Vector-Borne Diseases Systems Ecology in the Context of Climate Change: Understanding Transmission of Arthropod-Borne Pathogens Across Biological & Ecological Scales

A Virtual Workshop Sponsored by the Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
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Meeting Report

NIH National Institute of Allergy and Infectious Diseases

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Executive Summary

Organizers from the Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), brought together vector-borne disease (VBD) and data science experts to explore how systems biology (SysBio) can be applied to better understand VBDs within the ecosystems and environment in which those diseases exist. In accordance with NIAID's goals, the virtual workshop promoted communication and multidisciplinary collaboration among VBD and data science researchers, highlighted existing and needed resources, and identified opportunities to better understand applying SysBio and data science to ecological systems and environmental factors to improve VBD prevention and control.

Meeting Summary

SysBio tools and methods provide a unique perspective on the complexity of molecular interactions at the cellular, organ, and organism levels. These tools and methods can be applied at larger "scales" to better understand the complexity of VBDs within the ecosystems and environment in which those diseases exist. The relationships among pathogens, arthropod vectors, vertebrate hosts, and environmental factors (humidity, temperature, climate) strongly influence disease transmission as well as the effectiveness of preventative applications. Understanding these complex interactions is essential to prevent and control VBDs.

Workshop organizers provided a multidisciplinary environment for learning and discussion among VBD and data science experts. The workshop goals were to:

- Focus on VBDs at both the biological and ecological scales and consider how environmental conditions have an impact on the transmission of these diseases.
- Emphasize the application of data science principles as one way to study the complexity of these interactions.
- Identify gaps, challenges, and opportunities to better understand the ecological systems and environmental factors that influence the transmission of vector-borne pathogens.
- Develop a road map to address these challenges and improve VBD prevention and control.

The workshop took place over two days: Day 1 consisted of a keynote address, followed by oral presentations by investigators who study arboviruses, malaria, and tick-borne diseases. A Q&A/discussion session followed each presentation. Day 2 focused on how data science approaches—in particular, data integration and software/tool sharing—can contribute to the development of predictive models that provide actionable information. After a panel discussion on data integration and tool sharing, attendees divided into breakout groups that discussed one of two topics: 1) data integration priorities for modeling VBD across scales or 2) priorities for software, tools, and workflows for VBD modeling. Each group included a moderator and a rapporteur. These sessions were followed by a plenary discussion of breakout group findings and a panel discussion and reactions to those findings.

Appendix A contains the workshop agenda; Appendix B, speaker biographies; and Appendix C, a list of selected key publications.

June 22

Welcome by Adriana Costero-Saint Denis, DMID, NIAID

Dr. Costero-Saint Denis welcomed attendees to the virtual workshop and acknowledged the other NIAID organizers: Reed Shabman, DMID; Meghan Hartwick, Office of Data Science and Emerging Technologies (ODSET); and Wilbert Van Panhuis, ODSET. Dr. Costero-Saint Denis said the purpose of the workshop was to bring together experts in VBDs and data science to:

- Create a multidisciplinary environment for discussing VBDs at the biological and ecological scales.
- Understand how environmental conditions have an impact on disease transmission.
- Examine the role of data science principles in studying these complex interactions.

Dr. Costero-Saint Denis explained that the workshop was third in a series. The first workshop in 2021 focused on the pathogen-vector interactions scale. The second in 2022 applied systems approaches to study the complexity of pathogen-vector interactions. The current workshop aimed to look at VBD interactions at the pathogen-vector level, the ecological level, and the systems level. The workshop was associated with the NIH Climate Change and Health Initiative, an agencywide effort that includes funding opportunities and involves most NIH Institutes and Centers.

Session 1: Keynote

Scaling Forecasts to Matter: Vector-Borne Disease in a Changing World
Shannon LaDeau, Cary Institute of Ecosystem Studies

Dr. LaDeau addressed the complexities and uncertainties of predicting VBD emergence and transmission. She explained that most of researchers' current knowledge is through retrospective analyses—scientists know where pathogens emerge and can study the complex ecological conditions (e.g., deforestation, warming climate) that led to that emergence. The capacity to predict where and when VBDs will emerge next or become more endemic is still elusive.

The objective of ecological forecasts is to facilitate preparation, surveillance, and control, said Dr. LaDeau. When making predictions, researchers need to balance the tradeoff between precision vs. accuracy. For example, researchers might predict where emergent arboviral transmission to humans is most likely through determining where suitable habitat for a vector species occurs combined with where vectors are observed. The scaling may not be precise, but it is accurate enough to guide further research that scales in to where risk of local transmission to humans is high enough to warrant investment in preparation, surveillance, and control.

Dr. LaDeau emphasized the complexities of tracing back from ecological details during the life stages of a vector (mosquitoes, ticks). Information includes the environmental conditions and food sources at each life stage, and what vectors come in contact with after they emerge. Once emergence has occurred, human behavior comes into play.

Dr. LaDeau cited two intervention studies at the neighborhood scale to illustrate these complexities. One study in Baltimore tested whether mosquito populations can be reduced at the

block level by removing juvenile mosquito habitat (old tires, water pails, etc.) (D. Bodner (MS), LaDeau & Leisnham 2018). Results showed that the intervention did not decrease the mosquito population.

The second study in Duchess County, New York, tested whether Lyme disease incidents decreased meaningfully when tick populations were reduced using two commonly marketed strategies—bait boxes and fungal spray (Ostfeld, Keesing et al., Pathogens 2023; Keesing, Ostfeld et al., EID 2022; Ostfeld, Keesing et al., VBZD 2023). The number of nymphal ticks declined most significantly (about 50 percent) with bait boxes. Fungal spray was associated with a lower prevalence of nymphal ticks infected with Borrelia. Yards treated with both interventions saw no significant change in nymphal infection. Although the interventions resulted in fewer pet cases of Lyme disease infection in yards treated with either intervention, this did not translate to humans. There was no difference in numbers of humans infected across the study period.

Dr. LaDeau reemphasized the complexities of tracing ecological details through a vector's life cycle until a human bite occurs. Ticks, for example, must feed on animals, and the identity of those animals can change as the tick ages. The hosts can also move ticks to different locations. She noted that a forecasting model is being developed by Dr. John Foster (Cary Institute of Ecosystem Studies) that accounts for ticks' life stages, including what they feed on, and the climate and abiotic interactions at each stage. She cited the inability to predict precipitation as a persistent limitation in going beyond presence/absence forecasting to determine a vector's population size.

Dr. LaDeau concluded by challenging two concepts: 1) Researchers must produce observations that are able to be generalized and 2) Context-information cannot produce good predictions. She quoted Dr. Alkistis Elliot-Graves' statement that ecologists "need to be happier about making bad predictions" (Philosophy of Science Talk, GRC 2023). Predictions are needed to translate science into action, but also to refine researchers' understanding.

Because predictions can be high-stakes and urgent, researchers need:

- A standardized framework for defining objectives and acknowledging assumptions in research products.
- A community of practice that values predictions even when they are inaccurate/imprecise or incorrect.

Q&A/Discussion

In response to an audience question, Dr. LaDeau confirmed that the intervention used in the Baltimore study was to remove a substantial number of water-holding mosquito habitat containers (tires, cans, etc.).

One attendee commented that correlating the density of vectors to disease prevalence is sometimes misleading. Even if researchers can reduce the population of vectors, that may not translate directly to disease prevalence. Dr. LaDeau responded that the data in field vector systems often do not back up the principle that vector density is an important predictor of risk or

disease prevalence. She cited the high West Nile virus pools in mosquitoes across Baltimore, with no reported human cases. Finding the disease in the mosquitoes is not really associated with human infection. The flip side is shown in Zika data where researchers never found Zika in the mosquito pools tested, even when new human cases appeared. The time lag between testing for density in mosquito pools and the appearance of human cases makes it difficult to connect the two.

An audience member asked how and where Dr. LaDeau's Baltimore team counted mosquitoes before and after the intervention. She replied that researchers used one B-G Sentinel trap for every 50 meters, plus six other traps spread out over the same range where mosquitoes could enter the trap but could not get back out.

A meeting participant asked Dr. LaDeau whether vector abundance in urban environments decreases as the spatial extent of intervention increases. Dr. LaDeau noted that some of the blocks in the Baltimore study had roofless abandoned houses with trees growing out of them that were collecting water. Her team's research took place over blocks with different levels of abandonment. When there were no roofless abandoned buildings and the team could get rid of all water-holding container habitat, the intervention was effective. When researchers could not get rid of container habitat at the block level, intervention was not effective. Spatial scale and completion of the intervention play a big role.

Dr. LaDeau was asked for her thoughts regarding the observation that *Aedes aegypti* vector competence can be partitioned across geographical populations in a single state like Florida. The questioner asked whether such data would challenge the common use of vector abundance in estimating transmission risk. Dr. LaDeau replied that such data modify the association between abundance and risk. Human behavior and location are also factors.

An attendee asked Dr. LaDeau about the added value of prediction when it can be incorrect or inaccurate. Dr. LaDeau acknowledged that researchers do not like to make a wrong prediction. They get negative feedback and few rewards for making a prediction, testing it, and concluding they were wrong. She maintained that using a model to make a prediction, then evaluating why it was wrong is an incredible teaching opportunity. It is not the only way to refine science, but it is a powerful way to do so, she concluded.

Session 2: Example 1: Arboviruses

Within-to-Between Host Scaling: "Omics" of the Pathogen & Vector (Systems Biology)
Priya Shah, University of California, Davis

Dr. Shah discussed her team's research into the molecular requirements of host-switching arboviruses using SysBio approaches. The research focused on arthropod-borne flaviviruses—the mosquito and tick-borne small, single-stranded, positive-sense RNA (+ssRNA) viruses that are a major cause of human disease (dengue fever, yellow fever, congenital Zika syndrome, encephalitis). Dr. Shah's team studied primarily *Aedes*-borne flaviviruses. This diverse family also includes mosquito-borne flaviviruses transmitted by *Culex*; *Anopheles*-associated, insect-specific flaviviruses; tick-borne flaviviruses; and flaviviruses with no known vector.

Dr. Shah explained that her team zeroed in on a single cell within an infected host to observe what needs to happen in that cell for the virus to replicate successfully. The virus must:

- Get inside the cell through internalization and fusion.
- Replicate itself through translation, RNA replication, and assembly.
- Get out through maturation and the secretion process.

A flavivirus must co-op host cell pathways to accomplish all these tasks, and it does so through protein interactions. This basic replication cycle must be conserved in both the vector and vertebrate hosts.

Arboviruses represent a unique model system to understand the chemical constraints of virus replication and to answer the question: Does host-switching constrain host-protein interactions? Research began with the following steps (Shah et al., Cell 2018):

- Cloned the protein-coding sequences of the arbovirus into expression plasmids, expressing them in an easy-to-work-with cell line.
- Purified the viral proteins and any host proteins associated with them.
- Analyzed proteins by mass spectrometry.
- Subjected the data to quality control and scoring bioinformatically.
- Created networks of viral proteins and their interactions with host proteins, reducing thousands of data points to about several hundred high-confidence viral-host protein interactions for further analysis.

