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"A medida que un organismo aumenta su complejidad, el ritmo de lucha y consumación en la relación con su medio tiene variaciones y prolongaciones, y llega a incluir dentro de sí una interminable variedad de subritmos. Los designios de la vida se amplían y se enriquecen, la satisfacción es más compacta y tiene matices más sutiles."

John Dewey

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Resumen

En el contexto de las interacciones ecológicas entre virus, vectores y hospederos silvestres, se ha observado una relativa estabilidad a lo largo del tiempo. No obstante, el constante desarrollo y la explotación desmedida de los recursos naturales han ocasionado modificaciones en estas interacciones. Como resultado, han surgido brotes de enfermedades emergentes con impactos significativos en la salud humana, animal y la preservación de especies. Ejemplos notables de estas enfermedades emergentes incluyen el Denguevirus, el virus del Oeste del Nilo, el virus de St. Louis, la fiebre amarilla, el virus del Chikungunya y el Zikavirus, todos transmitidos por mosquitos.

En esta investigación, se pone a prueba el empleo del control biológico como una estrategia para regular poblaciones virales a través del uso de las interacciones virales, presentando una alternativa económicamente viable y ambientalmente sostenible para el control de plagas. Es crucial destacar que estas pruebas se realizan en modelos computacionales, y se subraya la importancia de llevar a cabo futuras evaluaciones exhaustivas y comparativas con la realidad ecológica fuera del modelo. Esta aproximación no solo busca comprender la viabilidad de la técnica en un entorno controlado, sino que también sienta las bases para posibles aplicaciones prácticas en la gestión de enfermedades virales y plagas en entornos reales.

Dentro del grupo de virus Flaviviridae, se destaca su capacidad de inducir infecciones persistentes en vectores, lo que permite la coexistencia de múltiples agentes infecciosos en una misma célula. Esta dinámica, conocida como coinfección (cuando interactúan en el hospedero al mismo tiempo) y superinfección (cuando un virus invade primero al hospedero y posteriormente se aloja el segundo virus), ha sido confirmada en entornos de cultivo celular y plantea interrogantes acerca de su influencia en la susceptibilidad del vector a diferentes arbovirus. Por lo tanto, el estudio integral de las comunidades virales, vectores y hospederos resulta fundamental para comprender las variables que inciden en las susceptibilidades y que serán analizadas en la presente tesis.

Para abordar esta complejidad, se han empleado diversas aproximaciones estadísticas y modelos analíticos, como los modelos compartimentales (SIR – Susceptible – Infectado - Recuperado), tradicionalmente usados en epidemiología. Estos modelos proveen una base para analizar las comunidades virales y discernir patrones emergentes que podrían contribuir a reducir la propagación de enfermedades infecciosas.

A pesar de la importancia de la diversidad viral en comunidades de hospederos y vectores, aún existe un vacío en la comprensión de su influencia. Los flavivirus se presentan como un modelo ideal, dada su inclinación a la coinfección, superinfección y exclusión. En esta investigación, se propone un modelo que considera la coocurrencia de los flavivirus, con el propósito de evaluar la magnitud y dirección de las interacciones virales. Se plantea la hipótesis de que las relaciones de facilitación (aumento en la replicación, transmisión o impacto de uno o varios virus) y exclusión (la reducción o inhibición de la replicación, transmisión o impacto de uno de los virus) dentro de las comunidades virales tienen un impacto directo en la prevalencia de estos virus tanto en vectores como en hospederos naturales.

Para simular estas interacciones complejas, se emplearán modelos basados en agentes (ABM), que permiten diseñar algoritmos que reflejen las reglas organizativas fundamentales. Lo destacable de este enfoque es la capacidad de dotar a los actores de inteligencia artificial, lo que les permite tomar decisiones y reaccionar ante las acciones de otros actores con los que interactúan.

Este trabajo de investigación se desarrolla a lo largo de los siguientes capítulos:

Capítulo I: Elección del Modelo Representativo

La influencia de las comunidades de hospederos, vectores y patógenos en los patrones de infección en la naturaleza es ampliamente reconocida. Para entender cómo estas complejas interacciones han afectado la propagación de enfermedades transmitidas por vectores, es fundamental identificar las especies clave de vertebrados (hospederos) e invertebrados (vectores) que desempeñan un papel central en la transmisión de estos simbiontes. Esta identificación es crucial para desarrollar estrategias preventivas específicas. Este estudio se basa en una compilación de datos globales extraídos de la literatura científica y tiene como objetivo identificar las especies hospederas relevantes en la transmisión global de flavivirus transmitidos por mosquitos, tales como el virus del Nilo Occidental, el virus de St. Louis, el virus del Dengue y el virus Zika, todos ellos de importancia en la salud animal y pública.

El análisis de la base de datos resultante, que engloba información sobre 1174 especies hospederas de vertebrados y 46 especies de vectores documentadas, nos ha permitido establecer redes de asociación entre estas especies. En particular, tres especies hospederas —*Mus musculus*, *Sapajus flavius* y *Sapajus libidinosus*— se destacan por su alta centralidad en la red, lo que sugiere que desempeñan un papel crucial en las interacciones dentro de la comunidad de flavivirus. Los métodos empleados y las especies identificadas como relevantes en esta red proporcionan nuevos conocimientos y coherencia, lo que podría guiar a los profesionales de la salud a repensar las estrategias de prevención y control, centrándose en las comunidades virales y sus interacciones. Además, estas técnicas de análisis de redes podrían ser beneficiosas para abordar otras enfermedades infecciosas que afectan tanto a la salud humana como animal.

Capítulo II: Descripción y Conformación de las Comunidades

Una vez identificadas las especies clave en la transmisión de flavivirus, se seleccionó la península de Yucatán como la ubicación idónea para recopilar datos que se incluirían en el modelo. Esta elección se sustenta en las altas prevalencias de flavivirus previamente reportadas en esta región (Farfan-ale et al., 2009).

Dentro de la península de Yucatán, se eligió Celestún como el lugar central para nuestro modelo, debido a la presencia de tres ecosistemas interconectados. Esta selección proporciona la oportunidad de evaluar tres comunidades distintas con su respectiva diversidad, lo que nos permite comprender sus variables y comparar su influencia en el modelo. Además, es importante destacar que Celestún se ubica a una distancia de aproximadamente 100 km de Mérida, lo que otorga una significativa relevancia en términos de salud pública, ya que existe la posibilidad de un contacto directo con una zona urbana de importancia.

Los ecosistemas presentes en Celestún abarcan Duna, Selva y Petén. Esta clasificación se basa principalmente en el tipo de vegetación predominante. La conformación de las comunidades que utilizaremos en nuestros modelos computacionales se basa en tres artículos con descripciones exhaustivas de la diversidad y abundancia en Celestún (Profile, 2006; Chablé-Santos y Sosa-Escalante, 2010; Hernandez-Perez et al., 2015), los cuales se detallan en el presente capítulo.

Capítulo III: Funcionamiento del Modelo

El desarrollo del modelo se llevó a cabo en la versión 6.1.1 del software NetLogo. Este programa destaca por su interfaz intuitiva que permite la observación de los elementos y acciones ejecutadas por los agentes dentro del modelo.

Dentro de esta representación, los elementos que ejecutan las acciones son denominados "tortugas". Se identifican dos clases de tortugas: hospederos y vectores. Ambas categorías de tortugas están equipadas con capacidades de inteligencia artificial. A estos agentes los dotamos con la capacidad de reconocer los virus a los que son susceptibles. Asimismo, pueden identificar a las tortugas en su proximidad y determinar su especie, así como la lista de enfermedades asociadas a ellas. Esta información resulta esencial para la aplicación de preferencias alimenticias y para comparar las listas de enfermedades, permitiéndoles contagiarse con un virus al cual sean susceptibles y aún no hayan contraído.

Capítulo IV: Estandarización del Modelo y Espacialidad

La biodiversidad nos otorga valiosos servicios ecosistémicos, entre ellos la protección de la salud al reducir el riesgo de infecciones mediante el "efecto de dilución". Este efecto es un mecanismo mediante el cual la diversidad de vertebrados disminuye la prevalencia de enfermedades en otros hospederos. En modelos previos del tipo SIR (Susceptible-Infectado-Recuperado), se examinó el efecto de dilución y su funcionamiento, pero surgió el desafío de incorporar la dimensión espacial. Para abordar este desafío, experimentamos con diferentes tipos de movimientos para los agentes (vectores y hospederos) y la distancia que pueden recorrer. Evaluamos la prevalencia máxima (calculada como el número de agentes infectados dividido por la población total, multiplicado por 100) en cada simulación.

Realizamos un total de cuatro modelos ABM (Agent-Based Models) distintos en NetLogo 6.1.1. con el objetivo de simular diversas situaciones ecológicas al modificar la susceptibilidad de los hospederos y vectores. En cada uno de los modelos probamos los tres tipos diferentes de movimiento. El primero es un movimiento lineal, donde el agente avanza en línea recta. El segundo es un movimiento aleatorio, más cercano a la realidad, pero debemos considerar que los organismos a menudo tienen objetivos en sus movimientos. El tercero representa un movimiento circular uniforme. En base a nuestros resultados, confirmamos que una mayor diversidad de especies en las susceptibilidades de la comunidad de hospederos potencia el efecto de dilución. Sin embargo, observamos que la diversidad de susceptibilidades en la comunidad de vectores tiene una influencia limitada en la prevalencia de enfermedades y en el efecto de dilución.

Nuestro análisis reveló que el tipo de movimiento no es un factor relevante para el efecto de dilución. Por el contrario, la distancia de movimiento surge como una variable que incrementa la prevalencia de enfermedades. Aunque dicho cambio en la prevalencia es sutil, es constante hasta que el desplazamiento alcanza el 1% de la superficie total. En última instancia, el efecto de dilución neutraliza los efectos de densidad dependientes de la prevalencia de enfermedades infecciosas en nuestro modelo, lo que abre nuevas interrogantes para futuras exploraciones.

Capítulo V: Preferencias alimenticias

Los mosquitos, al ser vectores esenciales, tienen la capacidad de transmitir una serie de enfermedades, siendo los flavivirus una de ellas. El éxito en la transmisión viral por mosquitos depende de su hábito de picar a especies susceptibles, no obstante, estos insectos presentan preferencias de alimentación específicas. Existen diversos estudios que documentan los variados patrones de estas preferencias. Contando con suficiente información sobre estos patrones, hemos desarrollado un modelo destinado a explorar el impacto de las preferencias alimenticias de seis tipos de mosquitos en la prevalencia de flavivirus en una comunidad que engloba mamíferos, aves, anfibios y reptiles. El objetivo principal de este análisis radica en comprender cómo la preferencia alimentaria de los vectores puede influir en la prevalencia de enfermedades infecciosas.

Los mosquitos seleccionados para el estudio son: *Aedes aegypti*, *Aedes albopictus*, *Culex nigripalpus*, *Culex quinquefasciatus*, *Culex stigmatosoma* y *Culex tarsalis*. Para evaluar la distribución entre las clases de hospederos, se compararon cuatro modelos implementados en NetLogo 6.1.1. Uno de ellos operó como un modelo nulo, sin considerar preferencias alimentarias, mientras que en los otros modelos se exploraron las preferencias de alimentación de los vectores. Los dos modelos restantes mantuvieron las mismas características, con la variante de incrementar la variable de movimiento para aumentar la probabilidad de encuentro con la especie preferida para picar.

Mediante la obtención de la prevalencia de la clase de hospedero, se concluyó que las preferencias alimentarias reducen la prevalencia máxima en una comunidad hospedera en comparación con un modelo sin considerar preferencias alimentarias. Asimismo, se identificó que el aumento del movimiento de hospederos y vectores reduce el efecto de dilución producido por las preferencias de alimentación, limitándolo al doble de su magnitud. Es importante resaltar la relevancia de este tipo de modelo en la identificación y descarte de variables importantes, como la diferenciación entre humanos y mamíferos, que demostró ser irrelevante en nuestro contexto de estudio.

Capítulo VI: Interacciones Virales

Los seres vivos mantienen interacciones constantes con otros organismos, y los virus no son una excepción. Entre las interacciones más reconocidas se encuentran la coinfección, la exclusión y la antigenicidad cruzada. Estos tipos de interacción influyen en sus capacidades de dispersión y, por ende, en la prevalencia viral de un ecosistema. Por lo tanto, el estudio de estas interacciones puede brindarnos beneficios al aprovechar las relaciones que favorezcan la disminución de las prevalencias virales que afectan la salud pública. El objetivo fundamental de este análisis es comprender cómo las interacciones virales pueden influir en la prevalencia de enfermedades infecciosas.

En este estudio, evaluamos cinco modelos distintos de ABM (Agent-Based Models). Los primeros cuatro modelos consideraron una única interacción: coinfección, exclusión, antigenicidad cruzada y antigenicidad especial del vector. El quinto modelo integró las cuatro interacciones trabajando en conjunto. Se emplearon dos tipos de agentes, hospederos y vectores. Los hospederos pueden infectarse en presencia de un vector infectado, mientras que los vectores pueden infectarse cuando están en proximidad de un hospedero infectado. Cada modelo se ejecutó en 1000 simulaciones.

La variable de respuesta evaluada fue la prevalencia de agentes infectados, es decir, el número total de agentes infectados dividido entre el total de agentes. En cada simulación del modelo, se consideró únicamente el valor máximo de prevalencia.

En conclusión, la diversidad viral contribuye a reducir la prevalencia tanto en los hospederos como en los vectores. Cuando los virus se encuentran en igualdad de condiciones, la prevalencia tiende a distribuirse homogéneamente en la población.

En un escenario donde interactúan dos virus, la interacción que ejerce la mayor reducción en la prevalencia viral es la antigenicidad cruzada. En cambio, cuando existe una comunidad viral con diversas interacciones, la exclusión surge como la interacción que más favorece la disminución de la prevalencia.

Capítulo VII: Interacción Viral en el Vector

Los arbovirus han desencadenado una significativa morbilidad y mortalidad, generando un enfoque investigativo intensivo en la esfera de la salud. Asimismo, el 90% de los arbovirus son transmitidos por mosquitos. Estos insectos actúan no solo como portadores de los arbovirus, sino también como reservorios de un grupo denominado "virus específicos de insectos" (ISV). Los ISV constituyen una categoría emergente con el potencial de disminuir la transmisión de arbovirus. Cuando los mosquitos se infectan con ISV, su capacidad vectorial de arbovirus se reduce, impactando así en la prevalencia. Esta característica hace que los ISV puedan considerarse como agentes de biocontrol. Enfocándonos en las interacciones virales a nivel comunitario, buscamos entender cómo una comunidad viral puede interactuar internamente para reducir la prevalencia.

Dentro de los virus con interacciones más estudiadas, destacan el *Culex flavivirus* (CxFv), el Virus del Nilo Occidental, el Virus de la Encefalitis de San Luis, el Virus del Dengue y el Virus Zika. En este contexto, empleamos un modelo basado en agentes para evaluar la influencia del CxFv en la prevalencia de flavivirus. Para lograrlo, ejecutamos cuatro modelos distintos en NetLogo 6.1.1. El primer par de modelos consiste en un modelo nulo sin CxFv ni antigenicidad cruzada (interacciones virales), y otro modelo nulo sin CxFv pero con antigenicidad cruzada. Luego, repetimos ambos modelos, añadiendo la presencia del CxFv.

Hemos seleccionado seis especies de vectores: *Aedes aegypti*, *Aedes albopictus*, *Culex nigripalpus*, *Culex quinquefasciatus*, *Culex stigmatosoma* y *Culex tarsalis*. La evaluación de la prevalencia se ha llevado a cabo en cada modelo, partiendo de la misma prevalencia inicial. Cada modelo se ejecutó 1000 veces y se examinó la prevalencia máxima de los vectores portadores de diferentes virus en cada simulación.

Nuestros hallazgos indican que los ISV pueden desempeñar un papel crucial en el control biológico de otros virus, reduciendo notablemente la prevalencia. Por ejemplo, en nuestro modelo, el CxFv disminuye la prevalencia de Zika y el Dengue. No obstante, su aplicación debe ser cuidadosamente estudiada y aplicada, ya que, en presencia de otros virus nocivos, podrían aumentar su propia prevalencia.

Capítulo VIII: Comparación de las Prevalencias Máximas en Tres Ecosistemas de Celestún: Duna, Selva, Petén

A lo largo del tiempo, las interacciones ecológicas entre virus, vectores y hospederos han mantenido una uniformidad en los ecosistemas, pero el desarrollo de las sociedades modernas y la explotación excesiva de los recursos naturales han dado lugar a cambios en estas interacciones. En consecuencia, emergen enfermedades que afectan tanto a la salud pública como animal, así como a la conservación de especies. Diversas enfermedades arbovirales afectan a la vida silvestre. En particular, los flavivirus inducen infecciones persistentes en los vectores, generando una competencia viral más intensa en su interior. Las infecciones persistentes no siempre experimentan interferencia viral, lo que permite la coexistencia de diferentes virus en una misma célula, manifestándose como coinfecciones (cuando interactúan simultáneamente en el hospedero) o superinfecciones (cuando un segundo virus infecta al hospedero después de que este ya haya sido invadido por otro virus).

Con el objetivo de examinar la influencia de las comunidades hospederas y virales, desarrollamos un modelo basado en agentes (ABM) en NetLogo 6.1.1. Celestún se seleccionó como entorno para nuestros modelos debido a su diversidad, conteniendo especies clave para la transmisión de flavivirus. En este contexto, evaluamos tres ecosistemas: Duna, Selva y Petén. Empleamos datos abundantes de la literatura y de informes para construir las comunidades de hospederos, organizándolas en función de su susceptibilidad. Luego, ejecutamos un modelo susceptible-infectado-recuperado (SIR) para cada comunidad. Para evaluar la prevalencia máxima, repetimos las simulaciones 1000 veces.

Nuestros resultados destacan que la Selva presenta la mayor prevalencia, mientras que el ecosistema del Petén exhibe la menor. Cabe resaltar la relevancia de la densidad en cada entorno, ya que esta variable puede aumentar o disminuir la prevalencia dentro de las comunidades. Por otro lado, los factores que más influyen en la reducción de prevalencia son las interacciones de exclusión viral y la participación de virus exclusivos de los vectores. La diversidad de susceptibilidades en todos los niveles biológicos propicia la aparición del efecto de dilución, tanto en vertebrados como en vectores, y en nuestro caso particular, en simbiontes (virus). Todas estas herramientas se presentan como valiosas para el control biológico y natural de enfermedades emergentes en diversos ecosistemas.

Capítulo IX: Conclusiones, Supuestos del Modelo y Posibles Sesgos.

Es fundamental recordar que los modelos computacionales, aunque poderosos, conllevan riesgos al ser altamente maleables y propensos a desviarse del objetivo original. En este capítulo, se presentan los supuestos que hemos incorporado en nuestro modelo, reconociendo que estos podrían variar en el mundo real y generar impactos diferentes a los resultados. Nuestra reflexión y retroalimentación se centran en los sesgos inherentes y el riesgo inherente al modelo, buscando una evaluación exhaustiva.

Aunque conscientes de estos desafíos, nuestro propósito es establecer las bases en torno a las variables pertinentes en la transmisión múltiple y las interacciones virales. A través de este trabajo, aspiramos a incursionar gradualmente en el ámbito de investigación y fomentar el control biológico, destacando la importancia de conservar la diversidad viral.

Palabras clave: comunidades virales, flavivirus, coocurrencia,
interacciones virales, efecto de dilución.

Abstract

The ecological interactions among viruses, vectors, and wild hosts have demonstrated relative stability over time. However, due to the development and excessive exploitation of natural resources, these interactions have undergone changes, leading to outbreaks of emerging diseases that impact both public health and animal well-being, along with species conservation efforts. Notable examples of these emerging diseases include Dengue virus, West Nile virus, St. Louis virus, Yellow fever, Chikungunya virus, and Zika virus, all transmitted by mosquitoes.

In this research, the use of biological control is being tested as a strategy to regulate viral populations through the utilization of viral interactions, presenting an economically viable and environmentally sustainable alternative for pest control. It is crucial to highlight that these tests are conducted using computational models, underscoring the importance of conducting future comprehensive and comparative assessments with the ecological reality outside of the model. This approach not only seeks to understand the feasibility of the technique in a controlled environment but also lays the groundwork for potential practical applications in managing viral diseases and pests in real-world settings.

In the context of Flaviviridae family viruses, they establish persistent infections within vector populations throughout their lifecycles. This dynamic fosters heightened viral competition within vectors rather than humans. Consequently, instances exist where viral interference is absent, enabling the coexistence of multiple infectious agents within a single cell. This results in coinfections (simultaneous interactions in the host) or super-infections (sequential invasions by different viruses). These phenomena have been effectively demonstrated in cell cultures, indicating that coinfections can potentially alter vector susceptibility to specific arboviruses. Consequently, comprehensive studies encompassing viral, vector, and host communities are imperative to understanding factors that influence susceptibility dynamics.

Analyzing such complex systems necessitates various statistical approaches and analytical models. For instance, deterministic compartmental models like Susceptible-Infected-Recovered (SIR) models, commonly utilized in epidemiology, offer insight into understanding viral dynamics within communities. This work underscores the importance of community-level viral analyses to uncover emergent patterns where diverse virus species collectively mitigate the dissemination of infectious diseases.

Presently, the impact of viral diversity on host and vector communities remains largely unexplored. Given flaviviruses' propensity for coinfection, superinfection, and exclusion, they serve as an ideal study model. Consequently, our study will construct a model considering the co-occurrence of flaviviruses to comprehend the scope and directionality of viral interactions. Our hypothesis posits that facilitation and exclusion interactions significantly shape viral prevalence in both vectors and their natural hosts. We anticipate that increased viral diversity will correlate with reduced infection prevalence in each species.

To gain insight into the intricate dynamics of these complex systems, we will employ agent-based models (ABMs). ABMs, designed around foundational organizational rules, allow the manipulation of variables to test various hypotheses. A notable advantage of this modeling approach lies in its incorporation of artificial intelligence (AI), empowering agents to make decisions and adapt based on interactions with other actors.

The forthcoming chapters of this research endeavor are outlined as follows:

Chapter I: Selection of the Representative Model

In the realm of infection dynamics within nature, the influence of host, vector, and pathogen communities is widely acknowledged. In the pursuit of comprehending the intricate impact of these complex systems on the prevalence of vector-borne diseases, a crucial initial step involves the identification of primary vertebrate (host) and invertebrate (vector) species responsible for propagating these microorganisms.

This identification lays the foundation for pinpointing pivotal species, thereby facilitating the development of targeted preventive strategies.

This study is anchored on an extensive compilation of a global database drawn from published literature. Its primary objective is to ascertain the pertinent host species driving the worldwide transmission of mosquito-borne flaviviruses. This encompasses renowned pathogens such as West Nile virus, St. Louis virus, Dengue virus, and Zika virus—entities that pose significant concerns to both public and animal health.

Central to our investigation is the meticulous analysis of a database encompassing 1174 vertebrate host species alongside 46 documented vector species. This endeavor has facilitated the construction of intricate association networks interlinking these species. Notably, three host species—*Mus musculus*, *Sapajus flavius*, and *Sapajus libidinosus*—stand out with considerably higher centrality values. This prominence signifies their pivotal roles within the realm of flavivirus community interactions.

The methodologies employed in this study, coupled with the identification of species holding relevance within the network, have endowed us with fresh insights and coherence. This valuable information could potentially guide health authorities in reevaluating their approaches to prevention and control. The emphasis here is on directing efforts toward viral communities and their interplay. Importantly, the network techniques employed herein also hold promise for addressing other infectious diseases that undermine the well-being of animals and humans alike.

Chapter II: Description and Composition of Communities

Having identified the pivotal species in the transmission of multiple flaviviruses, our attention shifted to the selection of a suitable locale where these species coexist harmoniously. In this pursuit, the Yucatan peninsula emerged as the optimal geographical area to acquire the requisite data for our model, primarily due to the documented high prevalence of flaviviruses in this region (Farfan-ale et al., 2009).

Within the expanse of Yucatan, our focus settled on Celestún as the quintessential site for our model's foundation. This choice is underscored by the presence of three distinct ecosystems, intricately interconnected. This strategic decision affords us the unique opportunity to dissect and analyze three diverse communities, each with its corresponding spectrum of diversity. This approach enables us to comprehend the variables at play and juxtapose their respective influences within the model's framework. Furthermore, it's important to highlight that Celestún is located at a distance of approximately 100 km from Merida, which holds significant relevance in terms of public health, as there's a possibility of direct contact with an important urban area.

Celestún encapsulates three predominant ecosystems: Dune, Jungle, and Peten. This classification hinges primarily upon the prevailing vegetation type in each ecosystem. Our selection process leaned on the insights gleaned from three pivotal articles, which provide a broad overview of the diversity and abundance observed in Celestún. These foundational references, namely Profile (2006), Chablé-Santos and Sosa-Escalante (2010), and Hernandez-Perez et al. (2015), constitute the bedrock upon which we structure the communities employed in our computational models. These intricacies are elaborated upon in the forthcoming chapter.

Chapter III: Model Functionality

The operational framework of the model transpired within the confines of NetLogo software, version 6.1.1. This software boasts a user-friendly interface, affording a clear visualization of the constituent elements and the actions executed by the agents nested within the model.

At the core of the model, two distinct classes of agents are instantiated: hosts and vectors, each endowed with the prowess of artificial intelligence. These agents are bestowed with the capacity to discern the viruses to which they stand vulnerable. Moreover, they exhibit the acumen to gauge the presence of neighboring agents, parsing their species classification and an inventory of afflictions they harbor. This duality of attributes serves a dual purpose: the former, to instigate the enactment of dietary predilections; the latter, to facilitate a juxtaposition of disease catalogues among agents, thereby enabling the acquisition of viruses to which they are susceptible yet remain unexposed.

Of particular note, the mosquitoes have been meticulously coded to procreate at intervals of 30 days, coupled with a finite lifespan oscillating between 15 to 30 days. This foundational premise lays the groundwork for the simulation's temporal dynamics. This chapter delves into the intricate mechanics underpinning the model's functionality, all orchestrated within the purview of NetLogo's user interface.

Chapter IV: Model Standardization and Spatial Considerations

Biodiversity bestows upon us an array of ecosystem services (Perrings et al., 2010), and among these, the safeguarding of health through the mechanism known as the "dilution effect." This phenomenon operates by capitalizing on the diversity of vertebrate species, which in turn diminishes the prevalence of diseases in other host species. While previous SIR models have explored the dilution effect and its underlying mechanisms, the challenge resided in integrating spatial configuration. In our pursuit, we embarked on the examination of various agent movements (both vector and host) and their corresponding ranges.

In our investigative framework, we scrutinized four distinct ABM models, meticulously executed within the framework of NetLogo 6.1.1., in order to simulate a spectrum of ecological scenarios. These models encompassed diverse movements: linear, random, and circular. While linear movement involves agents solely advancing forward, randomness mimics the inherent unpredictability of organismal motion. Circular movement, on the other hand, entails a uniform rotation. By delving into these models, we ascertained that heightened species diversity within host communities engenders the operation of the dilution effect. Conversely, the susceptibility diversity among vector communities exerts minimal influence on disease prevalence, thereby restricting the extent of the dilution effect.

