative importance scores for all traits are available in S2 pooled events report results from multiple time points as a single estimate

a) formerly known as Pteropus giganteus
b) The IUCN distribution maps erroneously include R. luctus, M. cyclotis, T. theobaldi, and P. pipistrellus in Kerala; however, these species are not found in Kerala [58, PO Nameer personal communication]

DISCUSSION

Our trait-based analyses identified four additional Indian bat species to target for surveillance for Nipah virus; two of these species occur within Kerala. Our predictions inform a research pipeline that should include serosurveys of these potential bat reservoirs and the 11 Indian bat species previously identified to have evidence of Nipah virus infection. Species that are sero- positive on these initial surveys should then undergo longitudinal spatiotemporal surveillance to detect shedding. Our predictions must be combined with local knowledge on bat ecology—including distribution, abundance, and proximity to humans—to design sampling plans that can effectively identify hosts that pose a risk to humans [60]. Moreover, sampling of bats should be combined with epidemiological, anthropological, ecological, immunological, and virological work to uncover the relations that drive transmission of virus from animals to humans. Nipah virus has a wide host breadth in both reservoir bat species and recipient animal species. Therefore, identifying the reservoir in a new location can be challenging. We used a systematic literature search to collate data from previous studies of Nipah virus in bats. We then prioritized surveillance of bats in Kerala, and more generally in India, on the basis of these data. We applied a trait-based generalized boosted regression that identified species with traits similar to those associated with serological or virological evidence of Nipah virus. Nipah virus was detected by PCR in only one species occurring in India, P. medius, which also is the known reservoir in Bangladesh. However, Nipah virus was detected by serology in many species. Eleven out of 112 bat species that occur in India, and seven of the 39 species that

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occur in Kerala, had serological evidence of Nipah virus exposure (most were sampled outside of India). Our work provides a list of species to guide early surveillance and should not be taken as a definitive list of reservoirs. A series of further studies are required to triangulate on the reservoir hosts that pose a risk to humans. A major reason these studies do not identify definitive reservoirs is because almost all previous Nipah virus studies relied on serology, but serological assays often lack specificity; detection of Nipah virus may represent cross-reactions to closely related viruses [61]. For example, multiple studies have shown cross reactivity among Hendra, Cedar, and Nipah viruses using glycoprotein assays [62–64]. It is likely that many of the positive tests reported here represent exposure to uncharacterized henipaviruses with antigenic similarity to Nipah virus. These viruses may or may not be zoonotic. PCR is specific and sensitive, and positive results demonstrate presence of Nipah virus RNA; however, the prevalence of Nipah virus is usually so low that large sample sizes are needed to yield positive detections [27, 65] outside of pulses of shedding [29, 36]). Therefore, PCR may not be informative in the early stages of identifying reservoirs. Serology remains an important tool for these initial surveys as long as the assays are interpreted correctly, and positive detections are followed by virological studies to detect shedding. These field surveys need to be followed by virological studies to characterize viruses and their zoonotic risk and then epidemiological studies to understand risk to public health [61]. In addition to suggesting potential reservoir species, the associative traits that predict reservoir capacity inform the ecology of potential bat reservoirs, which may guide epidemiological studies of Nipah virus infection. However, the utility of these traits as predictors of reservoir capacity should be interpreted as associative rather than causal. Some of the traits in the generalized boosted regression (see Supporting Information S2 Table) capture potential phylogenetic structure of Nipah virus hosts. For example, the relative importance of adult body length and forearm length could reflect the strong association of Nipah virus with medium to large Pteropodidae bats, although 'Pteropodidae' was not itself an important predictor. Beyond including bat families as taxonomic predictor variables, our analysis largely subsumes additional phylogenetic structure underlying patterns of Nipah virus seropositivity in bat species. It is likely that patterns of evolutionary relatedness among host species may underlie similarities in factors that determine host receptivity. Such factors may include functional receptors that enable viral entry into host cells and host factors required for viral replication [66, 67]. Patterns of co-divergence of hosts and viruses [68] are also reflected in host and viral phylogeny. The association of these traits with reservoir capacity should be elucidated by future phylogenetic comparative analyses of host traits, which will rely on expanded availability of relevant data (e.g., characterization of species level differences in functional receptors).