Dr. Shah's team used this process to identify interactions between dengue virus (DENV)-host proteins, DENV-*A. aegypti* proteins, and Zika virus (ZIKV)-human proteins. Bioinformatic approaches applied include gene enrichment and gene ontology to identify conserved protein interactions. The data that resulted revealed that Sec61 translocon facilitates transmembrane protein when the signal recognition particle (SRP) interacts with the SR receptor to insert a signal peptide into the translocon. Cotransins can inhibit this process (Garrison et al., Nature 2005).

Dr. Shah and her collaborators tested their hypothesis that, by targeting this pathway using cotransins CT8 and PS306, researchers could inhibit flavivirus replication in both human and mosquito cells. Results showed that modulation of Sec61 inhibits flavivirus replication of DENV and ZIKV in human and mosquito cells by significantly diminishing flavivirus infectious titer production and RNA replication. Dr. Shah said the results are a proof of concept that virus-host interactions conserved in the mammalian host and arthropod vector could be ideal targets for therapeutic intervention.

Dr. Shah said that the larger question of whether host-switching constrains arbovirus-host protein interactions is still a work in progress. However, researchers can now take advantage of the large-scale proteomic data for hundreds of protein interactions that are potentially conserved across multiple viruses or multiple vertebrate vector hosts and apply the computation tools developed for protein structure prediction. Researchers can take the improved predictions of human and vector protein structure from AlphaFold, for example, align them using algorithms

like FATCAT and ChimeraX, and dock host proteins with the viral proteins that researchers know interact. Scientists can then study the surfaces involved in these interactions and determine whether they occur on highly conserved surfaces.

Dr. Shah left the audience with two research questions that her team is beginning to explore:

- What will results show for other arboviruses such as yellow fever virus (primate-*aedes*), tick-borne flaviviruses (rodent-ixodes, human), and West Nile virus (avian-culex, human)?
- How will protein interaction dynamics change as mosquitoes experience higher temperatures? Researchers can take molecular-level data and start connecting it to ecological and global consequences.

Q&A/Discussion

An audience member asked Dr. Shah whether she has considered mapping protein interactions in cells of host/vectors that are not susceptible to DENV/ZIKV, such as *Culex* mosquitoes. This might give insight into whether barriers to infection are more related to entry, with host replication and/or immune invasion. Dr. Shah said her gut feeling is that barriers to entry are what explain vector competence.

An attendee asked whether any protein or group of proteins could be targeted in mosquitoes to detect that they were in contact with a viral (DENV or ZIKV) particle. Dr. Shah replied that she does not know if protein interaction data would be relevant, but she is interested in doing proteomics work in mosquitoes beyond the cellular level. There may be biomarkers of infection, such as structural proteins, that could be identified using proteomics or other biomarkers of infection. The growing field of single-cell proteomics may also have the sensitivity to identify viral proteins.

A questioner asked Dr. Shah to elaborate on how structure and docking predictions are validated in the lab. Dr. Shah said that her team has not yet validated results in the lab. The goal is to identify points of contact (specific amino acids that researchers think are responsible for the interaction), mutate those, and show biochemically that they cannot resolve that protein interaction. Researchers could also increase the temperature and test whether the protein interaction is still stable. Work on this idea is in the beginning stage.

The final questioner asked to what extent Dr. Shah thinks Genotype x Genotype (i.e., interactions between individual mosquito genotypes and the distinct viral serotypes) influence the epidemic potential of DENV on a macrogeographic scale. Dr. Shah said that the sequence variation is important. It is probably more important on the immune response scale as opposed to specific molecular interactions.

Climate Change & Vector-Borne Diseases: From Global Observations to Local Interventions
Rachel Lowe, Catalan Institution for Research and Advanced Studies (ICREA)/Barcelona Supercomputing Center (BSC), Spain

Dr. Lowe opened by noting the dramatic warming of global temperatures in the last several decades, which has been accompanied by an expansion of infectious diseases, such as dengue. The World Health Organization (WHO) estimates that half the world's population is at risk for mosquito-borne diseases, with billions more potentially at risk if the temperature rises by more than two degrees centigrade.

Dr. Lowe told attendees that she joined the BSC in 2022 to establish a new research team called the Global Health Resilience Group (GHRG). GHRG works with BSC's Climate Services and Air Quality Services groups to co-develop decision support systems for a more resilient and sustainable society. GHRG's work takes place across spatial domains, time horizons, and disciplines. The aim is to combine information at the global, regional, and national levels from sources such as satellites, forecast products, and socioeconomic indicators, with local information, such as disease surveillance. GHRG uses the information to develop decision models for early actions that help stop the emergence and spread of infectious diseases.

Dr. Lowe described GHRG's projects:

- Delayed and nonlinear combined effects of climate extremes (extremely wet, extreme drought) on dengue (Lowe, et al., The Lancet Planet Health, 2021) – The study began in Barbados and expanded to other locations, including Brazil, from 2001 to 2019. Hydrometeorological indicators combined with a spatial/temporal Bayesian model indicates showed an increased risk of dengue in both urban and rural areas three to five months following a drought event and immediately after extremely wet conditions. The impact of drought was more pronounced in urban settings. This may be due to drought mitigation through water storage, which can increase mosquito breeding sites. Study results have implications for the timing of standard interventions.

- Operational dengue early warning system for Vietnam (Felipe J Colón-González et al., PLOS Med, 2021) – The team combined 20 years of historical dengue cases, a hydrological model, and mosquito surveillance data with a model superensemble that captured different representations of how climate can impact the risk of dengue. Researchers then added seasonal climate forecasts to create probabilistic models to provide users with information on the probability of a province exceeding predefined epidemic thresholds.

- E4Warning: Early warning systems for infectious diseases in endemic and emerging settings – Dr. Lowe noted that the research focus is mosquito-borne disease. The newly started project looks to combine different approaches to modeling diseases in endemic settings. This includes monitoring the introduction of new invasive species or pathogens into the areas, combined with information from smart traps, human and mosquito interaction, and global travel data.

- Harmonizing multi-scale spatiotemporal data for health in climate change hotspots – The project looks at ways to build a robust evidence base to inform models. Dr. Lowe's team is working with partners in Brazil, Colombia, Peru, and the Dominican Republic, with a focus on climate change hotspots, particularly in cities, small islands, the Amazon

rainforest, and highlands. The aim is to develop tailored toolkits so users can rapidly gather all information needed to:

  - Understand environmental change and climatic influences on disease risk and a particular health outcome in their area.
  - Quickly develop decision support tools.

- Strategically gathered data will help researchers develop downscaling algorithms to understand how well satellite and analysis products are capturing changes on the ground.

- Implementing health impact-based modeling tool in BSC infrastructure - The tool would quantify and use climate information to predict the probability of infectious disease outbreaks. Researchers are taking advantage of the existing infrastructure at the BSC and have already produced a suite of open-source tools available on the Comprehensive R Archive Network (CRAN) to develop and analyze climatic indicators. The team is also working on an R package to develop impact-based forecasting tools for health that can be integrated into already-existing platforms.

Q&A/Discussion

An audience member asked Dr. Lowe how her team validates models that are calibrated and parameterized based on observation data given the complex, nonlinear, and interactive effects of these climate drivers on VBD transmission. The main way is through statistical validation approaches, said Dr. Lowe. Her team also does after-sample tests to see how well the model could perform on data it has not seen before.

An attendee asked Dr. Lowe whether early warning systems can be developed for countries/regions that are not yet endemic but at high risk (i.e., the United Kingdom) and whether these early warning systems take human mobility into consideration as a disease driver. Dr. Lowe said that her team's early warning project is looking at human mobility and developing climate suitability indicators that do not rely on disease data, since there have been only sporadic outbreaks of the diseases the project seeks to monitor. The team is tracking changes in climate suitability and overlaying connectivity between Europe and areas experiencing endemic DENV or malaria.

Data-Driven Approaches to Anticipate Vector-Borne Disease Transmission in a Rapidly Changing World

Integrating Data Across Ecological Scales in VBD Systems to Improve Predictions
Courtney Murdock, Cornell University, and Panel

Dr. Murdock framed the discussion by posing questions raised by the workshop theme. She noted that man-made environmental change is occurring at an unprecedented rate. Urbanization and land use are some of the defining challenges of the 21st century as far as changing the ecological relationships and processes that occur at each scale and across scales to affect mosquito-borne disease transmission.

Moving from the cell to the organismal level:

- What is the repeatability and robustness of within-host mechanisms characterized under one set of conditions to current and future field scenarios? The immune phenotype characteristics that researchers work with in the lab may not be the same phenotype that is expressed in different field conditions. Researchers may potentially be missing a lot of biological complexity that could scale up to affect dynamics at larger scales of organization. This has implications for understanding the mosquito-pathogen interactions as well as for novel vector control tools (Murdock et al., 2012 Proc Roy Soc B; Murdock et al., 2012 Nat Rev Microbial).

Moving from organismal to population level:

- How do we incorporate detailed knowledge of within-host mechanisms to understand variations in individual phenotypes?
- How can we incorporate these sorts of data into our mathematical models to inform our understanding of the prediction process or prediction?
- What are the potential issues of scaling up and certainty across different scales of organization to explain patterns of higher levels of organization? What are the impacts on our understanding of the transmission process and our ability to predict efficacy of novel control tools?
- What modeling frameworks would be appropriate for cross-scale inference? What are the limitations?

There is a myriad of abiotic and biotic factors that affect mosquito fitness, population dynamics, and the transmission process. The magnitude of these effects varies generally, and across different spatial and temporal scales. Researchers largely ignore biotic variation. The way in which data is collected may not reflect the relevant scale of inference (Cohen et al., 2016 PNAS).

Dr. Murdock presented questions from her own work to integrate data to understand population level dynamics across space and time:

- What is the appropriate spatial resolution for understanding the transmission process for enacting control?
- How do researchers downscale macro climate data? Using weather station data? Data logger data? Remotely-sensed land surface temperature?
- Do scientists scale indoor or outdoor environments?
- What other sources of variation may be important to consider?
- Should scientists model mosquito population dynamics explicitly, and what are the costs and benefits of doing so?
- What about scale mismatch in data collected?

Moving from the community to the biosphere level:

Different modeling approaches—statistical, mechanical, and process-based—are used to scale up transmission processes to understand global distribution of mosquito-borne disease. Researchers need to ask:

- What are the pros and cons of each approach?
- Can researchers extrapolate on work done on one population to a species-level response? How should genetic variation in predictive models be accounted for?
- How do researchers validate models that project future scenarios to assess uncertainty in model predictions? Researchers cannot access case study data from 50 years in the future and need to develop some level of comfort with uncertainty.

Dr. Murdock next presented steps to integrate data across multiple scales and improve predictions:

- Prioritize broader conceptual training in the foundations of VBD biology that spans multiple levels of biological organization.
- Emphasize both computational modeling skills as well as rigorous mechanistic empirical investigation at all scales of biological organization.
- Create funding mechanisms and scientific journals that support interdisciplinarity and cross-scale research. This will facilitate tackling the current challenges in predicting and controlling mosquito-borne disease.

Q&A/Discussion

One participant asked the panel about the best null models for prediction assessment. Dr. Lowe replied that her team's null model in the seasonal framework tends to be a seasonal average model. Dr. Murdock added that there is no doubt that local and expert knowledge of a system is highly informative. If someone lives and works within a system on a continual basis, there is a lot of intuition about how the system will behave. When researchers build models for forecasting and prediction, they also learn a lot about the systems. If scientists understand what the drivers are within a given system, they can predict how things might change in the future when the environmental variables change. There may seem to be consistency in the present, but this could change dramatically when temperatures warm or precipitation patterns change. By building a model, researchers are explicitly trying to understand the transmission process and use that knowledge to predict how the system might change when the surrounding environment changes.

