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The Global Expansion of Dengue: How *Aedes aegypti* Mosquitoes Enabled the First Pandemic Arbovirus

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Abstract

Dengue is an emerging viral disease principally transmitted by the *Aedes* (*Stegomyia*) *aegypti* mosquito. It is one of the fastest-growing global infectious diseases, with 100–400 million new infections a year, and is now entrenched in a growing number of tropical megacities. Behind this rapid rise is the simple adaptation of *Ae. aegypti* to a new entomological niche carved out by human habitation. This review describes the expansion of dengue and explores how key changes in the ecology of *Ae. aegypti* allowed it to become a successful invasive species and highly efficient disease vector. We argue that characterizing geographic heterogeneity in mosquito bionomics will be a key research priority that will enable us to better understand future dengue risk and design control strategies to reverse its global spread.

DENGUE THE DISEASE AND DENGUE THE VIRUS

Dengue is a self-limiting disease with a broad range of symptoms that make clinical diagnosis challenging (138). Classically characterized by high temperatures, headache, vomiting, myalgia, joint pain, and rash, dengue shares symptoms with many other common infectious diseases in its tropical setting (120). Only a small proportion of patients will see their illness develop into severe dengue, in which vascular leakage may pose a threat to life if not identified and managed appropriately (138). The majority of dengue cases (18–60%), however, have little or no contact with the healthcare system, as they are either asymptomatic or self-managed (8). These cases are still likely to be infectious but go undetected and thus impose a considerable challenge to disease surveillance and control (34, 128). Despite a mild disease outcome for the individual, the volume of these cases is the principal driver of the burden of dengue, with hospitals often overwhelmed with outpatient consultations, billions of hours of work or school missed, and many patients with chronic long-term infirmities, such as depression and fatigue (118, 129).

The dengue virus (DENV) is a single-stranded RNA virus and is the most globally prevalent member of the *Flavivirus* genus, which also includes viruses such as yellow fever (YFV), West Nile, and Zika that have also emerged as significant public health threats (38, 43). DENV exists in at least four genetically distinct clades often referred to as serotypes. A defining feature of this serotype grouping is that infection with one serotype confers lifelong immunity to that serotype and temporary (6 months–2 years) cross-immunity to the other serotypes. Infection with a heterotypic serotype is a major risk factor for developing severe dengue due to the mechanism of antibody-dependent enhancement (67, 110). However, it has been shown that within-serotype antigenic variation is almost as broad as between-serotype variation, suggesting a more complex genetic and immunological organization of DENV (66). This remains one of several different hypotheses for why DENV exhibits such year-on-year variability in case numbers and disease severity (63, 111).

THE EMERGENCE OF DENGUE FROM SYLVATIC CYCLES

DENV today exists in two distinct transmission cycles: a now ubiquitous human (urban) cycle, where the virus is transmitted between humans via an *Aedes* genus vector, and a more complex and ancient sylvatic cycle that sees occasional spillover to humans (133).

Much of our current understanding of sylvatic DENV comes from two research programs, one established in Senegal, where longitudinal entomological surveillance gives insight into entomological drivers of emergence (1), and the other in Malaysia, where more extensive nonhuman primate sampling aims to explore transmission dynamics in sylvatic hosts (133). These programs have proven the existence of permanent sylvatic cycles in Southeast Asia and Africa, with consistent identification of DENV in a broad range of nonhuman primate species and canopy-dwelling vector *Aedes* species (1, 52). How DENV is maintained in these sylvatic cycles remains unclear, but herd immunity combined with population turnover (2), vertical transmission in mosquito eggs (33), and environmental disturbance (82) have all been hypothesized to play a role in maintaining sustainable sylvatic transmission cycles.

Unlike YFV, DENV does not appear to have yet established a sylvatic cycle in South America. DENV has been documented in rodents, bats, marsupials, and primates across the continent, but only human-adapted viruses have so far been identified (31, 92). This suggests that these represent spill-back events into dead-end hosts likely due to increasing overlap between human and wildlife populations (92). As we have seen with YFV, establishment of a sustained sylvatic cycle of DENV in South America would jeopardize prospects for control and elimination, even in the presence of a highly effective vaccine.