Remarkably, our model indicated that the nature of agent movement does not substantially sway the dilution effect's potency. In contrast, the distance traversed by agents stands as a variable that amplifies prevalence. This increment, albeit modest, remains constant until reaching the threshold of covering 1% of the total terrain. Ultimately, the dilution effect negates the influence of density-dependent factors on infectious disease prevalence within our model, culminating in the elaboration of a comprehensive assessment of disease dynamics under the mantle of varying spatial conditions.

Chapter V: Feeding Preferences

Mosquitoes, acknowledged as paramount vectors, wield the capacity to disseminate diverse diseases. Among these afflictions reside the flaviviruses. The triumphant viral transmission through mosquitoes hinges on their selection of susceptible species as hosts. However, mosquitoes exhibit distinct feeding preferences, a facet that has sparked numerous studies elucidating the nuances of their dietary patterns. The available information sufficiently underscores these feeding predilections.

In our pursuit, we constructed a model tailored to assess the impact of the feeding preferences of six distinct mosquito species on the prevalence of flaviviruses within a community encompassing mammals, birds, amphibians, and reptiles. This analytical endeavor strives to unveil the extent to which vector feeding preferences could influence the prevalence of infectious diseases. Our chosen mosquito species encompass: *Aedes aegypti*, *Aedes albopictus*, *Culex nigripalpus*, *Culex quinquefasciatus*, *Culex stigmatosoma*, and *Culex tarsalis*. The comparative analysis involved four models executed through NetLogo 6.1.1.

Two models, one incorporating vector feeding preferences and another implementing the same with an elevated movement variable to augment the likelihood of encountering the preferred host, were compared against a null model devoid of feeding preferences. Our analyses centered on evaluating the prevalence within the host class, thereby deciphering the distribution patterns. Intriguingly, the incorporation of feeding preferences tangibly diminished the peak prevalence within the host community, diverging from the outcomes exhibited by the model sans feeding preferences. Additionally, augmenting host and vector mobility yielded a twofold reduction in the dilution effect attributed to feeding preferences, an outcome with implications for the prevalence within an ecosystem.

In summation, our model advances our comprehension of the interplay between vector feeding preferences and disease prevalence. Furthermore, we underscore the utility of this modeling paradigm in unearthing vital variables, exemplified by the insignificance of differentiating between humans and other mammals within our model.

Chapter VI: Viral Interactions

In the intricate tapestry of life, interactions are a constant, and viruses are no exception. Among their interactions, coinfection, exclusion, and cross-antigenicity stand out. These interactions wield substantial influence over their capacity to spread, thus influencing the viral prevalence within an ecosystem. Unveiling these dynamics holds promise for harnessing interactions that can mitigate the burden of infectious diseases on public health.

The essence of this inquiry lies in understanding how viral interactions ripple through infectious disease prevalence. Our exploration encompassed the evaluation of five distinct Agent-Based Models (ABMs). The first quartet of models each spotlighted a singular interaction—coinfection, exclusion, cross-antigenicity, and vector-specific antigenicity. In contrast, the fifth model amalgamated all four interactions. Central to our investigation were two categories of agents—hosts and vectors. In this paradigm, a host becomes susceptible to infection when in proximity to an infected vector, while an infected vector results from proximity to an infected host.

Our simulations unfolded across 1000 iterations per ABM, with the prevalence of infected agents—connoting the proportion of total agents infected—serving as our response variable. Each simulation yielded the maximum prevalence value. The overarching revelation pertains to the inverse correlation between viral diversity and prevalence within both host and vector populations. Should the viruses operate under equable conditions, the prevalence becomes evenly dispersed across the populace. Moreover, when two viruses interact, the interaction exerting the greatest dampening effect on prevalence proves to be cross-antigenicity. On the other hand, within a viral community characterized by diverse interactions, exclusion emerges as the interaction primed to attenuate prevalence to a significant degree.

In synthesis, this chapter delves into the crux of viral interactions, accentuating their potency in sculpting the prevalence dynamics of infectious diseases within diverse ecological contexts.

Chapter VII: Viral Interactions within the Vector Community

Arboviruses wield a significant toll on morbidity and mortality, prompting focused health research. These microorganisms find their transmission route in mosquitoes, serving as vectors for a staggering 90% of arboviruses. Yet, these mosquitoes are not merely reservoirs for arboviruses; they also harbor a subset known as insect-specific viruses (ISVs). These ISVs, a relatively nascent category, bear the potential to mitigate the transmission of arboviruses. Upon infection with ISVs, mosquitoes experience a dampened capacity to transmit arboviruses, consequently diminishing disease prevalence. Thus, ISVs emerge as potential biocontrollers. Our focus converges on the intricate interactions occurring within a viral community, aiming to comprehend how these interactions orchestrate a reduction in prevalence.

Among the studied viral interactions, a spotlight is cast on *Culex flavivirus* (CxFv), alongside other notable entities like West Nile Flavivirus, Saint Louis Encephalitis Virus, Dengue Virus, and Zika. Employing an agent-based model, we endeavor to discern CxFv's influence on flavivirus prevalence. Our exploration unfolds through four distinct models, executed via NetLogo 6.1.1. Initial forays encompass a null model bereft of CxFv and cross antigenicity (viral interactions), paralleled by another null variant excluding CxFv yet retaining cross antigenicity. These configurations are revisited with the inclusion of CxFv. Our focus span across 6 vector species: *Aedes aegypti*, *Aedes albopictus*, *Culex nigripalpus*, *Culex quinquefasciatus*, *Culex stigmatosoma*, and *Culex tarsalis*. Prevalence evaluations take center stage, with uniform starting prevalence across all initial models. A meticulous tally of 1000 model runs per configuration reveals maximal prevalence scenarios of vectors harboring distinct viruses for each simulation.

Our findings underscore the potency of ISVs as potent allies in the battle against viral ailments. CxFv, notably, emerges as a potent agent in curtailing Zika and DENV prevalence within our model. However, vigilance is crucial: harnessing ISVs necessitates careful scrutiny, for their coexistence with detrimental viruses could inadvertently amplify their prevalence. This chapter delves into deciphering intricate viral dynamics within the vector community, unveiling potential solutions while advocating astute evaluation of challenges in the quest for disease management.

Chapter VIII: Comparative Analysis of Maximum Prevalence across Three Ecosystems: Dune, Jungle, and Peten de Celestún

While ecological interactions between viruses, vectors, and hosts have maintained a semblance of equilibrium over time, the advent of modern societies and the unabated exploitation of natural resources has ushered in shifts in these dynamics. These changes have spawned the emergence of diseases, culminating in consequences for public and animal health, as well as species conservation. The realm of wildlife bears the brunt of various arbovirus-induced diseases. Flaviviruses, for instance, orchestrate persistent infections within vectors, fostering heightened viral competence within these organisms. However, such persistent infections don't always entail viral interference, thereby enabling the coexistence of multiple viruses within the same cell—a phenomenon known as coinfection when viruses interact in a host concurrently, or superinfection when a second virus invades a host already harboring another virus.

In a bid to examine the interplay of host and viral communities, an agent-based model (ABM) was crafted within NetLogo 6.1.1. Celestún was singled out as the backdrop for our simulations due to its rich biodiversity and the presence of keystone species critical to flavivirus transmission. Three distinct ecosystems were scrutinized: Dune, Jungle, and Peten. Drawing from the repository of literature, three comprehensive reports furnished the basis for constructing host communities, categorized by susceptibility. Executing the SIR model, we gauged maximal prevalence across multiple runs, repeated 1000 times. Unveiling the landscape, the Jungle emerged with the highest prevalence, in stark contrast to Peten, characterized by a lower prevalence.

Density wields an influential role within each ecosystem, its oscillations serving to augment or curtail prevalence amid communities. Additionally, the most conspicuous agents reducing prevalence included the interactions of viral exclusion and the participation of viruses exclusive to vectors. Remarkably, the diversity of susceptibilities, whether within vertebrates, vectors, or symbiotic entities like viruses, fosters the manifestation of the dilution effect. The suite of analytical tools showcased herein holds potential for shaping biological and natural interventions aimed at reining in emergent diseases, thereby orchestrating a balanced dynamic across diverse ecosystems.

Chapter IX: Conclusions, Model Assumptions, and Potential Biases

It is imperative to bear in mind that computational models bear an inherent peril, as their inherent malleability makes it exceedingly easy to veer off course from the intended goal. This might encompass the incorporation of superfluous variables or misguided assumptions, or even the omission of pivotal variables, all of which can indelibly impact our interpretations. In this chapter, we embark on a candid exploration of the assumptions woven into the fabric of our model—acknowledging

their potential fluidity in the real world, leading to divergent consequences for our findings.

Within this introspective exercise, we also cast a spotlight on the biases that could possibly infiltrate our model. With a conscientious approach, we delineate the associated risks that we have embraced within the model, shaping its trajectory for evaluation. Notwithstanding these complexities, our overarching aspiration hinges on fashioning a bedrock of fundamental variables governing multifarious transmission and viral interactions. In so doing, we forge a nascent path within this realm of research—a trajectory primed to unravel the intricate tapestry of biological control, underscored by the preservation of viral diversity.

While mindful of these challenges, our intent is to lay down the foundations surrounding the relevant variables in multiple transmission and viral interactions. Through this endeavor, we aspire to venture progressively into the realm of research and foster biological control, emphasizing the significance of preserving viral diversity.

Keywords: viral communities, flavivirus, co-occurrence, viral interactions, dilution effect.

Résumé

Les interactions écologiques entre les virus, les vecteurs et les hôtes sauvages sont demeurées relativement stables dans le temps. Cependant, avec le développement et l'utilisation excessive des ressources naturelles, ces interactions ont évolué, entraînant l'émergence d'épidémies de maladies qui affectent la santé publique, animale et la conservation des espèces. Certaines de ces maladies émergentes qui touchent la faune sauvage sont causées par des arbovirus tels que le Denguevirus (DENV), le virus du Nil occidental (WNV), le virus Chikungunya (CHIKV) et le virus Zika (ZIKV), tous transmis par des moustiques.

Dans cette recherche, l'utilisation du contrôle biologique est mise à l'épreuve en tant que stratégie pour réguler les populations virales par le biais de l'utilisation des interactions virales, présentant une alternative économiquement viable et écologiquement durable pour la lutte antiparasitaire. Il est crucial de souligner que ces tests sont réalisés à l'aide de modèles informatiques, mettant en évidence l'importance de mener des évaluations futures complètes et comparatives avec la réalité écologique en dehors du modèle. Cette approche vise non seulement à comprendre la faisabilité de la technique dans un environnement contrôlé, mais elle pose également les bases pour des applications pratiques potentielles dans la gestion des maladies virales et des ravageurs dans des environnements réels.

En revanche, les virus de la famille des Flaviviridae induisent une infection persistante chez les vecteurs tout au long de leur vie. Cela ouvre la porte à une compétition virale accrue au sein du vecteur plutôt que chez l'humain. Par conséquent, des cas ont été signalés où il n'y a pas d'interférence virale, permettant à divers agents infectieux de coexister dans une même cellule, engendrant ainsi des co-infections (lorsqu'ils interagissent simultanément chez l'hôte) ou des surinfections (lorsqu'un virus envahit d'abord l'hôte, puis un second virus s'y installe). Ces co-infections ont été avec succès testées en culture cellulaire, laissant entrevoir que de telles co-infections pourraient altérer la sensibilité des vecteurs à certains arbovirus. Par conséquent, une approche holistique pour étudier les

communautés de virus, de vecteurs et d'hôtes est essentielle afin de comprendre les facteurs influençant les susceptibilités.

Afin d'analyser ces systèmes complexes et de saisir les interactions au sein de ces communautés, différentes approches statistiques et modèles analytiques ont été déployés pour appréhender cette complexité. Parmi eux, les modèles compartimentaux déterministes couramment utilisés en épidémiologie, tels que les modèles Susceptible-Infected-Recovered (SIR), permettent d'analyser les virus à l'échelle communautaire et d'obtenir les informations recherchées.

Ces modèles ont été adaptés tant aux communautés de vecteurs qu'aux hôtes, mettant en lumière l'importance de la richesse en espèces dans la réduction de la prévalence des infections. Ainsi, ce travail souligne l'importance d'analyser les communautés virales pour identifier des schémas émergents où la diversité des espèces virales limite la propagation des maladies infectieuses.

Actuellement, l'impact de la diversité virale sur les communautés d'hôtes et de vecteurs demeure inexploré. Les flavivirus se présentent comme un excellent modèle d'étude en raison de leur propension à la co-infection, à la surinfection et à l'exclusion mutuelle. Dans cette étude, nous élaborerons un modèle prenant en compte la co-occurrence des flavivirus, visant à comprendre l'étendue et la directionnalité des interactions virales. Notre hypothèse postule que les relations de facilitation virale et d'exclusion influencent directement la prévalence de ces virus tant chez les vecteurs que chez leurs hôtes naturels. Nous anticipons qu'une plus grande diversité virale sera associée à une prévalence d'infection réduite au sein de chaque espèce.

Pour appréhender la dynamique de ces systèmes complexes, nous adopterons une approche de simulation des interactions. À cette fin, nous utiliserons des modèles à base d'agents, également connus sous l'acronyme anglais ABM (Agent-Based Models). Dans ces modèles, les algorithmes sont structurés selon des règles organisationnelles fondamentales, et diverses hypothèses peuvent être testées en manipulant les variables. Ce qui distingue particulièrement ce type de modélisation, c'est la possibilité d'attribuer une intelligence artificielle (IA) aux agents, leur permettant de prendre des décisions et de réagir aux décisions des autres agents avec lesquels ils interagissent.

Le développement de la recherche est présenté dans les chapitres suivants :

Chapitre I.- Choix du modèle représentatif

Il est largement établi que les schémas d'infection observés dans la nature peuvent découler des interactions entre les communautés d'hôtes, de vecteurs et d'agents pathogènes. Comprendre comment ces systèmes complexes influent sur l'incidence des maladies à transmission vectorielle nécessite une première étape : l'identification des principales espèces de vertébrés (hôtes) et d'invertébrés (vecteurs) qui propagent ces agents pathogènes. Cette démarche ouvre la voie à la reconnaissance des espèces essentielles pour élaborer des stratégies préventives ciblées. L'objectif de cette étude, basée sur une compilation de données issues de la littérature scientifique mondiale, vise à identifier les espèces hôtes pertinentes dans la propagation mondiale de flavivirus transmis par les moustiques. Parmi ces flavivirus figurent le virus du Nil occidental, le virus Saint-Louis, le virus de la dengue et le virus Zika, tous préoccupants pour la santé animale et humaine.

L'analyse de la base de données résultante, comprenant 1174 espèces hôtes vertébrées et 46 espèces vectrices, a permis de mettre en place des réseaux d'associations entre ces espèces. Trois espèces hôtes, à savoir *Mus musculus*, *Sapajus flavius* et *Sapajus libidinosus*, se distinguent par des niveaux de centralité nettement plus élevés, suggérant un rôle clé dans les interactions des communautés de flavivirus. Les méthodes employées ainsi que les espèces identifiées comme pertinentes au sein de ce réseau ouvrent de nouvelles perspectives et cohérences. Ces découvertes pourraient orienter les décisions des responsables de la santé en matière de restructuration des stratégies de prévention et de contrôle, en mettant davantage l'accent sur les interactions au sein des communautés virales. Il est également envisageable que d'autres maladies infectieuses, préjudiciables à la santé animale et humaine, puissent profiter de ces approches basées sur les réseaux

Chapitre II. Description et conformation des communautés

Une fois les espèces clés impliquées dans la transmission multiple des flavivirus identifiées, nous avons choisi la localité où ces espèces cohabitent. Nous avons déterminé que la péninsule du Yucatan était l'emplacement idéal pour recueillir les données nécessaires à notre modèle, étant donné que des prévalences élevées de flavivirus y ont été signalées (Farfán-ale et al., 2009).

Dans la région du Yucatán, nous avons sélectionné Celestún comme site optimal pour notre modèle. Cela s'explique par la présence de trois écosystèmes différents étroitement interconnectés. Cette configuration nous offre l'opportunité d'évaluer trois communautés distinctes avec leurs propres diversités respectives. Cette approche nous permettra de comprendre leurs variables spécifiques et de comparer leur influence au sein du modèle. De plus, il est important de souligner que Celestún est situé à une distance d'environ 100 km de Mérida, ce qui revêt une importance significative en termes de santé publique, car il existe la possibilité d'un contact direct avec une zone urbaine d'importance.

Les écosystèmes présents à Celestún sont les suivants : Dune, Jungle et Peten. Cette classification repose principalement sur le type de végétation prédominant dans chaque écosystème. Nous avons identifié trois articles principaux offrant une description générale de la diversité et de l'abondance à Celestún. Ces articles ont été utilisés comme base pour structurer les communautés que nous allons intégrer dans nos modèles de calcul (Profile, 2006 ; Chablé-Santos et Sosa-Escalante, 2010 ; Hernandez – Perez et al., 2015). Ces aspects sont détaillés dans le chapitre correspondant de notre étude.

Chapitre III. Fonctionnement du modèle

Le modèle a été élaboré à l'aide du logiciel NetLogo, en version 6.1.1. Ce logiciel présente une interface conviviale, permettant d'observer les éléments et les actions exécutées par les agents au sein du modèle.

Au sein de ce modèle, les éléments qui exécutent les actions sont appelés « tortues », nous avons créé deux catégories de tortues : les hôtes et les vecteurs. Ces tortues ont été pourvues d'intelligence artificielle. Les deux catégories de tortues sont capables de reconnaître les virus auxquels elles sont sensibles. Elles peuvent également identifier les autres tortues présentes à proximité, en déterminant leur espèce et leur liste de maladies. Cette capacité est utilisée pour mettre en œuvre les préférences alimentaires des tortues et pour comparer leurs listes de maladies respectives. Par conséquent, elles sont en mesure d'attraper un virus auquel elles sont sensibles mais qui ne leur a pas encore été transmis. En ce qui concerne les moustiques, nous avons programmé leur reproduction tous les 30 jours et leur durée de vie varie de 15 à 30 jours.

Ces paramètres et fonctionnalités ont été intégrés dans le modèle afin de simuler le comportement des agents (tortues hôtes et vecteurs) et d'observer comment leurs interactions influencent la transmission des virus dans le contexte des écosystèmes étudiés.

Chapitre IV. Standardisation et spatialité du modèle

La biodiversité nous offre une multitude de services écosystémiques, parmi lesquels la protection de la santé en atténuant les risques d'infection grâce à l'effet de dilution. L'effet de dilution est un mécanisme par lequel la diversité des espèces vertébrées réduit la prévalence des maladies chez d'autres hôtes. Les modèles SIR précédents (Susceptibles-Infectés-Récupérés) ont déjà exploré l'effet de dilution et son mécanisme, mais l'intégration de la dimension spatiale posait problème. Dans notre étude, nous avons testé divers types de mouvements pour les agents (vecteurs et hôtes) ainsi que les distances qu'ils peuvent parcourir.

Nous avons évalué la prévalence maximale (calculée comme le rapport du nombre d'agents infectés sur la population totale, multiplié par 100) pour chaque simulation. Dans cette optique, nous avons conçu quatre modèles ABM distincts dans le logiciel NetLogo 6.1.1. pour simuler différentes situations écologiques. Tout d'abord, un mouvement linéaire où l'agent se déplace uniquement en avant. Ensuite, un mouvement aléatoire, qui s'approche davantage de la réalité, même si les mouvements des organismes sont rarement totalement aléatoires étant donné qu'ils ont généralement des objectifs dans leurs déplacements. Le troisième type de mouvement était circulaire, où l'agent se déplace en mouvement circulaire uniforme.

À partir des résultats de notre modèle, nous confirmons que la présence d'une diversité accrue d'espèces dans les susceptibilités de la communauté hôte favorise l'effet de dilution. Cependant, en ce qui concerne la communauté de vecteurs, la diversité des susceptibilités a un impact limité sur la prévalence de la maladie et, par conséquent, un effet de dilution limité.

Notre modèle a révélé que le type de mouvement n'est pas un facteur déterminant pour l'effet de dilution. En revanche, la distance parcourue par les agents a un impact sur la prévalence. Même si l'augmentation de la prévalence due à la distance parcourue reste faible mais constante jusqu'à atteindre environ 1% de la surface totale.

En conclusion, l'effet de dilution a annulé les effets dépendant de la densité de la prévalence des maladies infectieuses dans notre modèle. Cela ouvre la voie à de nouvelles questions et réflexions pour de futures investigations

Chapitre V. Préférences alimentaires

Les moustiques sont largement reconnus comme étant les vecteurs les plus importants en raison de leur capacité à transmettre une variété de maladies, y compris les flavivirus. La transmission virale par les moustiques s'effectue lorsque les espèces sensibles sont piquées, cependant, les moustiques présentent des préférences alimentaires spécifiques. De nombreuses études ont documenté les différents modèles de préférences alimentaires des moustiques. Les informations disponibles sur ces habitudes alimentaires sont suffisamment riches. Dans cette optique, nous avons élaboré un modèle visant à évaluer l'influence des préférences alimentaires de six espèces de moustiques sur la prévalence des flavivirus au sein d'une communauté composée de mammifères, d'oiseaux, d'amphibiens et de reptiles.

L'objectif de cette analyse est de comprendre comment les préférences alimentaires des vecteurs peuvent influencer la prévalence des maladies infectieuses. Les espèces de moustiques que nous avons sélectionnées pour ce modèle sont : *Aedes aegypti*, *Aedes albopictus*, *Culex nigripalpus*, *Culex quinquefasciatus*, *Culex stigmatosoma* et *Culex tarsalis*. Nous avons comparé quatre modèles créés dans le logiciel NetLogo 6.1.1. Le premier modèle est un modèle de base sans prise en compte des préférences alimentaires, tandis que le deuxième modèle intègre les préférences alimentaires des vecteurs. Les deux autres modèles sont identiques, mais ils augmentent la variable de déplacement pour accroître la probabilité de rencontrer l'espèce préférée à piquer.

En évaluant la prévalence au sein de chaque classe d'hôtes, nous avons pu examiner leur distribution respective. Nos résultats indiquent que les préférences alimentaires des moustiques réduisent la prévalence maximale au sein de la communauté hôte par rapport à un modèle où ces préférences ne sont pas prises en compte. De plus, nous avons constaté que l'effet de dilution induit par les préférences alimentaires est doublé lorsque le déplacement des hôtes et des vecteurs est augmenté.

Notre étude met en évidence que les préférences alimentaires ont un effet significatif sur la réduction de la prévalence maximale pouvant survenir dans un écosystème donné. De plus, cet effet est amplifié lorsque les mouvements des hôtes et des vecteurs sont augmentés. Nous soulignons également l'importance de ce modèle pour exclure ou identifier des variables pertinentes, telles que la distinction entre les humains et les mammifères, qui ne se sont pas révélées pertinentes dans notre contexte.

Chapitre VI. Interactions virales

Les êtres vivants sont en perpétuelle interaction avec d'autres formes de vie, et les virus ne font pas exception à cette règle. Parmi les interactions virales les plus reconnues, on peut citer la co-infection, l'exclusion et l'antigénicité croisée. Ces interactions ont un impact sur leur capacité de dispersion et, par conséquent, sur la prévalence virale au sein d'un écosystème. Par conséquent, l'étude de ces interactions peut nous être profitable pour exploiter celles qui favorisent la réduction des prévalences virales ayant des répercussions sur la santé publique.

L'objectif de cette analyse est de comprendre comment les interactions virales peuvent influencer la prévalence des maladies infectieuses. Pour ce faire, nous avons évalué cinq modèles d'Agents-Based Models (ABM) distincts. Les quatre premiers modèles ont été conçus avec une interaction unique : la co-infection, l'exclusion, l'antigénicité croisée et l'antigénicité spécifique du vecteur. Le cinquième modèle combine ces quatre types d'interactions ensemble. Les agents du modèle sont répartis en deux catégories : les hôtes et les vecteurs. Un hôte peut être infecté s'il est en présence d'un vecteur infecté, et un vecteur peut être infecté s'il se trouve à proximité d'un hôte infecté.

Nous avons exécuté le modèle 1000 fois pour chaque configuration d'ABM. La variable de réponse que nous avons mesurée est la prévalence des agents infectés, c'est-à-dire le nombre total d'agents infectés rapporté au nombre total d'agents présents. Dans chaque simulation du modèle, nous n'avons pris en compte que la valeur maximale de la prévalence.

En conclusion, nos résultats montrent que la diversité virale entraîne une diminution de la prévalence chez les hôtes et les vecteurs. Si les virus présentent des caractéristiques similaires, la prévalence sera uniformément répartie dans la population. Lorsqu'il y a deux virus différents en interaction dans un environnement, l'interaction qui réduit le plus la prévalence virale est l'antigénicité croisée. En revanche, dans une communauté virale avec des interactions multiples, c'est l'interaction d'exclusion qui favorise principalement la réduction de la prévalence virale.

Chapitre VII. Interaction virale dans le vecteur

Les arbovirus engendrent une importante charge de morbidité et de mortalité, ce qui justifie une attention soutenue dans la recherche en santé. Environ 90% des arbovirus sont transmis par les moustiques. Ces insectes ne sont pas simplement des réservoirs pour les arbovirus, mais aussi pour un groupe de virus connus sous le nom de virus spécifiques aux insectes (ISV). Les ISV sont un groupe relativement nouveau, possédant le potentiel de réduire la transmission des arbovirus. Lorsqu'un moustique est infecté par un ISV, sa capacité à transmettre les arbovirus diminue, ce qui réduit la prévalence de ces derniers. Par conséquent, les ISV peuvent servir de biocontrôleurs.

L'étude se focalise sur les interactions virales au sein d'une communauté, cherchant à comprendre comment les virus peuvent interagir entre eux pour réduire la prévalence globale. Parmi les virus ayant des interactions bien étudiées figurent le *Culex flavivirus* (CxFv), le flavivirus du Nil occidental, le virus de l'encéphalite de Saint Louis, le virus de la dengue et le virus Zika. Un modèle basé sur des agents a été employé pour évaluer l'influence du CxFv sur la prévalence des flavivirus. Quatre modèles différents ont été exécutés à cet effet sur NetLogo 6.1.1. Le premier modèle est un modèle nul sans CxFv ni interactions virales, suivi d'un autre modèle nul sans CxFv, mais incluant des interactions virales. Ensuite, les deux modèles précédents ont été répétés en ajoutant CxFv. Six espèces de moustiques vecteurs ont été prises en compte : *Aedes aegypti*, *Aedes albopictus*, *Culex nigripalpus*, *Culex quinquefasciatus*, *Culex stigmatosoma* et *Culex tarsalis*.

