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REVIEW ARTICLE

The Coordinating Research on Emerging Arboviral Threats Encompassing the Neotropics (CREATE-NEO)

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Abstract

Arthropod-borne viruses, such as dengue, Zika, and Mayaro, are emerging at an accelerating rate in the neotropics. The **C**oordinating **R**esearch on **E**merging **A**rboviral **T**hreats **E**ncompassing the **Neo**tropics (CREATE-NEO) project, a part of the NIH-funded Centers for Research in Emerging Infectious Diseases (CREID) network provides a nimble and flexible network of surveillance sites in Central and South America coupled with cutting-edge modeling approaches to anticipate and counter these threats to public health. Collected data and generated models will be utilized to inform and alert local, regional, and global public health agencies of enzootic arboviruses with a high risk of spillover, emergence, and transmission among humans, and/or international spread. CREATE-NEO builds capacity *in situ* to anticipate, detect, and respond to emerging arboviruses at the point of origin, thereby maximizing the potential to avert full-blown emergence and widespread epidemics.

Key words: Virus emergence, pandemics, spillover and spillback, CREATE-NEO, CREID Network

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INTRODUCTION

In recent decades, Central and South America have experienced a series of emergence events, including but not limited to the following: (a) spillover of endemic arthropod-borne viruses (arboviruses) from wildlife reservoirs into humans; (b) exchange of emerging arboviruses; (c) re-emergence of arboviruses that were previously controlled by vaccination and/or vector control; (d) introduction and spread of novel arboviruses, and (e) spread of viruses to other regions. Furthermore, there is great concern that Zika virus (ZIKV), an arbovirus introduced in the western hemisphere as early as 2013, may establish an autochthonous sylvatic transmission cycle. More broadly, the enormous vertebrate and invertebrate biodiversity of the region harbors a broad range of arboviruses, in which the risk of emergence and spread among humans is unknown. A world experiencing economic globalization, rapid population mobility facilitated by jet travel, uncontrolled urban expansion and slummification, deforestation, land use repurposing, breakdown of public health structures in countries experiencing societal, economic, and political unrest, and global climate change all exacerbate the risk of arbovirus emergence in the neotropics.

The Coordinating Research on Emerging Arboviral Threats Encompassing the Neotropics (CREATE-NEO) provides a network of surveillance sites across Central and South America that are

geographically broad, encompass hotspots of biodiversity and different degrees of urbanization, and are well-integrated with appropriate modeling techniques that anticipate, mitigate, and counter the threat posed by emerging and resurging arboviruses. Therefore, collected surveillance and epidemiologic data and generated predictive models will be leveraged to forewarn public health agencies at the local, regional, and global levels of endemic arboviruses that could pose a particularly high risk of spillover, emergence, and/or international spread. The CREATE-NEO network will also be ready to detect the introduction of novel arboviruses from other continents and swiftly respond. The overarching goal of CREATE-NEO is to build local capacity to predict, detect, and respond to emerging arboviruses at the point of origin, thereby maximizing the potential to avert full-blown emergence and large-scale epidemics across the region and beyond.

CREATE-NEO OVERVIEW

Central and South America have borne the brunt of emerging arboviruses [1]. Emergence in this context has taken multiple forms, including the spillover of enzootic arboviruses from wildlife reservoirs into humans (e.g., Oropouche {OROV} [2] and Rocio {ROCV} [3], among others), exchange of emerging arboviruses within the region (e.g., Mayaro {MAYV} [4,5], Venezuelan equine encephalitis {VEEV} [6]), re-emergence of previously controlled arboviruses (e.g., yellow fever {YFV} and dengue {DENV} [1,7-11]), and introduction and spread of novel arboviruses (e.g., West Nile virus {WNV} [12,13], chikungunya {CHIKV} [14,15], and Zika {ZIKV} [16,17]). Furthermore, Central and South America have been exporting arboviruses to other regions (e.g., Madariaga {MADV} [18]) at increasing rates as global mobility has accelerated.

Of all the recent arbovirus introductions to Central and South America, the introduction of ZIKV as early as 2013 and the consequent surge in congenital Zika syndrome constituted a true calamity for the region, particularly Brazil [19]. There is considerable concern that ZIKV may spill back into an enzootic transmission cycle among non-human primates (NHPs) in the Americas, as YFV did centuries ago [20]. Establishment of a sylvatic ZIKV cycle would complicate control of virus transmission and render ZIKV eradication from the Americas unattainable. Although it received somewhat less attention, CHIKV was also introduced to the Americas in 2013 and exploded into a massive outbreak that created a staggering burden of clinical disease [21], sometimes resulting in prolonged disability [22]. Within the last decade, WNV was also introduced to Brazil, which now faces an imminent WNV outbreak [12,13]. All three viruses are now considered endemic in the neotropics.

Over the same time period, arboviruses that had previously been controlled via vaccination (YFV) or vector control (DENV) resurged dramatically [1,7-11]. Between 2016 and 2018, Brazil experienced an outbreak of yellow fever that was shocking in magnitude (the largest since the eradication of urban yellow fever in the region) and location (on the east coast of the country), which was perilously close to the mega-cities of Sao Paolo and Rio de Janeiro [7,23,24]. The thousands of human cases of yellow fever in this outbreak are thought to have been derived entirely from sylvatic transmission from non-human primate reservoirs. Moreover, 2019 had the highest number of DENV cases in the Americas in recorded history [25]. With the exception of a well-established vaccine for YFV and a controversial vaccine for DENV [26], there are currently no licensed vaccines to protect against infection with any of these viruses, and there are no licensed antivirals to alleviate disease.