A participant asked for the panel's opinion on the key tools and skills needed by the next generation of scientists. Panelists cited broader conceptual training that spans multiple levels, noting that it is a challenge to find collaborators that excel at different scales and work well together. Students need to learn computational and wet lab skills on the scale that research is conducted. Other scientists will not treat the data and care about the problem the same way that the researcher does. The trainees who can work in the field and at the bench as well as understand the computational modeling required will be more successful.

One way to accomplish that, commented Dr. Murdock, is for training programs to bring in students from different backgrounds with different skills to address similar questions about

infectious diseases. Training would promote an emphasis on gaining inference within a scale and how that inference can translate up or down scales. Trainees would work across different scales.

Session 3: Example 2: Malaria

Food as Information: The Comparative Evolutionary Biology of Host, Vector & Parasite Resource Consumption & Why This Matters in Malaria

Shirley Luckhart, University of Idaho

Dr. Luckhart's focus was the digestive system; specifically, the fact that arthropod vectors have something in common—blood feeding that introduces mammalian host biology directly into the arthropod vector.

She presented research that explored parasite transmission to mosquitoes:

- A study explored whether malaria-induced hypoargininemia, intestinal recruitment, and activation of mast cells could cause leaky gut in malaria (Jennifer Y. Chau et al., Host Response and Inflammation October 2013). Her team confirmed that low blood arginine levels lead to low nitric oxide levels, which results in mast cell activation in the gut and leaky gut to enteric pathogens such as salmonella.

- Published studies on basophil and mast cell activation in malaria concluded:
    - Both basophils and mast cells control malaria-induced leaky gut.
    - The activation of these cells drives early and persistent changes to the physical and immunological barriers of the gut.
    - Many factors in blood are modified by basophil and mast cell activation.
    - Mast cells and basophils are the major sources of histamine in our bodies and important sources of 5-HT.

- Work done by Dr. Luckhart's team showed that severe malaria is associated with elevated histamine and reduced 5-hydroxytryptamine (5-HT)—serotonin—in blood. Histamine and 5-HT are important insect neuromodulators.

- Dr. Luckhart's team then asked the question of whether activation of basophils and mast cells in malaria controls parasite transmission to mosquitoes (Donnelly et al., 2022a ImmunoHorizons). The team infected basophil-depleted and non-depleted mice and concluded:
    - Basophil depletion increased gametocytemia.
    - Basophil depletion had no effect on the prevalence of infection in mosquitoes fed on these mice.
    - However, basophil depletion increased intensity of infection in mosquitoes fed on these mice.

- A study posed the question: Based on these observations, could basophil activation be connected with parasite transmission? Mouse model studies concluded that depletion of the interleukin-18R (IL-18R) on basophils had no effect on infection intensity but decreased infection prevalence in mosquitoes (Donnelly et al., 2022b ImmunoHorizons).

The cytokine IL-18 is expressed early in malaria and can activate basophil synthesis of IL-4 and release of histamine.

- Based on previous research, Dr. Luckhart reframed the transmission question: Do levels of these two neuromodulators—histamine and 5-HT—at levels detected in malaria enhance parasite transmission to mosquitoes? Two recently published articles conclude that:
    - Provisioning of malaria-associated high histamine increased parasite transmission to mosquitoes, and provisioning of malaria-associated low 5-HT also increased parasite transmission to mosquitoes (Rodriguez, A.M. et al., 2021 Biomolecules; Briggs, A.M. et al., 2022 Frontiers in Physiology).
    - Further, a new study showed that malaria-associated levels of these combined factors increased infection with oocysts and sporozoites and significantly increased flight activity and visual responses, but somewhat decreased the tendency to take additional blood meals (Coles TA, Briggs AM, et al., 2023 Frontiers in Physiology).
    - A mosquito that feeds on an infected individual can become infected or not, but ingestion of these factors even in the absence of infection in mosquitoes could increase host-seeking behavior or infection success with subsequent blood meals.

- Dr. Luckhart concluded that the translation of malaria-induced allergy connects inflammation in the mammalian host to biology in the mosquito. This broad systems-level view of biology can be used to identify new targets to block vector-borne pathogen transmission.

Q&A/Discussion

An attendee asked Dr. Luckhart whether human cytokines have any biological effects in the mosquito. She replied that they do. Her team has looked at several cytokines and growth factors, including transforming growth factor beta-1, insulin-like growth factor, and insulin. Many of these compounds do have biological activity in vertebrate hosts.

Another workshop participant asked Dr. Luckhart how to translate research into the field to prevent or reduce transmission. She responded that elevated histamine and low serotonin levels in malaria contribute to the sense of illness as well as to pathology. Her team's work has shown that these can also increase transmission of parasites to mosquitoes. The idea would be to reverse the effects of these allergic mediators in the human host to reduce pathology and block transmission and/or directly target the pathways that are responding to these factors in the mosquito host to block transmission.

Nonlinear Impacts of Temperature Shape the Effects of Climate Change on Malaria Transmission

Erin Mordecai, Stanford University

Dr. Mordecai described the huge burden caused by VBDs, including the 96 million symptomatic cases of dengue each year and 445,000 deaths from malaria. These are happening in the context

of changes in climate; land cover; land use; the mobility of humans, animals, and goods; and humans introducing new species in new places while also driving species extinction. Dr. Mordecai's focus was on how climate change will affect malaria transmission.

The goal in research presented was to reconcile the disconnect between what is known from ectotherm physiology about the importance of nonlinear thermal responses and the assumption in VBD literature that the key life history traits of mosquitoes and parasites are responding monotonically, or even linearly, to temperature. The question to be answered was how temperature affects malaria transmission. Dr. Mordecai's team developed a temperature-dependent R0 model that was basically of function of the temperature-dependent traits of the mosquitoes and parasites.

Results showed:

- Strong evidence for nonlinear thermal responses in malaria-transmitting mosquitoes across traits, including bite rate, vector competence, parasite and mosquito development rates, and egg-to-adult survivorship (Mordecai et al., 2013, Ecol. Lett.). Combining the traits, the team determined that *Plasmodium falciparum* malaria transmission peaks at 77 degrees Fahrenheit (25 degrees Celsius). All previous mechanistic models using linear thermal responses had predicted an optimum of 89.6 degrees Fahrenheit (32 degrees Celsius). In a study that measured the malaria incidence in a cohort of children across locations in Kenya, thermal responses also predict human incidence, with a clear nonlinear response that also peaks at 77 degrees Fahrenheit (25 degrees Celsius) (Shah et al., 2019 Par & Vect.).

- Thermal optima and limits vary. There are some places where climate warming will speed up transmission, and these are the places where average temperatures are below the thermal optimum for malaria transmission. There are many places that are at or above 77 degrees Fahrenheit (25 degrees Celsius) where climate warming is going to slow transmission. Climate change will promote a shift in the locations for malaria suitability.

- Effects of temperature differ across different traits and across vector and parasite species (Villena et.al., 2022 Ecology).

- Models based on laboratory data can capture fairly coarse field patterns of temperature responses.

- Climate change will shift the suitability for transmission geographically and seasonally rather than broadly expanding transmission everywhere.

An important caveat is that all these temperature responses are likely to be mediated by human activities, including vector control activities to reduce transmission.

Dr. Mordecai concluded that while climate change has nonlinear effects on VBDs, those effects are also predictable based on models derived from laboratory and field data.

Q&A/Discussion

An attendee asked Dr. Mordecai what temperature is being measured (mean daily, nightly, distance from the ground, etc.) and how the daily temperature variation and rich microclimate variation are reflected. She replied that in laboratory experiments, the temperatures are constant because that is what is needed to drive a thermal performance curve. Researchers can then integrate over that curve to derive an estimate of how the R0 would be based on realistic temperature variation. The field validation takes coarse averages across seasons. Predictions of how climate change will affect transmission could be refined by:

- Looking at daily and seasonal temperature variation and integrated models over that predicted variation.
- Focusing on the most relevant microhabitat for mosquitoes and where they contact people.

Another participant asked about the effects of extreme climate events, particularly those that bring unprecedented rain and flooding and secondary malaria/dengue disasters. Dr. Mordecai replied that extreme events are a different dimension of climate change that are also expected to have large effects on VBD. Her work emphasizes that temperature is having direct effects on transmission, and those effects are detectable and predictable when looking for the correct nonlinear response to temperature.

Engaging "Other" Systems to Understand the Impact of Climate on Transmission
Luis Chaves, Indiana University, Bloomington, and Panel

Dr. Chaves presented research on incorporating realistic aspects of malaria biology into epidemiological models concerned with the control of malaria using interventions such as bed nets and vaccines. This includes addressing questions on the regulation of population dynamics using time-series data, particularly regarding interactions between different pathogens and the regulatory role of innate (bottom-up) and acquired (top-down) immunity (Chaves, et.al., 2009 Ecology). Dr. Chaves' team used qualitative loop analyses to examine interaction between *P. falciparum* and *P. vivax* at the population level, and the implications for within-host regulation of parasites. Analyses of monthly malaria time-series data from Vanuatu show that the dynamics of *P. falciparum* are not sensitive to *P. vivax*, whereas infections by the latter increase in response to those of the former. These results support within-host regulation of parasites and the need to better understand factors regulating malaria dynamics before developing control strategies.

Dr. Chaves also presented a study conducted in Kenya and Vanuatu showing that in impoverished areas, people are likely find alternative uses (i.e., fishing and crop protection) for their insecticide-treated bed nets (ITNs) (Keita Honjo, et al., January 2013 Parasitology). The ecosystem beyond living organisms (where users can gain more from applying nets to uses other than malaria protection) influences net use. There are levels of transmission for which it makes sense to use the nets for something else with no detrimental effect in the community. Results raise the question of how researchers should understand the context of transmission so that interventions have a positive impact on health and well-being.

Finally, Dr. Chaves presented a study of several factors that are normally not associated with driving land use change but may need to be addressed in the context of disease transmission (Bergmann and Holmberg, April 2016 Annals of the American Association of Geographers).

Q&A/Discussion

Dr. Chaves asked panel members to discuss training of future generations of researchers in multi-scale thinking. Dr. Luckhart said that better training is needed in how to communicate with people who do not work on the same biology or the same scale. A person cannot become master of all things but can become better at collaborating. A critical skill is to become conversant enough to communicate with others across all fields.

Dr. Mordecai added that finding common currencies across scales aids in this communication. Temperature is a good example because it affects everything from the cellular to the population and community levels. A transmission estimate is another common currency. The impacts of the allergy phenotype on mosquito vector competence could be translated to vectoral capacity or R0-type estimates that can then be scaled up.

Dr. Murdock agreed that it is impossible to expect everybody to be a master of all trades, but one can expose students to those in or outside their cohort who are asking similar questions at different scales and inference. This will facilitate the kind of communication needed for interdisciplinary work.

Dr. Chaves asked panel members to comment on ecological dynamics. Dr. Mordecai noted that mosquitoes can rapidly adapt to ecological conditions, including those imposed by humans, like bed nets and insecticides. She said there will be a question of what the competing evolutionary pressures on mosquitoes will be, including the selective pressures imposed by reaching upper thermal limits. Systematically assessing the evolutionary potential of thermal adaptation represents a huge gap in current literature. More studies are needed that capture gradients of evolutionary response to temperature. Beyond the genomic adaptation of individual mosquito populations, there is also the potential for ecological replacement.

