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Quantifying the potential pathways and locations of Rift Valley fever virus entry into the United States

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Summary

The global invasion of West Nile virus, chikungunya virus and Zika virus in the past two decades suggests an increasing rate of mosquito-borne virus (arbovirus) dispersal. Rift Valley fever virus (RVFV) is an arbovirus identified as a high-consequence threat to the United States (USA) because of the severe economic and health consequences associated with disease. Numerous studies demonstrate that the USA is receptive to RVFV transmission based on the widespread presence of competent mosquito species and vertebrate species. In this study, the potential pathways and locations of RVFV entry into the USA were quantitatively estimated to support a priori surveillance and RVFV prevention strategies. International movement data, ecological data and epidemiological data were combined to estimate the number of RVFV-infected mosquitoes entering the USA. Results suggest infected humans travelling by plane pose the highest risk of importing RVFV into the USA, followed by the unintentional transport of infected adult mosquitoes by ship and airplane. Furthermore, New York, New York, Washington DC, Atlanta, Georgia, and Houston, Texas, are implicated as the most likely regions of RVFV entry. Results are interpreted and discussed to support the prediction and mitigation of RVFV spread to the USA.

KEYWORDS
arboviruses, Emerging Disease, modelling, mosquitoes, prevention and control, Rift Valley fever, vector biology

1 | INTRODUCTION

The epidemiological landscape continues to be altered by international movement and globalization facilitating the dispersal of pathogens worldwide (Hatcher, Dick, & Dunn, 2012; Tatem, 2006). The impact of anthropogenic movement on vectorborne disease (arbovirus) systems was on display during fifteenth century yellow fever virus epidemics when *Aedes aegypti* [L.] mosquitoes reached the New World through ship traffic (Lounibos, 2002). The global invasion of West Nile virus (WNV), chikungunya virus (CHIKV) and Zika virus (ZIKV) into the Western Hemisphere in the past two decades suggests a more supportive landscape for vectorborne disease (arbovirus) dispersal (Fauci & Morens, 2016). Presumably, WNV reached the United States (USA) in 1999 when an infected mosquito was unintentionally transported by airplane to New York City (Bird & McElroy, 2016; Bogoch et al., 2016; Fauci & Morens, 2016; Lounibos, 2002; Powers, 2014). Human travel was also central to the transition of CHIKV from a sylvatic, forest dwelling arbovirus into an emerging global health issue (Powers, 2014). Most recently, the spread of ZIKV through human movement led to a global state of emergency (Bogoch et al., 2016). The movement of WNV, CHIKV and ZIKV emphasizes the unprecedented ease at which natural and anthropogenic processes continue to facilitate the spread of vectorborne pathogens.

Rift Valley fever virus (RVFV; family *Bunyaviridae*, genus *Phlebovirus*) is a mosquito-borne arbovirus that has considerable impact

on both human and livestock health throughout Africa and the Arabian Peninsula. It is the only virus that causes significant haemorrhagic fever in humans that also devastates agricultural systems with severe livestock morbidity and mortality (Bird & McElroy, 2016). Under the assumption of continued arbovirus dispersal, this study aims to quantitatively estimate how and where RVFV may reach the USA. Data from published resources on RVFV epidemiology, RVFV ecology and international movement were combined to (i) quantify pathways of RVFV entry into the USA, (ii) identify ports of entry, and (iii) distinguish which RVFV-endemic regions are directly connected to the USA. This modelling effort is intended to help mitigate the ever-increasing risk of RVFV invasion into the USA by postulating a priori estimates on pathways of viral entry that can help strategize cost-effective surveillance and management plans (Bird & McElroy, 2016; Fenichel, Horan, & Hickling, 2010; Kompas, 2015; Lounibos, 2002; Tatem et al., 2012).

1.1 | Background

The emergence of arboviruses in locations far removed from their original point of discovery (WNV, ZIKV, CHIKV), and the spread of exotic vector species to developed countries with seemingly advanced preventative infrastructures (*Ae. albopictus* [Skuse], *Ae. japonicus japonicus* [Theobald] and *Ae. notoscriptus* [Skuse]) underscores the challenge of biological invasion management (Peterson & Campbell, 2015; ProMed-mail, 2014). When the consequence of disease establishment results in an annual threat to public and animal health and economic prosperity, investments towards the prevention of disease emergence far exceed the economic return of managing an established arbovirus (Fenichel et al., 2010; Kompas, 2015). Unfortunately, the complex nature of biological invasions and infectious disease dynamics make them difficult to forecast, but simplified modelling efforts can help clarify biological assumptions, identify feasible pathways of invasion, and identify gaps in knowledge, all essential to organizing response strategies that support the proactive mitigation of disease establishment (Fenichel et al., 2010; Hethcote, 2009; Kompas, 2015).