Central and South America have also recently experienced an uptick in the spillover of endemic arboviruses from wildlife reservoirs into humans. This geographic region encompasses much of the world's diversity of vertebrate hosts and arthropod vectors [27,28], and as a result, many of the world's zoonotic viruses (Fig 1). Within this context, MAYV poses a specific threat [29,30]. MAYV is maintained in a sylvatic cycle involving non-human primates and *Haemagogus* mosquitoes, but readily spills over into humans, with a clinical presentation similar to and easily mistaken for chikungunya [31]. Importantly, the range of hosts and vectors responsible for maintenance of MAYV has not been completely characterized [32]. Phylogenetic analyses have revealed an exchange of MAYV viruses between Amazonia and the Caribbean, attributable to some combination of human movement between the regions and bird migration [5,33]. Similarly, MADV, which belongs to the eastern equine encephalitis virus complex, was initially exported from Brazil to other South and Central American countries [34-37], raising fears that MADV might move further into the Caribbean or North America. Outbreaks of Oropouche fever, attributable to spillover of midge transmitted OROV, have recently occurred in Brazil and Peru [2]. This virus is known to be maintained in a sylvatic reservoir, but the key host species in this cycle are not completely known and the risk of full-blown OROV emergence into human circulation is not fully understood.

While the viruses discussed above have already demonstrated a capacity for spillover, many additional viruses have been detected in wildlife or arthropod vectors in Central and South America; however, the risk of spillover and spread is presently unknown [38-40].

Unfortunately, the arbovirus spillover and spread rates in Central and South America are likely to accelerate in the future. Deforestation, already extensive in Central and South America, is expanding, primarily for commercial agriculture [41]. Forest conversion enhances contact between humans, and sylvatic vectors and viruses at land cover edges [42], thus favoring competent arbovirus

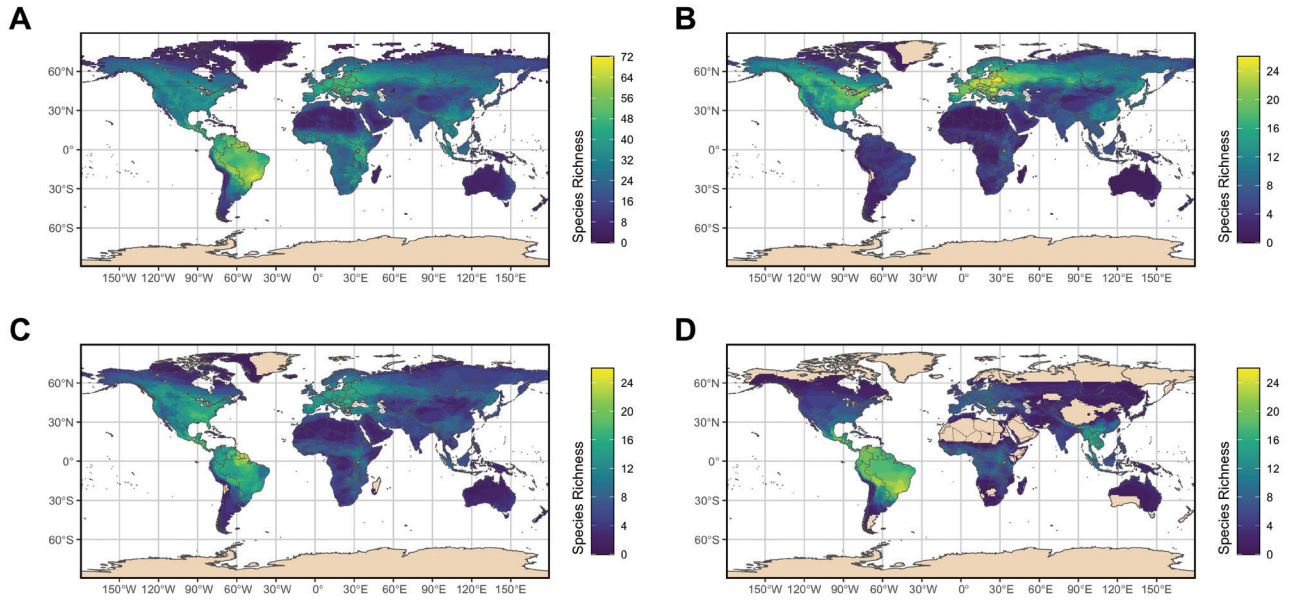

FIGURE 1 | Richness of zoonotic viruses A) across all mammal species currently associated with zoonoses, B) all mammal species associated with tick-borne diseases, C) all mammal species associated with mosquito-borne diseases, and D) all bats associated with zoonoses.

vectors [43] and precipitating arbovirus spillover [44]. Global climate change is also expected to shift vector and arbovirus distributions [45-47], and to facilitate spillover of novel arboviruses. Ongoing urbanization is clearly a boon to key urban vectors, such as *Aedes aegypti* [48] and *Ae. albopictus* [46,49], and may also promote spillover of novel arboviruses [50]. Globalization, especially transcontinental travel and relocation of humans, affords both vectors and arboviruses the opportunity to move rapidly into Central and South America from elsewhere, or conversely, from points of origin in Central and South America across the region or across the world [51-53]. For example, as of 22 September 2022, hundreds of thousands of Venezuelans have emigrated to Panama and Brazil [54]. The political, societal, and economic upheaval in Venezuela in recent decades has led to the breakdown of public health structures, which occupy a critical juncture in Central and South America, and exacerbated the resurgence and regional spread of pathogens [55-57], measles [58], malaria [59], as well as the spillover and cryptic circulation of novel pathogens [60].