Dr. Mordecai said that when scientists think about any intervention, they must engage communities as equal partners in the conversation. This includes helping to design experiments, determining the questions important to the communities, and engaging them in the process of working through studies and data analysis. To ignore social, behavioral, and cultural issues and macroeconomics is folly. Dr. Murdock applauded Dr. Chaves' research for connecting social, economic, and human systems and environmental systems with VBD transmission, not just for designing interventions but in the research itself.

Session 4: Example 3: Tick-Borne Pathogens

Tick-Skin Interactions at the Systems Biology Level

Joao Pedra, University of Maryland, Baltimore

Several years ago, a post-doctoral fellow who worked with Dr. Pedra observed that ticks secrete extracellular vesicles (Oliva Chavez et al., 2021 PMID). Researchers in other locations observed

the vesicle secretions as well.

These extracellular vesicles affect tick fitness. For example, if the biogenesis of vesicles is blocked by inhibiting the expression of a gene called Vamp 33 and the ticks feed on mice, they feed less and do not survive as well.

Tick vesicles affect the skin epidermis through dendritic epidermal T cells (DETCs). These cells represent only .5 to 1 percent of the epidermis and prompt the question: How is a cell that is so rare in the epidermis affected by the tick extracellular vesicles (EVs)? Dr. Pedra's team conducted an experiment that used two mouse genotypes—one with a DETC population and one depleted of DETCs. Researchers infected both mouse genotypes with ticks that had intact vesicles and ticks that had no or reduced vesicles. When researchers observed the keratinocyte population across these six permutations, a subcluster showed up only in mice that had the DETCs and no extracellular vesicles. The keratinocyte subcluster was enriched for wound healing pathways, suggesting vesicles act on gamma delta T cells and perhaps block the wound healing response during a tick bite (Liron Marnin, unpublished).

Further research through a combination of spatial transcriptomics, single-cell RNA sequencing, lineage tracing, and intraviral microscopy confirmed that tick EVs affect keratinocyte proliferation, disrupting epidermal repair during a bite. Results also showed that the tick feeding effect is spatially coordinated (Luisa Valencia, unpublished). Dr. Pedra concluded that ticks EVs affect the epidermal immune environment and the wound healing program. His team's ongoing research is focusing on the extent of coordination in the spatial program.

Q&A/Discussion

A participant asked Dr. Pedra to discuss the effect of the number of ticks on the immune environment and wound healing. Dr. Pedra responded that tick feeding is more complex and nuanced than is often portrayed in the literature. Vaccination strategies in the future may depend on how many ticks are feeding on the host—how many times people were bitten before they receive a vaccine. He confirmed that his research suggests that more ticks would potentially inhibit keratinocytes.

Another participant asked whether there is any role for EVs within the ticks themselves. Dr. Pedra said that EVs are universal and certainly play a role inside the tick. Current research by his team on how EVs are affected during Borrelia and Anaplasma acquisition shows that EVs change their numbers and may play a role in physiological processes.

Dr. Pedra was asked if modeling approaches would be useful in understanding bacteria/tick interactions. He answered that modeling would be interesting in systems immunology; for example, to predict an immune response in the context of vaccination.

A questioner asked for Dr. Pedra's thoughts on how the mechanisms he described are related to host competence more broadly. He replied that he would like to conduct research using guinea pigs because they may be a better model to understand what is happening during tick infestation, especially in the context of acquired immunity or repeated tick infestation. His work has already

shown that the immune response is more nuanced than predicted. Studies from 20 to40 years ago show that the immune response during a tick bite is very local. Researchers now have the technology available to show mechanistically how that works.

Integrating Multi-Scale Models, Including Earth Systems Models, to Create Climate-Driven Predictions for Tick-Borne Pathogen Spread
Carrie Manore, Los Alamos National Laboratory and Holly Gaff, Old Dominion University

Dr. Manore noted that her team has been working on a framework for modeling vector-borne pathogens in the context of climate, with an initial focus on mosquito-borne pathogens. The team is now looking to incorporate tick-borne pathogens. She said that Dr. Gaff is the tick modeling expert. Dr. Manore's team at Los Alamos is tackling the challenge to rapidly convert observations into knowledge to gain decision support and understanding of VBD systems that inform planning and intervention.

The team's high-level work combines data-driven and model approaches. Researchers look to combine real-time, voluminous, extremely noisy data with mathematical, statistical, and computational models to create forecasts of what would happen under various scenarios. The work requires collaborations across an interdisciplinary team (i.e., statistics, computer science, ecology, biology, chemistry, Earth systems, climate science, hydrology, epidemiology).

The team has been working for the past three years on the Climate Integrated Modular Model of Infectious Diseases (CIMMID). The final tool, to be finished this fiscal year, is a continental scale forecasting of mosquito-borne diseases with a mechanistic model so researchers can answer what-if questions. The current units that are part of CIMMID [Eco-Population Units, Earth System Model (E3SM), Vector Lifecycle Model, Epidemiological Model] could be replaced with other modules for different species (ticks), systems, or modeling approaches. Dr. Manore explained that many larger systems models work on square grid cells with fairly low resolution. Her team developed a finer scale grid for the eco-population units that better reflects the shape of the ecology to capture local mosquito population dynamics.

Dr. Gaff described her team's work on LYMESIM, an updated U.S. Department of Agriculture simulation model from the 1990s of blacklegged tick (*Acari: Ixodidae*) population dynamics and enzootic transmission of *Borrelia burgdorferi*. Much of the data her team has collected is hyperlocal, said Dr. Gaff.

Temperature and other aspects of climate come into play in two concepts of LYMESIM. One is Cohort Cumulative Degree Weeks (CCDWs), where each individual tick or individual cohort of ticks follows its own cumulation of temperature over time. CCDWs measure the number of weeks at a given temperature before an event occurs. When tick eggs are laid, for example, they must reach a certain number of CCDWs before they emerge. LYMESIM outcome measures include the density of infected nymphs (DIN), the density of all nymphs (DAN), and a measure of the surplus of questing nymphs.

Dr. Gaff emphasized the lack of long-term data and the need to support fundamental surveillance to understand hyperlocal, widely varying populations of ticks. She cited her team's long-term

data on blacklegged ticks in Virginia, New York, and Wisconsin/Minnesota. Model data compared with field data in Minnesota and Virginia show that while the model was not spot-on, it picked up many trends. By changing nothing in the model except the weather information from 2007-2016, Dr. Gaff's team was able to get a reasonable idea of the varying differential times, peaks, etc. for these two sites.

In New York, results were run with weather data as well as more host information. Dr. Gaff agreed with earlier comments that researchers must be able to "be wrong" in order to figure out the key drivers for any model. Researchers must understand the complex multiple components to pinpoint the data needed to validate a model in multiple locations.

Q&A/Discussion

A participant asked the panel to speak about the pros and cons of data reuse; for example, tick dragging and flagging vs. "submit a tick" (active vs. passive) programs. Dr. Gaff said that a researcher can get a lot of information from both. Community science programs can be helpful for collecting data in areas where individuals are motivated. The type of information collected is similar. From a modeling perspective, the consistent denominator of flagging or dragging the exact same transects in the exact same way monthly for 20 years is a useful validation set, whereas community science can have more variation in interest and participation.

One attendee asked how panel members determine the sources of uncertainty in multi-module models to find out if the limiting factors are the Earth systems models, the biological mechanisms, or something else. One of the approaches used by Dr. Manore's team is to dive into each model individually, explore what its uncertainty is, and see if there are specific data sources to validate that model. The team then connects two models at a time across the scale to look at uncertainty and how different drivers affect the output. The final step is to connect the whole model. She commented that it is difficult to disentangle which factor is affecting a model the most.

The panel was asked to discuss using complex models so they produce actionable information in a localized way. Dr. Manore said that more complicated is not always better. Sometimes a simpler model does a better job of capturing what is going on. Her team is now looking into subsets of data to determine which ones are the most informative in which places. Her team has also worked behind the scenes on figuring out the simplest model that can capture all the data needed. Dr. Gaff added that researchers need to match the model to the questions they are asking and avoid complexities that do not matter.

Environmental & Socio-Behavioral Determinants of Tick-Borne Disease Emergence Across Scales
Maria Diuk-Wasser, Columbia University, and Panel

Dr. Diuk-Wasser presented the risk factors for tick-borne disease:

- Hazard (potential source of harm) – Driven by pathogen and tick abundance and genotypes, which are influenced by both ecological-evolutionary processes and socio-

ecological processes.

- Exposure (likelihood of contact with pathogens) – Driven by human ecology and behavior, and human infections, which are influenced by socio-ecological processes.
- Vulnerability (the possibility that exposure causes harm) – Driven by age, socioeconomic and immune status, and genotype virulence, which are influenced by socio-ecological processes.

Dr. Diuk-Wasser defined risk as the combination of hazard, exposure, and vulnerability over the capacity to mitigate the risk.

Risk components can shift across land use gradients. In an urbanization gradient, for example, hazard increases in an area such as a park that may have more ticks. People's behaviors may increase their exposure if they go to the park, and the fact that they lack access to healthcare can increase their vulnerability (Diuk-Wasser et al., 2021 J. Med. Ent.). The compound association of these three factors is what determines the risk.

Dr. Diuk-Wasser noted that disease models contain a field component and a lab component to model the ecological processes. This is particularly important for ticks, because many things cannot be done in the lab for ticks that can be done for mosquitoes. For example, ticks' two-to-three-year life cycle makes it difficult to have a full model in terms of temperature. Lab work can simulate the processes of infection and look at transmission efficiency as one of the common currencies that may be used to scale up. For ecological processes, researchers can calculate R0 for host-pathogen and pathogen- tick, then use higher scale ecological patterns and genomic patterns to inform models.

Dr. Diuk-Wasser's team is currently focusing on social and human behavior factors. She and her colleagues are planning to develop agent-based models using radio-tracked animals that move through different landscapes. Humans move through the landscapes as well and an application called The Tick App will capture those movements. At this level of resolution, the team would like to run the model in different types of urban areas that can recreate how the system will operate across different levels of urbanicity. The range is not strong with temperature, but it is with host community distribution and human behavior. By having a mechanistic understanding of the interactions between human and animal behavior in a fragmented landscape, researchers can start building what-if scenarios in terms of different adaptive human behaviors.

In thinking of the models across scales, Dr. Diuk-Wasser presented them as thresholds for the emergence of pathogens. For example, her team is studying how landscape connectivity might drive deer abundance, which will determine a threshold R0 for ticks. If ticks become established and Lyme disease cases are reported, researchers can look at human behavior. For example, perceived risk may change in the population, with people taking measures for individual protection, and at the highest levels of enzootic transmission, implementing prevention and control interventions. The models across all these scales can be thought of as thresholds. The process will not be linear, with many points of feedback in the system.

Q&A/Discussion

Dr. Diuk-Wasser was asked if there are any simple temperature thresholds for tick-borne pathogen transmission or persistence that she could add to her model. She answered that a threshold would not be simple. The change in temperature will change the phenology. Ticks will move from a two-year cycle to a three, four, five, or six-year cycle. That will change the timing of feeding at all the stages, which will affect transmission in complicated ways. It is not a straightforward relationship. She noted that the R0 for ticks is high everywhere in the United States, so most of the limitations are linked to factors other than temperature.