RVFV is primarily transmitted through the bite of infected mosquitoes and utilizes wild and peridomestic animals as amplification hosts for enzootic and epizootic maintenance. The virus has been isolated from over 40 mosquito species and shown to be transmitted by at least six different mosquito genera (Turell et al., 2002, 2008). Current hypotheses suggest that certain species of floodwater mosquitoes, such as *Ae. (Neomelaniconion) mcintoshi (*Huang), maintain RVFV in an enzootic cycle during inter-epidemic periods by vertically infecting mosquito progeny through the process of transovarial transmission (Linthicum, Davies, Kairo, & Bailey, 1985). Unlike many medically important arboviruses that circulate between mosquitoes and humans in urban environments, such as CHIKV, dengue virus (DENV) and ZIKV, RVFV replicates in a variety of vertebrate and mosquito species, like WNV (Bird, Ksiazek, Nichol, & Maclachlan, 2009). However, unlike WNV, where humans and large mammals do not contribute to viral amplification, RVFV produces viral titres capable of infecting mosquitoes in both livestock animals and humans (Kasari, Carr, Lynn, & Weaver, 2008; Meegan, 1979). Animal vaccine programmes are making significant progress, yet targeting domestic animals might not be sufficient to break endemic transmission of RVFV in the USA if wild animals, like deer, are capable of enzootic maintenance and viral amplification (Hartley, Rinderknecht, Nipp, Clarke, & Snowder, 2011; Kakani, LaBeaud, & King, 2010; Rolin, Berrang-Ford, & Kulkarni, 2013). Should RVFV enter the USA, diagnosing the disease and controlling the spread of infected mosquitoes and vertebrates will pose a significant challenge to existing infrastructure (Britch & Linthicum, 2007). In the case of haemorrhagic diseases like RVFV, preventing viral emergence is significantly more efficient than dealing with the severe health and economic consequences associated with RVFV emergence or establishment (Basili & Belloc, 2015; Fenichel et al., 2010; Kompas, 2015).

Previous studies have explored potential vertebrate hosts, arthropod vectors and environments potentially conducive to RVFV transmission in the USA, but none have quantitatively evaluated pathways of entry into the USA (Barker, Niu, Reisen, & Hartley, 2013; Golnar, Turell, LaBeaud, Kading, & Hamer, 2014; Hartley et al., 2011; Kasari et al., 2008; Rolin et al., 2013). A qualitative assessment by Kasari et al. (2008) emphasized that it only takes a single RVFV-infected mosquito to introduce the disease. They concluded that 14 states are the most vulnerable to RVFV invasion: Alabama, California, Florida, Georgia, Maine, Maryland, Massachusetts, Minnesota, New Jersey, New York, Pennsylvania, South Carolina, Texas and Virginia. Kasari et al. (2008) also identified four feasible pathways of RVFV entry into the USA: the importation of infected animals, humans travelling after exposure to infection, mechanical transport of vectors and the smuggling of live virus. Our goal was synthesize data from various sources to quantitatively estimate which pathways are more likely to be involved in RVFV import and identify which ports are likely to be involved in RVFV dispersal to the USA.

2 | MATERIALS AND METHODS

2.1 | Movement data

Previous attempts to capture local and international human movement patterns have utilized census data, border traffic surveys, social media, satellites, mobile phones, flight traffic and shipping statistics (Tatem, 2014). Although a wealth of information exists to explore fine-scale movement patterns, accessing comprehensive data can be prohibitively expensive. At the risk of introducing more variability and uncertainty into this study, obtaining data was restricted to a variety of published resources and open-access databases. A detailed discussion of parameter estimation is provided in the Supporting Information. International flight data were obtained from the Department of Transportation's Bureau of Transportation Statistics T-100 International Segment as reported by US and foreign air carriers and curated by the Research and Innovation Technology Administration (Transtats US). Due to the nature of open-access, origin, destination, number of passengers and number of departures were only available

for direct international flights. Extensive maritime data are available through the Lloyd's List Intelligence database, but due to the excessive cost to acquire the data, ship movement data for this study were based on movement rates estimated by Drake and Lodge (2004) that used the Lloyd's List Intelligence database in 2004. Import data on tire and mammal trade were estimated from the United Nations Comtrade Database (UNComtrade, 2015). This searchable online database organizes trade statistics by commodity code, reporting nation and trading partner and is maintained by the United Nations Department of Economic and Social Affairs Statistics Division. Vertebrate movement data were combined with information from the CITES wildlife trade database, which holds over 13 million records of wildlife movement that can be queried and downloaded online (CITES). As mentioned previously, more details on parameter estimates are available in the Supporting Information available online.

2.2 | Model framework

The predictive framework for this analysis was modified from the methods of Kilpatrick et al. (2006) to quantify propagules of RVFV entry into the USA. Five pathways of RVFV introduction were considered: (i) infected adult mosquitoes arriving by airplane, (ii) infected adult mosquitoes arriving by ship, (iii) infected humans travelling by plane, (iv) infectious mammal import and (v) infected larvae travelling by tire import. The risk of infected humans travelling by ship was not considered in this model because the duration of maritime travel across the Atlantic Ocean is assumed to exceed the duration of an infectious viraemia in humans, which rarely lasts beyond 10 days in mammals (Golnar et al., 2014). Although alternative routes of mosquito invasion likely exist, such as the movement of container holding products like ornamental bamboo or lumber, the movement of used tires was used as the only surrogate for mosquito larvae dispersal in this model because it is the only pathway with available data documenting rates of mosquito infestation.

For each pathway, the number of infectious mosquitoes and infectious mammals entering the USA per year was estimated as the product of competent hosts (mosquitoes, humans or other mammals) arriving to the USA each year and the fraction likely to be infected with RVFV (Kilpatrick et al., 2006, 2006). To compare among pathways of import, the number of infectious vertebrate hosts arriving to the USA was converted into infectious mosquitoes by estimating the number of infectious mosquitoes resulting from feeding on an infected host (see Table 1) (Ba et al., 2012; Basio, Prudencio, & Chanco, 1970; Carneiro de Mendonca & Cerqueira, 1947; CITES; Craven et al., 1988; Diallo et al., 2005; Dobbs & Brodel, 2004; Drake & Lodge, 2004; Evans, Joyce, & Porter, 1963; Evans et al., 2008; Focks, Haile, Daniels, & Mount, 1993; Golnar et al., 2014; Hanafi et al., 2011; Herve, 1997; Highton & van Someren, 1970; Jeanmaire et al., 2011; Johansson et al., 2012; Jupp et al., 2002; Kilpatrick et al., 2006; Laird, 1952; Laird et al., 1994; Le Maitre & Chadee, 1983; Linthicum et al., 1985; Morvan, Rollin, Laventure, & Roux, 1992; Nie, Li, Li, Wang, & Gratz, 2004; Oda et al., 2002; Spielman & d'Antonio, 2002; Takahashi & Laird, 1984; Transtats US; Turell, Rossi, & Bailey, 1985; UNComtrade, 2015; Zeller, Fontenille, TraoreLamizana, Thiongane, & Digoutte, 1997). Finally, to account for travel duration, the number of days mosquitoes are expected to survive after arriving in the USA was multiplied by the number of infectious mosquitoes entering the USA per year for each pathway. The resulting values represent the number of infectious mosquito days per year (infectious mosquito days) resulting from each pathway and were used as a metric for RVFV invasion risk. It should be noted that this analysis does not consider seasonality or environmental receptivity, such as climatic conditions or habitat suitability, which are known to influence mosquito behaviour, abundance and survivorship. All parameter estimates are listed in Table 1 and defined in more detail in the supporting information.