La prévalence a été évaluée dans chaque modèle, avec des prévalences initiales identiques pour tous les modèles. Chaque modèle a été exécuté 1000 fois, et la prévalence maximale des vecteurs porteurs de différents virus a été évaluée pour chaque simulation. Les résultats montrent que les ISV, tels que le CxFv, peuvent apporter une contribution significative au contrôle biologique d'autres virus en réduisant considérablement leur prévalence. Par exemple, dans notre modèle, le CxFv réduit la prévalence du virus Zika et du virus de la dengue. Toutefois, l'utilisation des ISV nécessite une approche minutieuse et adaptée, car si ces virus coexistent avec d'autres virus nocifs, ils pourraient potentiellement augmenter leur prévalence.

Chapitre VIII. Comparaison de la prévalence maximale de trois écosystèmes : Duna, Selva, Petén de Celestún.

Les interactions écologiques entre les virus, les vecteurs et les hôtes étaient autrefois stables dans le temps. Cependant, avec le développement des sociétés modernes et l'exploitation excessive des ressources naturelles, ces interactions ont changé, conduisant à l'émergence de maladies qui affectent la santé humaine, animale et la conservation des espèces. Différentes maladies arbovirales touchent désormais la faune. Parmi celles-ci, les flavivirus sont particulièrement notables, car ils provoquent une infection persistante chez les vecteurs, générant ainsi une plus grande compétition virale à l'intérieur des vecteurs.

Cette compétition virale peut entraîner des situations où des virus coexistent dans la même cellule sans interférer les uns avec les autres, ce qui est appelé co-infection. Il peut également y avoir des cas où un premier virus infecte un hôte et permet ensuite à un second virus de s'introduire, ce qui est appelé surinfection. Pour examiner l'impact des communautés hôtes et virales, nous avons utilisé un modèle basé sur des agents (ABM) dans le logiciel NetLogo 6.1.1. Nous avons choisi Celestún comme cadre pour nos modèles en raison de sa grande diversité et de la présence d'espèces clés pour la transmission des flavivirus. Trois écosystèmes ont été évalués : Dune, Jungle et Petén.

Nous avons construit les communautés hôtes en nous appuyant sur la richesse d'information tirée de trois rapports. Les hôtes ont été classés selon leur susceptibilité, puis nous avons exécuté un modèle SIR (Susceptibles-Infectés-

Récupérés). À chaque simulation, nous avons calculé la prévalence maximale et répété cette étape 1000 fois. Nos résultats indiquent que la prévalence est la plus élevée dans la Jungle et la plus faible dans le Petén. La densité joue un rôle significatif dans chaque écosystème en influençant la prévalence au sein des communautés.

D'autre part, les mécanismes les plus influents pour réduire la prévalence sont l'interaction d'exclusion virale et la participation des virus à l'exclusion des vecteurs. La diversité des susceptibilités, qu'elle soit chez les vertébrés, les vecteurs ou les symbiotes (dans ce cas, les virus), facilite l'apparition de l'effet de dilution. Tous ces éléments s'avèrent utiles pour envisager des stratégies de contrôle biologique et naturel des maladies émergentes dans divers écosystèmes.

Chapitre IX. Conclusions, hypothèses du modèle et biais éventuels.

Il est essentiel de garder à l'esprit que les modèles informatiques sont potentiellement trompeurs, car ils peuvent être facilement adaptés, conduisant à des déviations par rapport à l'objectif initial. Il est possible d'introduire des variables superflues, de faire des hypothèses incorrectes concernant les variables, ou même d'omettre des variables pertinentes dans nos interprétations. Dans ce chapitre, nous exposons les hypothèses que nous avons formulées dans notre modèle. Nous sommes conscients que ces hypothèses peuvent varier dans le monde réel et influencer différemment nos résultats. Nous reconnaissons également les biais et les risques que nous avons acceptés dans notre modèle d'évaluation, en fournissant une rétroaction critique et une réflexion sur notre approche.

Néanmoins, il convient de noter que notre intention est de jeter les bases en identifiant les variables pertinentes liées à la transmission multiple et aux interactions virales. Cela permettra progressivement d'ouvrir de nouvelles perspectives dans ce domaine de recherche. En outre, notre objectif est de favoriser les méthodes de lutte biologique tout en préservant la diversité virale. Ce travail contribuera à mieux comprendre les mécanismes complexes de transmission des maladies et à développer des stratégies plus ciblées et efficaces pour contrôler les maladies émergentes dans un contexte écologique.

Mots-clés : communautés virales, flavivirus, co-occurrence, interactions virales, effet de dilution.

Introducción

El ser humano y el desarrollo de las sociedades modernas han impactado en todas las escalas, incluyendo el suelo, el aire, la tierra y todos los ecosistemas que existen en el planeta. El impacto ha sido tan amplio que incluso la era en la que vivimos se le ha llamado el Antropoceno (Steffen *et al.*, 2011).

El Antropoceno se distingue por el crecimiento poblacional del ser humano, lo cual ha demandado cambios sociales y demográficos como la urbanización, el incremento de la capacidad agropecuaria, la deforestación generalizada, el aumento de residuos y zonas para su deposición, y la redistribución del agua, por mencionar solo algunos (Gubler, 2002). Cada una de estas transformaciones ha generado cambios en las interacciones ecológicas dentro de las especies y entre especies, alterando la estructura y función de los ecosistemas; dentro de estos, los patrones de interacción virus-vector-hospedero se han modificado y acrecentado en la interfaz donde los animales domésticos, la fauna silvestre y las poblaciones humanas interactúan(Gould *et al.*, 2017a).

Dentro del Antropoceno, los sistemas biológicos han sido afectados de tal magnitud que incluso las enfermedades infecciosas han cambiado sus patrones de ocurrencia. Actualmente han ocurrido brotes y rebrotes de enfermedades a nivel mundial, como el virus de la Fiebre Amarilla (YFV), el Denguevirus (DENV), el virus del Oeste del Nilo (WNV), el virus de St. Louis (SLEV), el virus del Chikungunya (CHIKV) y el Zikavirus (ZIKV). Todas ellas ocasionadas por arbovirus transmitidos por mosquitos (Gould *et al.*, 2017b).

Los arbovirus infectan a diferentes especies de vertebrados y de mosquitos, y pueden dispersarse más rápidamente y alcanzar mayores extensiones con la ayuda de los sistemas de transporte global. Además, la dispersión de los virus puede favorecerse por las adaptaciones de diferentes especies de mosquitos a los entornos urbanos y perturbados. Estas adaptaciones incrementan su densidad poblacional y facilitan la transmisión y mantenimiento de virus en nuevos lugares donde antes no eran reportados (Eritja *et al.*, 2005).

Las interacciones ecológicas entre los virus, los vectores y los hospederos silvestres se han mantenido relativamente estables a lo largo del tiempo; sin embargo, con el desarrollo y el uso desmedido de los recursos naturales, estas interacciones han cambiado y se han reportado brotes de enfermedades emergentes que afectan la salud pública y animal, así como la conservación de especies. Algunas de estas enfermedades emergentes que afectan a la fauna silvestre son ocasionadas por los arbovirus.

Las enfermedades son parte natural de los ecosistemas. En lugares conservados donde los arbovirus han coexistido con sus hospederos, la mortalidad puede ser baja; por ejemplo, la mortalidad ocasionada por YFV en primates no humanos es muy baja en los bosques africanos (STRODE, 1951; Gould and Solomon, 2008; Gould *et al.*, 2017b). Sin embargo, en los primates del nuevo mundo, la mortalidad es alta y se desconoce la diversidad viral con la que estos virus patógenos coexisten. Es decir, si estas enfermedades se transmiten a lugares nuevos, su impacto será mayor en el ecosistema, como lo son las enfermedades emergentes.

El control biológico es un método que consiste en utilizar organismos vivos con el objetivo de controlar las poblaciones de otro organismo. Este método es el más económicamente viable, ecológicamente recomendable y autosostenible para el control de plagas (Badii and Abreu, 2006). Esta técnica ha sido ampliamente utilizada en el control de plagas insectiles, pero no por ello es exclusiva de este tipo de plagas (Arredondo Bernal and del Bosque, 2008). Por lo tanto, proponemos utilizar este tipo de control para reducir las prevalencias virales en cualquier ambiente ecológico. Para desarrollar la técnica de control biológico en otros entornos donde están involucrados vertebrados se requiere el desarrollo de modelos más específicos y avanzados, ya que se incluyen un sin número de variables al involucrar diferentes grupos de seres vivos, lo que incrementa la complejidad del sistema. Actualmente, encontramos muy pocas investigaciones relacionadas con las interacciones virales o la conformación de las comunidades virales que puedan aportar información para la aplicación del control biológico a nivel viral.

Para entender la complejidad de las infecciones y su impacto en diferentes especies, es necesario utilizar enfoques inclusivos y a diferentes escalas. En la mayoría de los casos, desconocemos la estructura y composición del viroma en el hospedero, definiendo el viroma como el conjunto de virus en un nicho ecológico. Este viroma puede favorecer o controlar la diseminación de las enfermedades infecciosas. Por lo tanto, es apremiante reconocer las interacciones naturales virus-vector-hospedero para entender procesos estables a lo largo del tiempo e identificar las variables que pueden reducir el impacto que estos pueden tener en la salud pública, animal y ecosistémica.

Los arbovirus son virus que requieren de artrópodos hematófagos para completar su ciclo de vida. Se han documentado 137 arbovirus zoonóticos. Dentro de estos arbovirus se reconocen tres familias con importancia en la salud pública: Flaviviridae, Togaviridae y Bunyaviridae. Sus reservorios principales son las aves y los pequeños mamíferos, mientras que sus vectores son los mosquitos y las garrapatas.

La familia Flaviviridae provoca una infección persistente a lo largo de la vida de los vectores. Esto da oportunidad a que se genere una mayor competencia viral dentro del vector y no sobre el humano. En consecuencia, se han reportado casos donde no hay interferencia viral y diversos agentes infecciosos pueden coexistir en la misma célula, originando coinfecciones (cuando interactúan en el hospedero al mismo tiempo) o superinfecciones (cuando un virus invade primero al hospedero y posteriormente se aloja el segundo virus). Estas coinfecciones han sido probadas en cultivos celulares con éxito (Salas-Benito and De Nova-Ocampo, 2015). Por lo tanto, hay evidencia que sugiere que las coinfecciones pueden alterar la susceptibilidad del vector a ciertos arbovirus (Bolling *et al.*, 2015a).

Dentro de la literatura, se han reportado coinfecciones del virus del Chikungunya y el virusdel Dengue en humanos (Furuya-Kanamori *et al.*, 2016). También se han reportado otros tipos de interacciones, donde se informa que el virus Nhumirim reduce la replicación viral de WNV, la encefalitis japonesa y la encefalitis de St. Louis. No obstante, esto solo ha sido probado en cultivos celulares (Bolling *et al.*, 2015a). Otro informe de competencia entre virus es entre CxFV y WNV, donde se sugiere que el CxFV reduce la replicación de WNV por competencia del vector, es decir, el vector puede transmitir solo uno de los virus(Bolling *et al.*, 2012, 2015a). Sin embargo, aún se debate esta interacción ya que no está completamente comprobada. Por otra parte, se han llevado a cabo estudios con huevos de mosquitos recolectados en Colorado, Estados Unidos, que al ser incubados y desarrollarse en el laboratorio, han reportado coinfecciones y asociaciones positivas entre esos mismos virus (CxFV y WNV)(Newman *et al.*, 2011). Ambos informes con resultados contrastantes sugieren interacciones complejas que representan un excelente modelo para acercarnos al entendimiento de las interacciones dentro de las comunidades virales y sus efectos en la prevalencia de las mismas.

Aparentemente, la diversidad y presencia de diferentes virus en un hospedero pueden deberse a factores bióticos y abióticos que restringen o facilitan su tamaño poblacional y su persistencia en el tiempo. Por lo tanto, estudiar las comunidades de virus, de vectores y de hospederos integralmente resulta fundamental para entender los factores que determinan estos ensambles.

Para analizar este tipo de sistemas complejos y entender las interacciones dentro de las comunidades, se han implementado diversas aproximaciones estadísticas y diferentes modelos analíticos para entender dicha complejidad. Un ejemplo de estos son los modelos determinísticos compartimentales comúnmente usados en epidemiología, como los modelos Susceptible-Infectado-Recuperado (SIR). Estos modelos se desarrollaron con aproximaciones poblacionales, pero se han adaptado a nivel de comunidades para entender el cambio en la prevalencia de los patógenos cuando se modifica la riqueza de especies dentro de la comunidad. De esta manera, este modelo nos permitirá analizar los virus a nivel de comunidad y obtener la información que buscamos.

Estos modelos se han adaptado tanto en comunidades de vectores como de hospederos y han señalado la importancia de la riqueza de especies en la disminución de la prevalencia de la infección (Roche *et al.*, 2013). Por lo tanto, este trabajo resalta lo valioso de realizar análisis a nivel de comunidad viral para encontrar patrones emergentes donde la diversidad de especies de virus reduce la capacidad de diseminación de enfermedades infecciosas. Aunque se han logrado avances importantes, existen muchos vacíos de información sobre estos patrones a nivel de comunidad viral, lo que lo convierte en un nicho importante de investigación. Sin embargo, no podemos dejar de lado la influencia de las comunidades de hospederos y vectores, por lo que también serán tomadas en cuenta como variables dentro de los modelos.

Actualmente, no se ha analizado la influencia de la diversidad viral en las comunidades tanto de hospederos como de vectores. Siendo los flavivirus un excelente modelo de estudio debido a su predisposición a la coinfección, superinfección y exclusión. Para este estudio, realizaremos un modelo que tome en cuenta la coocurrencia de los flavivirus. Con el fin de comprender la magnitud y direccionalidad de las interacciones virales. Nuestra hipótesis es que **las relaciones de facilitación** (aumento en la replicación, transmisión o impacto de uno o varios de estos virus) **y exclusión** (reducción o inhibición de la replicación, transmisión o impacto de uno de los virus) **dentro de las comunidades virales influyen directamente en la prevalencia de dichos virus tanto en los vectores como en sus hospederos naturales. Esperamos que, a mayor diversidad viral, encontraremos una menor prevalencia de infecciones en cada especie y por lo tanto aplicar estos conocimientos en el control biológico de virus.**

Para entender el dinamismo de estos sistemas complejos, utilizaremos otra aproximación que nos permita simular las interacciones. Para comprender esto, emplearemos los modelos basados en agentes, conocidos por sus siglas en inglés como ABM (Agent-Based Models). En estos modelos, se estructuran algoritmos sobre las reglas básicas organizativas y se pueden poner a prueba diversas hipótesis al manipular las variables. Lo más atractivo de este tipo de modelaje es que los actores pueden estar dotados de inteligencia artificial (IA), lo que les permite tomar decisiones además de retroalimentarse de las decisiones de los demás actores con los que interactúan (Balietti, 2012).

A modo de conclusión, en esta investigación se pone a prueba el empleo del control biológico como una estrategia para regular poblaciones virales a través del uso de las interacciones virales, presentando una alternativa económicamente viable y ambientalmente sostenible para el control de plagas. Es crucial destacar que estas pruebas se realizan en modelos computacionales, y se subraya la importancia de llevar a cabo futuras evaluaciones exhaustivas y comparativas con la realidad ecológica fuera del modelo. Esta aproximación no solo busca comprender la viabilidad de la técnica en un entorno controlado, sino que también sienta las bases para posibles aplicaciones prácticas en la gestión de enfermedades virales y plagas en entornos reales.

La tesis se presenta en los siguientes capítulos:

Capítulo I: Elección del Modelo Representativo

En este capítulo, se expondrán los pasos que se implementaron para construir la base de datos y aplicar la teoría de grafos para depurar los mismos. Se abordará la detección de las especies relevantes tanto de hospederos como de vectores en la transmisión múltiple de flavivirus.

Capítulo II: Descripción y Conformación de las Comunidades

Una vez identificadas las especies clave en la transmisión múltiple de flavivirus, se seleccionó la localidad donde cohabitaban estas especies y se establecieron las comunidades a comparar en los modelos finales. En este capítulo se detalla la elección del lugar y se ofrece una descripción de la diversidad de cada comunidad.

Capítulo III: Funcionamiento del Modelo

Este capítulo aborda la base funcional del modelo y proporciona una descripción del software utilizado para su programación.

Capítulo IV: Estandarización del Modelo y Espacialidad

Con el propósito de estandarizar el modelo a emplear, se utiliza un modelo matemático previamente establecido en la literatura y se traduce a lenguaje computacional. Se comparan los resultados para lograr la estandarización del modelo utilizado. A continuación, se lleva a cabo una comparación de los tipos de movimiento de los agentes dentro del modelo y se evalúa su influencia en la prevalencia viral.

Capítulo V: Preferencias Alimenticias

Se evalúa la influencia de las preferencias alimenticias dentro de nuestro modelo para identificar los cambios en la prevalencia atribuibles a esta variable.

Capítulo VI: Interacciones Virales

En este capítulo se explora la explicación de las interacciones virales reconocidas y se evalúa su efecto en la prevalencia viral. Posteriormente, se reconocen los cambios que estas interacciones producen.

Capítulo VII: Interacción Viral en el Vector

De manera específica, se evalúa el efecto de *Culex flavivirus* dentro del modelo para distinguir los cambios provocados por este virus exclusivo de vectores, pero con efectos indirectos sobre los hospederos vertebrados.

Capítulo VIII: Comparación de las Prevalencias Máximas en Tres Ecosistemas: Duna, Selva, Petén de Celestún

Se lleva a cabo una evaluación del modelo final en tres ecosistemas elegidos: Duna, Selva y Petén de Celestún. Se explica la influencia de las variables dentro del modelo para incrementar o disminuir las prevalencias virales. Se proponen estrategias de control biológico y reducción de las prevalencias virales dentro de estos ecosistemas, con la posibilidad de extrapolarlas a situaciones similares.

Capítulo IX: Conclusiones, Supuestos del Modelo y Posibles Sesgos

Este capítulo presenta los supuestos asumidos dentro del modelo, reconociendo que pueden variar en el mundo real y generar cambios diferentes en los resultados. Como forma de retroalimentación y reflexión, se describen los posibles sesgos y el riesgo aceptado en el modelo para su evaluación.

A modo de cierre podemos decir que para desarrollar el modelo, debemos abordar las preguntas fundamentales: ¿quién? (capítulo I), ¿dónde? (capítulo II) y ¿cómo? (capítulo III). Para llevar a cabo la ejecución del modelo, es esencial esclarecer algunas variables, como el movimiento de los agentes (capítulo IV). Es innegable que la transmisión de los flavivirus requiere que los mosquitos se alimenten de vertebrados, lo que conlleva preferencias alimenticias (capítulo V). Asimismo, es crucial evaluar las interacciones virales de manera individual para discernir su influencia directa y los posibles cambios o sinergias que puedan surgir al incorporar más variables (capítulo VI). Además, es conocido que los vectores albergan virus específicos que no afectan a los vertebrados (capítulo VII). Al abordar y analizar cada una de estas secciones, resulta más sencillo comprender y atribuir la influencia de cada variable en el modelo completo presentado en el capítulo VIII.

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Capítulo I. Elección del modelo representativo.

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Network Analysis of Hosts and Vectors in the Multiple Transmissions of Flavivirus

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Abstract

Background: It is well established that infection patterns in nature can be driven by host, vector, and symbiont communities. One of the first stages in understanding how these complex systems have influenced the incidence of vector-borne diseases is to recognize what are the major vertebrate (*i.e.*, hosts) and invertebrate (*i.e.*, vectors) host species that propagate those microbes. Such identification opens the possibility to identify such essential species to develop targeted preventive efforts.
Methods: The goal of this study, which relies on a compilation of a global database based on published literature, is to identify relevant host species in the global transmission of mosquito-borne flaviviruses, such as West Nile virus, St. Louis virus, Dengue virus, and Zika virus, which pose a concern to animal and public health.
Results: The analysis of the resulting database involving 1174 vertebrate host species and 46 reported vector species allowed us to establish association networks between these species. Three host species (*Mus musculus*, *Sapajus flavius*, *Sapajus libidinosus*, *etc.*) have a much larger centrality values, suggesting that they play a key role in flavivirus community interactions.
Conclusion: The methods used and the species detected as relevant in the network provide new knowledge and consistency that could aid health officials in rethinking prevention and control strategies with a focus on viral communities and their interactions. Other infectious diseases that harm animal and human health could benefit from such network techniques.

Keywords: DENV, Zika, SLEV, WNV, community ecology

Introduction

PATHOGENS THAT ARE potentially multihost, such as Zika virus (ZIKV), Dengue virus (DENV), and West Nile virus (WNV), represent a public health threat because of the burden they impose on affected communities (Gubler, 2002). Because the virus can use a variety of hosts as refuge, it is necessary to fully characterize their life cycles, vector, and host preferences, as well as their spatial and temporal dynamics to design novel preventive and control techniques (Taylor et al., 2001). To do so, it is possible to identify relevant hosts and vectors that propagate infections inside ecosystems through a network approach based on graph theory.

In multihost transmission, the fact that the pathogen can be transmitted (or not) through different host species may affect the infectious disease transmission, as explained by the dilution effect theory where a high hosts competence richness in a species assemblage tends to decrease pathogen prevalence (Dushoff, 1996; Haydon et al., 2002; Hess, 1996; Holt et al., 2003; Roche et al., 2013; Roddam, 2001; Sober and Steel, 2017; Woolhouse et al., 2001). In other words, the diversity of competencies and distributions of hosts and pathogens regulate

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the disease risk and may influence interactions in communities. For this reason, it is crucial to identify hosts and vectors of multihost parasites for effective control (Taylor et al., 2001).

While there is a wide range of hosts, there is also a large array of micro- and macroparasites that are frequently overlooked, but have the same kind of ecological interactions as any living being (Mihaljevic, 2012). Current approaches typically attempt to consider interactions between a couple of parasites, but very rarely with the entire parasite diversity or parasite communities (Abbate et al., 2018; Seabloom et al., 2015), and thus all the interactions that can be found between all of them (Dallas and Presley, 2014; Johnson et al., 2015; Nieto-Rabiela et al., 2018; Rynkiewicz et al., 2015).

To understand how diverse interactions among viral communities can influence the prevalence of an infection, we must first understand which host can acquire several parasites at the same time. With this knowledge, we may characterize the interaction network and identify significant hosts and vectors that could be targeted to control infectious diseases, allowing the network to be fractured or disassembled later and therefore lower disease prevalence or impact (Holme, 2017; Luke and Harris, 2007).

In this study, we compile a global database based on a literature review to identify which vertebrate and invertebrate species are infected by a given virus, using here four viruses that affect human and animal health (Farfan-Ale et al., 2010; Fernández-Salas et al., 2007; Ibáñez-Bernal et al., 1997). Then, we utilize graph theory to model this complex system and identify the connections between host species, vectors, and viruses to find nodes with a high degree that may represent potentially interesting targets.

Methods

The Flaviviridae family is well-known to be mostly mosquito-borne viruses (Bolling et al., 2012). As

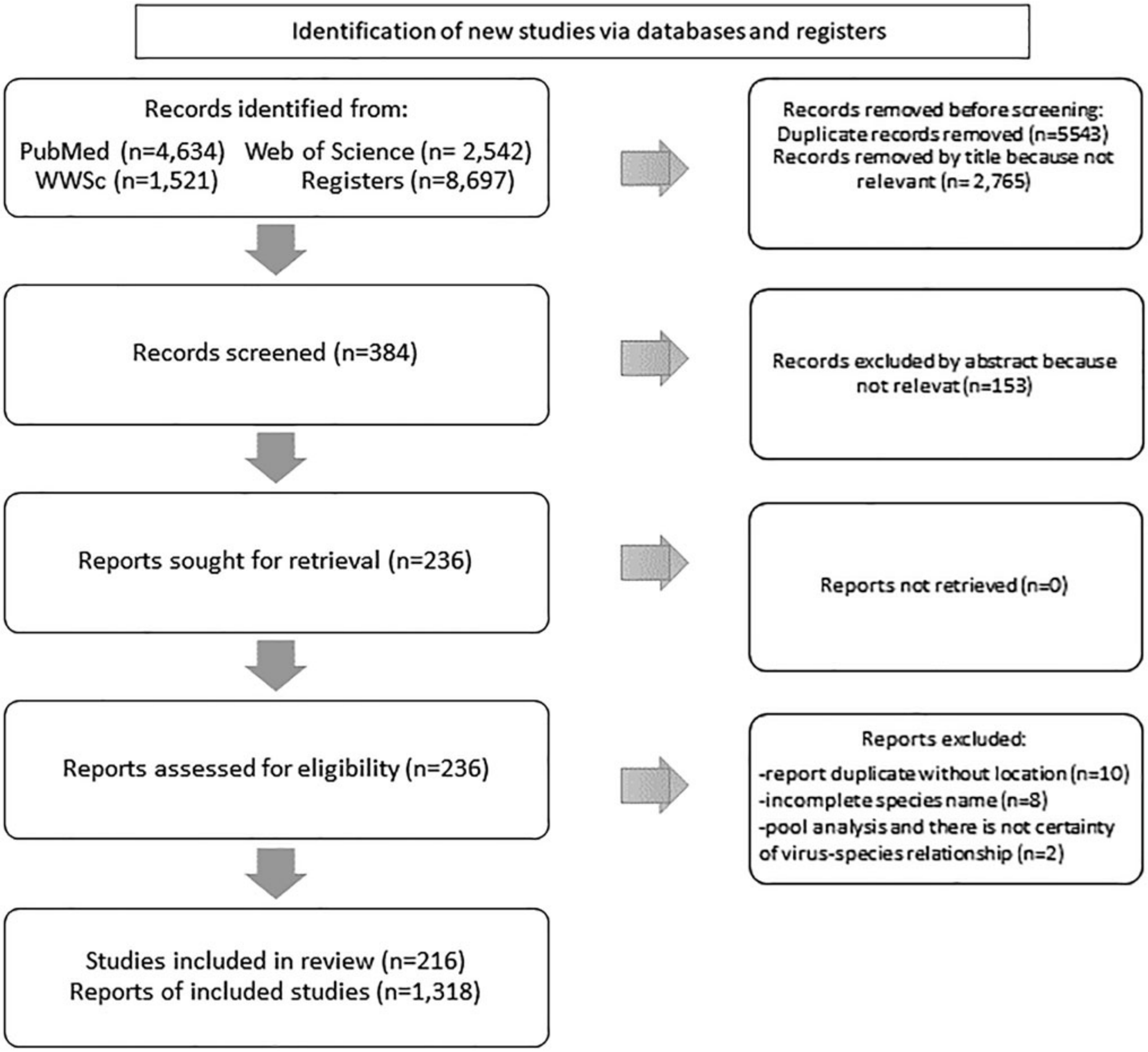

FIG. 1. PRISMA-style chart.

multipathogen/multihost dynamics, they frequently involve a variety of vector and host species (Hoyos et al., 2021). The WNV and the Saint Louis Encephalitis Virus (SLEV) have the most reported interaction in the literature (Bolling et al., 2015; Bolling et al., 2012; Salas-Benito and De Nova-Ocampo, 2015; Weaver and Barrett, 2004). The likelihood of contact would be substantially smaller in the case of a short-term infection. In this regard, they represent an excellent example of a multihost, multivector, multipathogen system that we can use in our research.