Dr. Gaff agreed that a temperature threshold is not straightforward. Researchers do not understand the metric to use for the temperature over the entire tick lifespan, let alone the pathogen. Dr. Pedra said it would be interesting to see how the cargo changes with different temperatures—for example, a tick feeding on a mouse vs. a lizard.

A participant raised the subject of how researchers collect data with the intention of linking scales as opposed to combining the data after the fact. Dr. Manore said that in a perfect world, there would be an iterative process between those who collect the data and those who focus on modeling data analytics. It would be helpful if researchers understood the open questions in each other's fields to identify the opportunities for dual use. Dr. Pedra said that his team's challenge is not collecting the data, but analyzing it due to a shortage of computational biologists.

The panel discussed research outcomes, targets, and scales of interest, especially in tick-borne diseases, where there are no good interventions at any scale. Dr. Manore said she is attempting to develop measurements and metrics that are comparable across models and sites. Dr. Pedra asked Dr. Shabman his perspective on the recruitment and compensation challenges when seeking computational biologists. Dr. Shabman acknowledged the need to bridge computational biology and data scientists with wet lab researchers and clinicians. DMID is co-hosting an event at the Society for Mathematical Biology to bring clinicians and mathematicians together to break silos and work together.

Dr. Van Panhuis agreed with the urgent need for quantitative computational scientists in the biomedical field, especially in infectious and immune disease research. He noted that ODSET is looking at options for training, establishing collaborations between different fields, and developing joint funding opportunities with other communities such as the National Science Foundation to create synergy, recognizing that it does not happen naturally. He said that NIAID is open to ideas about how to facilitate collaboration.

Dr. Van Panhuis then previewed the workshop agenda for Day 2, emphasizing the goal of producing actionable information. He explained that workshop participants will form breakout groups of 10 each to discuss one of two themes: data integration priorities for modeling VBD across scale, or priorities for computational resources for VBD modeling. He said that each group will rank resource and action priorities in its area.

Dr. Costero-Saint Denis adjourned the meeting.

June 23

Welcome Back & General Introduction to Data Integration & Computational Resources for VBD Systems Ecology Research, Wilber Van Panhuis, ODSET, NIAID

Dr. Van Panhuis introduced attendees to ODSET, which falls under NIAID's Office of the Director. ODSET's mission is to accelerate infectious and immune-mediated disease research with data science methods and technologies. This includes advancing research and training within and supported by NIAID to leverage data science. ODSET goals include making data easier to access, developing and improving the use of computational methods, and fostering a multidisciplinary community of biomedical and computational scientists.

Dr. Van Panhuis highlighted two areas of data and VBD research for the breakout groups to consider:

- Many organizations aim to advance data and computational resources. What are the most important resource gaps for VBD systems ecology research, including needed innovations?
- Biomedical scientists may not have the necessary skills to use computational methods and infrastructure.

Dr. Van Panhuis outlined some ideas to inform breakout discussions:

Data Integration

- Researchers are increasingly connecting both large-scale data systems and smaller databases to use together. The NIH Common Data Fund Ecosystem is an example, with 15 systems in the network.
- Workshop presentations have provided examples of the many studies that integrate data at different scales (cellular to population) and across domain areas (health, vectors, climate, etc.).
- Important innovations are needed to address data integration, data sources, data quality/uncertainty, data/metadata standards, and data discovery/access.

Computational Resources

- Many computational resources are being developed, but which are most important for VBD systems ecology research? This includes cloud-based platforms, software development, and collaborative workflows. These innovations allow researchers to collaborate using data that are too big to move from a centralized location or access software methods hosted in a centralized place.
- Spatial and Pattern Combined Smoothing (SPCS) and other advanced resources are necessary as biomedical research data increase in size and complexity, and the demanding nature of computational methods grow.
    - Workspace requirements may shift to accommodate workflow and tool sharing,

collaborative analytics, and centralized data access. Are these important for VBD ecology systems modeling? Which ones are most important?
- There is increasing inequality between those who do and do not have access to advanced computational resources and the skills to use them. What can be done to decrease these inequalities?
- Computational resources and infrastructure can improve reproducibility and model sharing. The challenges in these two areas are important topics in current scientific literature. Most computational models cannot be rerun by others to share results and sharing source code is often not effective.

Panel Discussion on Data Integration & Software/Tool Sharing for VBD Modeling

Guido España, Centers for Disease Control and Prevention (CDC); Sheetal Silal, University of Cape Town, South Africa

Dr. España, from the CDC's Center for Forecasting and Outbreak Analytics, talked about the data, methods, and tools that represent the best options for integrating climate and VBD models. He based his talk on his own experience with VBDs, particularly dengue.

Steps to Integrate Climate and VBD Models

1. Determine the relationship of climate and biological parameters (e.g., the dengue generation interval is highly sensitive to temperature).
2. Incorporate the mechanistic relationships of climate and parameters in epidemiology models. Agent-based models reproduce actions between humans and vectors. The models can assign biological parameters, such as biting rate and incubation period, to individual mosquitoes, and mechanistically reproduce the effect of an increase in temperature.
3. Use estimates of climate factors and other factors (such as vector abundance) to integrate with models (i.e., global predicted distribution of *A. aegypti*). Incorporating high-resolution data sets into models allows researchers to expand simulation regions.

Tools important to data integration include:

- Data translation tools that disentangle the direct impact of climate and interventions in disease dynamics.
- Tools that capture the heterogeneity in biological parameters. For example, why does vector abundance vary in different areas that have the same temperature?
- Models that can incorporate transmission dynamics, climate, and vectors.
- Tools that integrate data from different studies to help researchers understand what the values (vaccine efficacy, vector control) mean when implemented in a transmission model.
- Widely available data on human health outcomes.
- Open-source tools, including accessible data and models that can be shared.

Data Integration into Mechanistic Models to Characterize Transmission/Answer Health-Related Questions

Dr. Silal said her work focuses on eliminating malaria, primarily a disease of poverty endemic in low- and middle-income countries. Developing mechanistic models is important in understanding the drivers of residual malaria cases, which vary by country. The model used by Dr. Silal's team takes into account cost effectiveness and budget impact components so output can serve as an advocacy tool to secure funding toward malaria elimination.

Key Data Sets Needed for Malaria (generally transferable to many VBDs)

- Vector characteristics (e.g., species; biting behavior, including adaptation over time), density and population size relative to human population; environmental receptivity to a mosquito population; insecticide resistance; and changes in mosquito behavior.
- Climate data – rainfall, temperature, and elevation.
- Cyclical climatic patterns. The importance of this data has grown due to climate change.

Dr. Silal said that researchers must consider whether data exists at the granularity level required by the model. This may call for better surveillance or proxy measures. Multidisciplinary input from experts in other fields may also be required to help determine the correct data sets to use. VBD researchers are working more frequently with climate modelers because there is a need to understand the strengths and weaknesses of the data. Dr. Silal said this is particularly true when developing multi-decade scenarios.

Dr. Silal concluded that mechanistic models require knowing the drivers of transmission. It is important to recognize that not all drivers are biological. With malaria, for example, migration and economic patterns can be bigger drivers than local conditions and vector populations. Researchers must develop methods for incorporating appropriate data sets into mechanistic models. One example is establishing collaborative workflows, including repositories that help translate large data sets so they are ready to be incorporated into modeling.

Introduction & Instructions for Breakout Groups

Meghan Hartwick, ODSET, NIAID

Dr. Hartwick provided instructions for breakout group activities. The plan was for workshop attendees to divide into Zoom-supported groups of 10 people each to discuss one of two themes—data integration or computational resources. Each group chose a moderator and rapporteur.

Breakout Session Key Terms for Data Integration

Dr. Hartwick provided areas to focus on in breakout discussions:

- New sources of climate or disease data.
- Better or different climate or disease data.
- How to get data to follow the same standard or format.
- Easier discovery of existing data.
- Easier access to relevant data.

- Additional data-related innovations that participants want to discuss.

Breakout Session Key Terms for Computational Resources

- Standardized software, potentially available in a repository (e.g., CRAN, Python); downloadable and usable locally.
- Pipelines and workflows (Docker, bioinformatics platforms) that allow analysis to be done in the same way repeatedly.
- Algorithms (sharing needs).
- High performance computing (HPC), on-premises or cloud-based.

Each breakout group participated in two activities:

1) Rank the topics on the form provided in order of priorities. Attempt to reach consensus. Forms provide room for comment if a consensus cannot be reached or if attendees want to cite papers, resources, and packages, including those they use in their work.
2) Share an actual research experience (template provided). These can include an actual experience, a research goal, or an experience that should have been easier.

Presentation of Breakout Group Results & Plenary Discussion of Findings

Meghan Hartwick, ODSET, NIAID; Wilber Van Panhuis, ODSET, NIAID

Dr. Hartwick provided a brief overview of responses from the breakout sessions:

Data Integration

Three breakout groups composed of 10 participants each addressed the data integration theme. Groups did not always reach consensus and they produced a range of rankings for top priorities. Examples include:

- New sources of science or climate data – Two groups determined that this was the least important priority; one group ranked it as most important.
- Better or different climate or disease data – Two groups ranked this as the most important priority. One group ranked it third most important.
- Data following the same standard or format – The breakout groups produced a range of priority rankings, from third most important to third least important.
- Earlier discovery of existing data – The breakout groups produced a range of rankings, from least important to third most important.

Highlights From User Stories

Participants were provided the following template:

As a [role] who is working to study [research question or hypothesis], it would significantly accelerate my research if I could easily integrate [data 1] at [biological scale] with [data 2] at [biological scale] using [method].

- Role – Three participants submitted responses for their role, including an infectious disease and climate scientist, graduate/post-doctoral student, and principal investigator.
- Research question or hypothesis – Responses included VBDs, risk reduction through applied modeling, and the impact of climate change on VBDs.
- Data 1 – Responses included socio-demographic data, forecasted precipitation data, and vector-related data.
- Biological scale – Two responders chose biological scale; one chose organism scale.
- Data 2 – Responses included mechanistic or empirical data, vertebrate host data, and climate data.
- Biological scale – Answers encompassed molecular, organism/within host, between-host, population, and micro.

Computational Resources

Three breakout groups composed of 10 scientists each participated in the computational resources theme and produced a range of rankings for top priorities. Examples include:

- Standardized software packages – One group determined that this the least important priority; one group ranked it as very important.
- Shareable and reusable algorithms – The breakout groups produced a range of rankings, from moderately unimportant to most important.
- Analysis pipeline and workflow – Two groups ranked this as moderately important; one as most important.
- HPC environments – Two groups ranked these as moderately unimportant; one as most important.
- Additional tools or resources – Two groups ranked these of low importance; one as very important.

Highlights From User Stories

Template: As a [role] who is working in [research field], that are confronted by emerging and re-emerging VBDs, including [VBD], I use [computing resources] to [types of analysis] using [tools].