We estimated the number of RVFV infectious mosquito days resulting from airplane traffic (Table 2, Equation 1) by multiplying the annual number of direct flights entering the USA from RVFV-endemic countries (P) by the number of mosquitoes transported per plane (N_p), the fraction of mosquitoes expected to be female (x), the fraction likely to be infectious with RVFV (I_v), the fraction likely to transmit RVFV after adequate contact with a vertebrate (V_c) and the number of days mosquitoes arriving by plane are estimated to survive in the USA (D_p) (Transtats US). The number of RVFV infectious mosquito days resulting from ship traffic (Table 2, Equation 2) was estimated by multiplying the annual number of ships entering the USA per year from RVFV-endemic countries, based on a gravity model by Drake and Lodge (2004) (S), by the number of mosquitoes expected to be transported per ship (N_s), the fraction of mosquitoes expected to be female (x), the fraction of mosquitoes likely to be infected with RVFV (I_v), the fraction likely to transmit RVFV after an adequate contact with a vertebrate (V_c) and the estimated number of days mosquitoes transported by ship are estimated to survive in the USA (D_s) (Drake & Lodge, 2004). We estimated the number of RVFV infectious mosquito days resulting from vertically infected mosquito larvae (Table 2, Equation 3) transported in tires by multiplying the number of tire imports into the USA from RVFV-endemic countries (T) by the fraction of tires estimated to contain mosquitoes (O), the average number of mosquitoes per infested tire (μ), female mosquito sex ratio (x), adult emergence rate (E), transovarial infection rate (I_t), fraction likely to come from a RVFV infectious parent (I_v), fraction likely to transmit RVFV after an adequate contact with a vertebrate (V_c) and the estimated duration of mosquito infectiousness for mosquitoes emerging from tires in the USA (D_t). We estimated the number of infectious mosquito days resulting from infected mammals entering the USA (Table 2, Equation 4) by multiplying the number of mammals imported per year (M) (primate, carnivora, pholidota, perissodactyla, proboscidea, artiodactyla and unspecified live mammals), based on UN Comtrade and CITES trade data, by the estimated mammal infection rate (I_m), the number of infected mosquitoes resulting from feeding on an infected vertebrate (Υ), the fraction of mosquitoes likely to transmit virus after adequate contact with a vertebrate (V_c), and the number of days mosquitoes are expected to survive in the USA after feeding on an infected vertebrate (D_v) (CITES; UNComtrade, 2015). We estimated the number

TABLE 1 Notation, description, values and source of parameter estimates

Parameter	Description	Mean	SE	Reference
F	Mosquito biting rate	0.25	N/a	Spielman and d'Antonio (2002)
B_m	Fraction of Bloodmeals from Mammalian Host	0.52	N/a	Golnar et al. (2014)
A	Vector–host abundance ratio	2.5	N/a	Johansson et al. (2012)
H_c	Vertebrate infectiousness	0.33	N/a	Golnar et al. (2014)
X	Sex Ratio	0.5	N/a	See SI text
E	Emergence Rate	0.83	N/a	Focks et al. (1993)
Y	Number of infected mosquitoes resulting from feeding on infected vertebrates ($F \times B_m \times A \times H_c$)	0.11	N/a	See SI text
P	Planes to USA per year	3245	121	Transtats US
H	Humans arriving to USA per year	647,169	22558	Transtats US
S	Ships arriving to USA per year	1013	253	Drake & Lodge (2004)
T	Tires imported to USA per year	374,843	115842	UNComtrade (2015)
M	Live mammals imported to USA per year	285	88.6	UNComtrade (2015)
N_p	Number of mosquitoes transported/airplane	1	0.62	See SI text
N_s	Number of mosquitoes transported/ship	19	4.75	Nie et al. (2004)
O	Rate of tire infestation	0	N/a	See SI text
u	Number of mosquitoes/infested tire	7.7	2.76	Laird et al. (1994)
N_t	Number of mosquitoes/tire ($u \times O \times E \times x$)	0.002173	N/a	See SI text
I_v	Mosquito RVFV infection rate	0.00056	0.0001	See SI text
I_t	Transovarial RVFV infection rate	0.0024	0.0012	Laird et al. (1994)
W	Days RVFV IgG antibodies are detectable	150	N/a	Morvan et al. (1992)
G_m	IgG seroprevalence rates in mammals	0.098	0.097	See SI text
G_h	IgG seroprevalence rates in humans	0.028	0.006	Zeller et al. (1997)
D_m	Average mammalian infectious period	3.4	0.21	Golnar et al. (2014)
D_h	Average human infectious period	4.57	0.3	Golnar et al. (2014)
I_m	Estimated mammal infection rate ($D_m \times G_m$)/W	0.002	0.0001	See SI text
I_h	Estimated human infection rate ($D_h \times G_h$)/W	0.00085	0.0002	See SI text
V_c	Mosquito RVFV transmission rate	0.14	N/a	Golnar et al. (2014)
D_p	Lifespan of mosquito arriving by plane	15	2.5	Kilpatrick et al. (2006)
D_s	Lifespan of mosquito arriving by ship	5	2.5	See SI text
D_t	Lifespan of mosquito arriving by larvae	25	2.5	See SI text
D_v	Lifespan of mosquito infected by infected vertebrate	15	2.5	See SI text