Database

We searched for the name of the virus (''SLEV,'' ''WNV,'' ''DENV,'' and ''Zika'') and the words ''Mammal,'' ''Bird,'' ''Reptilian,'' ''Amphibian,'' or ''Vector'' and the word ''detection'' for example ''DENV AND (mammal OR bird OR reptile OR amphibian OR vector) AND (detection)'' in the Web of Science database, PubMed database and WorldWide science between the years 1990–2022. The virus, host, and vector, as well as the location and reference from which the virus was identified, were all examined to create a database with all these information.

Networks

We used the *igraph* package implemented in R software version 3.5.3 (R Core Team, 2017) to create three different networks (host-vector, virus-host, virus-vector), and their visualization has been done with the package ''visNetwork'' (Almende and Thieurmel, 2016) in the software R to detect the relevant vertebrate hosts and vectors in the multiple transmissions of flavivirus.

Host-vector network. First, we created a host-vector network to visualize all the interactions between host species. A bipartite and weighted network with the two types of nodes, vertebrate and invertebrate host (host and vector, respectively), has been constructed. When vertebrate hosts and vectors shared at least one of the four flaviviruses chosen, they were connected in the network. It is worth mentioning that this does not rule out the possibility that this interaction could be due to shared interactions with a third species not observed, but we assume the vertebrate and invertebrate species have the capability to facilitate the viral interactions inside them and disperse the virus. We ran a sensitivity test by creating a network with stronger connections (assuming a link when at least two or three viruses are shared, see Supplementary Appendix SA1), and the conclusions.

Virus-host and virus-vector network. Then, two other networks were constructed, one for hosts and one for vectors. Two types of nodes are involved in these networks: the virus and its hosts, which are connected with an edge if an infection has been reported. As a high-degree value suggests that they can host many viruses, they can present coinfections and

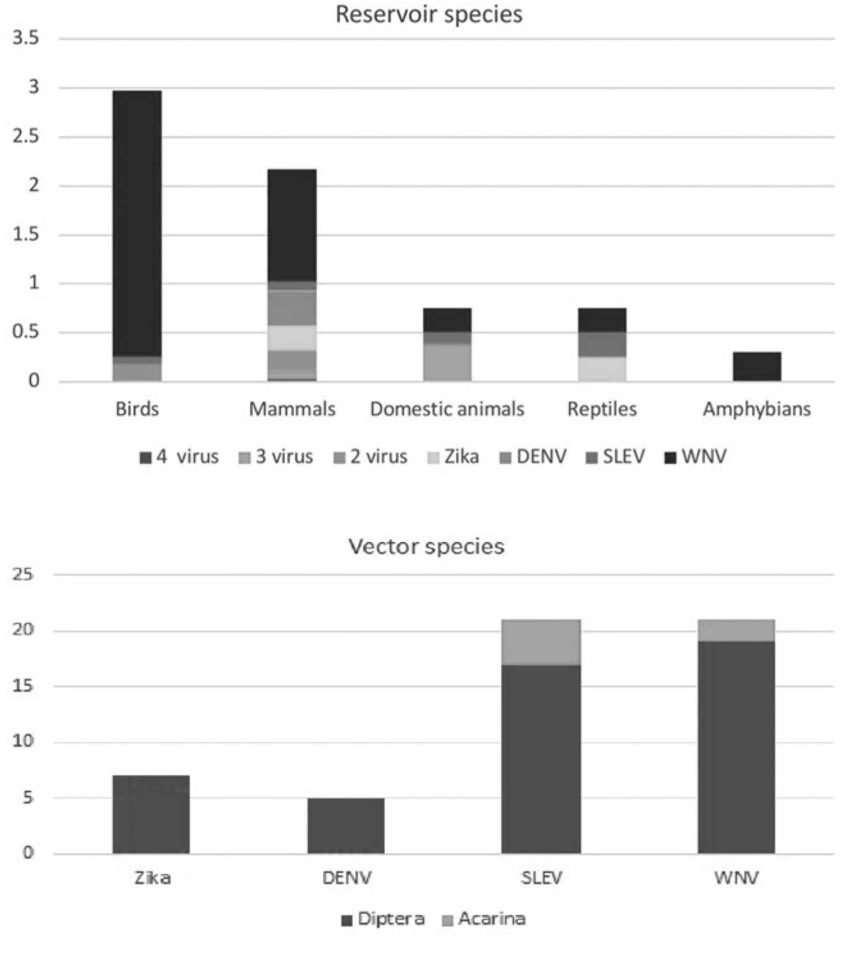

FIG. 2. Viral occurrence frequency in hosts and vectors. The *x* axis shows the type of host, the *y* axis shows how many species have been recorded in this type of host. In log 10, the graphic depicts the frequency of hosts in each class in each viral susceptibility group.

TABLE 1. TOP FIVE OF DEGREE AND BETWEENNESS IN THE VERTEBRATE HOST-VECTOR NETWORK

Vertebrate host				*Vector*		
Species	*Degree*	*Species*	*Betweenness*	*Species*	*Degree*	*Betweenness*
Mus musculus	54	*M. musculus*	2224.77	*Culex nigripalpus*	1200	37,483.94
Sapajus flavius	54	*S. flavius*	2224.77	*Culex quinquefasciatus*	1200	37,483.94
Sapajus libidinosus	54	*S. libidinosus*	2224.77	*Culex stigmatosoma*	1200	37,483.94
Equus caballus	43	*Artibeus lituratus*	1848.64	*Culex tarsalis*	1200	37,483.94
Myotis lucifugus	43	*Didelphis mammalialis*	1848.64	*Aedes taeniorhynchus*	1090	33,376.25

could be essential in viral interactions (mutations, cross-antigenicity, exclusion) inside them.

Network measurements. We measured different centrality values using this approach, including degree (the number of links for each node) and betweenness (the number of times a node acts as an intermediary to connect each possible pair of nodes) (Martínez-López et al., 2009; Newman, 2014, chap. 7; Nieto-Rabiela et al., 2019). These were calculated using the algorithms included in the ''IGRAPH'' (Csárdi and Nepusz, 2006) and ''NETWORK'' packages (Butts, 2008). In the multiple transmissions of flavivirus, network-level measures were effective for summarizing the ''big picture'' of the network and identifying the relevant vertebrate hosts and viruses.

Results

Database

WNV, SLEV, DENV, and ZIKV (Farfan-Ale et al., 2010; Fernández-Salas et al., 2007; Guerbois et al., 2016; Ibáñez-Bernal et al., 1997) were the viruses that we selected.

We found 8697 articles and the PRISMA graphic available in Fig. 1 explain the selection papers. There were 216 articles in English that fit the requirements since 1991 until November 2022. Among these articles, hosts were isolated in laboratory experiments and were thus omitted from further analysis. There were 1318 reports of vertebrate hosts that correspond to 1174 species. Finally, the final networks involve 1174 vertebrate host species, including 982 birds, 176 mammals, 7 domestic animals, 7 reptiles, and 2 amphibians (Fig. 2). There are 46 species on vectors (40 mosquitoes and 6 mites).

WNV has been found in 21 mosquito vector species and 1090 vertebrate host species, with the following distribution: 966 different bird species, 119 different mammal species, 3 reptile species, and 2 amphibian species. SLEV has been found in 21 mosquito species, 3 mite species, and 110 vertebrate hosts, including 85 bird species (2 of which are domestic), 23 mammalian species (2 of which are domestic), and 2 reptile species. Seven mosquito species have been identified infected by Zika, as well as 41 mammalian species, 2 reptile species, and 3 bird species, for a total of 46 vertebrate host species. Only mammals have been reported to have DENV, and we found 41 vertebrate host species and 5 mosquito vector species.

Vertebrate host-vector network

In the Vertebrate host-vector network, we found 1222 nodes with 25,415 edges after analyzing the 1174 vertebrate hosts and 46 vectors. This is a low-density network with a diameter of 4 and a density value of 0.033 (maximum value is 1). The average degree by species was 42.46 and the average distance between them was 744.18. Table 1 shows the top five vertebrate host and vector values; the rest of the data may be found in the Supplementary Material. The diameter suggests the diversification between the viral communities (greater number of viral combinations between hosts), while the density suggests that the viral communities of the hosts are more diverse (greater number of viruses within the same host).

Virus-vertebrate host network

The network with four viruses (ZIKV, WNV, SLEV, DENV) for a total of 1178 nodes and 1287 links, we analyzed 1174 vertebrate hosts and 4 viruses. With a diameter of 4, the density is 0.001. The average degree was 2.15 and the average distance was 775. Table 2 shows the top five vertebrate host and virus values; the rest of the information is available in the Supplementary Material.

Relevant vertebrate hosts to have viral co-occurrence

We found 86 species with the capability to host two different viruses (Supplementary Appendix SA1). *Mus musculus*, *Sapajus flavius*, and *Sapajus libidinosus* are the species with the capability to host the four different viruses and the last two with distribution in Brazil. The species with the capability to host three viruses were *Alouatta carava*, *Rattus rattus*, *Myotis lucifugus*, *Artibeus jamaicensis*, *Equus caballus*, and *Sigmodon hispidus*. *A. jamaicensis* can host WNV, SLEV, and DENV; and *S. hispidus* and *E. caballus* can host WNV, SLEV, and Zika. Results are consistent with previous research (Sotomayor-Bonilla et al., 2021).

Virus-vector network

We looked at 50 nodes spread across 46 vectors and 4 viruses (Zika, WNV, SLEV, and DENV). With a low density of 0.044 and a diameter of 6, the network includes 54 linkages. The average degree was 2.16 and the average distance

TABLE 2. VERTEBRATE HOSTS AND VIRUSES TOP FIVE OF DEGREE AND BETWEENNESS IN THE VIRUS-VERTEBRATE HOST NETWORK

Sorted by degree		
Species	*Degree*	*Betweenness*
Mus musculus	4	8113.19836
Sapajus flavius	4	8113.19836
Sapajus libidinosus	4	8113.19836
Alouatta caraya	3	6014.618332
Artibeus jamaicensis	3	6014.618332

Table 3. Vectors and Viruses Top Five of Degree and Betweenness in the Vertebrate Host Simple Network

Node	*Degree*	*Betweenness*
Aedes aegypti	3	202
Aedes albopictus	3	202
Culex nigripalpus	2	168
Culex quinquefasciatus	2	168
Culex stigmatosoma	2	168
Culex tarsalis	2	0

between them (betweenness) was 56.9. *Aedes aegypti* and *Aedes albopictus* have higher values than Zika, implying that they play an important role in world flavivirus transmission. Table 3 shows the top five viruses and vectors in terms of degree and betweenness values, with the rest of the data in the Supplementary Material.

Relevant vectors to have viral co-occurrence

Ae. aegypti and *Ae. albopictus* can host Zika, SLEV, and DENV, and *Culex nigripalpus*, *Culex quinquefasciatus*, *Culex stigmatosoma*, and *Culex tarsalis* can transmit SLEV and WNV.

Discussion

In this study, we discovered that only 4 virus species from the same family are linked with more than 1000 host species and 30 vector species. We have been able to identify different species presenting unusual characteristics in terms of the network metrics, suggesting that they can play a larger role than other species in viral transmission. Our main important result shows that *C. nigripalpus* is ranked first in the central values of the vertebrate host-vector network, and then third in the centrality values of the virus-vector network. This is because *C. nigripalpus* has a large number of vertebrate hosts, the vector is more important among the three components because it connects them all. Therefore, our results show that the control focus should be on *C. nigripalpus* in American continent, but in a global level *C. quinquefasciatus*.

In our network, the centrality values were higher in rodents and bats than in the other host species, except in one bird species (*Bubulcus ibis*). They are all considered invasive or generalist species with a wide range of distribution (Fowler and Cubas, 2001, chap. 9). They are potentially significant species in transmission because they may host a variety of viruses, have a high rate of interaction with host species, and can transfer viruses (Becker et al., 2018; Egoscue, 1976; Erazo et al., 2019). Regarding vectors, mites are not relevant for viral transmission, according to their low centrality values, and some investigations imply that mites are not always able to complete the cycle for some infections (Whitaker et al., 2009). As there is not much information about them, this judgment may be limited. On the opposite, *Culex* spp. are competent vectors, as shown in Fig. 3, because they have a greater impact on virus dissemination and are linked to viruses like WNV and SLEV, which have many vertebrate hosts recognized (Crockett et al., 2012; Newman et al., 2011).

Our study suffers of several caveats that need to be discussed. Due to the amount of the available data, the study was conducted at a worldwide scale rather than at a local one. It is therefore important to be careful with a potential local interpretation of the results. But to fully understand the system, modeling potential networks are required, rather than relying solely on published data that provide results for the local reality (Cooper et al., 2012). In this case, we assume a link between two host species when a virus infects two host species, despite the fact that they could have acquired the virus through interaction with a third host species.

We performed a sensitivity analysis with a network where we assume a link only if two viruses were shared by two hosts and our conclusions remain consistent (diameter of 4 and a density value of 0.020). We also want to reinforce that in the network, we are not saying that a link is a direct interaction, much less a physical one, but rather a vector/host in which a greater number of the flaviviruses that we select in our research transit. Therefore, these bases are a point of interest to understand, study, and monitor the existent of real transit through them, either with the help of more species between them. If there is communication, mutation or viral changes in one of these hosts/vectors could reach the other in a matter of a few years without us realizing it.

The next step is elucidating the information of the relevant nodes suggested by the betweenness of the network. The interesting point is to locate which host species can serve as a bridge between viruses. The importance of these bridges can be revealed by the number of connections associated to each of these host species (Pastor-Satorras et al., 2014). We mean that if a host has the capacity to host the four viruses, it is more likely that viral mutations occur in those hosts or that

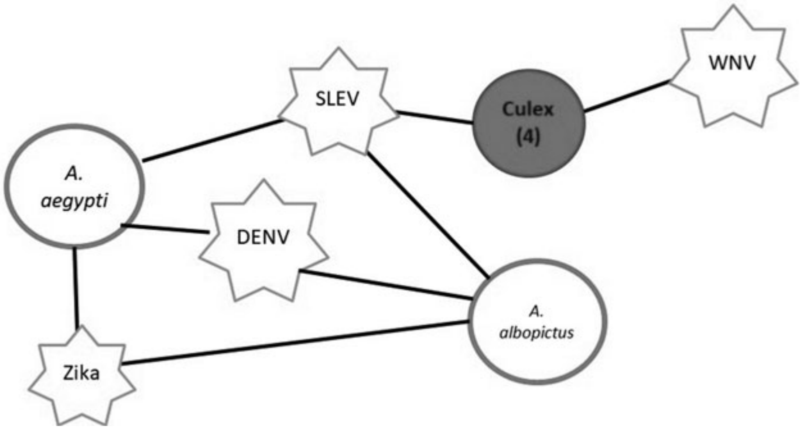

FIG. 3. Relevant vectors Network. Viruses are represented by *star*, vectors by *circle*, and associations by connections. *C. nigripalpus*, *C. quinquefasciatus*, *C. stigmatosoma*, and *C. tarsalis* are represented by the *red circle*.

these hosts can help us in epidemiological control by propagating attenuated viruses, with crossed antigenicity or excluding the problem virus of the virus. However, this requires gathering more data of positive and negative hosts at a local scale to characterize more precisely these networks and offer a surveillance/control opportunity.

Meta-analyses give us the advantage of processing a larger amount of data with a low budget and finding and rediscovering patterns on a large scale. But it always carries several biases since the researcher does not have control over the method of collecting information in the field as it would be in their own investigation. However, we can apply inclusion and exclusion criteria trying to modify these biases. In our investigation, we work with the information available, and it should be updated. We did not find information on true negatives that would clarify ‘‘ditches'' between species. But research biases are great opportunity niches in future research. There is also a temporal bias since the samplings have been conducted at different times. To minimize the temporal bias, we assume the capacity of the host species to host the virus, but we do not take current circulation into account.

Another bias is the oversampling and the undersampling biases in different regions, so we do not take their location into account. We cannot detect global patterns using our network, because the American continent (America) contains more species that share viruses than the other continents by oversampling. In contrast, we found only two flaviviruses of the four reported in Europe, and both viruses share a nonvertebrate host. To fully comprehend the system, extrapolation and modeling potential networks are required, rather than relying solely on published with geographical information data that provide results for the spatial-temporal reality (Cooper et al., 2012). Our objective is to locate the appropriate species in multiple transmissions focusing on viral communities inside the host, we prefer to apply prospective thinking in this scenario.

Conclusion

Flaviviruses are a large group of viruses that have a significant impact on human and animal health. Understanding the interactions between various vertebrate and invertebrate hosts and viruses can provide us with the information we need to make better decisions. So that these findings may help us develop control measures to control some flaviviruses, as well as other viruses, bacteria, parasites, or organisms in more complicated epidemiological situations.

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Authors' Contributions

F.N.-R.: conceptualization, data curation, formal analysis, investigation, methodology, and writing—original draft. F.E.: methodology. B.R.: supervision and validation writing—reviewing and editing. G.S.: supervision and writing—reviewing and editing.

Author Disclosure Statement

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Supplementary Material

Supplementary Material
Supplementary Appendix SA1

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Capítulo II. Descripción y conformación de las comunidades

En el capítulo anterior, se detalló el proceso de detección de las especies clave en la transmisión múltiple de flavivirus en México. Sin embargo, las 12 especies identificadas no son suficientes para el desarrollo adecuado de un modelo. Por lo tanto, es necesario conformar las diferentes comunidades a evaluar.

Durante nuestra búsqueda en todo México, identificamos la península de Yucatán como el lugar idóneo para obtener la información necesaria para incluir en el modelo, debido a las altas prevalencias de flavivirus reportadas en esta región (Farfan-ale *et al.*, 2009).

Dentro de la península de Yucatán, encontramos que Celestún cumple con las condiciones ideales para nuestro modelo, ya que cuenta con tres ecosistemas diferentes que están estrechamente conectados. Esta característica nos brinda la oportunidad de evaluar tres comunidades distintas, cada una con su propia diversidad. De esta manera, podemos comprender las variables específicas de cada comunidad y comparar su influencia dentro del modelo. Además, la ubicación de Celestún, a aproximadamente 100 km de Mérida, es relevante. Mérida es la duodécima ciudad más poblada de México, lo que refuerza la influencia de la población en los ecosistemas y, a su vez, la influencia de los ecosistemas en la salud pública (https://www.inegi.org.mx/datos/). La cercanía entre estos dos lugares también respalda la similitud entre ellos, lo que a su vez permite la extrapolación y aplicación de los resultados obtenidos en la ciudad de Mérida.

Los ecosistemas presentes en Celestún son los siguientes: Duna, Selva y Petén. Esta clasificación se basa principalmente en el tipo de vegetación existente en cada uno de ellos (Guadarrama *et al.*, 2018). Para la conformación de las comunidades a utilizar en nuestros modelos computacionales, nos apoyamos en tres artículos que proporcionan una descripción detallada de la diversidad y abundancia en Celestún (Profile, 2006; Chablé-Santos and Sosa-Escalante, 2010; Hernandez-Perez *et al.*, 2015).

En la siguiente figura se presentan las comunidades que hemos elegido para cada uno de los modelos:

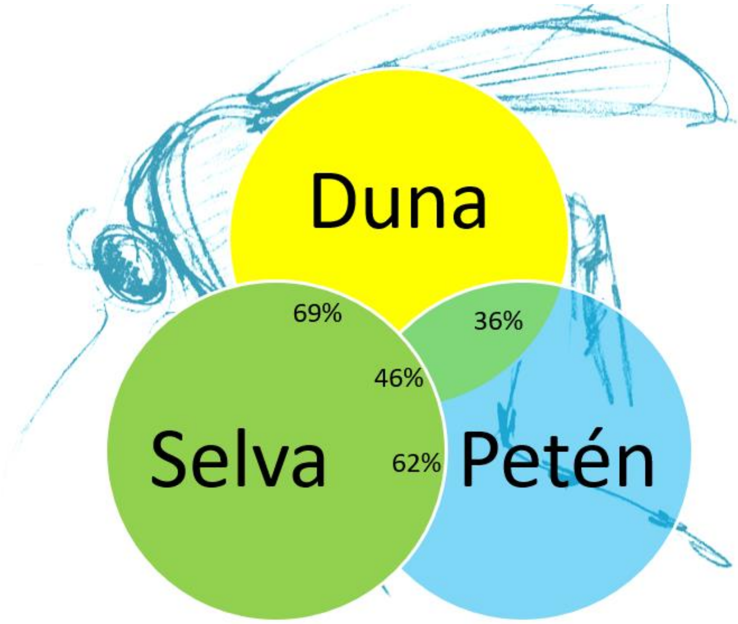
	DUNA	SELVA	PETEN	CLASE	DENV	SLEV	WNV	ZIKA
Agelaius phoeniceus	9			Ave		X	X	
Amazona albifrons		18		Ave			X	
Aratinga nana	4	53	19	Ave			X	
Ardea herodias	1			Ave		X	X	
Artibeus intermedius	2	14	12	Mammal	X			
Artibeus jamaicensis		1	5	Mammal	X	X	X	
Artibeus lituratus	1	6	10	Mammal	X		X	
Attila spadiceus		2	7	Ave			X	
Bubo virginianus			1	Ave			X	
Buteo brachyurus	1			Ave			X	
Buteo magnirostris		2		Ave			X	
Buteo nitidus			1	Ave			X	
Buteogallus anthracinus	2	1		Ave			X	
Calidris mauri	35			Ave			X	
Campylorhynchus yucatanicus	8			Ave			X	
Caracara plancus	1			Ave			X	
Cardinalis cardinalis	24			Ave		X	X	
Casmerodius albus	1	3		Ave			X	
Cathartes aura (no susceptible)	6(187)	4(109)	4(57)	Ave				
Chordeiles acutipennis	2			Ave			X	
Coccyzus minor	1			Ave			X	
Columbina passerina	7	14		Ave		X	X	
Columbina talpacoti	10			Ave		X	X	
Crotophaga sulcirostris	22	27		Ave			X	

Cyanocompsa parellina		1		Ave			X	
Cyanocorax yncas	2	16	14	Ave			X	
Cyclarhis gujanensis		2		Ave			X	
Dasypus novemcinctus	7	7		Mammal		X	X	
Dendrocygna autumnalis	3	3		Ave			X	
Dendroica coronata	4			Ave			X	
Dendroica dominica	1	5	2	Ave			X	
Dendroica magnolia	3	7	3	Ave			X	
Dendroica palmarum	3			Ave			X	
Dendroica petechia	4		1	Ave			X	
Dendroica virens		2		Ave			X	
Didelphis marsupialis	14	14		Ave	X		X	
Dives dives	1	21		Ave			X	
Egretta caerulea	1			Ave			X	
Egretta thula	1			Ave			X	
Empidonax minimus	3	21		Ave			X	
Eumomota superciliosa	4	1		Ave			X	
Falco sparverius	1			Ave		X	X	
Glaucidium brasilianum	2	7	8	Ave			X	
Habia fuscicauda			2	Ave			X	
Helmitheros vermivorum			2	Ave			X	
Larus atricilla	1			Ave			X	
Leptotila verreauxi	4	16	4	Ave			X	
Melanerpes aurifrons	2	26	7	Ave			X	
Melanoptila glabrirostris	1			Ave			X	
Mimus gilvus	44	1		Ave			X	
Mniotilta varia		3		Ave			X	
Molothrus aeneus	1	35		Ave			X	
Momotus momota			3	Ave			X	
Mus musculus	1			Mammal	X	X	X	X
Mycteria americana	2	4		Ave			X	
Myiarchus tuberculifer	4	3		Ave			X	
Myiozetetes similis		15		Ave			X	
Odocoileus virginianus	21	21		Mammal		X	X	
Ortalis vetula	5	27	14	Ave			X	
Pachyramphus aglaiae	3	3		Ave			X	
Pandion haliaetus	1			Ave			X	
Parula americana	2	9		Ave			X	
Passerina ciris	1	3		Ave			X	
Pelecanus erythrorhynchos	2			Ave			X	
Pelecanus occidentalis	32			Ave			X	

Penelope purpurascens			5	Ave			X	
Philander opossum			8	Ave				X
Picoides scalaris	1	6		Ave			X	
Pitangus sulphuratus		7		Ave			X	
Polioptila albiloris	20			Ave			X	
Polioptila caerulea	3	10	13	Ave			X	
Procyon lotor	30	30		Mammal			X	
Pteronotus parnellii		6		Ave	X			
Pyrocephalus rubinus	6			Ave			X	
Quiscalus mexicanus	17	3		Ave		X	X	
Saltator atriceps		1		Ave			X	
Seiurus aurocapilla		4	1	Ave			X	
Seiurus motacilla	2		1	Ave			X	
Thamnophilus doliatus	1	5		Ave			X	
Tiaris olivaceus		1		Ave			X	
Tringa flavipes	10			Ave			X	
Troglodytes aedon	1			Ave		X	X	
Turdus grayi		30		Ave			X	
Tyrannus melancholicus	13	4	2	Ave			X	
Tyrannus vociferans		1		Ave			X	
Vireo griseus	8	10	1	Ave			X	
Vireo pallens	14	7		Ave			X	
Wilsonia citrina			5	Ave			X	
Zenaida asiatica	4	14	4	Ave			X	
Zenaida macroura	4			Ave		X	X	

Nota: Se añadió la especie *Cathartes aura*, que no es susceptible, al modelo para representar a toda la población no susceptible. Entre paréntesis se indica el número total de ejemplares añadidos en el modelo.

En la siguiente figura, se representa el porcentaje de especies compartidas entre las comunidades de los diferentes ecosistemas. Como se puede observar, existe un alto grado de superposición entre estas comunidades debido a que se trata de la misma localidad y los ecosistemas están en estrecho contacto.



En relación a los vectores, se verificó la presencia de las especies de mosquitos en Celestún utilizando la plataforma "species" de CONABIO (http://species.conabio.gob.mx/). Identificamos la presencia de cuatro especies de mosquitos en los ecosistemas de Celestún. Es importante destacar que se trata de la misma comunidad de vectores presente en los tres ecosistemas seleccionados. Las susceptibilidades de estas especies se presentan en la figura siguiente.

	CxFv	WNV	SLEV	Zika	DENV
Aedes aegypti			X	X	X
Culex nigripalpus		X	X		
Culex quinquefasciatus	X	X	X		X
Culex stigmatosoma		x	x		

Capítulo III. Funcionamiento del modelo.

Descripción de NetLogo

El modelo se desarrolló utilizando el software NetLogo en su versión 6.1.1 (Wilensky, 1997). Este software ofrece una interfaz amigable que permite la observación de los elementos y las acciones que llevan a cabo los agentes dentro del modelo.

Es importante resaltar que en NetLogo, los elementos que ejecutan las acciones son denominados "tortugas", las cuales se posicionan en una cuadrícula de 16x16 (esta dimensión es ajustable). Además, este entorno tiene una configuración toroidal, lo que significa que si una tortuga alcanza uno de los bordes, reaparecerá en el extremo opuesto de manera continua.