There is an urgent global need for broad and integrated surveillance networks to better confront the rising threat of emerging and resurging arboviruses [61]. This need was recognized by the National Institutes of Health (NIH), with the issuance of a Funding Opportunity Announcement (FOA [RFA-AI-19-028]) on 4 April 2019, calling for the establishment of a coordinated Centers for Research on Emerging Infectious Diseases (CREID) network in regions around the globe where emerging and re-emerging infectious disease outbreaks are likely to occur. The **C**oordinating **R**esearch on **E**merging **A**rboviral **T**hreats **E**ncompassing the **Neo**tropics (CREATE-NEO), 1 of the 10 funded CREIDs, integrates arbovirus surveillance across the region with summarizing and predictive modeling efforts to better anticipate and counter arbovirus emergence (Fig 2). Since its inception, CREATE-NEO has built local capacity, including comprehensive genomic surveillance, allowing teams to detect, predict, and respond to emerging arboviruses at the point of origin. CREATE-NEO teams have been able to quickly redirect their resources to respond to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), thus allowing CREATE-NEO teams to inform local and regional policy makers and public health authorities [62-64].

The major areas of concentration for CREATE-NEO involve the following:

1. **Virus discovery in wildlife and arthropod vectors in Central and South America.** Members of CREATE-NEO have discovered, characterized, and annotated many known and new viruses in wildlife and vectors in Central and South America, select examples of which are listed below in Table 1. Additionally, our group was the first to report evidence of a natural ZIKV infection in neotropical, non-human primates in Brazil [77], and a lack of evidence for SARS-CoV-2 spillover in wild, non-human primates across several surveyed locations in Brazil [64].
2. **Development of novel diagnostic assays.** Detecting and distinguishing arbovirus infections in human populations among asymptomatic and symptomatic individuals are important CREATE-NEO activities. Without sensitive and specific diagnostics, fever symptoms can go undiagnosed or be misdiagnosed. We have developed affordable, easy-to-use, rapid, paper fluidic tests to detect and distinguish DENV and ZIKV

FIGURE 2 | Overview of CREATE-NEO surveillance of humans (human icon), vectors (mosquito icon), and wildlife (monkey icon) in Central and South America.

[79] without crossover, thus permitting unambiguous virus identification. Our partners are currently developing nanoparticle-based methods for virus detection and pandemic preparedness [80], initially targeting neglected arboviruses (e.g., Ilheus [ILHV] and ROCV viruses) with enormous potential for emergence and posing a significant impact on public health.

3. **Identification of key vectors and hosts in a regional hotspot for arbovirus spillover and spillback.** CREATE-NEO is coupling geographically- and taxonomically-broad surveillance of arthropods and vertebrates with remote sensing and machine learning to predict the distribution of both known and as-yet undiscovered host-vector networks that sustain

TABLE 1 | Examples of viruses discovered by CREATE-NEO partners in Central and South America.

Country	Host	Virus name	Virus family	Ref.
Colombia	Mosquitoes	Sinu virus	*Orthomyxoviridae*	[65]
Brazil; Trinidad & Tobago	Mosquitoes	Trinity virus	*Peribunyaviridae*	[66]
Brazil; Panama; Ecuador	Mosquitoes, birds	Gamboa serogroup	*Peribunyaviridae*	[67]
Panama	Mosquitoes	PanAr 395145 and PanAr 395144	*Peribunyaviridae*	[68]
Colombia	Mosquitoes	Chiqui virus	*Reoviridae*	[69]
Panama	mosquitos	Gamboa mosquito virus	*Flaviviridae*	[70]
Panama	Mosquitoes	Mercadeo virus	*Flaviviridae*	[71]
Peru	Mosquitoes	La Tina virus	*Flaviviridae*	[72]
Peru	Mosquitoes	Arboretum, Puerto Almendras	*Rhabdoviridae*	[73]
Colombia	Mosquitoes	Balsa virus	*Rhabdoviridae*	[39]
Panama	Mosquitoes	Rio Chico	*Rhabdoviridae*	[39]
Brazil	Amphibians	Cuiaba virus	*Rhabdoviridae*	[74]
Peru; Brazil	Mosquitoes	Piura, Loreto, and Santana viruses	*Negeviridae*	[75]
Colombia, Panama, Peru, Brazil	Mosquitoes	Wallerfield, Brejeira, and San Bernardo viruses	*Negeviridae*	[76]
Brazil	NHPs	Zika virus	*Flaviviridae*	[77]
Mexico	Mosquitoes	Zika Virus	*Flaviviridae*	[17]
Panama	Equids	Venezuelan equine encephalitis and Eastern equine encephalitis	*Togaviridae*	[78]

transmission of key arboviruses. The close integration of empirical sampling with these modeling approaches is a highly innovative aspect of the proposed work [81–85].