Other traits with high relative influence included aridity (mean precipitation [mm]/mean potential evapotranspiration [mm]), the maximum latitudinal extent of each species geo- graphic range, the richness of mammal species found within a species' geographic range, and the trophic level of each species. In general, our analysis suggests Nipah virus-positive bats in this region tend to be herbivorous or omnivorous species whose geographic ranges overlap with tropical desert (arid) habitats, maximally extending to the northern limit of the tropical belt and overlapping with a high diversity of other mammal species (S1 Fig). Given that bats from arid habitats may forage more widely when water or food resources become limited in dry years, it is also possible that Nipah virus transmission may occur with increasing contact between multiple bat species mixing at higher densities around limited resources [24]. A current constraint on progress towards understanding the epidemiology of Nipah virus in India is the dearth of virologic and taxonomic studies on bats in India. The majority of studies used for these analyses were conducted outside of India and no studies, to our knowledge, investigated Nipah virus in Kerala prior to this outbreak. India encompasses many different bioregions. The outbreak in Kerala shows that the ecological niche for Nipah virus is very wide and could include the entire distribution of P. medius, as well as the distributions of other potential reservoirs proposed here. Studies in wildlife and humans must cover this broad geography to assess future risk in India. Moreover, the last comprehensive and systematic taxonomic study on the bats in India was conducted more than a century ago. There are several cryptic species or species with unresolved taxonomic status in India, and it is possible that species with Nipah virus detections outside of India may have been misidentified. Therefore, our conclusions may change after detailed and systematic taxonomic studies are done on Indian bats. Once serological evidence of Nipah virus is detected in potential reservoir hosts, longitudinal spatial and temporal surveillance of these hosts will be necessary. Detection of virus at a single point in time and space conveys limited information and could represent a spillover event from another species. To confirm reservoirs status of a species, virus must be consistently found within that species [69].

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Moreover, maintenance of henipaviruses can be extremely dynamic. Seasonal, annual, interannual, or stochastic pulses of shedding can be driven by extinction and recolonization of virus among bat populations or episodic shedding in response to stress (see discussions in [26]). Therefore, discriminating viral maintenance versus spillover, and characterizing shedding dynamics, requires intensive sampling over time and space.

Identifying reservoir hosts and then characterizing the diversity of their viruses and their virus shedding patterns are critical steps in understanding spillover. However, the transmission of Nipah virus from bats to humans requires alignment of a number of other ecological and epidemiological factors [67], including bat and human behaviors that expose humans to an infectious dose of Nipah virus. In Bangladesh and Australia, bat and human behaviors facilitate exposure to Nipah and Hendra virus, respectively, when bats exploit human food. In Bangladesh, bats contaminate human-harvested date palm sap [7]. In Australia, bats exploit food from trees in peri-urban areas when native winter food sources are cleared [26, 70]. When pulses of virus shedding in bats coincide with bat and human or horse contact through food, spillover is more likely to occur [71]. Understanding these important interfaces requires a variety of epidemiological studies including niche and spatial risk modeling [72], as well as animal and human behavioral studies [7, 11]. In addition to sampling bat reservoir hosts, sampling plans should consider that henipaviruses could be maintained in domestic recipient hosts. These hosts, with closer and more frequent contact with humans, can become bridge hosts for human infections [36]. For example, Nipah virus was repeatedly introduced into intensive commercial pig populations in Malaysia. These repeated introductions of Nipah virus into pig farms allowed accumulation of herd immunity and the conditions for long term persistence and regional spread that facilitated transmission to humans [10]. To narrow potential spillover pathways to humans in India, studies should consider susceptible domestic animal species with husbandry that facilitates virus persistence (e.g., intensive commercial farming systems with high turnover of animals).

CONCLUSION

Projecting the risk of Nipah virus outbreaks in humans requires identification of the reservoir hosts and the dynamics of Nipah virus within those hosts. Our predictions inform initial sampling that can be followed by a sequence of studies that investigate the bat species highlighted here. The machine learning approaches presented here can be the first step in a research pipeline to eventually understand the mechanisms underpinning epidemiologically important cross-species contacts.

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APPENDIX

Figure-1: Epidemiologic curve of Nipah virus disease (NVD) outbreak, Kozhikode, Kerala, India, 2018, by date of illness onset