Aplicando los conceptos mencionados previamente, nuestro modelo incluye dos tipos de tortugas: "hospedero" y "vector". Estas tortugas están programadas con inteligencia artificial. Ambos tipos de tortugas pueden identificar los virus a los que son susceptibles. También tienen la capacidad de reconocer a las tortugas a su alrededor, lo que les permite identificar la especie y la lista de enfermedades de otras tortugas. Esta funcionalidad es esencial para aplicar las preferencias alimenticias y permitir que las tortugas se contagien de virus a los que son susceptibles y que aún no han adquirido.

En el caso de los mosquitos, se les ha programado para que puedan reproducirse cada 30 días y, posteriormente, morir. La esperanza de vida de los mosquitos oscila entre 15 y 30 días.

A continuación, se proporcionan los fundamentos del código y una explicación de su utilidad en el modelo.

Creación de las tortugas

```
create-aedesaeyis 14
 [setxy random-xcor random-ycor
  set Life-Span 15 + random 30
  set es-vector True
  set enfermedades (list "DENV")
  set tick-infeccion -1
 ]
```

Se empleó una instrucción similar para cada una de las tortugas, donde se especificó su especie (*Aedes aegypti*), el número de individuos a crear (en este ejemplo es de 14), su ubicación inicial en un parche aleatorio, su esperanza de vida (en el caso de ser un vector), y la lista de enfermedades con las que inician. Además, se incluyó un contador de los días transcurridos desde la infección, que es útil para modelar las interacciones de antigenicidad cruzada.

Este enfoque de programación uniforme para las tortugas permitió establecer las características y comportamientos esenciales de los diferentes agentes en el modelo. Al definir parámetros como la especie, la cantidad, la posición inicial y las enfermedades asociadas, así como el seguimiento de los días desde la infección, se creó una base sólida para simular las interacciones virales y evaluar el impacto en la prevalencia y dinámica de las enfermedades en las comunidades estudiadas.

Acción de las tortugas

```
ask aedesaeyis
 [forward 1
  rt 50
  aedesaeyi-cn-cs-infecta-hospedero
  set Life-Span Life-Span - 1
  set sick sick - 1
  set es-vector True
  vector-muere
    ]
```

Para cada una de las especies se empleó una instrucción muy similar. Inicialmente, se invoca la especie (*Aedes aegypti*) y se le indica que se desplace 1 parche. Luego, se le solicita que gire 50 grados, logrando así un movimiento más natural. En el caso de que una especie sea un vector, se reduce en un día su esperanza de vida y se decrementa en un día su período de enfermedad. Si la esperanza de vida llega a cero, la especie fallece.

La instrucción para la transmisión de infecciones se describe a continuación. Es relevante señalar que solo una especie (*Cathartes aura*) no incorpora esta instrucción, ya que no es susceptible y simplemente avanza.

Este enfoque coherente en la programación de las especies permite simular con mayor precisión sus movimientos y comportamientos dentro del modelo. La inclusión de instrucciones para la transmisión de infecciones también es fundamental para evaluar la propagación de enfermedades y su impacto en las poblaciones estudiadas.

Instrucción de contagio

```
to aedesaeyi-cn-cs-infecta-hospedero
 let enfermedad-mosco enfermedades
 ifelse   any? turtles-here with [breed = humanos and sick >  0]
 [ ask one-of turtles-here with [ breed = humanos and sick >  0]
    [ contagia-humano-ac enfermedad-mosco
    set sick 7
    show enfermedades  ]]
 [ ifelse   any? turtles-here with [breed = humanos and sick <  0]
 [ ask one-of turtles-here with [ breed = humanos and sick <  0]
    [contagia-humano-exc enfermedad-mosco
    set sick 7
    show enfermedades  ]] ...
```

Se presenta aquí un fragmento de la instrucción, dado que en realidad es bastante extensa. Se procede a consultar a la tortuga (*Aedes aegypti*) si hay algún humano en su proximidad que tenga un registro de más de 0 días enfermo. En caso afirmativo, se lleva a cabo una comparación entre las listas de enfermedades. Si se identifica alguna enfermedad que no esté presente en ambas listas, la tortuga contagia al humano, quien a partir de entonces registra 7 días de enfermedad.

Recordando la instrucción previa, cada día que transcurre implica una disminución de un día en el contador de días enfermo. La antigenicidad cruzada se activa a partir del séptimo día de enfermedad. Con esto en mente, se cuentan con dos listas de infección: una antes de que la antigenicidad cruzada entre en acción (días 7 a 0) y otra después de su activación (menos de 0).

En caso de no encontrar un humano con las características mencionadas, la tortuga busca individuos con días de enfermedad menores a 0 y utiliza la lista de infección correspondiente para contagiar a dicho individuo.

Este proceso sigue el orden de hospederos según las preferencias alimenticias de los vectores (tal como se describe en el capítulo V), hasta encontrar un hospedero susceptible o hasta recorrer la lista sin éxito. Este proceso funciona de manera recíproca, ya que los hospederos también contagian a los vectores.

Identificación de listas de enfermedades

La instrucción que sigue es complicada de describir, pero hemos añadido explicaciones en negrita con el objetivo de clarificar su propósito.

```
to-report mePuedeDar-aedesaeyi [virus]
 let i 0
 let j 0
 let meDa True
 if member? virus enfermedades  ; Si ya enfermó que no enferme otra vez
    [set meDa False]
 while [i < length enfermedades and meDa]
; para cada enfermedad que tiene un vector en su lista de enfermedades
 [ set j 0
   let enfermedad  item i  enfermedades ; sacar la enfermedad i
   while [j < length listaaedesaeyi and meDa]
```

```
; revisar si el virus al que se enfrenta  esta en la lista de exclusión de la
enfermedad que tiene
   [   let excluye item j listaaedesaeyi
   if first excluye = enfermedad and member? virus sublist excluye 1 length excluye
     [  set meDa False  ]
     set j j + 1   ]
    set i i + 1  ]
 report meDa
end

to contagia-aedesaeyi [virusLista]
  let i 0
 while [i < length virusLista]
 [
 let virus item i virusLista
 if mePuedeDar-aedesaeyi virus
 [ set enfermedades insert-item 0 enfermedades virus]
   set i i + 1  ]
end
```

A continuación, mostramos un ejemplo de lista de exclusión, la primer posición es del virus al que nos referimos (SLEV) y los subsiguientes son lo virus con los que se excluye. De este modo todo virus que no se encuentre subsiguiente a su nombre puede ser adquirido por el vector.

```
set listaaedesaeyi [["SLEV" "CxFv" "DENV" "WNV" "Zika"] ["Zika" "CxFv" "DENV"
"SLEV" "WNV"]["DENV" "CxFv" "Zika" "SLEV" "WNV"]
   ["Nada" "CxFv" "WNV"]]
```

Reproducción de los vectores

En la literatura se reporta la transmisión vertical (transmisión directa de un simbionte a su descendencia) de CxFv por tal motivo incluimos dos instrucciones de reproducción, una para los vectores no portadores de CxFV y la segunda para los portadores de CxFV ya que heredan la infección a su descendencia. La descendencia consiste en 5 ejemplares.

```
to reproduce-vector-CxFv
   if  ticks > 0 and ticks mod 30 = 0
 [ask turtles with [es-vector = True and enfermedades = (list "CxFv")]
```

```
   [ hatch 5 [ fd 1 ] ] ]
end

to reproduce-vector
  if ticks > 0 and ticks mod 30 = 0
 [ask turtles with [es-vector = True and enfermedades != (list "CxFv")]
   [ hatch 5
     [ fd 1
  set enfermedades (list "Nada")] ] ]
end
```

Como variable respuesta del modelo evaluamos la prevalencia máxima, calculada como el número total de agentes infectados dividido entre el total de agentes para cada simulación. Esta prevalencia se calculaba para vectores, hospederos y la prevalencia total (vectores y hospederos en conjunto).

Utilizando los fundamentos explicados previamente, se procedió a desarrollar el código completo, realizando ajustes específicos para cada una de las especies. De esta forma, se aseguró el cumplimiento de sus susceptibilidades y preferencias alimenticias. Debido a la longitud y la repetitividad del código en su totalidad, consideramos que no es necesario incluirlo en su totalidad.

Capítulo IV. Estandarización del modelo y espacialidad.

Spatial configuration and dilution effect in agent-based models

Abstract

Biodiversity provides us with numerous ecosystem services, one of which is health protection through the mitigation of infection risks attributed to the "dilution effect." This mechanism involves the diversity of vertebrates decreasing disease prevalence in other host populations. While prior SIR (Susceptible-Infected-Recovery) models have examined the dilution effect and its mechanisms, incorporating spatial configuration posed a challenge. We conducted experiments with various movement types for agents (vectors and hosts) and explored the distances they could cover. We assessed the maximum prevalence ((number of infected agents/total population) * 100) in each simulation across 4 distinct Agent-Based Models (ABMs) implemented in NetLogo 6.1.1, aiming to replicate diverse ecological scenarios. Our exploration encompassed three movement patterns: linear, where agents moved forward only; random, which, while not entirely random due to organisms often having directional intent, approximated realism better; and circular, wherein agents exhibited uniform circular movement. Our findings reaffirm that greater species diversity in the host community's susceptibilities supports the operation of the dilution effect. In contrast, diversity in vector community susceptibilities minimally influences disease prevalence, resulting in a limited dilution effect. Surprisingly, we identified that movement type holds negligible relevance for the dilution effect within our model. Instead, movement distance emerged as a pivotal variable impacting prevalence. Although changes in prevalence remained modest, they were consistent until movement covered roughly 1% of the total surface area. Importantly, the dilution

effect counteracted the density-dependent effects of infectious disease prevalence in our model. In summary, our study underscores the crucial role of species diversity within host communities for the dilution effect to be effective, while revealing limited influence from vector susceptibility diversity. We also challenge the conventional assumption that movement type significantly impacts the dilution effect, highlighting movement distance's more substantial role. Our findings shed light on the complex dynamics of disease prevalence in the context of spatial configurations and diverse ecological scenarios.

Introduction

Biodiversity serves as a source of various ecosystem services(Perrings *et al.*, 2010), notably including health protection through the attenuation of infection risks, a phenomenon referred to as the "dilution effect"(Estrada-Peña, 2009). The dilution effect operates as vertebrate diversity curtails disease prevalence in other host populations (Ostfeld and Keesing, 2012). Three key mechanisms underpin the action of the dilution effect within an ecological community. Firstly, vectors must exhibit generalist behavior, devoid of strong food preferences. Second, the host community should encompass a multitude of susceptible species. Lastly, interaction between species within the host community is essential (Ostfeld and Keesing, 2000).

The dilution effect has been explored across various natural instances, such as Lyme disease, *Batrachochytrium dendrobatids*, and West Nile Virus(Ostfeld and Keesing, 2000; Swaddle and Calos, 2008; Searle *et al.*, 2011; Civitello *et al.*, 2015). However, grasping the role of species diversity in diminishing disease prevalence demands not only recognition of natural examples but also theoretical comprehension of intricate interactions, coupled with empirical testing to comprehend the mechanics underlying this phenomenon.

Previous work, notably Roche *et al.*, 2013, validated this assumption within a mathematical model, reporting a decrease in disease prevalence with heightened diversity in host susceptibilities. Conversely, an escalation in prevalence was observed with increased diversity in vector susceptibilities, owing to vector abundances. Our study aims to determine whether this pattern holds true without altering vector and host abundances, by introducing spatial configuration through a computational Agent-Based Model (ABM).

While the previous model sought to elucidate the dilution effect's mechanism, the ABM functions at an individual scale, offering the ability to manipulate host and vector movement types and distances. Importantly, the influence of spatial configuration on the dilution effect has not yet been examined.

Although exposure to infectious diseases influences epidemiological prevalence (Organización Panamericana de la Salud, 2011), studies incorporating spatiality have predominantly focused on epidemiological investigations, often using geolocation and Geographic Information Systems (GIS) (Auchincloss *et al.*, 2012). Yet, the impact of movement patterns on vector-borne diseases, whether in wildlife or isolated environments, has remained largely unexplored. As such, we assess the effects of three movement patterns.

Model description

In a bid to maintain comparability with Roche et al., 2013, we utilized closely aligned parameters. While Roche et al. employed a mathematical model in MATLAB(MATLAB, 2018) to compute prevalence rates with life history variables but without spatiality, our approach leveraged ABMs in NetLogo 6.1.1 to incorporate spatial variables. This enabled a comparison between information derived from mathematical and ABM models.

Our simulation established a versatile disease model applicable to diverse mosquito-borne diseases. The model followed an SIR (Susceptible-Infected-Recovered) compartmental framework, with agents transitioning between states of susceptibility, infection, and recovery. The probability of infection was determined for each model as illustrated in Figure 1. The simulation operated in daily time steps and continued until no susceptible agents remained.

Purpose

Our study seeks to discern how the diversity of susceptibility within vector and host species (agents), coupled with spatial configuration, influences the prevalence of infectious diseases in an ABM context. A central objective is to identify the potential presence or absence of the dilution effect.

Model environment

We evaluated four distinct ABM models using NetLogo 6.1.1 (NetLogo: Wilensky, 1999). Two agent types, hosts and vectors, were considered. Each model incorporated 1000 hosts and 300 vectors. Agents could exist in two states: infected or susceptible. Hosts could become infected when in the same patch as an infected vector, while vectors could be infected when in proximity to an infected host. Infection probabilities varied across models based on community susceptibility. Hosts recovered within 7 days, while vectors had lifespans ranging from 15 to 30 days and reproduced at a rate of 5 vectors per 30 days. Refer to Figure 1 for a summary of initial parameters.

Figure 1: Initial parameters of each simulation

ABMs Models				
Name	species	community species	vector	Community vectors
Initial hosts infected	0	0	0	0
Initial vectors infected	300	300	100	100
Number of host species	1	10	1	1
Number of vector species	1	1	1	10
Probability to be infected (host susceptibility)	1	0.2-1	1	1
Probability to be infected (vector susceptibility)	1	1	1	0.2-1

Evaluation

We executed the model 1000 times for each ABM configuration, with a maximum runtime of 100 days. The variable of interest, prevalence of infected agents, was computed by dividing the total number of infected agents by the total number of agents and then multiplying by 100 for each day. Within each model run, we extracted the maximum prevalence value across the 100 days.

Spatial

We introduced modifications to the spatial configuration in two dimensions: movement type and distance covered by agents. We hypothesized that these factors could influence prevalence in the models.

Type of movement.

Three distinct movement types were tested to simulate diverse ecological scenarios:

1. Linear movement: Agents moved straight ahead. Although unrealistic, it served as a simple model.
2. Random movement: A more realistic movement type, accounting for organisms' objectives in their movements. This movement was derived from the wolf-sheep predation model in NetLogo (Wilensky, 1997).
3. Circular movement: Agents exhibited uniform circular movement, akin to a macro-scale representation of a home range in ecology.

Distance moved

We employed a standardized surface spanning patches -16 to 16, equivalent to a 33x33 square patch grid in NetLogo. The simulation included movements of 1, 5, 10, 20, 30, and 50 patches based on the movement types described earlier. To assess the realism of this scale, we calculated the percentage of surface traversed by agents: 0.09%, 0.45%, 0.91%, 1.83%, 2.75%, and 4.59%, respectively.

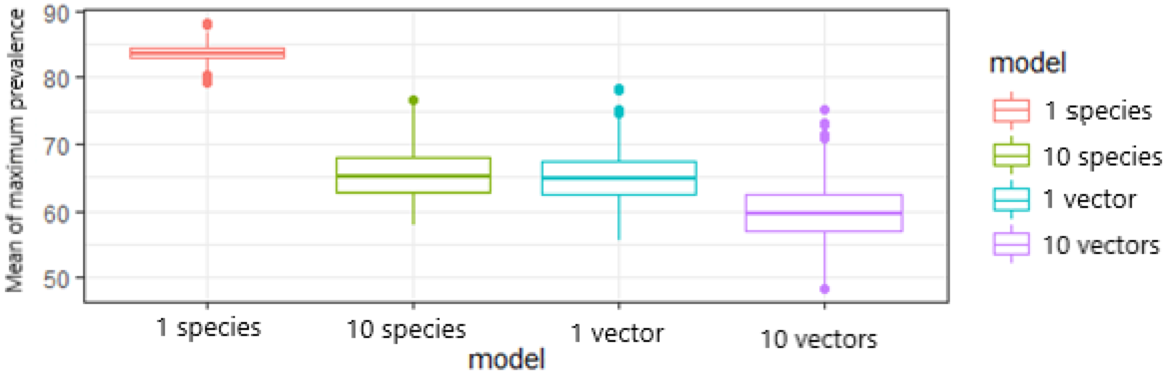
Density

Subsequently, we tested eight different agent densities, calculated as the number of agents (vectors and hosts) divided by the number of patches. The density values tested were 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, and 2. In each density scenario, we again computed the maximal prevalence from 1000 simulations of each model.

Results

To assess the influence of diversity susceptibility, we analyzed the 1000 maximum prevalence results for the ABM species with ABM community and ABM vector with ABM community vector, calculating significant differences. We employed the Wilcoxon Mann-Whitney test due to non-normal distribution and heterogeneous variances (Fay and Proschan, 2010) to compare populations. Both comparisons yielded significant differences: 18.38 and 5.1537 respectively. Notably, increased diversity in agent susceptibility led to a decrease in prevalence in both cases. It's interesting to observe that host distances were approximately three times greater than those of vectors, a finding consistent with Roche's mathematical model (Roche *et al.*, 2013) . This implies comparability between the two models.

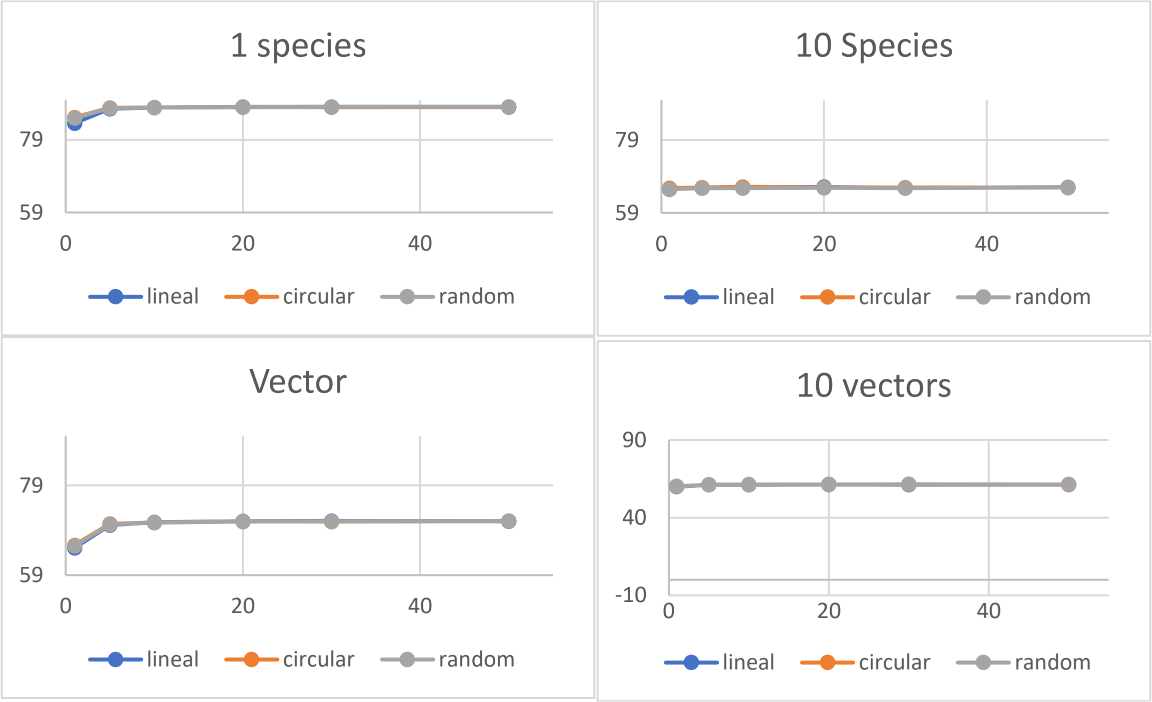
Figure 2: A boxplot depicting the four diversity susceptibility models.



Spatial

We can see in the figure 2 the lack of influence on the spatial configuration in our models. At each scale we identify unstable behavior on prevalence when the diversity of susceptibilities is added but the difference is to stretch.

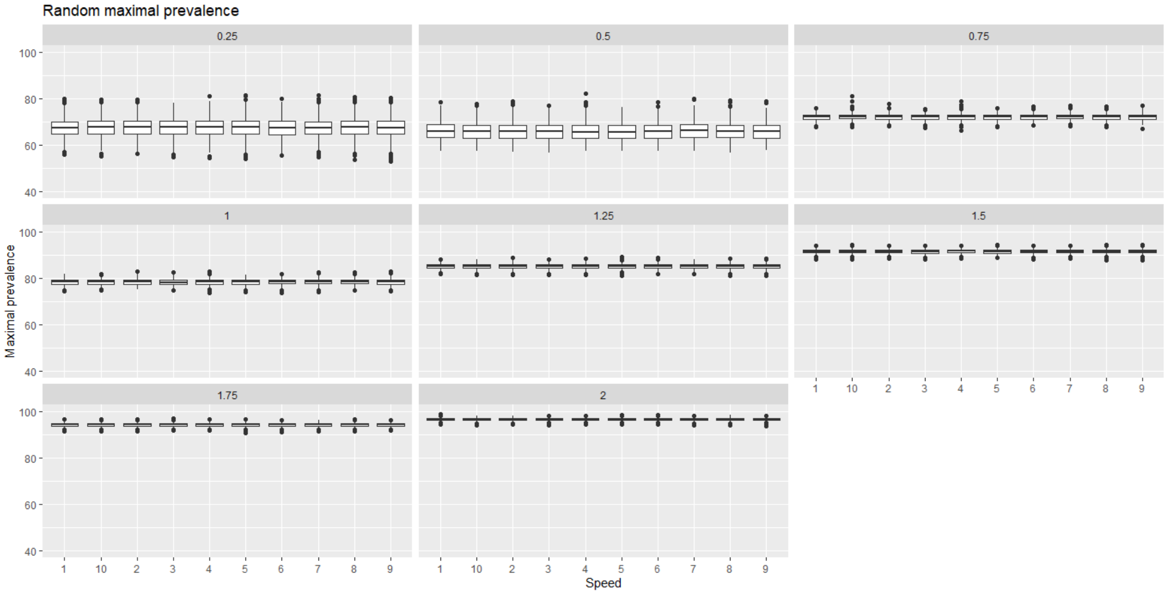
Figure 3. Influence of the spatial movements in the four models (at same scale).



Density

In our density tests, we focused on the 4 models using random movement with 10 different movement distances (1 to 10 patches). Notably, we observed no significant changes in the maximal prevalence across most models, except for the case where susceptibility diversity was absent.

Figure 4. Maximal prevalence in the random movement model without diversity testing density.



Discussion

This study marks the first attempt to evaluate the influence of spatial configuration on the dilution effect, and our findings indicate that while the type of movement doesn't appear to significantly affect the effect, the distance covered by agents does impact prevalence.

We have confirmed through our model that a higher species diversity in the susceptibilities of the host community indeed allows the dilution effect to operate effectively. On the contrary, the diversity in susceptibilities of the vector community has a limited impact on the prevalence of diseases and the dilution effect.

Moreover, our results align with previous findings (Roche et al. 2013) showing that it's the abundances of vectors that amplify prevalence. When vector abundances are held constant, we do not observe the same amplification effects. Nevertheless, we must be cautious in making broad generalizations about movement effects as our model has specific assumptions. For instance, it assumes a high contagious rate and a small surface area. Factors such as food preferences that influence vector movement are not included. Further research with adjusted variables is necessary to gain deeper insights into the impact of movement patterns on the dilution effect.

Our study also highlights that the distance of movement plays a crucial role in prevalence. Although the change in prevalence is modest, it remains constant until agents cover approximately 1% of the total surface. This threshold could serve as a valuable reference point for understanding how movement influences epidemiology management efforts.

Regarding density, we observed that diversity of susceptibilities nullifies the impact of density on prevalence. However, in cases lacking susceptibility diversity, higher density leads to a significant increase in prevalence. This suggests that the dilution effect counteracts density-dependent effects on disease prevalence in our model. This presents an intriguing area for further exploration, both practically and within our model.

Computational models offer the advantage of precise agent behavior specification, as demonstrated by the spatial movement in our model. Nevertheless, we must exercise caution and thoroughly understand each modified parameter's implications. Parsimony remains key – the simplicity of mathematical models can efficiently solve numerous problems.

Conclusion

In conclusion, our model reconfirms that greater species diversity in host susceptibilities facilitates the dilution effect. Conversely, diversity in vector susceptibilities has a limited impact. Movement type seems inconsequential, while movement distance influences prevalence. Our findings also reveal that the dilution effect counteracts density-dependent prevalence effects.

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Capítulo V. Preferencias Alimenticias.

Feeding preference influence in a flavivirus ABM

Abstract

Mosquitoes are widely recognized as significant vectors capable of transmitting several diseases, including flaviviruses. Successful viral transmission occurs when mosquitoes bite susceptible species, but their feeding preferences play a crucial role in this process. Numerous studies have documented various feeding patterns in mosquitoes. Building upon this information, we've developed a model to assess the impact of feeding preferences of six mosquito species on the prevalence of flaviviruses within a community comprising mammals, birds, amphibians, and reptiles. The primary objective of this analysis is to comprehend how the feeding preferences of vectors influence the prevalence of infectious diseases. The chosen mosquito species for this study are *Aedes aegypti*, *Aedes albopictus*, *Culex nigripalpus*, *Culex quinquefasciatus*, *Culex stigmatosoma*, and *Culex tarsalis*. We've compared four models using NetLogo 6.1.1: a null model without feeding preferences, a model incorporating feeding preferences of the vectors, and two additional models that retain feeding preferences while increasing the movement variable to enhance the likelihood of encountering the preferred host species. Prevalence within host classes has been calculated to assess distribution among them. Our findings indicate that feeding preferences of the vectors reduce the maximal prevalence within a host community when compared to a model lacking feeding preferences. Moreover, the effect of feeding preferences is halved when displacement (movement) of hosts and vectors is increased, thereby diminishing the dilution effect caused by feeding

preferences. The results highlight the potential of feeding preferences to lower the maximum prevalence within an ecosystem. This reduction is further magnified when host and vector movement is enhanced. This model underscores the significance of ruling out or recognizing critical variables, as exemplified by the insignificance of differentiating between humans and other mammals in our specific model. In conclusion, this research contributes to our understanding of how feeding preferences of mosquito vectors can impact the prevalence of flaviviruses within a diverse ecological community. The insights gained from this study could have important implications for disease management and prevention strategies.

Introduction

Mosquitoes hold significant importance as vectors due to their capability of transmitting various diseases (Takken and Verhulst, 2013; Öhlund, Lundén and Blomström, 2019). Among the diseases they transmit are flaviviruses, a group of viruses with potential public health implications (Crockett *et al.*, 2012). Due to their disease-transmitting potential, mosquitoes have been a subject of extensive research. Effective viral transmission by mosquitoes is contingent on their biting of susceptible species; however, mosquitoes do not indiscriminately bite any potential host. Instead, they are guided by specific attractants related to their potential food sources. These attractants can include odorants, color, body heat, body mass, gender, climate, physiology, and even the presence of animal parasites (Takken and Verhulst, 2013; Hoyos *et al.*, 2021).