4. **Novel insights into arbovirus transmission and cross-protection from clinical studies.** CREATE-NEO leverages ongoing human cohorts in geographically-, demographically-, and ecologically-distinct regions in Central and South America that are hyper-endemic for various constellations of arboviruses to gain insight into how pre-existing immunity influences clinical outcomes upon infection. Understanding this interplay between different arboviruses mediated by cross-protection or enhancement is a highly innovative aspect of the proposed work that will influence vaccine design, enhance vaccine efficacy, and predict the risk of future arbovirus epidemics.

CONCLUSION

CREATE-NEO is responding to the rising threat of emerging arboviruses in the Americas by linking a group of Brazilian, Panamanian, and US scientists into a network that integrates arbovirus surveillance in vectors, wildlife, and humans across Central and South America. The data generated are analyzed with cutting-edge phylogenetic, statistical, and modeling approaches to better anticipate and counter arbovirus emergence. Close relationships with local, regional, and global public health agencies allow the timely transfer of information on emerging arboviruses to agencies tasked with responding to such events; however, our ultimate goal is to head off emergence events at the source by building local capacity within Panama and Brazil that will expand the already impressive abilities at these sites to collect and assay key samples *in situ*.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Marcondes CB, Contigiani M, Gleiser RM. Emergent and reemergent arboviruses in South America and the Caribbean: why So Many and Why Now? J Med Entomol. 2017;54(3):509-532.
2. Romero-Alvarez D, Escobar LE. Oropouche fever, an emergent disease from the Americas. Microbes Infect. 2018;20(3):135-146.
3. de Souza Lopes O, Coimbra TL, de Abreu Sacchetta L, Calisher CH. Emergence of a new arbovirus disease in Brazil. I. isolation and characterization of the etiologic agent, Rocio virus. Am J Epidemiol. 1978;107(5):444-449.
4. Mavian C, Rife BD, Dollar JJ, Cella E, Ciccozzi M, Prosperi MCF, et al. Emergence of recombinant Mayaro virus strains from the Amazon basin. Sci Rep. 2017;7(1):8718.