The discovery that every human DENV serotype clade has a sylvatic ancestor is suggestive that the circulation of the four current DENV serotypes in the human cycle arose through multiple independent zoonotic events, with the most recent occurring approximately 850 years ago (27, 126, 134). Both African and Asian origins have been suggested as the source of human-adapted DENV (52). The *Aedes* (*Stegomyia*) *furcifer* vector (in Africa) and *Aedes* (*Stegomyia*) *albopictus* (in Asia) have been found in abundance in environments at the edge of forests, and this, along with their high plasticity in host feeding habits, makes them likely bridge vectors of sylvatic dengue (32, 33, 98, 143).

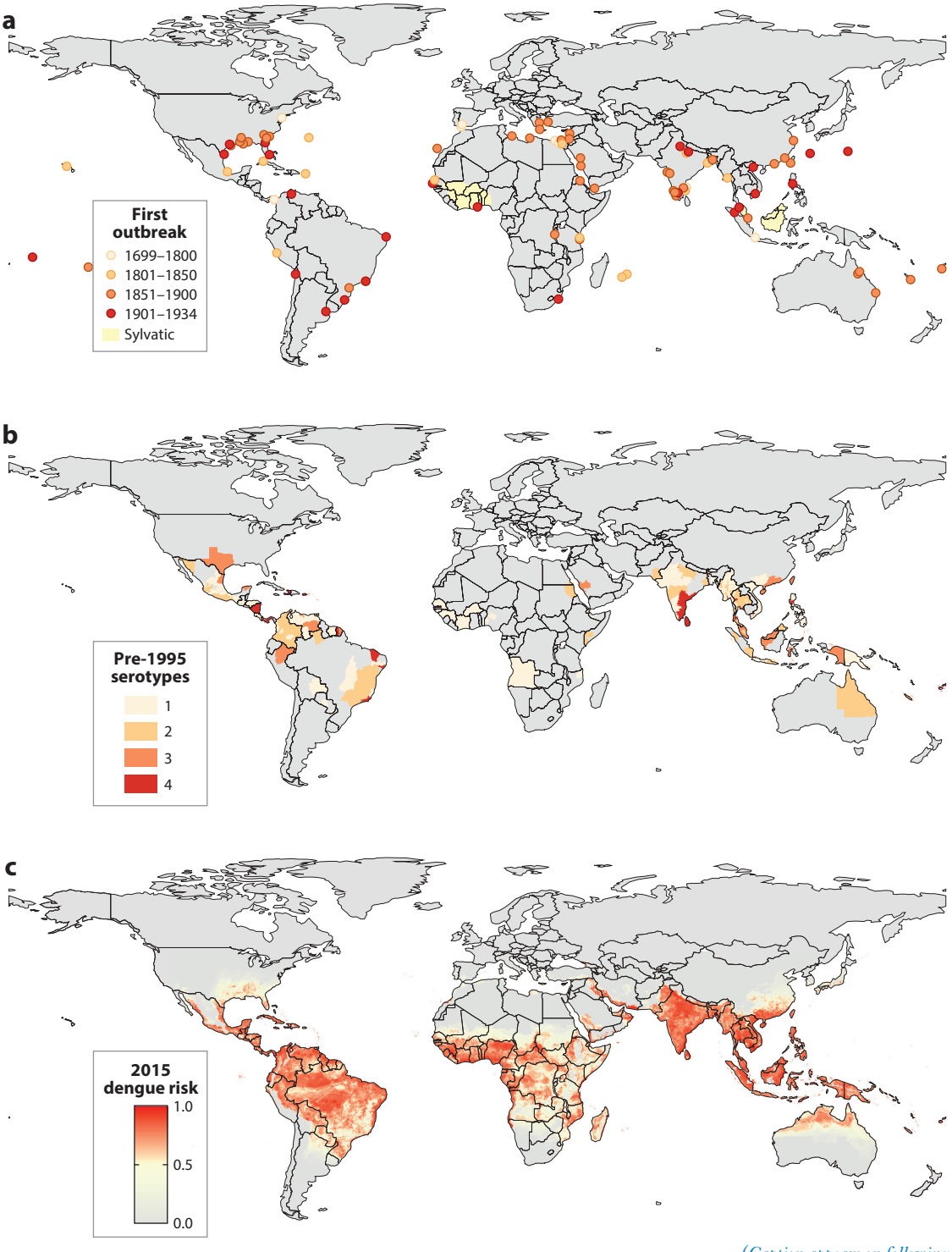
GLOBAL SPREAD OF DENGUE

Following emergence, the global spread of dengue can broadly be divided into three distinct phases: (*a*) the first urban outbreaks, (*b*) the co-circulation of serotypes, and (*c*) consolidation (**Figure 1**).

With DENV-specific diagnostics not becoming available until the 1950s, much of our understanding of the early history of dengue, reviewed in detail by Gubler (47), comes from searching historical literature for dengue-like illness. While the oldest description dates back to an epidemic in China in 992, historical reports of dengue-like illness only begin to emerge with any regularity around the eighteenth and nineteenth centuries (47). These reports detail outbreaks confined to specific cities with brief (one- or two-year) durations that fit the profile of single DENV serotype epidemics. These early reports are highly geographically diverse, with occurrences from all continents in the tropical and subtropical world; the Indian subcontinent, the Caribbean, and the southern United States reported multiple outbreaks over this time (**Figure 1**). These historical outbreaks have led some to suggest that early shipping routes, and in particular the slave trade, caused the first global dengue pandemic between 1779 and 1916 (47, 57). However, with only one serotype circulating at a time, this collection of short-lived, sporadic outbreaks lacked the regularity and severe clinical outcomes of contemporary dengue transmission.