It is crucial to emphasize that feeding preference patterns vary across mosquito species. Extensive research has detailed these distinct feeding preferences. Some patterns are consistent, while others describe more specific subgroups within the mosquito population (Daugherty *et al.*, 2011; Muñoz *et al.*, 2012; Takken and Verhulst, 2013; Hoyos *et al.*, 2021). Furthermore, each mosquito species can exhibit either generalist or specific feeding preferences The literature contains reports on class preferences such as birds or mammals, and certain mosquito species exhibit preferences for specific host species, such as crows or robins (*Turdus migratorius*) (Kilpatrick *et al.*, 2006).

These feeding preferences play a role in altering transmission dynamics and potential prevalence within populations. The influence of feeding preferences on disease transmission is particularly evident in studies on the West Nile Virus (WNV), where certain avian species have been identified as amplifying transmission due to mosquito feeding preferences (Kilpatrick *et al.*, 2006). Some studies have estimated transmission risks based on diet composition, further highlighting the impact of mosquito feeding preferences on disease transmission (Kilpatrick *et al.*, 2006; Richards *et al.*, 2006; Muñoz *et al.*, 2012; Del Cid *et al.*, 2018).

While a wealth of information exists on feeding patterns and their influence on vector-borne disease transmission, there are additional interacting elements that can shape the system. The diversity of mosquito species and susceptible hosts can modify the effects of feeding preferences on disease transmission dynamics. Thus, we have developed a model to assess the impact of feeding preferences of six mosquito species on the prevalence of flaviviruses within a community comprising mammals, birds, amphibians, and reptiles.

Model description

Purpose

The primary aim of this analysis is to explore how the feeding preferences of mosquito vectors influence the prevalence of infectious diseases. We have focused on flaviviruses as a model due to the diversity of mosquito species that act as their vectors.

Model environment

We selected six mosquito species known to transmit flaviviruses: *Aedes aegypti*, *Aedes albopictus*, *Culex nigripalpus*, *Culex quinquefasciatus*, *Culex stigmatosoma*, and *Culex tarsalis*. These mosquitoes are well-studied, and we extracted their feeding preferences from the literature. To obtain this information, we conducted searches on Web of Science using the scientific names of the mosquitoes and the term "feeding preference" (results shown in Table 2). Each of these mosquito species can bite a wide variety of animals, which we categorized into classes: mammals, birds, amphibians, reptiles, and humans (human separated from mammals due to *Aedes aegypti*'s preference for humans).

We compared four models using NetLogo 6.1.1 (NetLogo: Wilensky, 1999). The models included a null model without feeding preferences, a model incorporating the feeding preferences of the vectors, and two additional models retaining feeding preferences but increasing the movement variable to enhance the likelihood of encountering preferred host species. The movement value chosen was 10 based on previous experiments (Chapter IV). The models evaluated host prevalence as an indicator. Each model included 1000 hosts and 300 vectors, and feeding preferences were attributed according to the hierarchy in Table 1. The prevalence within host classes was assessed to evaluate distribution. Hosts and vectors in the model could either be infected or healthy. Infection could occur when a host and a vector shared the same space and the vector bit the host; similarly, vectors could become infected after biting an infected host. Vectors could reproduce and die (see appendix for further details).

Table 1: Hierarchy of Feeding Preferences in the Model

Mosquito	Order
Aedes aegypti ***Aedes albopictus*** ***Culex nigripalpus***	Humans Mammals Birds Amphibious Reptiles
Culex quinquefasciatus	Birds Mammals

	Humans Amphibious Reptiles
Culex stigmatosoma	Mammals Birds Humans Amphibious Reptiles
Culex tarsalis	Mammals Humans Birds Amphibious Reptiles

Evaluation

Each model was executed 1000 times to ensure robustness in the results. We calculated the prevalence of infected hosts for each virus separately, allowing for individual evaluation. The maximum prevalence value observed in each simulation was considered for analysis.

Results

While we found relevant literature on mosquito feeding preferences, it's noteworthy that only a limited number of studies quantified these preferences or performed comparisons between different host classes or species. The researchers contributing to this body of work are from diverse countries including the USA, Thailand, India, Italy, and Australia. The studies were published between 2005 and 2019.

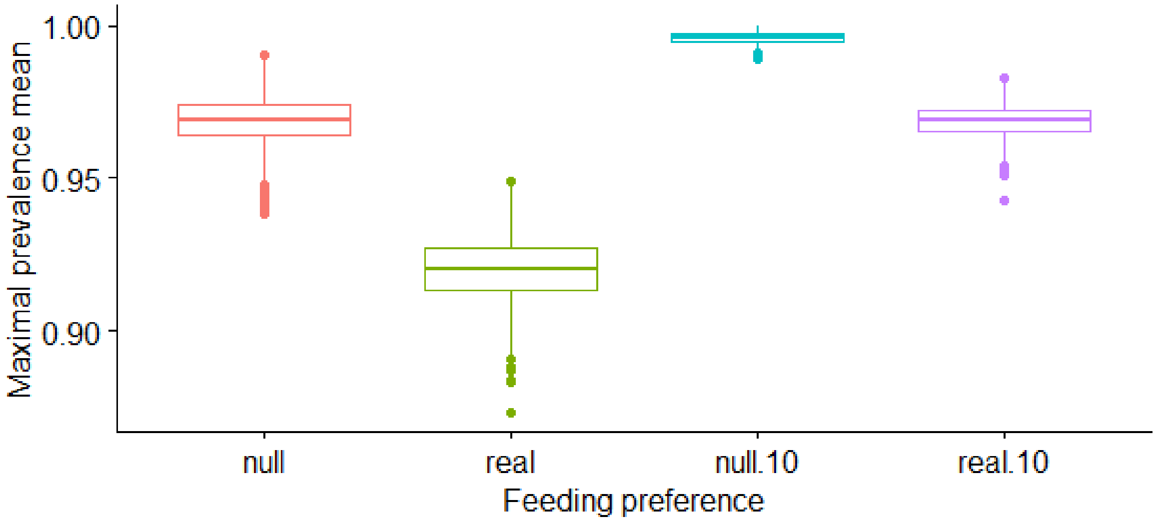
Table 2. Mosquitoes' feeding preference in the literature.

Mosquito	Feeding preference	Reference (DOI)
Aedes aegypti	99% humans	https://doi.org/10.1093/jmedent/42.5.844
	80-99% humans	10.1186/s13071-019-3405-z
	70% humans 18% mongooses 6% dogs 3% cats 3% birds	10.1093/jme/tjz037
	99% humans	10.1093/jmedent/42.5.844
Aedes albopictus	49% human	10.1007/s00436-015-4634-5

	80% human 20% others	10.1603/0022-2585(2006)43[543:hpoaad]2.0.co;2
	79-96% humans (city) 23-55% humans (rural)	10.1089/vbz.2009.0007
Culex nigripalpus	Preference of birds	10.1089/vbz.2013.1501
	33.9% birds 64.3% mammals	10.1603/ME09168
Culex quinquefasciatus	51% birds 27% cats 5% iguanas 3% dogs 3% rats 3% opossums	10.1093/jme/tjz037
	No difference between birds	10.1089/vbz.2018.2381.
	59.9% birds 39.2% mammals	10.1603/ME09168
Culex stigmatosoma	98.6% birds 1.2% mammals 1% reptiles	10.1093/jme/tjx154
Culex tarsalis	41.4% mammals 58.5 % birds 0.1% reptiles 2.8% mammals (Winter) 97.2% birds (Winter)	10.1093/jmedent/4.3.315
	81% mammals 18% birds 1% reptiles	10.1603/me11272

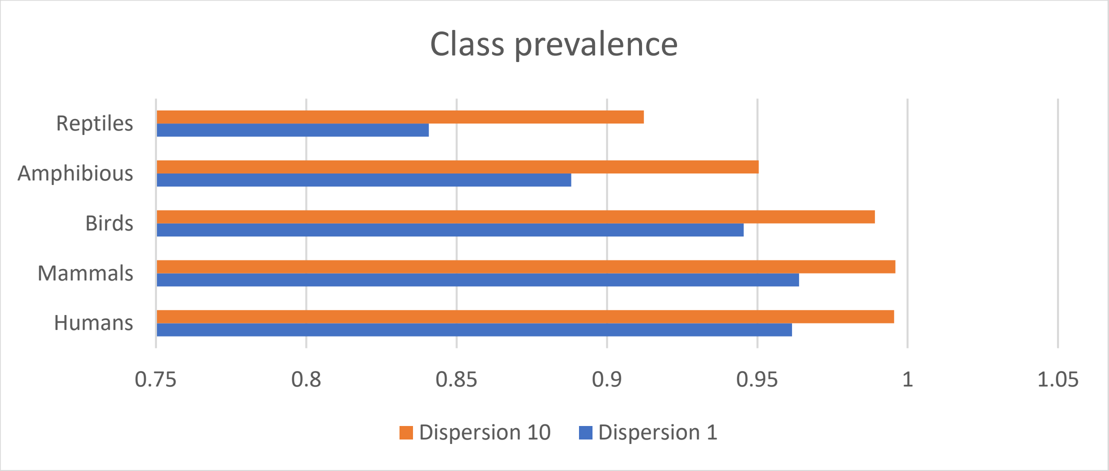
We tested normality and homogeneity of variances of the maximal prevalence in each simulation. Finally, we compare the populations with Wilcoxon Mann Whitney (Fay and Proschan, 2010). Both comparisons are significant with a difference in location of 0.04 and 0.02 respectably (figure 1). There is difference between the four groups but the reduction of the maximal prevalence by the feeding preference influence is two times bigger when they have reduced movement distance.

Figure 1. Boxplot of maximal prevalence in the four tested models.



We can see the low difference between mammals and human in the maximal prevalence because half of vectors prefer the human over the mammals (Figure 2.) The class maximal prevalence does not change when change the movement distance; it is consistent.

Figure 2. Class Prevalence in the models with feeding preference.



Discussion

We found that feeding preferences reduce the maximal prevalence in a host community when compared to a model without feeding preferences. Feeding preferences have a dilution effect on the communities However, this relationship is not straightforward. When we consider the displacement of species, this dilution effect changes. In our model, we observed a relationship between displacement and feeding preference, with displacement reducing the dilution effect of feeding preferences.

We can speculate that displacement increases contact rates, making it easier for mosquitoes to find their preferred food when displacement is lower. Therefore, an important variable to explore in future research is the contact rate with feeding preferences and displacement to understand the relationship and identify key points.

Furthermore, we discovered that the division between humans and mammals at the end of our study was not relevant, as they tend to exhibit similar class prevalence. Interestingly, the number of mosquitoes that prefer humans over mammals is equal to the number of mosquitoes that prefer mammals over humans.

As with any model, certain assumptions are necessary to test variables and establish general trends. However, we acknowledge that feeding preferences in mosquitoes can change dramatically due to environmental factors. Reports indicate that the feeding preference of the same mosquito species can vary based on available food, microhabitat overlap, and seasonal influences (Tempelis and Washino, 1967; Valerio *et al.*, 2010; Farajollahi *et al.*, 2011) Additionally, mosquitoes can learn from their experiences, and their feeding preferences can be influenced by host defense mechanisms (Takken and Verhulst, 2013). Our model assumes standard values and lacks flexibility in capturing the plasticity of mosquito feeding preferences.

Conclusion

In conclusion, food preferences reduce the maximum prevalence that can occur in an ecosystem, and this effect diminishes as the movement of hosts and vectors increases. We also emphasize the significance of this modeling approach in identifying important variables, such as the lack of differentiation between humans and mammals, which turned out to be irrelevant.

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Capítulo VI. Interacciones virales.

Viral interactions as prevalence reducers

Abstract

Living beings are in a constant state of interaction with each other, and viruses are no exception to this rule. Among the various interactions they engage in, coinfection, exclusion, and cross antigenicity are particularly well recognized. These interactions influence their dispersal capabilities and consequently the viral prevalence within an ecosystem. Therefore, studying these interactions can provide insights that enable us to leverage them for the purpose of reducing viral prevalence, which is crucial for public health considerations. The aim of this analysis is to understand the influence of viral interactions on the prevalence of infectious diseases. We evaluated five different Agent-Based Model (ABM) scenarios. The first four models focus on individual interactions: coinfection, exclusion, cross antigenicity, and vector-specific antigenicity. The fifth model incorporates all four interaction types working in conjunction. In these models, there are two types of agents: hosts and vectors. Hosts can become infected when they are exposed to infected vectors, while vectors can become infected when they are in close proximity to infected hosts. We conducted 1000 model runs for each ABM scenario. Our response variable was the prevalence of infected agents, which is the ratio of infected agents to the total number of agents. For each model run, we recorded only the maximum prevalence value reached during the 100 ticks. In conclusion, our findings suggest that viral diversity contributes to a decrease in prevalence both among hosts and vectors. When viruses are under equal conditions, the prevalence tends to be distributed uniformly across the population.

In cases where two viruses are present in an environment and interact, cross antigenicity emerges as the interaction that most effectively reduces prevalence. On the other hand, in communities featuring multiple viral interactions, exclusion appears to be the interaction that promotes the most significant reduction in prevalence.

Introduction

The interactions between viruses, vectors, and wild hosts within ecosystems have traditionally exhibited stability over time. However, due to the development and overexploitation of natural resources, these interactions have undergone changes, resulting in reported outbreaks of emerging diseases that impact both public health and animal well-being, as well as species conservation efforts (Suzán *et al.*, 2015; Johnson, Roode and Fenton, 2016). Various emerging diseases affecting wildlife have been documented (Harvell *et al.*, 2002; Woolhouse, Haydon and Antia, 2005; Jones *et al.*, 2008).

To comprehend the complexity of infections and their effects on different species, a comprehensive approach across different scales is essential (Mihaljevic, 2010). Often, the structure and composition of the virome within a host—defined as the collection of viruses within an ecological niche—remain unknown. This virome may influence the transmission of infectious diseases, either promoting or inhibiting their spread (Bergner *et al.*, 2019; Nieto-Rabiela *et al.*, 2021 Hence, recognizing natural virus-vector-host interactions becomes imperative to understanding long-term stability and identifying variables capable of mitigating their impact on public health, animal health, and ecosystem dynamics.

Certain viruses, like those belonging to the Flaviviridae family, establish persistent infections within vectors throughout their lifecycles (Reisen *et al.*, 2008; Bolling *et al.*, 2012; Salas-Benito and De Nova-Ocampo, 2015). This persistence provides ample opportunity for heightened viral competition within vectors as opposed to among humans. Consequently, scenarios have been observed where viral interference is absent, enabling various infectious agents to coexist within the same cell, leading to coinfections, exclusions, and cross antigenicity.

Coinfection, a term used when two viruses successfully infect a vector or host concurrently, contrasts with exclusion, which arises when both viruses attempt infection but only one succeeds (May and Nowak, 1995, Bergua *et al.*, 2014). Furthermore, interactions can be time-dependent, as seen in cross antigenicity. In this case, successful infection by two viruses occurs only if the second virus arrives within seven days of initial contact with the first virus. If the second virus arrives after seven days, its infection attempt fails, resulting in cross antigenicity (Yanow *et al.*, 2020 While these coinfections have been demonstrated in cell cultures (Salas-Benito and De Nova-Ocampo, 2015, they can influence vector susceptibility to arboviruses (Bolling *et al.*, 2015).

More complex interactions, less clearly defined, have been discussed in various studies, such as the interaction between *Culex flavivirus* (CxFv) and West Nile Virus (WNV) within vectors. Research involving cell cultures has yielded highly variable responses (Kent, Crabtree and Miller, 2010; Newman *et al.*, 2011; Bolling *et al.*, 2012, 2015; Salas-Benito and De Nova-Ocampo, 2015). While some studies suggest no interaction, others report coinfections or exclusions. One common thread across these studies is the critical role of timing and sequence of cellular infection in determining interaction types. Although a consensus has been reached that CxFv and WNV interactions are insignificant after day 14, the period between days 0 and 14 remains a topic of debate. For instance, Bolling *et al.*, 2012 identified a negative interaction between hours 84 and 156, whereas the negative interaction began after day 7 when using a Honduran strain. Considering this, we propose the concept of vector-specific antigenicity interaction, where viruses cannot co-infect between days 7 and 14. We favor the extended exclusion period since its impact on mosquito prevalence, if negligible, suggests an even weaker rationale for a shorter exclusion period between hours 84 to 156.

Evidently, the diversity and presence of viruses within a host can be attributed to both biotic and abiotic factors that influence their population size and persistence over time (Bolling *et al.*, 2012, 2015). As such, comprehensively studying virus, vector, and host communities is imperative to deciphering the factors shaping these complex assemblages.

Analyzing these intricate systems and understanding their inter-community interactions has necessitated the use of diverse statistical methods and analytical models to capture such complexity. These models have been adapted for both host and vector communities, consistently highlighting the significance of species richness in infection prevalence (Roche *et al.*, 2013). Consequently, this work underscores the importance of analyzing viral communities to identify patterns where the diversity of virus species curtails the potential for infectious disease spread. While notable progress has been made, substantial knowledge gaps remain at the viral community level, constituting a vital avenue for future research. Nevertheless, the influence of host and vector communities cannot be overlooked and will be considered as variables within these models.

To grasp the magnitude and directionality of viral interactions, we hypothesize that facilitation and exclusion relationships directly impact the prevalence of these viruses in both vectors and their natural hosts. Our hypothesis posits that greater viral diversity leads to lower infection prevalence in each species. To unravel the dynamics of these intricate systems, we will employ Agent-Based Models (ABMs). These models incorporate algorithms based on fundamental organizational rules and allow for the testing of various hypotheses through manipulation of variables. Notably, actors within ABMs can be endowed with artificial intelligence, enabling decision-making and interactions based on feedback from other actors (Balietti, 2012).

Model description

Purpose

The objective of this analysis is to comprehend how viral interactions influence the prevalence of infectious diseases.

Model environment

We assessed five distinct ABM models, implemented using NetLogo 6.1.1 (NetLogo: Wilensky, 1999). The first four models focused on individual interactions: coinfection, exclusion, cross antigenicity, and vector-specific antigenicity. The fifth model combined all four interaction types. The agents consisted of two categories: hosts and vectors. Across all models, there were a total of 150 hosts and 150 vectors. Agents could exist in either of two states: infected or susceptible. Hosts became infected when in proximity to infected vectors, while vectors could become infected when near infected hosts. Vectors had a lifespan spanning 15 to 30 ticks and reproduced, with each vector producing five offspring every 30 ticks.

Coinfection model

This model incorporated two viruses, labeled "A" and "B". Both viruses had the capacity to coinfect both hosts and vectors simultaneously.

Exclusion model

This model also utilized two viruses, "A" and "B". However, these viruses could not simultaneously infect hosts or vectors. An agent could only become infected by one of the two viruses.

Cross Antigenicity

This model also utilized two viruses, "A" and "B". However, these viruses could not simultaneously infect hosts or vectors. An agent could only become infected by one of the two viruses.

Vector special antigenicity model.

This model involves two viruses, designated as "A" and "B". The vectors are unable to be infected by either of these viruses during the period spanning days 7 to 14 post-infection. However, before day 7 or after day 14, the vectors can be infected by both viruses. In the host, the interaction mirrors that of coinfection.

Model with the four interactions

In this comprehensive model, we incorporated five viruses named alphabetically: "A", "B", "C", "D", and "E". Among these, only the virus "A" engages with the other four viruses. The interactions with virus "A" vary across the remaining viruses. With virus "B", coinfection is possible. Virus "C" induces exclusion of virus "A". Virus "D" exhibits cross antigenicity with virus "A". Lastly, virus "E" triggers a response analogous to the vector special antigenicity observed with virus "A".

ABMs Models					
Name	Coinfection	Exclusion	Cross antigenicity	Vector special antigenicity	Model with the four interactions
Initial hosts infected	0	0	0	0	0
Initial vectors infected	100	100	100	100	125
Host’s total	150	150	150	150	150
Vector’s total	150	150	150	150	150
Number of viruses	2	2	2	2	5

Evaluation

We conducted 1000 simulations for each ABM, with a time limit of 100 ticks. The response variable was the prevalence of infected agents, representing the total number of infected agents divided by the total number of agents. For each simulation run, we extracted the maximum prevalence value observed within the 100 ticks. Additionally, we computed the mean prevalence for each virus across all simulations.

Results

The summarized results are presented in Table 1 for host populations and Table 2 for vector populations. We calculated the mean maximum prevalence values based on the different interactions evaluated in the ABM. For instance, we computed the mean prevalence of virus "A" across its various interaction scenarios ("A", "AB", "AC", "AD", and "AE") and similarly for virus "B" ("B" and "AB"). We employed the mean calculation to address the variable number of categories for different viruses, with the exception of exclusion where viruses do not coexist within the same host.

The findings displayed in Tables 1 and 2 suggest a tendency toward homogeneously distributed prevalence values. In the cases of coinfection, exclusion, and vector special antigenicity, the prevalence tends to converge around 0.5. For cross antigenicity, the prevalence value deviates slightly, centering around 0.3, but remains consistently distributed between the two viruses.

Table 1. Mean of maximum prevalence in hosts

Virus / Model	Coinfection	Mean Coinfection	Exclusion	Cross antigenicity	Mean Crossantigenicity	Vector special antigenicity	Mean vector special antigenicity
A	0.22	0.52	0.47	0.32	0.3	0.23	0.53
B	0.22	0.52	0.47	0.32	0.3	0.23	0.53
AB	0.82		0	0.29		0.83	

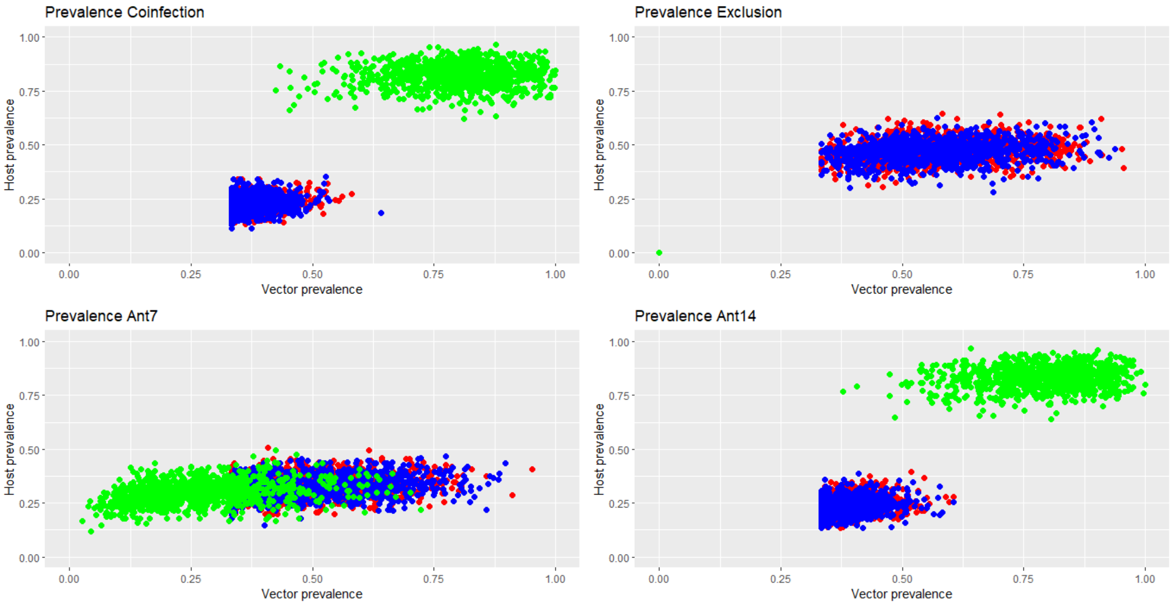
Table 2. Mean of maximum prevalence in vectors

Virus / Model	Coinfection	Mean coinfection	Exclusion	Cross antigenicity	Mean crossantigenicity	Vector special antigenicity	Mean vector special antigenicity
A	0.37	0.58	0.57	0.49	0.37	0.38	0.58
B	0.37	0.58	0.57	0.51	0.38	0.38	0.58

AB	0.8		0	0.26		0.79	

In figure 1 we cannot see the difference in the prevalence values between coinfection and vector special antigenicity. The lower prevalence value is in cross antigenicity.

Figure 1 Viral prevalence in the four interactions.



Coinfection (upper left), exclusion (upper right), cross antigenicity (lower left) vector special antigenicity (lower right).

In table three, we see a similar trend, the prevalence tends to be distributed homogeneously among all viruses, that is, being 5 viruses it tends to 0.2. Only the "C" virus that is excluded with the other 5 presents much lower values.

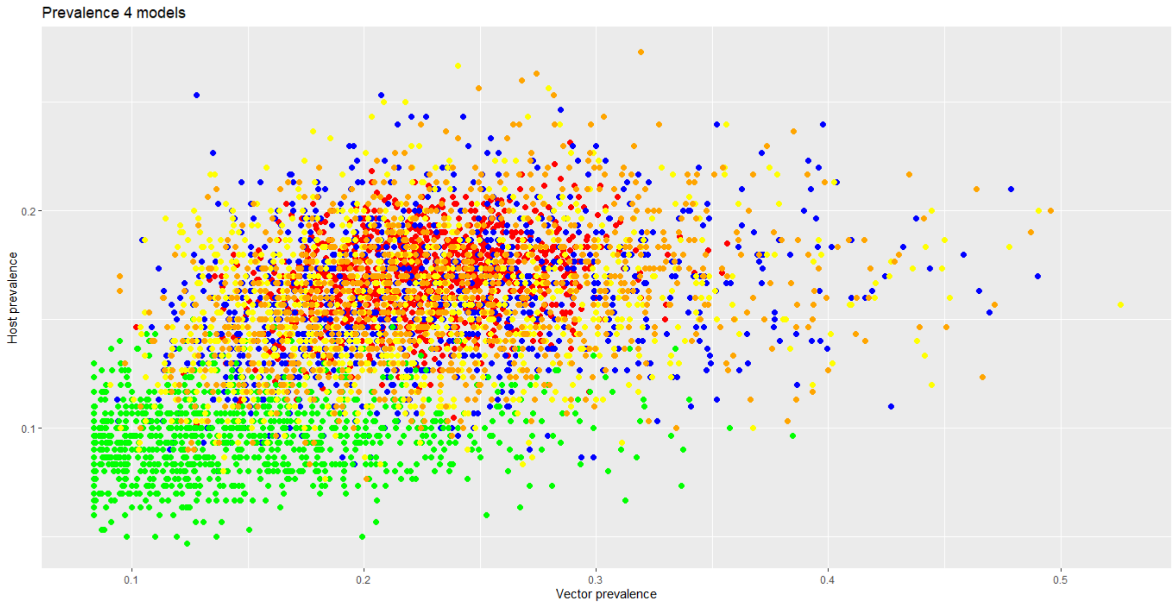
Table 3. Mean of maximum prevalence in hosts and vectors. Model with the four interactions.