5. Calisher CH, Gutiérrez E, Maness KS, Lord RD. Isolation of Mayaro virus from a migrating bird captured in Louisiana in 1967. Bull Pan Am Health Organ. 1974;8(3):243-248.
6. Scherer WF, Dickerman RW, Ordonez JV, Seymour C, 3rd, Kramer LD, Jahrling PB, et al. Ecologic studies of Venezuelan encephalitis virus and isolations of Nepuyo and Patois viruses during 1968-1973 at a marsh habitat near the epicenter of the 1969 outbreak in Guatemala. Am J Trop Med Hyg. 1976;25(1):151-162.
7. Faria NR, Kraemer MUG, Hill SC, Goes de Jesus J, Aguiar RS, Iani FCM, et al. Genomic and epidemiological monitoring of Yellow Fever virus transmission potential. Science. 2018;361(6405):894-899.
8. Kallas EG, D'Elia Zanella LGFAB, Moreira CHV, Buccheri R, Diniz GBF, Castiñeiras ACP, et al. Predictors of mortality in patients with Yellow Fever: an observational cohort study. Lancet Infect Dis. 2019;19(7):750-758.
9. Cunha MS, da Costa AC, de Azevedo Fernandes NCC, Guerra JM, Dos Santos FCP, Nogueira JS, et al. Epizootics due to Yellow Fever virus in Sao Paulo State, Brazil: viral dissemination to new areas (2016-2017). Sci Rep. 2019;9(1):5474.
10. Pinheiro TM, Mota MTO, Watanabe ASA, Biselli-Périco JM, Drumond BP, Ribeiro MR, et al. Viral immunogenicity determines epidemiological fitness in a cohort of DENV-1 infection in Brazil. PLoS Negl Trop Dis. 2018;12(5):e0006525.
11. Williams M, Mayer SV, Johnson WL, Chen R, Volkova E, Vilcarromero S, et al. Lineage II of Southeast Asian/American DENV-2 Is Associated with a Severe Dengue Outbreak in the Peruvian Amazon. Am J Trop Med Hyg. 2014;91:611-620.
12. Silva ASG, Matos ACD, da Cunha MACR, Rehfeld IS, Galinari GCF, Marcelino SAC, et al. West Nile virus associated with equid encephalitis in Brazil, 2018. Transbound Emerg Dis. 2019;66(1):445-453.
13. Castro-Jorge LA, Siconelli MJL, Ribeiro BDS, Moraes FM, Moraes JB, Agostinho MR, et al. West Nile virus infections are here! Are we prepared to face another flavivirus epidemic? Rev Soc Bras Med Trop. 2019;52:e20190089.
14. Weaver SC, Lecuit M. Chikungunya virus and the global spread of a mosquito-borne disease. N Engl J Med. 2015;372(13):1231-1239.
15. Naveca FG, Claro I, Giovanetti M, de Jesus JG, Xavier J, Iani FCM, et al. Genomic, epidemiological and digital surveillance of chikungunya virus in the Brazilian Amazon. PLoS Negl Trop Dis. 2019;13(3):e0007065.
16. Aliota MT, Bassit L, Bradrick SS, Cox B, Garcia-Blanco MA, Gavegnano C, et al. Zika in the Americas, year 2: what have we learned? What gaps remain? A report from the Global Virus Network. Antiviral Res. 2017;144:223-246.
17. Guerbois M, Fernandez-Salas I, Azar SR, Danis-Lozano R, Alpuche-Aranda CM, Leal G, et al. Outbreak of Zika Virus Infection, Chiapas State, Mexico, 2015, and First Confirmed Transmission by Aedes aegypti Mosquitoes in the Americas. J Infect Dis. 2016;214(9):1349-1356.
18. Silva MLCR, Auguste AJ, Terzian ACB, Vedovello D, Riet-Correa F, Macário VMK, et al. Isolation and characterization of Madariaga virus from a horse in Paraiba State, Brazil. Transbound Emerg Dis. 2017;64(3):990-993.
19. Gubler DJ, Vasilakis N, Musso D. History and emergence of Zika virus. J Infect Dis. 2017;216(suppl_10):S860-S867.
20. Althouse BM, Vasilakis N, Sall AA, Diallo M, Weaver SC, Hanley KA. Potential for Zika virus to establish a sylvatic transmission cycle in the Americas. PLoS Negl Trop Dis. 2016;10(12):e0005055.
21. Moreira J, Bressan CS, Brasil P, Siqueira AM. Epidemiology of acute febrile illness in Latin America. Clin Microbiol Infect. 2018;24(8):827-835.
22. Ali S, Gugliemini O, Harber S, Harrison A, Houle L, Ivory J, et al. Environmental and social change drive the explosive emergence of Zika virus in the Americas. PLoS Negl Trop Dis. 2017;11(2):e0005135.
23. Silva NIO, Sacchetto L, de Rezende IM, Trindade GS, LaBeaud AD, de Thoisy B, et al. Recent sylvatic Yellow Fever virus transmission in Brazil: the news from an old disease. Virol J. 2020;17(1):9.
24. Sacchetto L, Silva NIL, Rezende IM, Arruda MS, Costa TA, Mello EM, et al. Neighbor danger: Yellow Fever virus epizootics in urban and urban-rural transition areas of Minas Gerais state, during 2017-2018 Yellow Fever outbreaks in Brazil. PLoS Negl Trop Dis. 2020;14(10):e0008658.
25. PAHO. Dengue in the Americas reaches highest number of cases recorded. In *PAHO*. 2019.
26. Halstead SB. Dengvaxia sensitizes seronegatives to vaccine enhanced disease regardless of age. Vaccine. 2017;35(47):6355-6358.
27. Rylands AB, Mittermeier RA. The diversity of the new world primates (Platyrrhini): an annotated taxonomy. In *South American Primates: Comparative Perspectives in the Study of Behavior, Ecology, and Conservation*. Edited by Garber PA, Estrada A, Bicca-Marques JC, Heymann EW, Strier KB. New York: Springer; 2009:23-54.
28. Antonelli A, Zizka A, Carvalho FA, Scharn R, Bacon CD, Silvestro D, et al. Amazonia is the primary source of neotropical biodiversity. Proc Natl Acad Sci U S A. 2018;115(23):6034-6039.
29. Esposito DLA, Fonseca BALD. Will Mayaro virus be responsible for the next outbreak of an arthropod-borne virus in Brazil? Braz J Infect Dis. 2017;21(5):540-544.
30. Mackay IM, Arden KE. Mayaro virus: a forest virus primed for a trip to the city? Microbes Infect. 2016;18(12):724-734.
31. Figueiredo ML, Figueiredo LT. Emerging alphaviruses in the Americas: chikungunya and Mayaro. Rev Soc Bras Med Trop. 2014;47(6):677-683.
32. Celone M, Okech B, Han BA, Forshey BM, Anyamba A, Dunford J, et al. A systematic review and meta-analysis of the potential non-human animal reservoirs and arthropod vectors of the Mayaro virus. PLoS Negl Trop Dis. 2021;15(12):e0010016.
33. Terzian AC, Auguste AJ, Vedovello D, Ferreira MU, da Silva-Nunes M, Sperança MA, et al. Isolation and characterization of Mayaro virus from a human in Acre, Brazil. Am J Trop Med Hyg. 2015;92(2):401-404.
34. Benvenuto D, Cella E, Fogolari M, De Florio L, Borsetti A, Donati D, et al. The transmission dynamic of Madariaga virus by bayesian phylogenetic analysis: molecular surveillance of an emergent pathogen. Microb Pathog. 2019;132:80-86.
35. Luciani K, Abadía I, Martínez-Torres AO, Cisneros J, Guerra I, García M, et al. Madariaga virus infection associated with a case of acute disseminated encephalomyelitis. Am J Trop Med Hyg. 2015;92(6):1130-1132.
36. Vittor AY, Armien B, Gonzalez P, Carrera JP, Dominguez C, Valderrama A, et al. Epidemiology of Emergent Madariaga Encephalitis in a Region with Endemic Venezuelan Equine Encephalitis: Initial Host Studies and Human Cross-Sectional Study in Darien, Panama. PLoS Negl Trop Dis. 2016;10(4):e0004554.
37. Carrera JP, Bagamian KH, Travassos da Rosa AP, Wang E, Beltran D, Gundaker ND, et al. Human and equine infection with alphaviruses and flaviviruses in Panama during 2010: a Cross-sectional study of household contacts during an encephalitis outbreak. Am J Trop Med Hyg. 2018;98(6):1798-1804.
38. Catenacci LS, Ferreira M, Martins LC, De Vleeschouwer KM, Cassano CR, Oliveira LC, et al. Surveillance of arboviruses in primates and sloths in the Atlantic Forest, Bahia, Brazil. Ecohealth. 2018;15(4):777-791.
39. Contreras MA, Eastwood G, Guzman H, Popov V, Savit C, Uribe S, et al. Almendravirus: a proposed new genus of rhabdoviruses isolated from mosquitoes in tropical regions of the Americas. Am J Trop Med Hyg. 2017;96(1):100-109.
40. Marklewitz M, Dutari LC, Paraskevopoulou S, Page RA, Loaiza JR, Junglen S. Diverse novel phleboviruses in sandflies