See supporting information for further description of parameters.

of infectious mosquito days resulting from infected humans entering the USA (Table 2, Equation 5) by multiplying the annual number of passengers entering the USA on direct flights from RVFV-endemic countries based on US Transtats data (P) by the RVFV human infection rate (I_h), the number of infectious mosquitoes resulting from feeding on a viraemic vertebrate (Υ), fraction of mosquitoes likely to transmit RVFV after adequate contact with a mammal (V_c), and the number of days mosquitoes are expected to survive in the USA after feeding on an infected mammal (D_v) (Transtats US).

Like any modelling effort, parameter estimation is limited by available data. Recognizing that data availability is a shortcoming to this effort, a thorough literature review was completed on the unintentional transport of mosquitoes in order to generate realistic parameter estimates. A standard error was utilized to generate a 95% confidence interval around each parameter estimate to account for uncertainty in the estimates. The bounds of parameter space were then used to assess the error in risk (i.e., infectious mosquito days) calculated for each pathway of RVFV dispersal. In addition to estimating a deterministic minimum and maximum level of risk for each pathway of dispersal, a pseudorandom function in MATLAB 9.1 (The MathWorks Inc., Natick, MA, 2000) was used to explore how stochasticity can influence risk. The pseudorandom selection process selects random values from normally distributed parameter space defined by a 95% confidence interval. When only one data point was available, confidence intervals were defined as 50% more or less than the mean parameter estimate. The standard deviation of the

TABLE 2 Equations for quantifying infectious Mosquito Days per year

Equation	Pathway of RVFV entry	Function
1	Mosquitoes arriving by plane	$P \times N_p \times x \times I_v \times V_c \times D_p$
2	Mosquitoes arriving by ship	$S \times N_s \times x \times I_v \times V_c \times D_s$
3	Mosquitoes arriving through tire trade	$T \times O \times H \times E \times x \times I_t \times I_v \times V_c \times D_t$
4	Infected imported mammals	$M \times I_m \times Y \times V_c \times D_v$
5	Infected travelling humans	$H \times I_h \times Y \times V_c \times D_v$

Estimates listed in Table 1.

results after 10,000 iterations was used to calculate the interval that contains 95% of all possible outcomes.

2.3 | Spatial risk

The spatial risk of RVFV entry into the USA and exit from endemic regions was illustrated using ArcGIS (Figures 1 and 2). Because data from UN Comtrade and CITES provide no information on origin or destination of imported tires and animals, spatial figures only reflect direct airplane traffic, human travel on direct flights and ship movement. It was assumed that all direct international flights were final destinations, even though many are likely temporary points of entry into the USA for travellers and imported resources.

3 | RESULTS

3.1 | Pathways of introduction

Based on our synthesis, 3,245 direct flights, 1,013 ships, 374,873 tires, 285 live animals and 647,169 humans were estimated to enter the USA from RVFV-endemic countries annually (Table 1). It is estimated that 1.4 adult mosquitoes, 19 adult mosquitoes and 0.002 adult mosquitoes will be transported by flight, ship and tire, respectively. From these movement patterns, it is estimated that 24,661 mosquitoes will enter the USA from RVFV-endemic regions every year. According to CITES, the following wild mammals have been imported to the USA from RVFV-endemic regions from 2008 to 2012: Artiodactyla (*Oryx leucoryx*), Carnivora (*Acinonyx jubatus*, *Caracal caracal*, *Felis nigripes*, *Leptailurus serval*, *Panthera leo* and *Proteles cristata*), Perissodactyla (*Ceratotherium simum simum*), *Primates* (*Allenopithecus nigroviridis*, *Callithrix jacchus*, *Cebus capucinus*, *Cercopithecus mitis*, *Chiropotes satanas*, *Chlorocebus aethiops*, *Galago moholi*, *Otolemur crassicaudatus* and *Pan troglodytes*) and Proboscidea (*Loxodonta africana*) (UNEP-WCMC, 2014).

Results indicate that infected humans entering the USA on airplanes from RVFV-endemic regions account for 95% of the RVFV infectious mosquito days in the USA. According to model results, 127 infectious mosquito days (Confidence interval [CI]: 34–220) result from human travel, 3.8 infectious mosquito days (CI: 0–22) result from shipping, 2.7 infectious mosquito days (CI: 0–6) result from air traffic, 0.14 infectious mosquito days (CI: 0.04–0.25) result from mammal imports and 0.004 infectious mosquito days (CI: 0–0.01) result from tire importation each year (Table 3). A standard error is utilized to generate a 95% confidence interval around each parameter estimate when applicable. When multiple data points were unavailable, a confidence interval was created as 50% and 150% of the value. A deterministic minimum and maximum level of risk was calculated using the standard error of parameter estimates, and a pseudo-random function in MATLAB 9.1 was used to explore how stochasticity can influence risk (Figure S1). Results from deterministic and stochastic methods used to evaluate the uncertainty in model results converge on similar conclusions. Overall, the USA is estimated to receive 133.7 infectious mosquito days per year.