Virus / Model	Hosts	Vectors	Hosts mean	Vectors mean	
A	0.09	0.21	0.16	0.22	Rojo
B	0.12	0.22	0.15	0.22	Azul
C	0.19	0.30	0.09	0.15	Verde

D	0.12	0.22	0.15	0.21	Amarillo
E	0.12	0.21	0.16	0.23	naranja

Figure 2 illustrates the distribution of viral prevalence across different interactions. It is evident that the prevalence values follow a similar pattern across viruses, except for the red "A" virus. Notably, the red virus does not exhibit the same degree of extreme prevalence values as observed in the other viruses. In contrast, the green "C" virus maintains a more contained prevalence distribution due to its exclusionary interaction with all other viruses. This distinction in prevalence patterns highlights the varying impact of different interactions on the viral prevalence within the ecosystem.

Figure 2 Viral prevalence from the four interactions.



virus A-red, virus B-blue (coinfection), virus C-green (exclusion), virus D-yellow (cross antigenicity), virus E-orange (vector special antigenicity).

Discussion

Overall, our findings emphasize the influence of viral interactions on prevalence and shed light on important considerations for understanding disease dynamics. It's evident that when viruses interact in terms of prevalence, they tend to exhibit homogeneous distribution, particularly when the viruses possess equal capabilities to infect the same hosts. This underscores the need to avoid overestimating prevalence reduction solely due to increased viral diversity.

Our results indicate no significant difference in viral prevalence between coinfection interactions and the special antigenicity of vectors. The 7-day exclusion period characteristic of vector special antigenicity did not significantly impact prevalence, behaving similarly to coinfection. Consequently, distinguishing between these interaction types might not be relevant in future modeling efforts. Notably, cross antigenicity exhibited the lowest viral prevalence when two viruses interacted, while exclusion emerged as the interaction with the lowest prevalence among five-virus interactions. This could be attributed to the competitive dynamics between two viruses compared to the more complex scenario involving interactions among five viruses.

Importantly, our study focused on interactions under equal viral conditions, warranting further exploration of variables like infectivity, latency period, and infection. Likewise, variables associated with hosts and vectors, such as susceptibility diversity and population dynamics, were not considered in this study.

Conclusion

In conclusion, our research underscores how viral diversity contributes to prevalence reduction in both host and vector populations. Furthermore, in scenarios involving viral interactions, the prevalence reduction is most pronounced in cases of cross antigenicity. Conversely, in diverse viral communities, the interaction with the greatest prevalence reduction is exclusion. These insights shed light on the intricate interplay between viruses, hosts, and vectors, offering valuable directions for understanding and managing infectious disease dynamics.

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Capítulo VII. Interacción viral en el vector.

CxFv as control of flavivirus prevalence

Abstract

Arboviruses pose a significant threat to public health, contributing to substantial morbidity and mortality. Among these viruses, mosquitoes are responsible for transmitting around 90% of them. Notably, mosquitoes not only act as reservoirs for arboviruses but also harbor a distinct group called insect-specific viruses (ISVs). This emerging group of ISVs presents a promising avenue for reducing arbovirus transmission. When mosquitoes are infected with ISVs, their ability to transmit arboviruses diminishes, leading to a decrease in prevalence. This unique property positions ISVs as potential biocontrollers for disease management. Focusing on the interactions within a viral community is crucial to grasp how different viruses can collaboratively reduce prevalence. Among the well-studied interactions are those involving *Culex flavivirus* (CxFv), West Nile Flavivirus, Saint Louis Encephalitis Virus, Dengue Virus, and Zika. Employing an agent-based model, we sought to understand the impact of CxFv on flavivirus prevalence. We developed four distinct models using NetLogo 6.1.1: two null models without CxFv and cross antigenicity, and two corresponding models incorporating CxFv. The vector species chosen encompassed *Aedes aegypti*, *Aedes albopictus*, *Culex nigripalpus*, *Culex* *quinquefasciatus*, *Culex stigmatosoma*, and *Culex tarsalis*. Our evaluation centered on prevalence, and all initial models began with the same initial prevalence. Each model underwent 1000 simulations, and the maximal prevalence of vectors infected with different viruses was assessed for each simulation. Our findings unveiled the potential of ISVs, particularly CxFv, in significantly aiding the biological control of other viruses by substantially reducing prevalence. For instance, our model demonstrated that CxFv led to a decreased prevalence of Zika and Dengue viruses. Nonetheless, prudent caution must be exercised in the study and application of ISVs. The possibility of co-occurrence with other harmful viruses raises the concern that ISVs could inadvertently elevate the prevalence of these pathogenic agents. In conclusion, our research underscores the promise of ISVs, such as CxFv, as valuable tools for managing viral diseases transmitted by mosquitoes. By reducing prevalence, ISVs offer a potential biocontrol strategy. However, careful investigation and strategic implementation are necessary to ensure that the presence of ISVs does not inadvertently lead to unintended consequences in disease dynamics.

Introduction

Arboviruses contribute significantly to both morbidity and mortality, warranting dedicated health-focused research(Vasilakis and Tesh, 2015; Roundy *et al.*, 2017). Mosquitoes are responsible for transmitting around 90% of these arboviruses. However, mosquitoes not only act as reservoirs for arboviruses but also serve as hosts for a distinct group known as insect-specific viruses (ISVs) (Öhlund, Lundén and Blomström, 2019).

ISVs, a relatively novel group, hold promise in reducing arbovirus transmission (Öhlund, Lundén and Blomström, 2019). When mosquitoes are infected with ISVs, their capacity to transmit arboviruses diminishes, consequently leading to a reduction in prevalence. This unique characteristic positions ISVs as potential biocontrollers. While biocontrol measures have traditionally aimed at reducing pest populations, it is also crucial to consider their potential role in occupying ecological niches to prevent the colonization of those niches by other viruses (Newman *et al.*, 2011; Bolling *et al.*, 2015; Öhlund, Lundén and Blomström, 2019). Hence, our focus lies in comprehending how interactions within a viral community can collaboratively reduce prevalence.

Our previous research revealed that when viruses possess similar characteristics, prevalence tends to be uniformly distributed across the population. In this study, we delve into viruses with distinct characteristics, each with their own interactions such as coinfection, exclusion, or cross antigenicity. However, an intriguing question arises: how does the introduction of an ISV into the viral community influence prevalence (See Chapter VI).

To elucidate the impact of ISVs on prevalence among vectors and hosts, we have employed an Agent-Based Model. We primarily investigate viruses with well-documented interactions, including *Culex flavivirus*, West Nile Flavivirus, Saint Louis Encephalitis Virus, and Dengue Virus. Notably, established interactions exist between these viruses involving cross antigenicity (Newman *et al.*, 2011; Maharaj *et al.*, 2018). These interactions are not necessarily reciprocal. Additionally, we introduce the Zika virus into the model (Romo *et al.*, 2018). This choice is driven by our need for a virus that does not interact with other viruses, resembling a null model, while still belonging to the flavivirus group.

Methods

We employed an agent-based model to investigate the impact of *Culex flavivirus* (CxFv) on the prevalence of flaviviruses. Our study encompassed four distinct models, all implemented using NetLogo 6.1.1 (NetLogo: Wilensky, 1999). Initially, we established two null models: one lacking CxFv and cross antigenicity interactions, and another without CxFv but featuring cross antigenicity interactions. Subsequently, we replicated both null models while introducing CxFv.

Our selection of vector species included six types: *Aedes aegypti*, *Aedes albopictus*, *Culex nigripalpus*, *Culex quinquefasciatus*, *Culex stigmatosoma*, and *Culex tarsalis*. These mosquitoes, identified as keystones in the transmission of multiple flaviviruses (as discussed in Chapter I), were chosen due to their central role in the transmission dynamics. While these mosquitoes can host five different flaviviruses, they exhibit varying degrees of susceptibility to each one, as outlined in Table 1.

The established interactions within the literature encompass coinfection cases such as SLEV-WNV, CxFv-DENV, and CxFv-SLEV-WNV. Cross antigenicity has been reported between SLEV and WNV, with its onset occurring on day seven for SLEV and WNV, and day four for DENV. Furthermore, the vectors are capable of vertical transmission of CxFv, allowing its inheritance (Bolling *et al.*, 2012)

In our model, we introduced 1000 hosts to each model and strategically distributed the vector population to achieve uniform initial prevalence (as detailed in Table 1). To maintain consistent initial prevalence between models without CxFv and those with its addition, we incorporated a healthy population. With each model iteration, we conducted 1000 simulations and assessed the maximal prevalence of vectors infected with different viruses.

Table 1 Vector susceptibility and initial populations

	CxFv	**WNV**	**SLEV**	**Zika**	**DENV**	**Health**	**50**
Aedes aegypti			10	60	20	4	94
Aedes albopictus	20		10		20	4	54
Culex nigripalpus		15	10			4	29
Culex quinquefasciatus	20	15	10		20	4	69
Culex stigmatosoma		15	10			4	29
Culex tarsalis	20	15	10			4	49
Population	60	60	60	60	60	24	324
Prevalence	0.19	0.185	0.19	0.19	0.185		0.92592593
	CxFv	WNV	SLEV	Zika	DENV	Health	
Aedes aegypti			10	60	20	10	100
Aedes albopictus			10		20	10	40

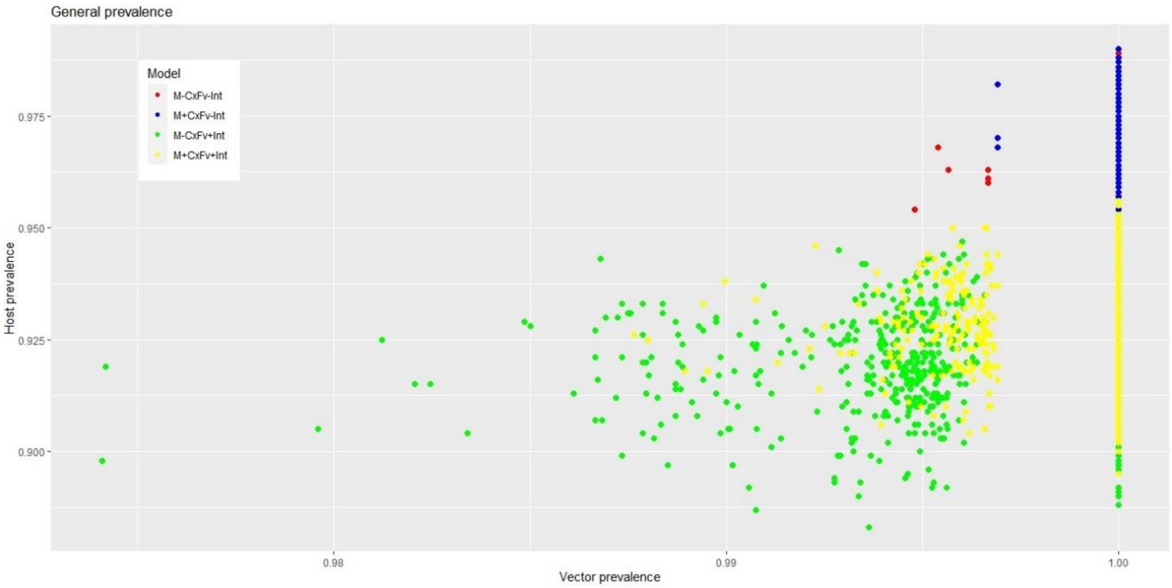
Culex nigripalpus		15	10			10	35
Culex quinquefasciatus		15	10		20	10	55
Culex stigmatosoma		15	10			10	35
Culex tarsalis		15	10			10	35
Population		60	60	60	60	60	300
Prevalence	0	0.2	0.2	0.2	0.2		0.8

Results

During our assessment of overall prevalence, a substantial number of simulations revealed maximal vector prevalence reaching a value of one. This indicates a scenario where the entire vector population becomes infected by the viruses, leading to maximum prevalence. Notably, among the groups displaying lower prevalence in vectors, we identified those without viral interactions, depicted in green and yellow in Figure 1.

Similarly, when considering host prevalence along the Y-axis, a similar trend emerges. The models devoid of viral interactions tend to exhibit higher prevalence values, while those incorporating viral interactions generally manifest lower prevalence levels. This observation underscores the potential of viral interactions to contribute to reduced prevalence within both vectors and hosts.

Figure 1. General Prevalence



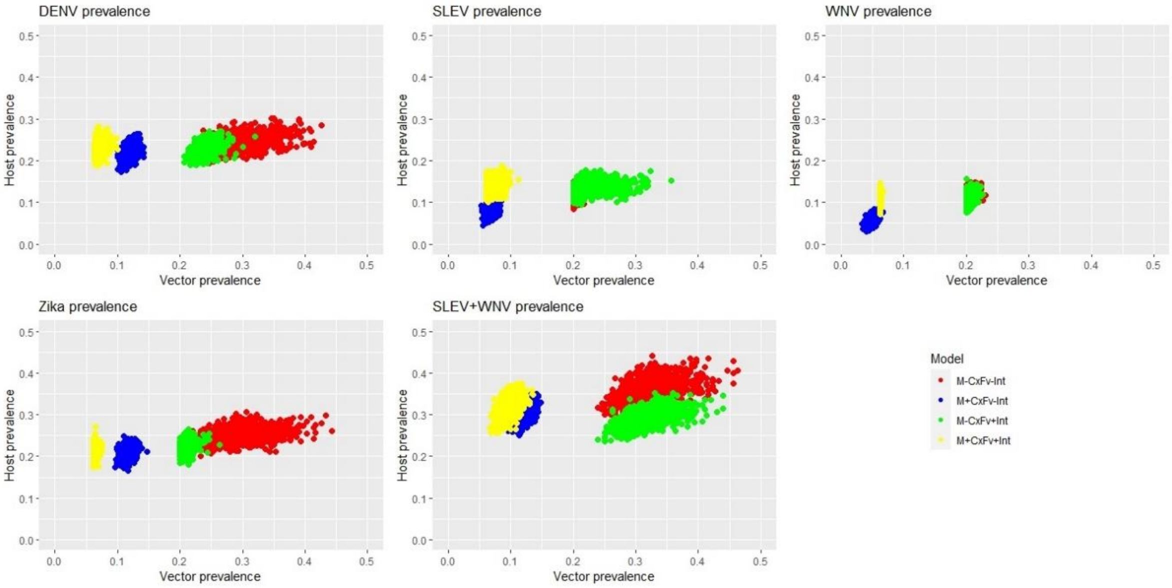
In Figure 1, a notable similarity emerges in the prevalence patterns between DENV and Zika, as well as SLEV and WNV. In the cases of DENV and Zika, the host prevalence remains relatively consistent across the four models, whereas the vector prevalence experiences variation. Notably, the model with CxFv but without viral interactions consistently achieves the lowest prevalence, followed by the introduction of viral interactions. The model without CxFv but with viral interactions occupies the third position, and the model with viral interactions removed ranks last. This suggests that in DENV and Zika, the presence of CxFv plays a more pronounced role in reducing vector prevalence compared to the impact of viral interactions. Nonetheless, the interactions still contribute to a decrease in prevalence.

For SLEV and WNV, the absence of CxFv appears to lead to little variation between the models without CxFv, irrespective of viral interactions. Among the models incorporating CxFv, those with null viral interactions lead to a slight reduction in host prevalence. Vector prevalence remains consistent between the last two groups for SLEV, while for WNV, viral interactions serve to narrow the variability in vector prevalence and maintain a higher prevalence compared to the models without CxFv.

In essence, the presence of CxFv effectively reduces vector prevalence, while null viral interactions marginally reduce host prevalence.

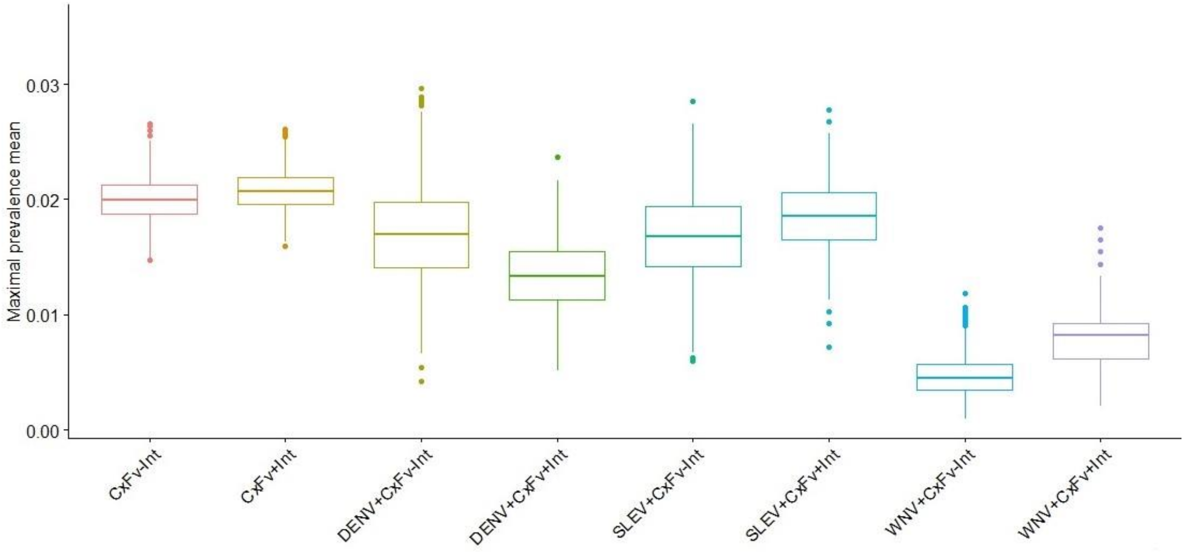
In the interaction between SLEV and WNV, evaluating maximal prevalence reveals minimal disparity in vector prevalence between models with CxFv. The model with viral interactions slightly outperforms the model without viral interactions, both demonstrating reduced vector prevalence compared to the models without CxFv. Within the models without CxFv, vector prevalence remains uniform, while host prevalence is notably lower in the group with viral interactions (Figure 2).

Figure 2. Prevalence by virus.



In Figure 3, we present a boxplot to compare the prevalence of CxFv across different viruses. The data suggests that vector prevalence tends to increase when viral interactions are introduced, with one notable exception being the coinfection of CxFv with DENV. In this specific case, the vector prevalence experiences a reduction upon the addition of viral interactions. This phenomenon can likely be attributed to the early activation of viral interactions in the case of DENV, occurring on day 4. Such an early activation appears to counteract the typical trend of increased vector prevalence associated with viral interactions.

Figure 3. CxFv prevalence by virus.



Discussion

In our study, we have observed that the presence of the insect-specific virus (ISV), specifically *Culex flavivirus* (CxFv), has the potential to change the prevalence of the viral community. However, this effect is not uniform across all viruses, and the way in which prevalence changes varies for different viruses. We have identified distinct patterns between viruses that can coexist and those that cannot.

For viruses like Dengue (DENV) and Zika, which do not typically coinfect, the presence of CxFv reduces their prevalence to a greater extent in vectors than viral interactions. However, the interactions themselves also contribute to reducing the prevalence. On the other hand, for viruses like Saint Louis Encephalitis Virus (SLEV) and West Nile Virus (WNV) that can cooccur, the patterns are more similar, with the presence of CxFv reducing vector prevalence and viral interactions reducing host prevalence to some extent.

When evaluating the combined prevalence of SLEV and WNV, which can both infect susceptible vertebrates, we find that the presence of viral interactions has a larger impact on changing prevalence than the inclusion of an ISV. This suggests that natural interactions among viruses have a more significant influence on prevalence reduction compared to the introduction of ISVs, at least in our model. Therefore, we suggest prioritizing the study of natural viral interactions over the incorporation of ISVs. It's important to note that more experiments are needed to understand untested variables and potential costs associated with carrying co-occurring viruses in vectors, as these costs could affect the observed benefits of ISVs.

In the case of CxFv prevalence with each virus, we found that adding viral interactions leads to a decrease in DENV prevalence due to the short restriction period of only 4 days. On the other hand, the prevalence of other viruses increases as the restriction period extends to around 7 days. This indicates that the use of ISVs as a control strategy should be approached cautiously, as there could be counterproductive effects. It's crucial to conduct further research to understand the impact of carrying co-occurring viruses on vectors, including potential costs to life expectancy or quality. The potentiation observed in our model might not necessarily translate directly to real-world scenarios.

Conclusion

In conclusion, ISVs like CxFv have the potential to reduce the prevalence of harmful viruses such as Zika and DENV. However, their application requires careful study and consideration, as co-occurrence with other harmful viruses could lead to unintended consequences and increased prevalence.

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Capítulo VIII. Comparación de las prevalencias máximas de tres ecosistemas: Duna, Selva, Petén de Celestún.

Model of flavivirus in three ecosystems of Celestun

Abstract

Over time, ecological interactions among viruses, vectors, and hosts have experienced shifts due to the development of modern societies and the extensive use of natural resources. These changes have led to the emergence of diseases that impact public health, animal health, and species conservation, particularly those caused by arboviruses. Among these, flaviviruses are notable for their ability to establish persistent infections within vectors, enhancing their viral competence. However, persistent infections don't always result in viral interference, allowing different viruses to coexist within the same cell, leading to coinfections or superinfections. To investigate the impact of both host and viral communities, we employed an Agent-Based Model (ABM) using NetLogo 6.1.1. The chosen scenario for our models was Celestun, a location with rich biodiversity that includes keystone species in flavivirus transmission. We assessed three distinct ecosystems: Dune, Jungle, and Peten. Drawing from existing literature, we built host communities based on their susceptibility levels and implemented an SIR (Susceptible-Infectious-Recovered) model. Each run produced a maximal prevalence value, and we repeated the process 1000 times. Our findings revealed varying prevalence rates across the ecosystems, with the Jungle showing the highest prevalence and Peten exhibiting the lowest.

Notably, the density within each ecosystem played a crucial role in influencing prevalence levels. Furthermore, we identified two significant factors that reduced prevalence: viral exclusion interactions and the involvement of viruses exclusively targeting vectors. The diversity in susceptibilities observed across different biological levels facilitated the emergence of what is known as the "dilution effect." This effect is more pronounced when there is diversity in vertebrates, vectors, or other symbionts, such as viruses. These insights and tools have the potential to contribute to the biological and natural control of emerging diseases in diverse ecosystems.

Introduction

The ecological interactions between viruses, vectors, and hosts were once relatively stable over time. However, with the development of modern societies and the excessive use of natural resources, these interactions have changed, leading to the emergence of diseases that impact public and animal health, as well as species conservation. Various arboviruses infect wildlife. In conserved ecosystems where arboviruses have coexisted with their hosts, the mortality rate tends to be low. For instance, the mortality rate among nonhuman primates due to yellow fever is quite low. However, in new world primates, the mortality rate is high (STRODE, 1951; Gould and Solomon, 2008; Gould *et al.*, 2017). We lack knowledge about how other viruses in the environment interact with flaviviruses and how coinfections either facilitate or control disease dissemination. Therefore, recognizing the natural interactions among viruses, vectors, and hosts is essential for understanding long-term stability and identifying variables that can mitigate the impact on public, animal, and ecosystem health.

Arboviruses are viruses that rely on hematophagous arthropods to complete their life cycle. Among the 137 zoonotic arboviruses, three families are of zoonotic relevance: Flaviviridae, Togaviridae, and Bunyaviridae. The primary reservoirs for these viruses are birds and small mammals, with mosquitoes and ticks serving as their vectors. Humans are incidental hosts and do not contribute to the transmission cycle. Currently, only the Dengue virus has a cycle involving mosquitoes and humans, independent of another animal reservoir (Gubler, 2002; Weaver and Barrett, 2004).

Flaviviruses establish persistent infections throughout the vector's life cycle, leading to greater viral competence within the vector rather than in humans. These persistent infections don't always involve viral interference, and different viruses can coexist within the same cell, resulting in coinfections (when multiple viruses interact in the host simultaneously) or superinfections (when a second virus infects the host after the initial virus invasion)(Salas-Benito and De Nova-Ocampo, 2015). Coinfections have been successfully demonstrated in cell cultures. Evidence suggests that coinfections can alter vector susceptibility to arboviruses (Bolling *et al.*, 2015).

Furuya-Kanamori et al.(2016) reported coinfections of Chikungunya and Dengue viruses in humans. However, coinfection is not the only type of interaction. Nhumirim has been found to reduce the replication of WNV, Japanese encephalitis, and St. Louis encephalitis, albeit only in cell cultures(Bolling *et al.*, 2015). Other reports suggest competence between CxFV and WNV. They propose that CxFV reduces WNV replication through vector competence, meaning the vector can transmit only one virus(Bolling *et al.*, 2012, 2015), However, this interaction is still under discussion due to lack of testing. On the contrary, Newman´s (*et al.*, 2011) in Colorado, USA, involved collecting mosquito eggs, incubating and developing them in the laboratory, and detecting coinfections and a positive association between the same viruses, WNV and CxFV. These contrasting research outcomes indicate complex interactions and provide an excellent model for comprehending interactions within viral communities and their impact on prevalence.

Methods

To assess the influence of host and viral communities, we developed an Agent-Based Model (ABM) using NetLogo 6.1.1 We selected Celestun as the scenario for our models due to its rich biodiversity, housing key species responsible for flavivirus transmission (as discussed in Chapter IV), spanning across three distinct ecosystems in close proximity. The diversity and abundance in each of these ecosystems have been comprehensively studied and documented (Profile, 2006; Chablé-Santos and Sosa-Escalante, 2010; Hernandez-Perez *et al.*, 2015). Additionally, Celestun is in close proximity to the human settlement of Merida adding relevance in public health.

We focused our evaluation on three ecosystems: Dune, Jungle, and Peten. To construct the host communities, we utilized abundance data from three reports(Profile, 2006; Chablé-Santos and Sosa-Escalante, 2010; Hernandez-Perez *et al.*, 2015) available in the literature. The detailed descriptions of the host communities can be found in the Appendix. Non-susceptible species were aggregated and treated as a single category of non-susceptible species. Given that certain species were represented by only one individual in the population, we duplicated the populations to ensure at least two specimens for assessing prevalence. The total number of host and vector species can be found in the appendix.

To determine mosquito distribution in the region, we utilized data from the C3/CONABIO platform SPECIES (http://species.conabio.gob.mx). We identified four keystone mosquito species crucial for flavivirus transmission (as discussed in Chapter IV): *Aedes aegypti*, *Culex nigripalpus*, *Culex quinquefasciatus*, and *Culex stigmatosoma*. Their susceptibility levels are presented in the table. In our model, we integrated feeding preferences for the mosquitoes based on the hierarchical Table 1 from our previous work, and the same reproduction dynamics were applied (as detailed in Chapter V).

Table 1. Vector susceptibility

	CxFv	**WNV**	**SLEV**	**Zika**	**DENV**
Aedes aegypti			x	x	x

Culex nigripalpus		x	x		
Culex quinquefasciatus	x	x	x		x
Culex stigmatosoma		x	x		

Viral Interactions

The species within our communities are capable of hosting several flaviviruses, including CxFv, DENV, SLEV, WNV, and Zika. Notably, CxFv exclusively infects invertebrates. The susceptibility levels of each host and vector to these flaviviruses are provided in the appendix.