from the Panama Canal area, Central Panama. J Gen Virol. 2019;100(6):938-949.
41. FAO. *State of the World's Forests 2016*. Rome: Food and Agriculture Organization of the United Nations; 2016:1-126.
42. Faust CL, McCallum HI, Bloomfield LSP, Gottdenker NL, Gillespie TR, Torney CJ, et al. Pathogen spillover during land conversion. Ecol Lett. 2018;21(4):471-483.
43. Burkett-Cadena ND, Vittor AY. Deforestation and vector-borne disease: forest conversion favors important mosquito vectors of human pathogens. Basic Appl Ecol. 2018;26:101-110.
44. Jones BA, Grace D, Kock R, Alonso S, Rushton J, Said MY, et al. Zoonosis emergence linked to agricultural intensification and environmental change. Proc Natl Acad Sci U S A. 2013;110(21):8399-8404.
45. Tabachnick WJ. Climate change and the arboviruses: lessons from the evolution of the dengue and Yellow Fever viruses. Annu Rev Virol. 2016;3(1):125-145.
46. Kraemer MUG, Reiner RC, Brady OJ, Messina JP, Gilbert M, Pigott DM, et al. Past and future spread of the arbovirus vectors Aedes aegypti and Aedes albopictus. Nat Microbiol. 2019;4(5):854-863.
47. Fouque F, Reeder JC. Impact of past and on-going changes on climate and weather on vector-borne diseases transmission: a look at the evidence. Infect Dis Poverty. 2019;8(1):51.
48. Carvalho FD, Moreira LA. Why is Aedes aegypti linnaeus so successful as a species? Neotrop Entomol. 2017;46(3):243-255.
49. Messina JP, Brady OJ, Golding N, Kraemer MUG, Wint GRW, Ray SE, et al. The current and future global distribution and population at risk of dengue. Nat Microbiol. 2019;4(9):1508-1515.
50. Hassell JM, Begon M, Ward MJ, Fèvre EM. Urbanization and disease emergence: dynamics at the wildlife-livestock-Human interface. Trends Ecol Evol. 2017;32(1):55-67.
51. Mayer SV, Tesh RB, Vasilakis N. The emergence of arthropod-borne viral diseases: a global prospective on dengue, chikungunya and Zika fevers. Acta Trop. 2017;166:155-163.
52. Rezza G. Dengue and chikungunya: long-distance spread and outbreaks in naive areas. Pathog Glob Health. 2014;108(8):349-355.
53. Ryan SJ, Carlson CJ, Mordecai EA, Johnson LR. Global expansion and redistribution of Aedes-borne virus transmission risk with climate change. PLoS Negl Trop Dis. 2019;13(3):e0007213.
54. Anonymous. Refugees and Migrants from Venezuela. (November 21, 2022).
55. Rodríguez-Morales AJ, Suárez JA, Risquez A, Cimerman S, Valero-Cedeño N, Cabrera M, et al. In the eye of the storm: infectious disease challenges for border countries receiving Venezuelan migrants. Travel Med Infect Dis. 2019;30:4-6.
56. Paniz-Mondolfi AE, Tami A, Grillet ME, Márquez M, Hernández-Villena J, Escalona-Rodríguez MA, et al. Resurgence of vaccine-preventable diseases in Venezuela as a regional public health threat in the Americas. Emerg Infect Dis. 2019;25(4):625-632.
57. Grillet ME, Hernández-Villena JV, Llewellyn MS, Paniz-Mondolfi AE, Tami A, Vincenti-Gonzalez MF, et al. Venezuela's humanitarian crisis, resurgence of vector-borne diseases, and implications for spillover in the region. Lancet Infect Dis. 2019;19(5):e149-e161.
58. Elidio GA, Franca GVA, Pacheco FC, Ferreira MM, Pinheiro JDS, Campos EN, et al. Measles outbreak: preliminary report on a case series of the first 8,070 suspected cases, Manaus, Amazonas state, Brazil, February to November 2018. Euro Surveill. 2019;24(2):1800663.
59. Rodríguez-Morales AJ, Suárez JA, Risquez A, Villamil-Gómez WE, Paniz-Mondolfi A. Consequences of Venezuela's massive migration crisis on imported malaria in Colombia, 2016-2018. Travel Med Infect Dis. 2019;28:98-99.
60. Page KR, Doocy S, Reyna Ganteaume F, Castro JS, Spiegel P, Beyrer C. Venezuela's public health crisis: a regional emergency. Lancet. 2019;393(10177):1254-1260.
61. Bloom DE, Cadarette D. Infectious disease threats in the twenty-First century: strengthening the global response. Front Immunol. 2019;10:549.
62. Banho CA, Sacchetto L, Campos GRF, Bittar C, Possebon FS, Ullmann LS, et al. Impact of SARS-CoV-2 Gamma lineage introduction and COVID-19 vaccination on the epidemiological landscape of a Brazilian city. Commun Med (Lond). 2022;2:41.
63. Estofolete CF, Banho CA, Campos GRF, Marques BC, Sacchetto L, Ullmann LS, et al. Case study of Two Post vaccination SARS-CoV-2 infections with P1 variants in CoronaVac vaccinees in Brazil. Viruses. 2021;13(7):1237.
64. Sacchetto L, Chaves BA, Costa ER, de Menezes Medeiros AS, Gordo M, Araújo DB, et al. Lack of evidence of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spillover in free-living neotropical non-human primates, Brazil. Viruses. 2021;13(10):1933.
65. Contreras-Gutiérrez MA, Nunes MRT, Guzman H, Uribe S, Suaza Vasco JD, Cardoso JF, et al. Sinu virus, a novel and divergent orthomyxovirus related to members of the genus Thogotovirus isolated from mosquitoes in Colombia. Virology. 2017;501:166-175.
66. Lima JA, Nunes Neto JP, Castro KS, Travassos da Rosa APA, Tesh R, Nunes MRT, et al. Characterization of Triniti virus supports its reclassification in the family Peribunyaviridae. J Gen Virol. 2019;100(2):137-144.
67. Chiang JO, Marciel de Souza W, Teixeira Nunes MR, Acrani GO, Paes de Andrade Travassos da Rosa A, Mesquita de Freitas N, et al. Characterization of the Gamboa virus serogroup (Orthobunyavirus Genus, Peribunyaviridae Family). Am J Trop Med Hyg. 2018;98(5):1502-1511.
68. Rogers MB, Gulino KM, Tesh RB, Cui L, Fitch A, Unnasch TR, et al. Characterization of five unclassified orthobunyaviruses (Bunyaviridae) from Africa and the Americas. J Gen Virol. 2017;98(9):2258-2266.
69. Contreras-Gutiérrez MA, Guzman H, Cardoso JF, Popov VL, Nunes MRT, Uribe S, et al. Genome sequence of Chiqui virus, a Novel reovirus isolated from mosquitoes collected in Colombia. Microbiol Resour Announc. 2018;7(12):e00881-e00818.
70. Shi M, Lin XD, Vasilakis N, Tian JH, Li CX, Chen LJ, et al. Divergent viruses discovered in arthropods and vertebrates revise the evolutionary history of the flaviviridae and related viruses. J Virol. 2016;90(2):659-669.
71. Carrera JP, Guzman H, Beltrán D, Díaz Y, López-Vergès S, Torres-Cosme R, et al. Mercadeo virus: a Novel mosquito-specific flavivirus from Panama. Am J Trop Med Hyg. 2015;93(5):1014-1019.
72. Guzman H, Contreras-Gutierrez MA, Travassos da Rosa APA, Nunes MRT, Cardoso JF, Popov VL, et al. Characterization of three new insect-specific flaviviruses: their relationship to the mosquito-Borne flavivirus pathogens. Am J Trop Med Hyg. 2018;98(2):410-419.
73. Vasilakis N, Castro-Llanos F, Widen SG, Aguilar PV, Guzman H, Guevara C, et al. Arboretum and Puerto Almendras viruses: two novel rhabdoviruses isolated from mosquitoes in Peru. J Gen Virol. 2014;95(Pt 4):787-792.
74. Vasilakis N, Tesh RB, Widen SG, Mirchandani D, Walker PJ. Genomic characterisation of Cuiaba and Charleville viruses: arboviruses (family Rhabdoviridae, genus Sripuvirus) infecting reptiles and amphibians. Virus Genes. 2019;55(1):87-94.
75. Vasilakis N, Forrester NL, Palacios G, Nasar F, Savji N, Rossi SL, et al. Negevirus: a proposed new taxon of insect-specific viruses with wide geographic distribution. J Virol. 2013;87(5):2475-2488.
76. Nunes MRT, Contreras-Gutierrez MA, Guzman H, Martins LC, Barbirato MF, Savit C, et al. Genetic characterization, molecular epidemiology, and phylogenetic relationships of insect-specific viruses in the taxon Negevirus. Virology. 2017;504:152-167.