3.2 | High-risk ports

Based on flight and shipping data, the risk of RVFV entry is estimated to be highest in the Eastern region of the USA (Figures 1,2 and Figure S2), specifically in New York City, Washington D.C. and Atlanta. These cities account for 34%, 25% and 18% of the annual infectious mosquito days, respectively. Houston, Texas (6.1%); Boston, Massachusetts (3.1%); Jacksonville, Florida (2.7%); Milwaukee, Wisconsin (1.4%); New Orleans, Louisiana (1.3%); Baltimore, Maryland (1.1%); Tacoma, Washington (1%); and Oakland, California (1%), account for the majority of remaining risk. Duluth, Minnesota; Laplace, Louisiana; Los Angeles, California; Miami, Florida; Philadelphia, Pennsylvania; Seattle, Washington; Long Beach, California; San Diego, California; Portland, Oregon; Savannah, Georgia; Corpus Christi, Texas; Pittsburgh, Pennsylvania; Bangor, Maine; Bayport, Houston; Birmingham, Alabama; Cincinnati, Ohio; Orlando, Florida; Newark, New Jersey; Cleveland, Ohio; Colorado Springs, Colorado; White Plains, New York; Rochester, New York; Dover, New Hampshire; Fayetteville, Arkansas; Fort Lauderdale, Florida; Lexington, Kentucky; and Louisville, Kentucky, each account for less than 1% of the infectious mosquitoes travelling to the USA.

According to available international movement data, the following countries are theoretical sources of RVFV export into the USA: Angola, Burkina Faso, Cameroon, Egypt, Ethiopia, Gabon, Guinea, Kenya, Mali, Mauritania, Mozambique, Niger, Nigeria, Saudi Arabia, Senegal, South Africa, The Gambia, Uganda, Yemen and Zimbabwe. Among these countries, 99% of export risk is estimated to originate from nine countries: South Africa (25%), Saudi Arabia (18%), Nigeria (15%), Senegal (14%), Egypt (13%), Ethiopia (9%), Kenya (2%), Angola (2%) and Mozambique (1%). Specifically, the following port cities were identified: Johannesburg, South Africa (6%); Lagos Nigeria (5%); Dakar, Senegal (5%); Cairo, Egypt (4%); Addis Ababa, Ethiopia (3%); Jeddah, Saudi Arabia (3%); Riyadh, Saudi Arabia (2%); Yanbu, Saudi Arabia (1%); and Durban, South Africa (1%).

4 | DISCUSSION

Previous studies emphasize the receptivity of the USA to a RVFV invasion. These efforts have outlined feasible routes of RVFV entry

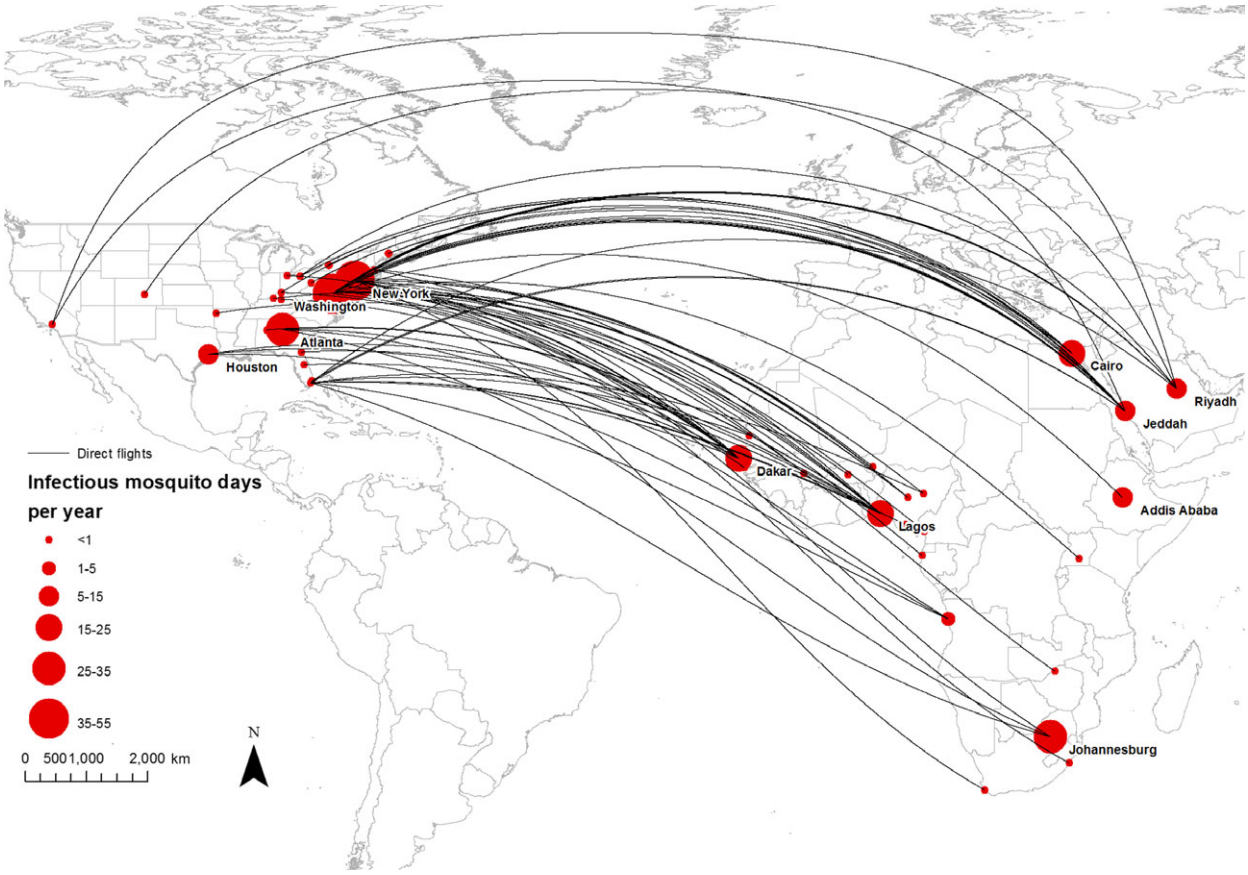

FIGURE 1 The risk of importing Rift Valley fever virus to the USA through flight traffic. This radial flow map illustrates the spatial risk of Rift Valley fever virus entering the USA through flight traffic (mosquitoes and humans). Radial lines represent direct international flights from cities in countries with historical RVFV activity. Red circles symbolize the magnitude of infectious mosquito days entering or leaving each port