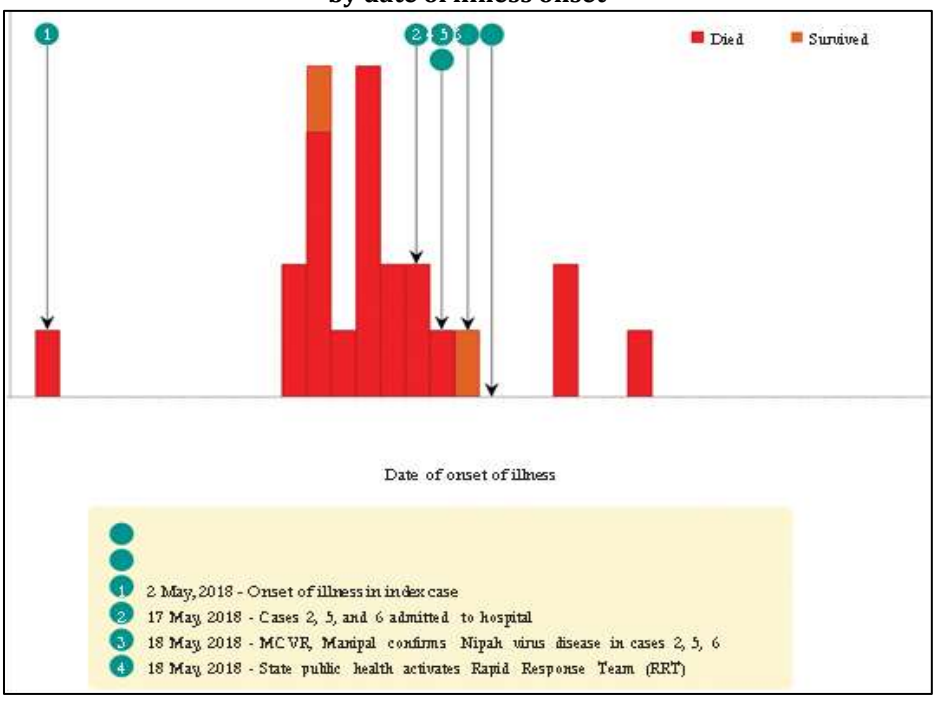

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Figure-2: Clades that include Nipah-virus seropositive bats

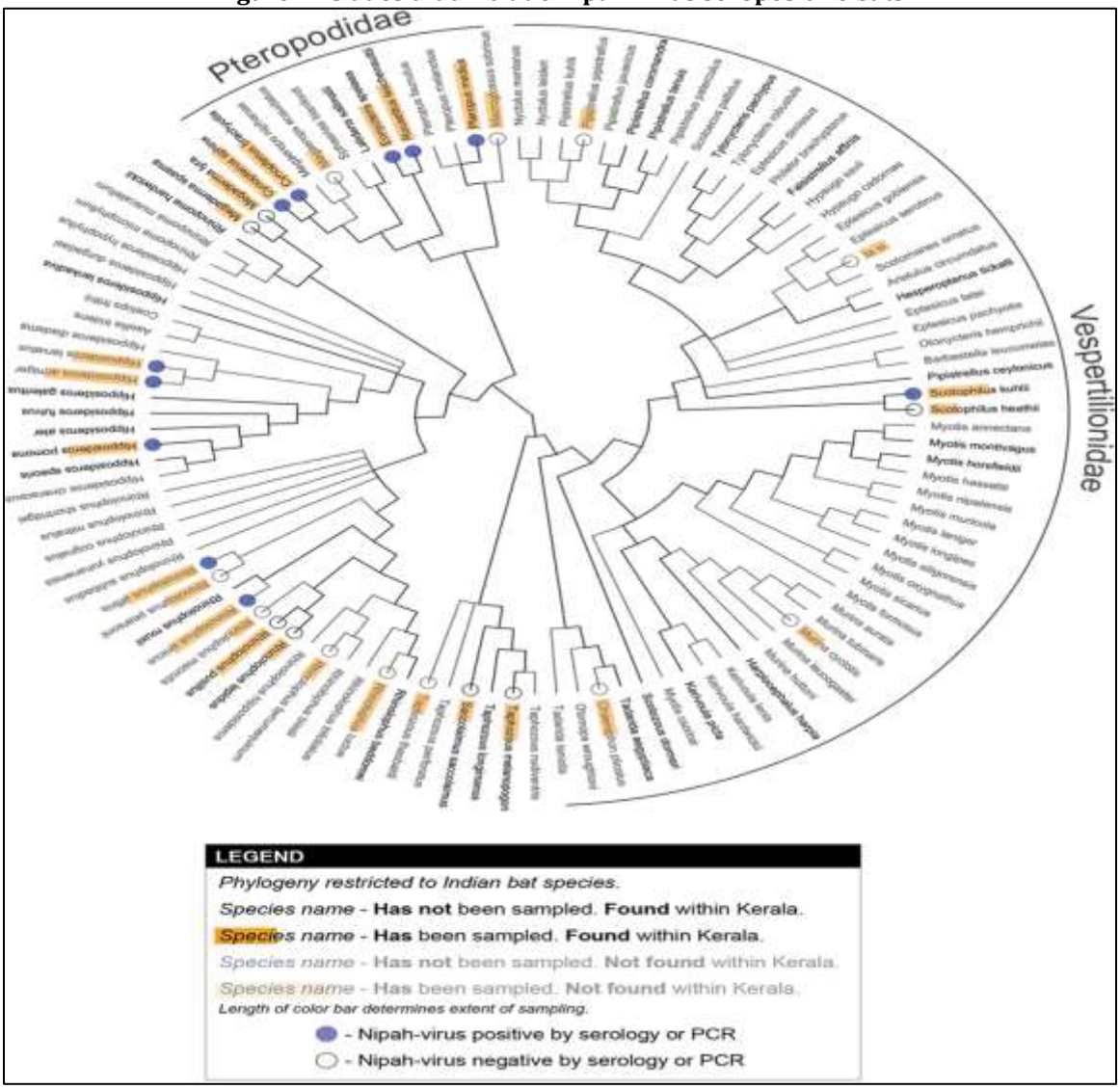

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Figure-3: Phylogeny of Indian bats and Nipah virus detections