77. Terzian ACB, Zini N, Sacchetto L, Rocha RF, Parra MCP, Del Sarto JL, et al. Evidence of natural Zika virus infection in neotropical non-human primates in Brazil. Sci Rep. 2018;8(1):16034.
78. Carrera JP, Forrester N, Wang E, Vittor AY, Haddow AD, López-Vergès S, et al. Eastern equine encephalitis in Latin America. N Engl J Med. 2013;369(8):732-744.
79. Bosch I, de Puig H, Hiley M, Carré-Camps M, Perdomo-Celis F, Narváez CF, et al. Rapid antigen tests for dengue virus serotypes and Zika virus in patient serum. Sci Transl Med. 2017;9(409):eaan1589.
80. de Puig H, Bosch I, Salcedo N, Collins JJ, Hamad-Schifferli K, Gehrke L. Multiplexed rapid antigen tests developed using multicolored nanoparticles and cross-reactive antibody pairs: implications for pandemic preparedness. Nano Today. 2022;47:101669.
81. Hendy A, Hernandez Acosta E, Valério D, Mendonça C, Rodrigues E, Júnior JTA, et al. The vertical stratification of known and potential vectors of sylvatic arboviruses at the Adolpho Ducke forest reserve in Manaus. Brazil Sci Rep. 2020;10(1):18254.
82. Hendy A, Hernandez-Acosta E, Chaves BA, Fé NF, Valério D, Mendonça C, et al. Into the woods: changes in mosquito community composition and presence of key vectors at increasing distances from the urban edge in urban forest parks in Manaus, Brazil. Acta Trop. 2020;206:105441.
83. Hendy A, Valério D, Fé NF, Hernandez-Acosta E, Mendonça C, Andrade E, et al. Microclimate and the vertical stratification of potential bridge vectors of mosquito-borne viruses captured by nets and ovitraps in a central Amazonian forest bordering Manaus, Brazil. Sci Rep. 2021;11(1):21129.
84. Silva NIO, Albery GF, Arruda MS, Oliveira GG, Costa TA, de Mello ÉM, et al. Ecological drivers of sustained enzootic Yellow Fever virus transmission in Brazil, 2017-2021. bioRxiv. 2022:2022.10.19.512702.
85. Fischhoff IR, Castellanos AA, Rodrigues J, Varsani A, Han BA. Predicting the zoonotic capacity of mammal species for SARS-CoV-2. Proc Biol Sci. 2021;288:20211651.