The end of the Second World War precipitated a rapid increase in global trade, travel, and urbanization that has long been suspected to have aided the next wave of dengue expansion (46). For the first time, multiple serotypes could co-circulate in major cities, leading to dengue hemorrhagic fever (DHF), or what would now be diagnosed as severe dengue (51). The rise of hyperendemicity (continuous co-circulation of more than one serotype) in the Americas was delayed by the Pan American Health Organization (PAHO)'s three-decade-long attempt to eliminate *Aedes* (*Stegomyia*) *aegypti* to prevent epidemics of urban yellow fever. Between 1947 and 1962, *Ae. aegypti* was eliminated from over 20 countries through intensive vertically organized campaigns that allowed access to indoor mosquito breeding habitats and made extensive use of DDT (112, 142). In contrast, in countries such as the United States, where the program was decentralized and community led, nationwide *Ae. aegypti* elimination was never achieved (112). When enthusiasm for the project waned in the 1970s, *Ae. aegypti* began to resurge (47), regaining much of its original distribution by the time the program was officially disbanded in 1985 (69, 89).

The final phase of the expansion of dengue was its global consolidation. This began in the late 1990s, when DENV transmission moved beyond major cities to more rural areas to become a ubiquitous threat throughout the tropical world (15, 122). Since 1995, the number of subnational areas reporting dengue and *Ae. aegypti* has trebled (**Figure 2**). Major urban areas maintain high viral diversity, with frequent urban–rural travel ensuring that even smaller communities can maintain high DENV prevalence (111). Increasing international movement, and thus introduction of DENV via viremic humans, has also made maintaining dengue-free status challenging even with intensive vector control programs. A key example of this is the resurgence of dengue in Singapore,



(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

The expanding global distribution of dengue. (*a*) Cities with evidence of dengue-like illness prior to 1935 and the approximate range of sylvatic dengue (47, 52). (*b*) The cumulative number of dengue serotypes reported in each area in the period 1945–1994 (first administrative units or equivalent-sized countries) (87). (*c*) The contemporary (2015) predicted global distribution of dengue risk (86).

which has DENV seroprevalence levels >50% despite successful control in the 1970s and 1980s and continued intensification of their vector control programs (96, 136). The high risk of reintroduction now presents a hurdle for modern dengue control programs, placing a renewed emphasis on coordination in global dengue control efforts (139).