- Role – Three participants submitted responses. One identified the whole "team" as the story participant. The other two were a staff researcher and a graduate/post-doctoral student.
- Research fields – Responses included epidemiology (chosen by all participants), public health, mathematical modeling, or artificial intelligence (AI), data science, data standardization/meta, ontologies, statistics/biostatistics, bioinformatics, atmospheric science and geography, and geography.
- VBD – Responders answered malaria, dengue, Zika, chikungunya, Rift Valley fever, yellow fever, West Nile fever, Lyme, and trypanosomiasis.
- Types of analysis – Answers included statistical/biostatistics analysis (all responders),

mathematical or AI/machine learning (ML) modeling, predictive modeling/forecasting, image analysis, agent-based modeling, and bioinformatics, computer/cloud computing, "didn't have access to HPC and cloud computing resources."
- Tools – Participant responses included Google Earth Engine (Java script), R(biomed), R(Bayes TPC RPC), Python, Matlab, Maple, GIS, Used R, MCMC inference (Rstan).

Plenary Discussion

Dr. Van Panhuis moderated a plenary discussion of breakout group results.

Workshop participants elaborated on the issues discussed in their breakout groups:

HPC
The availability of HPC is what generated its high or low rankings. HPC can be thought of as a gatekeeper for computational resources. Unequal access within countries and geographical regions is a factor in HPC's ranking as a computational resource. Researchers who lack HPC access rank it as a high priority. Those who already have HPC access focus on other concerns, including future innovations. Inequality of access can influence other computational resource priorities as well.

New Data/Existing Data
Group members debated whether generating new data is a higher priority than making existing data more discoverable/reusable. Useful data is already available in many different places, but not everybody knows where or how to locate these resources. When a researcher finds the data inadequate, augmenting existing data is important, especially when using bigger models (AI/ML/neural networks).

The research community is moving toward mechanistic models. AI and neural networks rely upon a good map of the relationship between different nodes. It will be difficult for neural maps to capture activity when researchers lack a good knowledge of data that has already been published or cannot access it in a standardized format. Scientists want to avoid duplicating effort. Standardized, open access databases are important in this endeavor.

Analysis Pipelines and Workflows
Shareable and Reusable Algorithms

Two breakout groups ranked analysis pipelines and workflows as moderately important, while one group ranked them most important. Discussion points included:

- The systems and infrastructure for developing a modeling pipeline (data cleaning, data access processing, estimations) should be resources that can be shared among groups from a centralized place as an alternative to researchers running these procedures on their own computers in their own labs.
- The group that ranked pipelines and workflows as moderately important considered development of a training pipeline as critical. There is no use having an integrated algorithm if no one understands how to use it. People may not have the skills and

experience to leverage centralized workflows.

- A chicken-and-egg situation can arise where researchers cannot develop the workflow if they do not have sufficient computing. It makes no sense to build a big computational pipeline if there is nothing to run it on and people are not trained to use it. This issue will become more important as people increasingly work with large-scale molecular data, satellite images, etc.
- There is a general acknowledgement across science that workflows must be provided. To do this, researchers often must generate the actual data that is used to train the models, or ask authors to share their raw data set. Source code sharing runs into problems when the data are sensitive, recipients cannot rerun source code in their computer environment, or the data are privately negotiated.
- There are valid reasons for people not wanting to or being unable to share. Generating reliable data sets is difficult. There are ways, however, to pull the data at the right step in the workflow under negotiated authorization/permission requirements.

Dr. Van Panhuis concluded that the connection between the computational sciences and the biomedical/biological science/ecology of VBDs is not an easy bridge to make.

Panel Discussion & Reaction to Breakout Group Findings

Guido España, Centers for Disease Control and Prevention (CDC); Sheetal Silal, University of Cape Town, South Africa; Mauricio Santos Vega, University of Los Andes, Colombia

Panel members discussed several topics from the breakout group findings:

Dr. España noted:

- There is more than one type of model in VBD research and each has its own data needs.
- When discussing new sources of data vs. better sources of data, what does "better" mean? A different resolution? More standardization? When there are a lot of data sources, none may meet the quality standard required by the research. There is often worse resolution in low-income countries when studying human movement, landscape, urban vs. rural, etc. Meanwhile, those who will be affected the most by climate change and VBDs are in these low-income countries.
- Dr. España's group prioritized access to current data resources over new data sources. Even with an abundance of data sets, inequality is an issue if they are not discoverable and accessible, or if access depends on where the researcher is in the world. When scientists can access better data sources, they can operate better models.

Dr. Silal noted:

- Lowering the cost of access to HPC is one way to alleviate inequalities. Options to increase access include incorporating it into grant funding and forming nontraditional partnerships with private donors to fund HPC/internet access.

- Signposting could be used to alert researchers about where to access data sets, with or

without access gateways. The context in which data was collected is equally important. A facility that provides signposting could also provide contextualization of the data, so users have the information to analyze and interpret it. Dr. Silal's team is working on signposting for a community-run repository that shows where the data is located and the proper ways to access it.

- Modelers need to be good at communication. Her breakout group discussed not only the reproducibility of code, but of entire pipelines, so that other analysts can validate the work or use it going forward. Analysts must also be aware of whom they are serving with their work. In many cases, the work is for the betterment of health and saving lives, and to inform decisionmakers who have the power to act on the analysis output. Therefore, analysts must be able to communicate with experts outside their fields and think about reproducibility in a broader sense.

Dr. Santos Vega echoed the need for more reproducible pipelines, more data sets, increased accessibility, the need for standardization, and clarity on the assumptions about data sets and how they were collected. He also discussed:

- Multiple VBD data sets will come from low-income countries and are going to be noisy. Better models and methods are needed to deal with data that is hard-to-obtain, noisy, incomplete, and scattered.

- Collaboration with climate scientists is needed to quantify the role of climate in disease transmission. Researchers often think only in terms of long-term trends in temperature increases, and fail to consider covariates such as rainfall, humidity, extreme climate events, and droughts. Researchers need to consider how mechanisms are operating for these other types of variables.

- Researchers must recognize the uncertainty of climate data.

- There is room for improvement on how to get new sources of biological data into models. Simpler microscopic models are needed for variables such as humidity and rainfall.. Data from experiments and field work are going to be important. Researchers in the global south need increased funding to pursue this research.

Collaboration with Climate Scientists

- Dr. Silal said she started collaborating as the result of an open grant application for malaria modeling. Climate researchers realized as they were drafting their application that they needed disease modeling for the grant and began collaborating with Dr. Silal. The first thing her team did was organize a course with climate scientists to discuss data sets, when they should be used, and what the uncertainties are with each of them. The climate scientists are now learning about malaria modeling. Climate change is here to

stay so it is important to learn about each other's field.

- Dr. Silal mentioned her involvement in setting up a community of practice on climate sensitive disease modeling as a result of a Wellcome Trust workshop. She said the effort is in its inception and she will be reaching out to analysts from different fields as the network forms. The goals are to improve modeling methodologically, better understand the data, and establish an equitable community of practice. Dr. España noted that the CDC's Center for Disease Forecasting and Analytics is making disease forecasting a priority and is connecting open source, enterprise-grade software models. He declared that connecting across fields will make humanity better prepared for future epidemics.

- Participants emphasized the importance of assessing under what circumstances models are useful and reliable and where they are not. Researchers need to develop a framework, structure, or methods to compare and improve predictions of different models.

- Dr. España said that uncertainties about models must be communicated in an open and reliable way, including uncertainty in the inputs and the calibrations. Dr. Silal said it is also important to explain what a model is producing. Was it a forecast, a projection, or a scenario? These are three different things that could be validated in three different ways. Understanding the difference helps to alleviate misinterpretations.

- Dr. Santos Vega echoed the emphasis on communicating uncertainty. He added that scientists do not develop models only for predictions. Models are also created to understand and quantify mechanisms. Dr. Van Panhuis concluded that it would be helpful to have a structural way to better communicate these tested pathways.

Adjourn

Drs. Van Panhuis and Costero-Saint Denis thanked workshop participants, panelists, and moderators. Dr. Costero-Saint Denis acknowledged Brian Pinton and the rest of the NIAID Meet team for technology support and adjourned the meeting.

Appendix A: Agenda

Day 1

10:00-10:10 AM: Welcome, Introduction; Adriana Costero-Saint Denis, NIAID
10:10- 10:35 AM: Scaling forecasts to matter: vector-borne disease in a changing world; Shannon LaDeau, Cary Institute of Ecosystem Studies
10:35-10:45 AM: Questions/Discussion; Moderator: Adriana Costero-Saint Denis NIAID

Example 1: Arboviruses, Moderator: Courtney Murdock, Cornell University

10:45-11:05 AM (15 min talk, 5 min Q&A): Within-to-between host scaling: "Omics" of the pathogen & vector (systems biology); Priya Shah, UC Davis
11:05-11:25 AM (15 min talk, 5 min Q&A): Climate change and vector-borne diseases: from global observations to local interventions; Rachel Lowe, ICREA/BSC, Spain
11:25-11:45 AM: Data-driven approaches to anticipate vector-borne disease transmission in a rapidly changing world; Courtney Murdock, Cornell University, and panel

Example 2: Malaria, Moderator: Luis Chaves, Indiana University, Bloomington

11:45 AM-12:05 PM (15 min talk, 5 min Q&A): Food as information: the comparative evolutionary biology of host, vector and parasite resource consumption and why this matters in malaria; Shirley Luckhart, University of Idaho
12:05-12:25 PM (15 min talk, 5 min Q&A): Nonlinear impacts of temperature shape the effects of climate change on malaria transmission; Erin Mordecai, Stanford University
12:25-12:45 PM: Engaging "other" systems to understand the impact of climate on transmission; Luis Chaves, Indiana University, Bloomington, and panel
1:00-1:15 PM: Break

Example 3: Tick-borne pathogens: Moderator: Maria Diuk-Wasser, Columbia University

1:15-1:35 PM (15 min talk, 5 min Q&A): Tick-Skin Interactions at the Systems Biology Level; Joao Pedra, University of Maryland, Baltimore
1:35-1:55 PM (15 min talk, 5 min Q&A): Integrating Multi-Scale Models, including Earth Systems models, to Create Climate-Driven Predictions for Tick-borne Pathogen Spread; Carrie Manore & Holly Gaff, Los Alamos Labs, Old Dominion Univ.
1:55-2:15 PM: Environmental and socio-behavioral determinants of tick-borne disease emergence across scales; Maria Diuk-Wasser, Columbia University, and panel
2:15 – 2:30 PM: Questions/Discussion; Reed Shabman, NIAID
2:30 PM: Adjourn; Reed Shabman, NIAID

Day 2

10:00-10:15 AM: Welcome back and General Introduction to data integration and model sharing for VBD; Wilbert Van Panhuis, NIAID
10:15-10:45 AM: Panel discussion on data integration and software/tool sharing for VBD modeling; Guido Espana; Mauricio Santos Vega; Sheetal Silal, CDC/CFA; University of Los Andes, Colombia; University of Cape Town
10:45-11:00 AM: Introduction and Instructions for breakout groups; Meg Hartwick NIAID

Moderated breakout groups

11:00-11:45 AM: Breakout theme 1, Data Integration Priorities for modeling VBD across scales, or Breakout theme 2: Priorities for software, tools, and workflows, for VBD modeling; Participants will be assigned to breakout groups to discuss one of the themes with a moderator and rapporteur
11:45-12:15 PM: Break
12:15-12:50 PM: Plenary discussion of breakout group findings; Breakout rapporteurs
12:50-1:00 PM: Break
1:00-1:30 PM: Panel discussion and reaction to breakout group findings; Guido Espana, CDC/CFA, Mauricio Santos Vega, University of Los Andes, Colombia, Sheetal Silal, University of Cape Town
1:30 PM: Adjourn

Appendix B: Speaker, Moderator, Panelist Biographies

NIAID Welcome & Meeting Introduction

Adriana Costero-Saint Denis, Ph.D., Program Officer, Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID)

Dr. Adriana Costero-Saint Denis is the DMID Vector Biology Program Officer. DMID's Vector Biology program supports more than 100 grants that span basic, translational, and clinical research on the most significant arthropod vectors of human diseases, as well as snails reservoirs of Schistosoma parasites. Basic research topics include molecular and mechanistic studies of pathogen-vector interactions; vector/vertebrate host interactions; vector biology, ecology, and behavior; and identification of approaches that will interrupt or decrease pathogen transmission. The Vector Biology Program also supports translational research to assist in the development of novel vector control interventions and the assessment of their epidemiological and clinical impact on transmission.