Dr. Nikos Vasilakis is currently a professor with tenure and Vice Chair for Research in the Department of Pathology at the University of Texas Medical Branch (UTMB) in Galveston, TX. He earned his BA and MA degrees in biology from Hofstra University and his PhD in experimental pathology from UTMB. He worked for a number of years in the pharmaceutical industry, where he developed vaccine candidates for pediatric diseases based on alphavirus gene delivery systems. His collaborative research program has been at the vanguard of research on the ecology and evolution of arboviruses and their vectors, as well as their pathogenesis, virus–mosquito, and virus–host interactions, for which our experimental studies have led to over 180 peer-reviewed publications (i10-index = 136). He has been recognized by Clarivate as a highly cited researcher continuously since 2019 and as World's Top 2% Scientist by the 2022 Stanford University Annual Influence Ranking. As a senior faculty member of the World Reference Center for Emerging Viruses and Arboviruses (WRCEVA), he utilizes next generation sequencing (NGS) to discover, characterize, and annotate new and novel viruses that could lead to the development of successful countermeasures for a number of veterinary and human diseases. He was awarded in 2009 with the Young Investigator Award and elected as chair of the American Committee on Arthropod-borne Viruses (ACAV) and as fellow of the American Society of Tropical Medicine and Hygiene, in 2015 and 2016, respectively. His research program is supported by grants by the National Institutes of Health and pharmaceutical industry contracts. His currently funded Centers for Research in Emerging Infectious Diseases (CREID), The **C**oordinating **R**esearch on **E**merging **A**rboviral **T**hreats **E**ncompassing the **N**eotropics (CREATE-NEO) (Hanley and Vasilakis co-PIs), provides a nimble and flexible network of surveillance sites in Central and South America coupled to cutting-edge modeling approaches in order to anticipate and counter emerging arboviruses.

For her entire career, **Dr. Kathryn A. Hanley** has been fascinated by the interactions between hosts and pathogens, and how these interactions shape pathogen transmission and virulence. Kathy graduated *magna cum laude* with a major in biology from Amherst College, and she completed her PhD in biology at the University of California, San Diego. She did her post-doctoral research at the University of California, Davis, the University of Maryland, and the National Institutes of Health (NIH), where she participated in the development of the NIH dengue virus vaccine. Since joining the New Mexico State University in 2004, her lab has been at the forefront of research on the ecology and evolution of viruses transmitted by Aedes mosquitoes, including dengue, Zika, chikungunya, and yellow fever virus. They have conducted groundbreaking field research on the ecology, spillover, and spillback of sylvatic arboviruses and their vectors around the world. They have also made significant advances via laboratory studies on arbovirus evolution and on the interaction between arboviruses and the mosquito RNA interference response. More recently, they have launched a study of the ecology and emergence of vesicular stomatitis virus. Kathy is currently a regents professor of biology at NMSU and a visiting scientist at the Cary Institute of Ecosystem Studies. She is a past president of the Rio Grande branch of the American Society for Microbiology and a past chair of the American Committee on Arthropod-borne Viruses (ACAV). She is the recipient of the ACAV Dalrymple-Young award for research excellence and the NMSU College of Arts and Sciences award for excellence in graduate student mentorship. She is currently a co-principal investigator of CREATE-NEO (Coordinating Research on Emerging Arboviral Disease Threats Encompassing the Neotropics), one of ten NIH-funded centers for research on emerging infectious diseases.