into the USA, identified competent hosts for RVFV transmission in the USA, and discussed characteristics that make regions in the USA prone to RVFV invasion, such as high traffic ports, significant ruminant populations and a level of connectivity to endemic regions (Golnar et al., 2014; Kasari et al., 2008; Linthicum et al., 2008; Turell et al., 2013, 2015). In support of proactive RVFV prevention strategies, we completed a quantitative synthesis using published and publically available data. Results quantitatively estimate the relative risk of dispersal pathways and identify which regions are most likely to be involved in the theoretical introduction of RVFV to the USA.

While the process of biological invasion is often stochastic, the global movement of ZIKV, DENV and CHIKV demonstrates a propensity for arboviruses to spread through human movement. Results from this synthesis strongly implicate human travel as the most likely source of RVFV entry into the USA (Table 3). More than two billion passengers fly every year all around the world in a timeframe shorter than most arbovirus incubation periods (Tatem et al., 2012). The dispersal of RVFV by humans is presumably high considering infected individuals can produce an infectious viraemia and international travellers are known to be exposed to RVFV (Durand et al., 2001; Hartley et al., 2011; Meegan, 1979; Rolin et al., 2013). For example, in 2015, an immunocompromised kidney transplant patient originating from Mali, but having lived in France for several years, was diagnosed with RVFV after returning to France from a visit to Mali (Haneche et al., 2016). Further, observations from accidental laboratory exposures and disease outbreaks since the 1930s show humans indeed produce a viraemic titre within the range of $10^{4.1}$–$10^{8.6}$ Lethal $Dose_{50}$ (Meegan, 1979; Smithburn, Mahaffy, Haddow, Kitchen, & Smith, 1949). Although the extent of human infectiousness is unknown, the presence of a measurable RVFV titre indicates a certain probability of infectiousness that cannot be ignored (Lord, Rutledge, & Tabachnick, 2006). Although the resolution of available movement data was limited, and network-based analyses of movement were not possible, direct flight data provide a means to estimate the role of human movement in the theoretical introduction of RVFV into the USA even though it likely vastly underestimates the potential role of humans in RVFV dispersal through international flight traffic. Nonetheless, results from this analysis emphasize a clear need to understand the role humans can play in RVFV transmission (Kasari et al., 2008; Rolin et al., 2013). With a history of human travellers importing arboviruses into the USA, such as DENV, ZIKV and CHIKV, clear clinical case definition is essential to promptly diagnose, treat, and manage imported viral cases, especially if the aetiological agent may be RVFV.

Numerous studies have identified ship and airplane traffic as important vehicles of pest dispersal (Basio et al., 1970; Carneiro de