Reed Shabman, Ph.D., Program Officer, DMID, NIAID

Dr. Reed Shabman has more than 15 years of research experience in the fields of genomics, virology, immunology, and cell and molecular biology. He is currently a Program Officer in DMID's Office of Genomics and Advanced Technologies (OGAT), where he oversees the Systems Biology Program. He has extensive familiarity with mosquito-transmitted virus research and has played lead roles in mapping both mosquito and tick draft genomes. Before joining NIAID, he was a Lead Scientist at the American Type Culture Collection (ATCC) and an Assistant Professor at the J. Craig Venter Institute (JCVI). Dr. Shabman received his doctoral training at the University of North Carolina at Chapel Hill and performed postdoctoral work at the Icahn School of Medicine at Mount Sinai in New York.

Wilbert Van Panhuis, M.D., Ph.D., Director, Office of Data Science and Emerging Technologies (ODSET), NIAID

Dr. Wilbert Van Panhuis is a globally recognized leader in the use of data science for public health research. His focus has been on building large-scale, multidisciplinary international partnerships for data sharing, data integration, and data-driven research on infectious diseases. He conceived and developed Project Tycho, a data repository that comprises more than 125 years of detailed, standardized U.S. infectious disease surveillance data not previously available in an accessible format. Dr. Van Panhuis also established and directed the inaugural Coordination Center for the Models of Infectious Disease Agent Study (MIDAS). He received his M.D. from the Free University Medical Center in Amsterdam, and a Ph.D. in Infectious Disease Epidemiology from the Johns Hopkins Bloomberg School of Public Health. Prior to joining NIAID, he served for 12 years as a faculty member in Epidemiology and Biomedical Informatics at the University of Pittsburgh.

Meghan Hartwick, Ph.D., Data Scientist, ODSET, NIAID

During her Ph.D. work in Molecular and Evolution Systems Biology (MESB) at the University of New Hampshire and MSc work in Conservation Medicine with Tufts University, Dr. Meghan Hartwick developed mathematical models and bioinformatic approaches to predict public health risk from emerging water and foodborne microbial pathogens. She has contributed to advancing data science in infectious disease research through publications in high-impact journals, as a deputy editor of the Journal of Public Health Policy, and a Senior Fellow with Tufts InFORMID leading international research projects and training for the next generation of data scientists to promote data-driven solutions for complex health challenges. As a Data Scientist in ODSET, Dr. Hartwick is contributing to the development of the NIAID Data Ecosystem and the management of our Data Science research initiatives.

Session 1. Keynote

Shannon LaDeau, Ph.D., Cary Institute of Ecosystem Studies

Dr. Shannon LaDeau is a community and disease ecologist who serves as Senior Scientist and the G. Evelyn Hutchinson Chair in Ecology at Cary Institute of Ecosystem Studies, Millbrook, NY. She is also an Associate Editor for the Ecological Society of America's *Ecosphere* journal and serves on the Science, Technology, and Education Advisory Board for the National Ecological Observatory Network (NEON). Her research program integrates empirical and model-based studies to better understand how species interactions, abiotic filters, and environmental stochasticity influence community function in real (often urban) landscapes. Her work emphasizes disease or transmission-related functions using data-model integration. Dr. LaDeau's most recent focus is understanding and forecasting arthropod vector abundances, traits, and associated human risk in the context of global change. She received her Ph.D. from Duke University and a National Science Foundation (NSF) Bioinformatics Postdoctoral Fellowship to support her disease ecology research jointly at the Smithsonian Institution and The Ohio State University.

Session 2. Example 1: Arboviruses

Courtney Murdock, Ph.D., Cornell University

Dr. Courtney Murdock is associate professor, Department of Entomology, Cornell Institute of Host-Microbe Interactions and Disease, College of Agriculture and Life Sciences. A consistent theme of her research has been the application of ecological and evolutionary theory to inform which knowledge gaps are crucial to fill in order to improve the performance of predictive models of VBD transmission and disease management strategies. Dr. Murdock's research typically spans multiple scales of ecological organization, from within-host processes up to population and community-level dynamics. Her work employs a trans-disciplinary and integrative approach, adopting theory and techniques from the fields of ecology, evolutionary biology, behavioral ecology, genetics, virology, parasitology, medical entomology, statistics, immunology, and mathematical modeling. Dr. Murdock's approach involves carefully designed, rigorous experiments in the lab and under semi-field conditions, combined with field studies and

modeling, to provide insight into relevant mechanisms driving mosquito-borne disease transmission in the field. She is passionate about mentoring students at all levels of education and maintaining a diverse and inclusive research/teaching environment.

Priya Shah, Ph.D., University of California, Davis

Dr. Priya Shah is an Assistant Professor in the Department of Chemical Engineering and in the Department of Microbiology and Molecular Genetics. She started her lab at UC-Davis in 2017. Dr. Shah studies virus-host interactions using global proteomics approaches. This research serves as a starting point for hypothesis generation on how viruses hijack cellular pathways to facilitate replication, and in the process disrupt key physiological functions to cause disease. Dr. Shah established the global landscape of dengue- and Zika virus-host protein interactions using a comparative proteomics approach. This broad and unifying view of flavivirus-host protein interactions revealed flavivirus-human and flavivirus-mosquito protein interactions relevant to pathogenesis and conserved mechanisms of replication. Her group at UC-Davis continues to dissect these flavivirus-host protein interactions with molecular detail, and identify new protein interactions for other arboviruses, with a focus on protein interactions conserved across vertebrate and vector hosts. Dr. Shah received her B.S. in Chemical Engineering from MIT and her Ph.D. in Chemical Engineering at UC-Berkeley. She pursued her postdoctoral training at UC-San Francisco.

Rachel Lowe, Ph.D., Catalan Institution for Research and Advanced Studies (ICREA)/Barcelona Supercomputing Center (BSC)], Spain

Dr. Rachel Lowe is an ICREA Research Professor, leading the Global Health Resilience Group at the BSC's Earth Sciences Department. She also holds a Royal Society Dorothy Hodgkin Fellowship at the London School of Hygiene & Tropical Medicine. Dr. Lowe's research involves co-developing policy-relevant methodological solutions to enhance surveillance, preparedness, and response to climate-sensitive disease outbreaks and emergence. Her published work has focused on the viability of integrating seasonal climate forecasts in early warning systems for infectious diseases in Latin America, the Caribbean, and Southeast Asia. She is a member of the World Meteorological Organization COVID-19 research task team and was a contributing author of the Intergovernmental Panel on Climate Change Sixth Assessment Report (WGII) chapter on risks across sectors and regions. Dr. Lowe is Director of the Lancet Countdown in Europe, a new transdisciplinary collaboration tracking progress on health and climate change. She coordinates two Wellcome Trust digital technology, climate, and health projects that aim to provide robust data and modeling tools to build local resilience against emerging infectious disease threats in climate change hotspots.

Session 3. Example 2: Malaria

Luis Fernando Chaves, Ph.D., Indiana University, Bloomington

Dr. Luis Chaves is an Associate Professor of Environmental Health at Indiana University, Bloomington. Before coming to Indiana, he was an Associate Researcher and External Consultant at Instituto Conmemorativo Gorgas de Estudios de la Salud (Gorgas Memorial Health

Research Institute) in Panamá (2017-2022); an external faculty member of the Entomology Masters at Universidad de Panamá (2020-2022); a senior researcher at INCIENSA (Costa Rican Institute for Research and Training on Nutrition and Health) in Costa Rica (2018-2019); and an assistant professor at the Nagasaki University Institute of Tropical Medicine (2013-2016) in Japan. Dr. Chaves had postdoctoral training on the mathematical modeling of coupled natural and social systems from Hokkaido University as a Japan Society for the Promotion of Science Fellow (2010-2012), and in vector ecology and environmental studies at Emory University (2008-2010), where he was a member of the NIH-RAPIDD (Research and Policy on Infectious Disease Dynamics) group on VBDs. Dr. Chaves has directed research projects in Costa Rica, Panamá, the United States, Venezuela, and Japan and has participated in many research projects around the globe. In this process, Dr. Chaves has mentored a diverse group of students at different stages in their training. His research results have been published in more than 120 papers, mainly focused on insect vectors, VBDs, and other diseases sensitive to environmental change.

Shirley Luckhart, Ph.D., University of Idaho

Dr. Shirley Luckhart is a Professor in the Department of Biological Sciences and in the Department of Entomology, Plant, Pathology, and Nematology at the University of Idaho. She is also Co-Director of the Institute for Health in the Human Ecosystem. Her work for the past 28 years has focused on mosquito and malaria biology, including animal and human disease pathology, as well as host immunity and parasite transmission. While her work has been primarily lab-focused, Dr. Luckhart's early background in disease ecology, forestry, and wildlife biology has grounded the research with collaborative field studies as well. Since the early days of -omics, Dr. Luckhart has been fascinated by cell signals and transduction pathways that are conserved across evolutionary time in host-parasite interactions across plants, animals, and humans. In this context, her group is well-known for studies of the transfer of bioactive molecules between mammalian hosts and mosquitoes at the blood feeding interface, including peptides and proteins, hormones, small molecules, and drugs. To perturb conserved host-parasite interactions and test the importance of this biology, her team has provisioned a wide variety of bioactive molecules, peptides and proteins, hormones, and small molecules to *Anopheles stephensi*, with concomitant analyses of signaling biology, metabolism, host seeking and flight behavior, parasite growth, and parasite transmission to and infection of adult female mosquitoes.

Her current work in the mosquito host has been inspired by her prior and continuing work in the mammalian host, including metabolic and immune responses to parasite infection, as well as published literature from plants, non-arthropod invertebrates, and completely unrelated pathosystems. Research questions generally focus on the mammalian host responses that result in changes in blood bioactive factors that are ingested by mosquitoes, whether these changes in blood factors inhibit or amplify parasite transmission. Research also focuses on how this interface can be manipulated to block transmission. Ultimately, however, her team thinks about how this biology evolved and seeks to understand its fundamental role in the organism and how it can be leveraged to improve health and well-being in complex systems.