Certain interactions exist between these flaviviruses. Specifically, CxFv can engage in coinfection with DENV, SLEV, and WNV. Beyond these interactions, only SLEV and WNV can interact with each other. As a result, the vector encompasses ten possible viral communities, while the hosts encompass five potential viral communities. A comprehensive description of these interactions is presented in Table 2, which has been included in the appendix alongside corresponding details for each species.

Table 2. Possible viral communities.

	CxFv	**DENV**	**SLEV**	**WNV**	**Zika**
Vector/host		x			
Vector/host			x		
Vector/host					x
Vector	x				
Vector/host				x	
Vector/host			x	x	
Vector	x	x			
Vector	x		x		
Vector	x			x	
Vector	x		x	x	

The host species have been categorized into 11 susceptibility possibilities, each of which has been detailed in Table 3, found in the appendix. This classification system proved essential for the development of our programming code. Each variable within these categories serves to differentiate potential coinfections and the temporal variations in cross antigenicity. Notably, each susceptibility classification corresponds to a unique set of exclusions within the code, allowing for accurate modeling of interactions.

Similarly, the vector species underwent a similar categorization process, but with the addition of *Culex flavivirus*—a virus exclusive to vectors, as discussed in Chapter VII. This expanded classification system for vectors enhances the fidelity of our model by accounting for the specific dynamics involving *Culex flavivirus*.

For further details on these categorizations and their implications for our research, please refer to Table 3 in the appendix, which provides a comprehensive breakdown of the host and vector susceptibility classifications along with their corresponding attributes and considerations.

Table 3 Possible susceptibilities.

Susceptibility	Code	DENV	SLEV	WNV	Zika	Viruses
	mam	x	x	x	x	4
	nodn		x	x	x	3
	nozika	x	x	x		3
	slev-zika		x		x	2
	ave		x	x		2
	den-slev	x	x			2
	den-wnv	x		x		2
	zika				x	1
	anf			x		1
	den	x				1
	slev		x			1

Within the model, vectors have the capacity to acquire the virus when coming into contact with an infected host, and vice versa—a reciprocal transmission scenario. This bi-directional infection dynamic has been integrated into the model to capture a more accurate representation of real-world interactions.

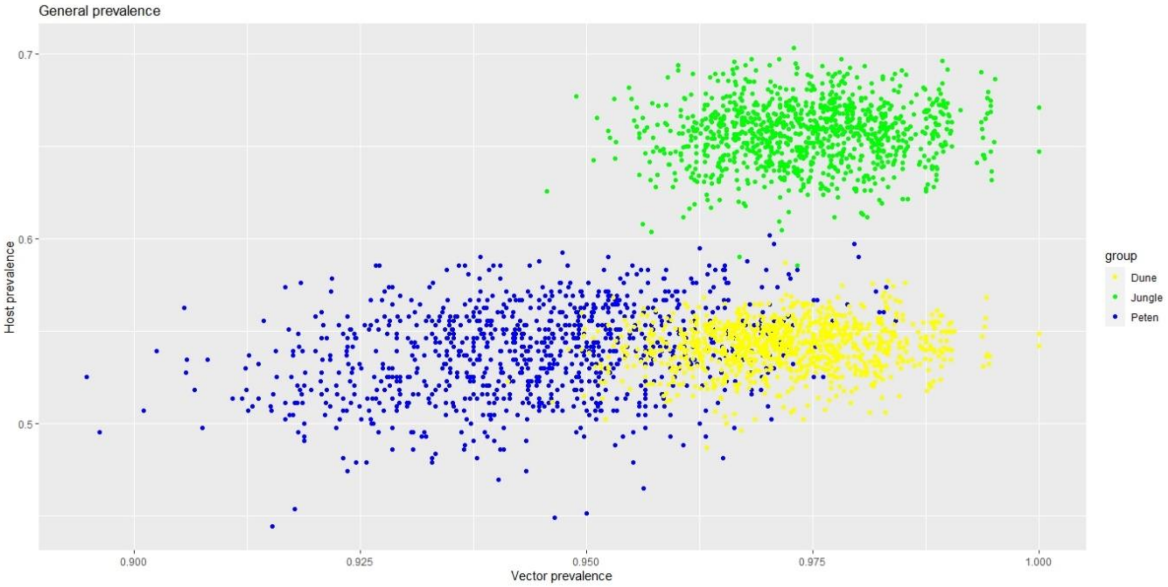
We have constructed three distinct models for each ecosystem—Dune, Jungle, and Peten—each with their own set of variables representing communities and abundance specific to that ecosystem. Our evaluations focused on identifying the maximal prevalence achieved in these models through each simulation run.

By implementing these ecosystem-specific models and assessing the peak prevalence attained in various simulation instances, we aim to gain a deeper understanding of the interplay between the host, vector, and viral communities within each ecosystem. This approach allows us to capture the nuanced dynamics of disease transmission and prevalence in different ecological contexts.

Results

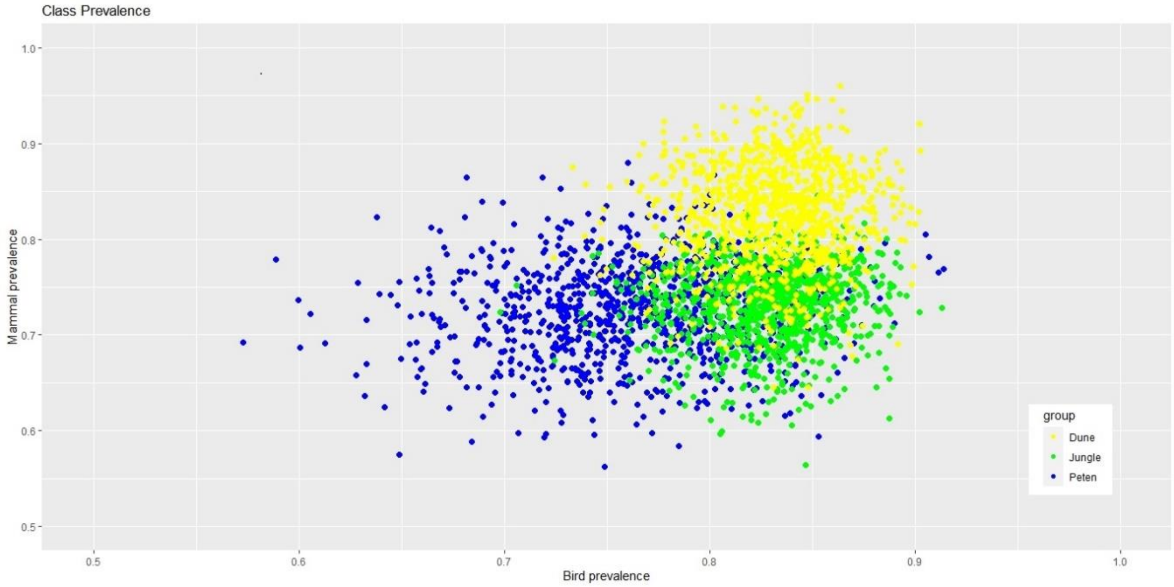
In the general prevalence graph, we can see that the Jungle ecosystem has the highest values of prevalence. Between Dune and Peten are similar in host prevalence, but Dune have higher maximal prevalence in vectors. The variation of the Peten vectors is bigger.

Figure 1. General prevalence



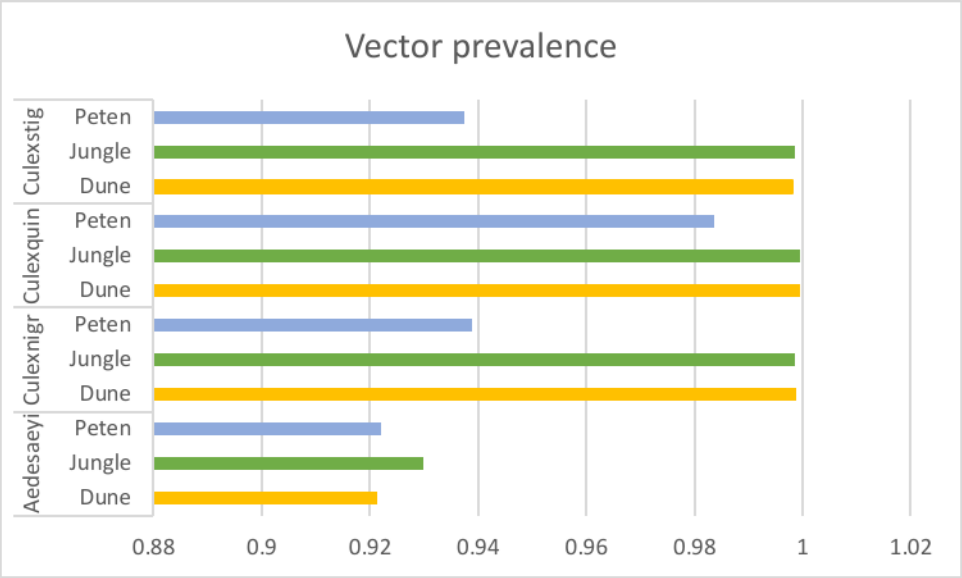
When we evaluate by classes, Dune have a little more mammals' prevalence than the others and Peten have more variance in the bird prevalence.

Figure 2. Class prevalence.



Inside the vectors the Peten has the less prevalence between the ecosystems. The Jungle is the ecosystem where the *Aedes aeyipti* have the less prevalence (figure 3).

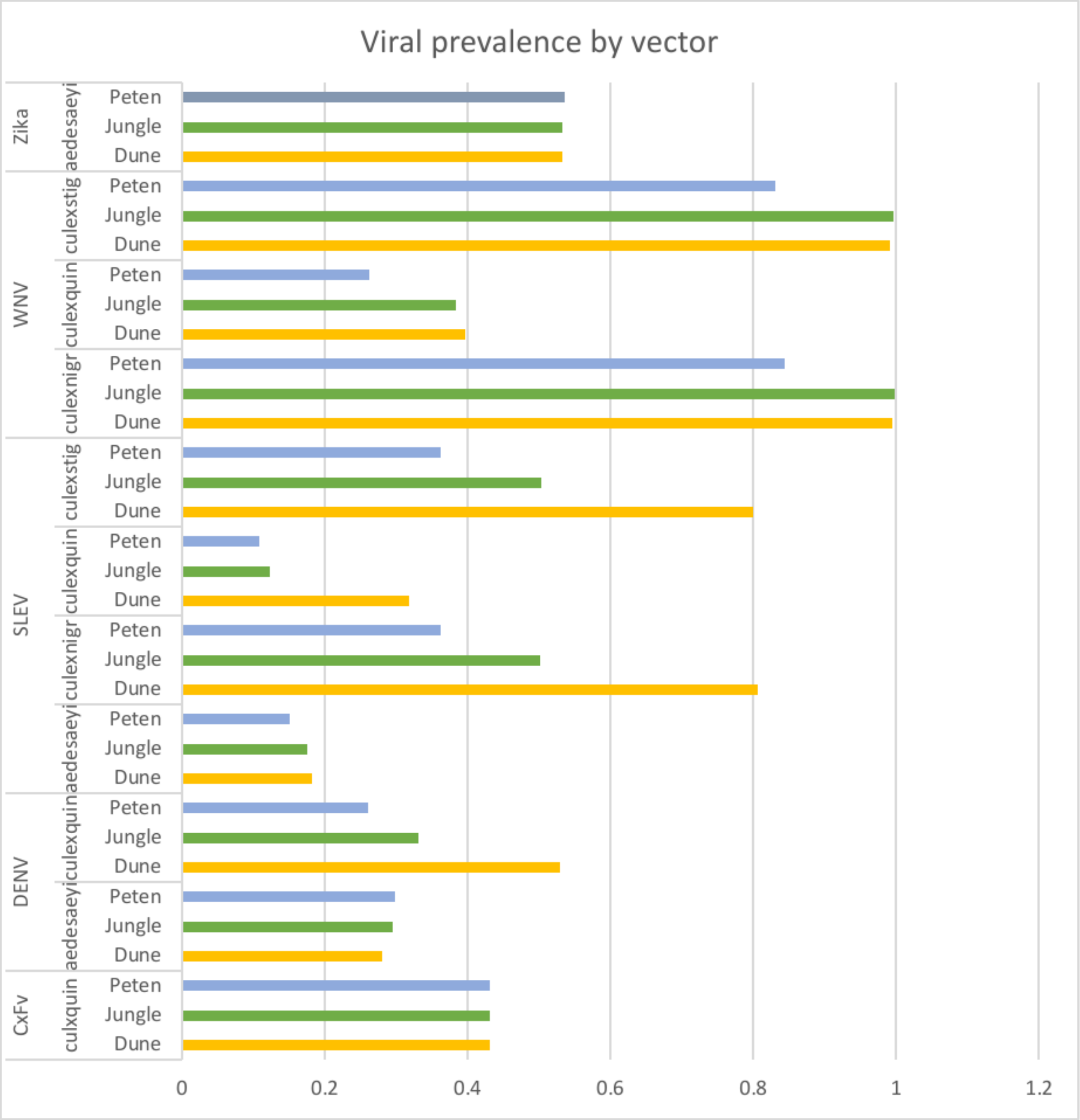
Figure 3. Vector prevalence



The highest prevalence is attributed to WNV due to its abundance of hosts, which facilitates easier dissemination. This elevated prevalence aligns with the virus's ability to exploit a larger pool of susceptible hosts for transmission. Interestingly, the prevalence of CxFv and Zika remains the same across the models due to the presence of only one susceptible species in the models, leading to a uniform prevalence pattern for these viruses.

In the case of DENV, the maximal prevalence is observed in *Culex quinquefasciatus* within the Dune ecosystem. Conversely, *Culex nigripalpus* and *Culex stigmatosoma* primarily serve as reservoirs for SLEV in the Dune ecosystem, resulting in high prevalence values for this virus. The prevalence of WNV exhibits lower values in *Culex quinquefasciatus*, which can be attributed to its susceptibility diversity and interactions with CxFv. Interestingly, Aedes aegypti and *Culex quinquefasciatus* consistently exhibit lower values of SLEV prevalence across all ecosystems, as depicted in Figure 4.

Figure 4. Viral prevalence by vector



The species-specific graphs, which provide information about their sizes, are available in the appendix for reference. Notably, among the species graphs in the general prevalence context, Artibeus intermedius consistently exhibits low prevalence levels across all three ecosystems. This can likely be attributed to its susceptibility to only DENV, which limits its role in harboring and transmitting other viruses. Additionally, Philander opossum also demonstrates low prevalence, but this is primarily due to its presence in only one ecosystem and susceptibility to a single virus, Zika.

Upon closer examination of prevalence by virus, it becomes evident that mammals such as Artibeus jamaicensis and Artibeus lituratus exhibit lower prevalence levels in the context of WNV, while Mus musculus displays lower prevalence in the case of SLEV. This observed low prevalence among these mammalian species can be attributed to their broader viral susceptibility. In other words, they are susceptible to a variety of viruses, leading to a more evenly distributed prevalence across different viral strains, as discussed in Chapter VI.

Discussion

Following the pattern established in our results, our discussion will proceed from a general overview to specific observations. It's evident that the Jungle ecosystem holds the highest prevalence rates, while the Peten ecosystem exhibits the lowest prevalence levels. This prevalence discrepancy might be attributed to ecosystem density. By calculating the density through the division of the species count in each ecosystem by the number of patches in the model, we found that the Dune ecosystem boasts a density of 1.76, the Jungle ecosystem 2.17, and the Peten ecosystem 0.62. As previously discussed in Chapter IV, density profoundly impacts flavivirus transmission, and this influence is mirrored in our observed prevalence patterns.

Shifting focus, while the Dune ecosystem maintains similar prevalence levels in vertebrates compared to the Peten ecosystem, it shows higher prevalence levels in vectors. This divergence can be attributed to the Dune's elevated vertebrate density, which potentially raises prevalence. However, these Dune vertebrates are more diverse, introducing a multitude of susceptibility factors that facilitate the dilution effect. In contrast, the vector population remains uniform and thus doesn't gain from diversity advantages.

Analyzing at the species level, conventional expectation might suggest that species with higher susceptibility would exhibit greater prevalences. However, our findings reveal the contrary. This observation can be elucidated by the participation of species susceptible to a single virus, in tandem with viral interactions. In essence, viruses seem to establish a more suitable niche within monosusceptible species, consequently reducing coinfections or superinfections in species with multiple susceptibility.

An intriguing observation pertains to Aedes aegypti, the vector with the lowest prevalence. This can be attributed to its susceptibility to Zika, serving as the sole Zika-susceptible vector in the model. As established, the Zika virus excludes other selected flaviviruses, notably exerting the strongest influence in reducing prevalence, as detailed in Chapter VI.

Similarly, within the Culex group, *Culex quinquefasciatus* presents the lowest prevalence rates. This mosquito is the sole vector susceptible to *Culex flavivirus* among the analyzed vectors. As we've discussed in Chapter VII, viruses exclusive to vectors significantly diminish their prevalence, safeguarding the population at large.

These observations collectively highlight the intricate interplay between ecological factors, susceptibility diversity, and viral interactions, which collectively shape disease prevalence dynamics within ecosystems. By considering these complex dynamics, we can formulate targeted strategies for disease management that are tailored to the unique ecological context of each ecosystem.

Conclusion

We can emphasize the influence of density in each ecosystem, which can either increase or decrease prevalence within the communities. Additionally, the most significant factors that contribute to reducing prevalence are the viral exclusion interactions and the presence of viruses exclusive to vectors. The diversity of susceptibilities at various biological levels facilitates the emergence of the dilution effect, whether it pertains to diversity in vertebrates, vectors, or symbionts (in our case, viruses). These insights and tools are invaluable for the biological and natural control of emerging diseases within diverse ecosystems.

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Capítulo IX. Conclusiones, supuestos del modelo y posibles sesgos.

Debemos recordar que los modelos computacionales son peligrosos ya que son muy maleables y es muy fácil desviarse del objetivo, incluir variables innecesarias o asumir variables de manera incorrecta o no tomarlas en cuenta dentro de nuestras interpretaciones (Crouch and Haines, 2004; Crawley, 2007). Por tal motivo, consideramos necesario incluir un capítulo en el que describiremos los supuestos del modelo y los posibles sesgos que podemos observar a partir de ellos.

El primer punto a considerar dentro de nuestro modelo es el tiempo. Nuestro modelo sucede a una alta velocidad, donde se asume que cada día los mosquitos pican a algún hospedero una vez y que los hospederos contagian a los hospederos una vez al día. Es decir, las tasas de infección son muy altas. Tampoco se incluyeron las variables de recuperación de los hospederos ni su reproducción, pero el periodo en el que sucede nuestro modelo es tan corto que involucraría muchos otros ajustes y una posible desviación hacia variables innecesarias dentro del modelo.

Además, no incluimos una probabilidad de contagio, es decir, que todos los contagios ocurrían. Lo decidimos de este modo porque estaríamos incluyendo más variables y, como sabemos, en los modelos menos, es más, y nos regimos por el principio de parsimonia. Elegimos enfocarnos más en las posibles interacciones dentro de la comunidad viral. Las implicaciones que esto tiene es que se alcanzan las prevalencias máximas en un tiempo muy corto y se obtienen prevalencias mucho más altas de las que son naturales. En la realidad, no todos los piquetes transmiten el virus y adquirir el virus no garantiza que puedas transmitirlo, ya que se requieren niveles altos de viremia para que pueda ocurrir.

Tampoco tomamos en cuenta el periodo que tarda el organismo en presentar la viremia ni el tiempo en que son portadores. Priorizamos la enfermedad; es decir, debido al tipo de código que desarrollamos, debimos ordenar las enfermedades a contagiar y dimos prioridad a la coinfección, asumiendo que un ser vivo ya infectado normalmente padece inmunosupresión e incrementa su probabilidad de contraer otras infecciones.

En nuestra simplificación del modelo, todos eran transmisores. Actualmente, se han reconocido infinidad de variables que pueden influir en estos lapsos, desde la edad de los ejemplares hasta el estado fisiológico y el sistema inmune. Incluso la susceptibilidad propia de cada ejemplar determinada por la genética (Thrall, Biere and Antonovics, 1993; Hawley and Altizer, 2011). Existen un sinnúmero de variables que suelen abstraerse y reducirse muchas veces a una simple probabilidad, y es correcto usarlas, siempre y cuando no se olvide el trasfondo que conlleva su empleo.

Las interacciones virales que consideramos en nuestro estudio involucran en su mayoría estudios de laboratorio (Fang and Reisen, 2006; Reisen *et al.*, 2008; Kent, Crabtree and Miller, 2010; Newman *et al.*, 2011; Bolling *et al.*, 2012, 2015b; Salas-Benito and De Nova-Ocampo, 2015; Chotiwan *et al.*, 2016; Requena-castro *et al.*, 2017; Schultz, Frydman and Connor, 2018; Maharaj *et al.*, 2018). Definitivamente, representan un sesgo, ya que no reconocemos si ocurren naturalmente o en qué medida podemos encontrarlos en la naturaleza. A pesar de ello, decidimos realizar esta investigación de este modo con el fin de resaltar las interacciones virales como posibles controladores biológicos y fomentar los reportes o aislamientos desde una perspectiva más cercana a la comunidad viral dentro del hospedero y menos desde el punto de vista aislado. Si logramos inspirar esta visión en el futuro, obtendremos reportes más fiables y útiles para retroalimentar teoría y práctica.

Las susceptibilidades que utilizamos también asumen que con una sola vez que el virus se aisló de la especie, la consideramos susceptible. Somos conscientes de que puede ser un hallazgo incidental, que el aislamiento del virus no implica necesariamente su capacidad de transmitirlo y que el hecho de que una población pueda albergarlo en una zona geográfica determinada no muestra necesariamente su universalidad, ya que pueden existir variables abióticas o bióticas que en otras condiciones no permitirían la infección. Sin embargo, en muchas ocasiones, la información negativa es aún más difícil de corroborar. Es decir, los reportes negativos de aislamiento de simbiontes en los muestreos suelen ser infravalorados y poco registrados en los artículos, por lo que también instamos a la comunidad científica a reportar el número de resultados negativos para tener estimaciones cada vez menos sesgadas.

Reconocemos que las preferencias alimenticias son muy plásticas; se ha reportado que pueden cambiar según la localidad, la composición de la comunidad de hospederos de la región, la época del año y la cercanía a asentamientos urbanos o instalaciones animales.

También sabemos que la actividad de los vectores está más fuertemente influenciada por las condiciones ambientales, como la temperatura. Tampoco consideramos que algunas aves son migratorias o insectívoras, y estas últimas reducirían las poblaciones de mosquitos dentro de su comunidad. Aún más importante, asumimos que las prevalencias iniciales dentro de los mosquitos comenzaban en 0.16 para nuestros 5 virus, ya que queremos evaluar cómo se elevan y compararlas entre ellos; sin embargo, en la realidad, las prevalencias iniciales son muy diferentes entre los virus, algunos siendo muy elevados, como se ha reportado en el caso del WNV, con un 70% de prevalencia en los mosquitos (Farfan-ale *et al.*, 2009).

El conocimiento de las dinámicas de prevalencia a lo largo del tiempo es otro aspecto crucial que hemos considerado. Aunque nuestra focalización principal recae en las prevalencias máximas de cada simulación, nuestro propósito es integrar los virus como componentes intrínsecos de las dinámicas ecológicas, evitando así los picos que suelen ser resultado de las intervenciones humanas en los ecosistemas. No obstante, también es innegablemente relevante comprender la evolución de la prevalencia a medida que transcurre el tiempo y reconocer su progresión.

Los ecosistemas son entidades en constante transformación y cambio, impulsados por diversos factores como los ciclos estacionales y anuales, entre otros. En consecuencia, cualquier reporte o investigación relacionada con su ecología debe estar sujeto a actualizaciones y adaptaciones constantes. Además, es fundamental considerar que a medida que construimos modelos más específicos, su aplicabilidad en situaciones similares podría verse limitada. A pesar de esta limitación inherente, nuestra intención radica en sentar las bases fundamentales al resaltar las variables relevantes en la transmisión múltiple y las interacciones virales. Así, buscamos abrir gradualmente nuevos horizontes en este ámbito de investigación y fomentar el control biológico y el efecto de dilución mediante la conservación de la diversidad viral.

La presente tesis representa un avance significativo en el campo de la ecología de enfermedades infecciosas al investigar las interacciones ecológicas entre virus, vectores y hospederos silvestres desde múltiples perspectivas. A través de un enfoque holístico y una combinación de enfoques metodológicos innovadores, se han logrado contribuciones valiosas que enriquecen nuestra comprensión de los sistemas biológicos complejos y sus dinámicas. Las conclusiones de esta tesis arrojan luz sobre diversos aspectos que tienen implicaciones fundamentales tanto para la salud humana como para la conservación de especies.

En primer lugar, la identificación de especies clave de hospederos y vectores en la transmisión de flavivirus proporciona una base sólida para el diseño de estrategias preventivas y de control. Esta caracterización detallada de las comunidades biológicas involucradas en la transmisión viral permite un enfoque más focalizado en la prevención y control de enfermedades transmitidas por vectores.

La utilización de modelos basados en agentes (ABM) ha permitido simular con mayor precisión las complejas interacciones entre hospederos, vectores y virus. A través de estos modelos, se han explorado diversos escenarios que van desde las preferencias alimenticias de los vectores hasta las interacciones virales en el vector mismo. Estos modelos han proporcionado conocimientos profundos sobre cómo estas interacciones influyen en la prevalencia de enfermedades infecciosas en diferentes ecosistemas.

Además, el análisis de la influencia de los virus específicos de insectos (ISV) en la capacidad vectorial de los mosquitos para transmitir arbovirus destaca la posibilidad de utilizar agentes de control biológico para reducir la prevalencia de enfermedades. Esta investigación ofrece una perspectiva prometedora para el desarrollo de estrategias de control más sostenibles y efectivas.

Una contribución clave de esta tesis radica en la evaluación comparativa de las prevalencias máximas en diferentes ecosistemas de Celestún. Esta comparación ha revelado patrones importantes en la distribución y prevalencia de enfermedades en función de la diversidad de hospederos, vectores y sus interacciones. Estos hallazgos son cruciales para la identificación de factores clave que determinan la propagación de enfermedades en diferentes entornos y, por lo tanto, tienen implicaciones significativas para la formulación de estrategias de control adaptadas a contextos específicos.

En conjunto, esta tesis no solo ofrece una visión integral de las interacciones ecológicas entre virus, vectores y hospederos, sino que también presenta un enfoque metodológico innovador mediante el uso de modelos basados en agentes. Las conclusiones y los hallazgos de esta investigación no solo amplían nuestro conocimiento fundamental sobre las dinámicas de enfermedades infecciosas, sino que también tienen el potencial de influir en la formulación de políticas de salud pública, estrategias de conservación de especies y el desarrollo de enfoques de control biológico más eficaces y sostenibles en un mundo en constante evolución.

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