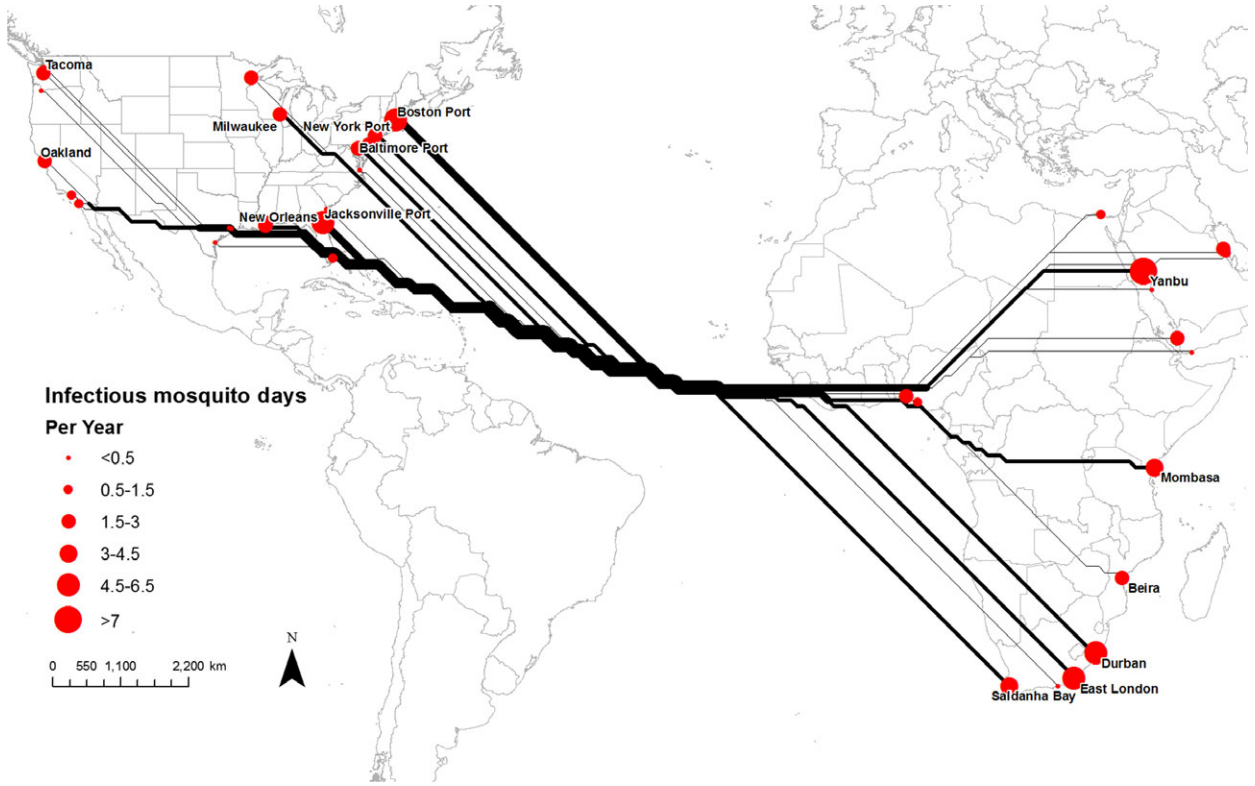

FIGURE 2 The risk of importing Rift Valley fever virus to the USA through ship traffic. This distributive flow map illustrates the spatial risk of Rift Valley fever virus entry into the USA through ship traffic. Red circles symbolize the magnitude of infectious mosquito days entering the USA per year or leaving ports in countries with endemic RVFV activity. Black lines represent the flow of risk from regions with RVFV activity to ports in the USA

TABLE 3 Estimated risk of Rift Valley fever virus entry into the United States by introduction pathway

Pathway of entry	Annual arrival/year	Fraction likely to transmit	Duration	IMD (CI)
Mosquito by plane	$(3245)^{P}(1.41)^{Np}$	$(0.00056)^{Iv}(0.14)^{Vc}$	15	2.69 (0.13–9.8)
Mosquito by ship	$(1013)^{S}(19)^{Ns}$	$(0.00056)^{Iv}$ $(0.14)^{Vc}$	5	3.7 (0–23)
Larvae by tire	$(374843)^{T}(7.7)^{O}(0.5)^{x}(0.83)^{E}$	$(0.0024)^{I}$ $(0.00056)^{Iv}(0.14)^{Vc}$	25	0.0039 (0–0.04)
Mammal Import	285^{M}	$(0.002)^{Im}(0.33)^{Hc}(0.11)^{Y}(0.14)^{Vc}$	15	0.14 (0.03–0.34)
Human travel	647169^{H}	$(0.00085)^{Ih}(0.33)^{Hc}(0.11)^{Y}(0.14)^{Vc}$	15	127 (42–267)

Duration = Number of days the mosquito is expected to remain infectious (Di); IMD = Estimated Infectious mosquito days per year and confidence interval (CI); See parameter estimates listed in Table 1 for more detail.

Mendonca & Cerqueira, 1947; Dobbs & Brodel, 2004; Evans et al., 1963; Laird, 1952; Le Maitre & Chadee, 1983; Takahashi & Laird, 1984). This study indicates shipping traffic and flight traffic pose a comparable level of risk for introducing RVFV-infected mosquitoes into the USA. Access to movement data likely impacts estimates of RVFV-infected mosquito transport by ships more than by airplane. Direct flights are likely responsible for the majority of mosquito introduction scenarios; however, the movement of ships remains more chaotic and is simplified by this model. Many variables, such as travel speed, ship itinerary and route, can impact estimates on the role of ship movement in the transport of RVFV-infected mosquitoes. Methods to control the dispersal of medically and agriculturally significant arthropods, such as the application of pesticides and the use of attractants to bait hitchhiking pests are likely to impact the interpretation of these results (Dobbs & Brodel, 2004). However, no surveys document the widespread use of these practices nor do any studies indicate whether the application of these control methods is changing over time. Even more, the actual rates of mosquito infestation arriving on flights or ships are likely to be different across the world. However, in the absence of any studies documenting contemporary rates of mosquito infestation on ships or planes entering the USA, we must rely on published studies from alternative international ports to generate realistic rates. Overall, this synthesis has taken a conservative approach to estimating the role of ship traffic in the import of RVFV-infected mosquitoes by assuming voyage between countries with endemic RVFV and US ports takes 10 days.

Realistically, ships are likely to move between ports at much slower speeds; however, without appropriate records to estimate movement patterns between ports all ports were treated equally to permit post hoc evaluations when more fine-scale data are attained. It remains unclear how many mosquitoes survive ship or plane transport and how many mosquito species entering these vessels are capable of transmitting RVFV as all mosquito species cannot vector RVFV (Turell et al., 2008). Without proper data to answer these two biological questions, the role of ship and flight traffic in the dispersal of RVFV-infected mosquitoes is likely overestimated. Nonetheless, results of this model suggest RVFV-infected mosquitoes can feasibly enter the USA through ship and flight vessels suggesting that these pathways cannot be overlooked; especially considering flight traffic is the putative pathway of WNV entry into New York in 1999 (Lounibos, 2002; Tatem et al., 2012).

Mammal imports were estimated to result in less than one infectious mosquito day per year (Table 3), which is presumably an overestimate based on supporting information. Trade bans preventing rinderpest and foot-and-mouth disease already indirectly minimize trade in the USA with RVFV active regions. These restrictions likely already constrain the movement of RVFV infectious ruminants into the USA (Kasari et al., 2008; Rolin et al., 2013). Furthermore, in the absence of viral recrudescence or autophagous tissue–tissue transmission among individuals, voyage across the Atlantic Ocean will likely exceed the maximum eight-day infectious period that has been recorded in mammals (Golnar et al., 2014; Kasari et al., 2008; Rolin et al., 2013). Animals entering through less traditional routes, like pets or illegal wildlife, may pose a higher risk of RVFV introduction should animals travel by plane and quarantine procedures not be followed. This is especially relevant for artiodactyls, primates, carnivores and lagomorphs, which have been implicated as potentially high-risk amplification hosts in the USA (Golnar et al., 2014; Kasari et al., 2008).