Erin Mordecai, Ph.D., Stanford University

Dr. Erin Mordecai is Associate Professor in the Biology Department of Stanford University. She is also a Senior Fellow in the Woods Institute for the Environment, a Faculty Fellow in the King Center on Global Development and the Center for Innovation in Global Health, and a faculty affiliate of Bio-X and the Institute on Human-Centered Artificial Intelligence. She has been recognized by the Ecological Society of America as an Early Career Fellow. Dr. Mordecai's research focuses on the ecology of infectious disease, with an interest in how climate, species interactions, and global change drive infectious disease dynamics in humans and natural ecosystems. Her research combines mathematical modeling and empirical work. Dr. Mordecai received her Ph.D. in Ecology, Evolution, and Marine Biology from the University of California – Santa Barbara. She completed a two-year NSF postdoctoral research fellowship in the Intersection of Biology and Mathematical and Physical Sciences and Engineering at the University of North Carolina at Chapel Hill and North Carolina State University.

Session 4. Example 3: Tick-Borne Pathogens

Maria Diuk-Wasser, Ph.D., Columbia University

Dr. Maria Diuk-Wasser is Professor and Director of Graduate Studies in the Department of Ecology, Evolution, and Environmental Biology. Her research uses a combination of empirical and analytical approaches to unravel the socio-environmental factors driving the emergence of VBDs, with a particular focus on tick-borne illnesses. Her current investigations revolve around understanding tick-borne diseases as interconnected natural human systems. She evaluates the risk of these diseases by considering the combined impact of pathogen distribution and abundance (referred to as the "hazard"), human exposure influenced by human ecology and behavior, and social vulnerability. Dr. Diuk-Wasser's research encompasses various spatio-temporal scales, ranging from molecular to continental levels, and she employs modeling frameworks informed by both laboratory and field experiments. She received her Ph.D. from the University of California – Los Angeles, followed by postdoctoral training and an Assistant Professor position at the Yale School of Public Health.

Over the past two decades, Dr. Diuk-Wasser has led numerous large-scale projects funded by federal agencies, aiming to assess the patterns and processes underlying the emergence of tick-borne diseases. Notable projects she has spearheaded include the investigation of the "Emergence of babesiosis in the United States," the development of a "Spatial risk model for *Ixodes scapularis*-borne Borrelia," the exploration of "Tradeoffs between specialist and generalist strategies for host immune evasion in a vector-borne bacterium," and the examination of "Eco-social interactions influencing human exposure to ticks and the Lyme disease agent in anthropogenic landscapes" as part of the CNH2-L program. Maria plays a key leadership role in the Northeast Regional Center for Excellence in Vector-Borne Diseases and has contributed as an author to the 5th National Climate Assessment (NCA5).

Joao Pedra, Ph.D., University of Maryland, Baltimore

Dr. Joao Pedra is a Professor of Microbiology and Immunology, President of the American Society for Rickettsiology, Chair of the NIH Transmission of Vector-Borne and Zoonotic Diseases Study Section, and Chair of Admissions for the Molecular Microbiology and Immunology Graduate Program at the University of Maryland School of Medicine. His research program is directed toward understanding tick-borne diseases. His group determined the existence of an atypical Immune Deficiency circuit in the *Ixodes scapularis* tick that safeguards against the Lyme disease spirochete *B. burgdorferi* and the rickettsial bacterium *Anaplasma phagocytophilum*. The team discovered that eicosanoids regulate a non-canonical NLRC4 inflammasome pathway upon rickettsial infection. Researchers demonstrated the anti-inflammatory properties of a tick salivary protein on Nod-like receptor signaling pathways during pathogen colonization of the mammalian host. Dr. Pedra spearheaded a study group with other investigators to tackle the problem of genetically manipulating obligate intracellular bacteria. His group showed that extracellular vesicles from ticks affect dendritic epidermal T cells and promote distinct bacterial outcomes in the mammalian host. Dr. Pedra has managed trainees in different career stages (*e.g.*, undergraduates, graduate, and post-doctoral fellows) and in 2022, received the Dr. Mark E. Shirtliff Ph.D. Student Mentor Award, Graduate Program in Life Sciences at the University of Maryland School of Medicine.

Carrie Manore, Ph.D., Los Alamos National Laboratory (LANL)

Dr. Carrie Manore is an Applied Mathematician and Deputy Group Leader, Theoretical Biology and Biophysics, at LANL. She specializes in modeling ecological systems and infectious disease spread. Her work ranges from theory and model analysis to data-driven predictions of disease. Dr. Manore has modeled human, plant, livestock, and wildlife disease across the world in collaboration with dozens of scientists from a broad range of disciplines and national/international organizations. Dr. Manore received a Ph.D. in Mathematics, with a minor in Ecosystem Informatics, from Oregon State University. She was a postdoctoral researcher at Tulane University, modeling mosquito-borne diseases such as West Nile virus and dengue. Dr. Manore received an NSF Science, Engineering, and Education for Sustainability (SEES) Fellows grant to model emerging infectious diseases in a changing environment, and published research of multi-scale models for livestock, plant, and human diseases. Her research with colleagues on constructing rigorous biosurveillance networks for detecting emerging outbreaks received an award for Outstanding Research Article in *Biosurveillance* from the International Society for Disease Surveillance. She was awarded a Director's Postdoctoral Fellow at LANL in T-6 (Theoretical Biology and Biophysics) and A-1 (Information Systems and Modeling) for "Development and Application of Multi-scale Models for Disease Forecasting."

Holly Gaff, Ph.D., Old Dominion University

Dr. Holly Gaff is Professor and Chair of the Department of Biological Sciences at Old Dominion University (ODU). Dr. Gaff's research interests have focused mainly on studying the ecology of ticks and tick-borne diseases through an active surveillance project and mathematical modeling. She has published more than 75 peer-reviewed articles and obtained funding from various government agencies, including NIH, CDC, the Department of Defense, and the U.S.

Department of Agriculture. Dr. Gaff currently leads the ODU Tick Research Team—a group of faculty, graduate, and undergraduate students working to better understand the ecology of ticks and tick-borne pathogens in Virginia. The ODU Tick Research Team has been running a long-term active tick surveillance program in Virginia since 2009, which has led to the discovery and mapping of tick populations moving into and across the state. Dr. Gaff earned her Ph.D. in Mathematics at the University of Tennessee, Knoxville. She also holds an honorary appointment at the University of KwaZulu-Natal and works with scientists throughout southern Africa on the challenges of ticks and tick-borne pathogens.

Session 5: Panel Discussion on Data Integration & Software/Tool Sharing for VBD Modeling

Guido España, Ph.D., Centers for Disease Control and Prevention (CDC)

Dr. Guido España recently joined the CDC Center for Forecasting and Outbreak Analytics (CFA) as Senior Service Fellow. He previously served as Research Assistant Professor at the University of Notre Dame and the National University of Colombia. Dr. España's research is focused on supporting public health decision making with the use of mathematical and computational models to understand the dynamics of infectious diseases, particularly the evaluation of vaccine impact and vector control in VBDs. Additionally, he is interested in estimating the impact of non-pharmaceutical and pharmaceutical interventions on the dynamics of the COVID-19 pandemic. Dr. España has published extensively at the intersection of VBD and modeling, including his work evaluating COVID-19 non-pharmaceutical interventions and agent-based models for dengue virus transmission and chikungunya mitigation. Dr. España holds a Ph.D. in Electrical Engineering from National University of Colombia and an M.Sc. in Engineering, Industrial Automation from the National University of Colombia.

Sheetal Silal, Ph.D., University of Cape Town, South Africa

Dr. Sheetal Silal is the Director of the Modelling and Simulation Hub, Africa (MASHA), an Associate Professor in the Department of Statistical Sciences at the University of Cape Town (UCT), and an Honorary Visiting Research Fellow in Tropical Disease Modelling at the Nuffield Department of Medicine at Oxford University. Dr. Silal's primary area of research is mathematical and statistical modeling of infectious diseases to model the control and elimination of malaria, COVID-19, pertussis, and other infectious diseases in South Africa, sub-Saharan Africa, and globally. During the COVID-19 pandemic, she led the development of COVID-19 dynamic transmission models as part of the South African COVID-19 Modelling Consortium (SACMC) and has published extensively, integrating differential equation modeling and agent-based simulation to predict the dynamics and control of infectious diseases. Dr. Silal holds a Ph.D. in Mathematical Modeling of Infectious Diseases and an M.Sc. in Operations Research in Development.

Session 8: Panel Discussion & Reaction to Breakout Group Findings

Mauricio Santos Vega, Ph.D., Universidad de Los Andes, Colombia

Dr. Mauricio Santos Vega is a mathematical biologist with a research focus on the interface

between ecology, climate, economics, and urbanization. More specifically, his interests are at the intersection of the ecology of infectious diseases, urban ecology, and public health. Using mainly methodologies that combine statistical and mathematical models, he studies how environmental and demographic factors at different spatiotemporal scales affect the dynamics of vector-borne diseases (such as malaria) in urban settings. Dr. Santos Vega studied Biology at the Pontificia Universidad Javeriana in Bogotá, followed by an M.Sc. in Ecology and Evolutionary Biology at the University of Michigan, Ann Arbor, and a Ph.D. in Ecology and Evolution from the University of Chicago.

Appendix C: Selected Key Publications

- Virus-Host Flavivirus Use Case:
  - Shah PS, et al. Comparative Flavivirus-Host Protein Interaction Mapping Reveals Mechanisms of Dengue and Zika Virus Pathogenesis. Cell. 2018 Dec 13;175(7):1931-1945.e18. doi: 10.1016/j.cell.2018.11.028. PMID: 30550790; PMCID: PMC6474419.
- Virus-Vertebrate Flavivirus Use Case:
  - Fishburn AT, et al. Zika virus NS4A hijacks host ANKLE2 to promote viral replication. bioRxiv 2022.03.15.484510; doi: https://doi.org/10.1101/2022.03.15.484510. This article is a preprint and has not been certified by peer review.
- Virus-Vector, Review:
  - Petit MJ, Shah PS. Mapping Arbovirus-Vector Interactions Using Systems Biology Techniques. Front Cell Infect Microbiol. 2019 Jan 7;8:440. doi: 10.3389/fcimb.2018.00440. PMID: 30666300; PMCID: PMC6330711.
- Virus-Vector Flavivirus Use Case:
  - Gestuveo RJ, et al. Analysis of Zika virus capsid-Aedes aegypti mosquito interactome reveals pro-viral host factors critical for establishing infection. Nat Commun. 2021 May 13;12(1):2766. doi: 10.1038/s41467-021-22966-8. PMID: 33986255; PMCID: PMC8119459.
- Vector Genomes and AlphaFold Integration:
  - Yates AD, et al. Ensembl Genomes 2022: an expanding genome resource for non-vertebrates. Nucleic Acids Res. 2022 Jan 7;50(D1):D996-D1003. doi: 10.1093/nar/gkab1007. PMID: 34791415; PMCID: PMC8728113.
- VEuPathDB Technological Advances:
  - Amos B, et al. VEuPathDB: the eukaryotic pathogen, vector and host bioinformatics resource center. Nucleic Acids Res. 2022 Jan 7;50(D1):D898-D911. doi: 10.1093/nar/gkab929. PMID: 34718728; PMCID: PMC8728164.
- Mosquito Metabolomics:
  - Horvath TD, Dagan S, Scaraffia PY. Unraveling mosquito metabolism with mass spectrometry-based metabolomics. Trends Parasitol. 2021 Aug;37(8):747-761. doi: 10.1016/j.pt.2021.03.010. Epub 2021 Apr 22. Erratum in: Trends Parasitol. 2021 Jun 25;: PMID: 33896683; PMCID: PMC8282712.