Studies demonstrate that RVFV can vertically pass from infected female mosquitoes to their offspring, which creates a theoretical opportunity for infected mosquito larvae to enter the USA through tire trade (Hartley et al., 2011; Kasari et al., 2008; Kilpatrick et al., 2006) Although the transportation of immature mosquitoes in tires is one of the major routes of documented mosquito dispersal globally, our model suggests the risk of infected larvae entering the USA by tire transport would be negligible. Even more, vertical infection of RVFV has only been recorded in one species of mosquito (Linthicum et al., 1985). Although the transportation of mosquitoes through the movement of cargo freights and the transportation of lumber from RVFV-endemic regions to the USA are potential introduction scenarios, no records of mosquito interceptions in cargo freights or lumber trade have been documented in the literature.

According to our model, the risk of RVFV entry into the USA through human travel, airplane traffic and shipping transport is expected to concentrate in the East Coast (New York, Washington D.C. and Atlanta) (Figure 1,2, and Figure S2). Similar to the introduction of WNV into North America in 1999, New York is estimated to receive the most RVFV infectious mosquito days per year representing 34% of all potential exposure. Yet, it is important to consider environmental receptivity when interpreting these results. This model does not consider cold winters that may be present in locations like New York, which would dramatically reduce the opportunity for mosquitoes to transmit RVFV (Barker et al., 2013). Southern US climates are more likely to support mosquito activity year-round, and it seems reasonable that these regions would therefore be more receptive to RVFV establishment than mid-Atlantic and north-eastern ports of entry. For example, Houston, Texas, may be of particular risk due to warm climatic conditions, an abundance of livestock, and an extreme abundance of salt marsh mosquitoes (*Aedes sollicitans* [Walker]): laboratory competent vectors of RVFV known to reach population densities sufficient to exsanguinate cattle (Abbitt & Abbitt, 1981; Gargan, Clark, Dohm, Turell, & Bailey, 1988; Golnar et al., 2014).

If RVFV does enter the USA, state and county public health departments and the associated vector-control agencies will be critical members of the outbreak response. Our model compares the relative importance of various countries in exporting RVFV to the USA under the assumption all have similar levels of RVFV activity. Countries with endemic RVFV, such as Egypt, Saudi Arabia, Yemen, Sudan, Mauritania, Senegal, Gambia, South Sudan, Kenya, Tanzania, Mozambique, Zambia, Zimbabwe, Namibia, Madagascar and South Africa, are arguably more likely to be involved in the spread of RVFV to the USA. However, of 32 known countries with RVFV activity, only 20 demonstrate a level of risky connectivity with the USA. Among these countries, about 99% of the estimated RVFV introduction propagules originate from South Africa, Saudi Arabia, Nigeria, Senegal, Egypt, Ethiopia, Kenya, Angola and Mozambique. As such, task forces should be increasingly vigilant of these particular countries during active RVFV outbreaks. Of course, because the virus is known to persist at low levels in the environment among enzootic animal reservoirs and vectors, there is always a level of introduction risk.

Understanding how anthropogenic processes affect vectorborne disease systems can guide research and policy development. Invasion biology is a complex process that necessitates a number of simplifying assumptions. Due to the nature of this project, this quantitative synthesis is based on published and open-access data that originate from various resource materials. Without specific field data to estimate parameters, there is an expected level of uncertainty in our results. Additionally, a number of assumptions made throughout the model will influence results. It is important to note that the total number of humans entering the USA from RVFV-endemic regions is potentially grossly underestimated considering available movement data only include direct flights into the USA even though travellers routinely change flights at international ports before returning to the USA. Furthermore, the role of ship traffic in RVFV dispersal is likely overestimated as voyage times were conservatively estimated assuming ships do not stop at multiple locations during movement between ports in RVFV active regions and the USA. Fine-scale human movement data and epidemiological parameters within and

around affected regions can help further identify patterns of release and mitigate damages associated with RVFV transmission. Additionally, this study focuses on direct connections between RVFV-endemic countries and the USA, and although this is the process by which WNV arrived to the Western Hemisphere (Lounibos, 2002; Tatem et al., 2012) we know that "stepping stone" processes are also possible where RVFV could first become introduced and established in Central or South America and then spread to the USA. This indirect route is how CHIKV and ZIKV have made their way into the Western Hemisphere and then into the continental USA (Fauci & Morens, 2016).

5 | CONCLUSION

Previous studies discuss feasible routes of RVFV entry into the USA and demonstrate that receptive environments with competent mosquito species and vertebrate species exist (Barker et al., 2013; Golnar et al., 2014; Kakani et al., 2010; Kasari et al., 2008; Linthicum et al., 2008). Results of our synthesis expand upon those findings by quantifying the potential role of different pathways and ports in the introduction of RVFV. Results indicate that human travel is the highest risk route of RVFV entry into the USA, followed by the unintentional import of mosquitoes on ships and planes. The risks of mammal and tire imports are likely overestimated and predicted to be low. Risk of RVFV entry is expected to be concentrated on the East Coast in cities such as New York, Washington DC, and Atlanta, and likely to originate from South Africa, Saudi Arabia, Nigeria, Senegal, Egypt, Ethiopia, Kenya, Angola and Mozambique. These results are intended to guide resource prioritization to help support proactive prevention efforts, inform regional vector-control programs and help future vaccination programs target strategic animal populations at risk for exposure.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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