As with all emerging diseases, ascertainment bias (disentangling expansion of disease from expansion of reporting of disease) is a challenge. The post–Second World War expansions coincide with the development of hemagglutination inhibition (HI) assays that provided the first laboratory diagnosis of dengue (50). Wider adoption of electronic surveillance systems since the mid-1990s; the development of global clinical guidelines for diagnosis in 1986, 1997 and 2009; and the wider use of polymerase chain reaction (PCR)–based and point-of-care serological rapid tests in the 2000s all likely improved dengue surveillance (50, 121, 137, 138). Understanding if or how increases in urbanization, travel, and climate change have affected the global expansion of dengue is therefore problematic when the relationships between these factors may be confounded by changes in disease surveillance. What is clear is that, while it is highly plausible that all of these factors affect dengue expansion, current research on the topic often falls short of the requirements for causal inference (5).

FURTHER EXPANSION OF DENGUE

Understanding drivers of global dengue expansion is important for predicting whether dengue will continue to expand. Both continental Europe and the United States were historically endemic, are

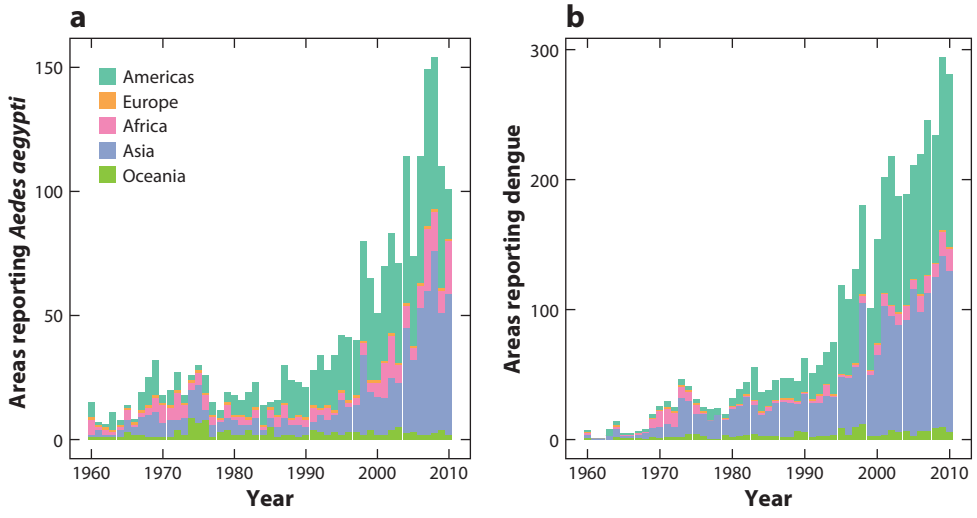


Figure 2

The rise in the global number of areas (first administrative level, e.g., state) reporting (*a*) *Aedes aegypti* and (*b*) dengue. Data taken from References 70 and 87.

at the fringes of the current distribution of dengue, and have had recent small outbreaks (47, 81, 101). Historically, it was thought that human–vector contact was too low in these areas because humans spend most of their time in well-screened, air-conditioned buildings that are unfavorable for mosquitoes (104). However, recent large outbreaks in Madeira, Portugal (2012) (123) and southern Florida (2009) (101) have brought this assumption into question. Wider use of virus-sequencing tools offers the promise of reconstructing detailed chains of transmission, as was done for the Zika outbreak in Florida (44). This revealed high heterogeneity in onward transmission following imported infectious cases and suggested that large outbreaks are possible, and indeed probable, if the number of imported cases is high enough and if they are introduced into certain vulnerable population groups. With future North–South travel projected to increase (59), and given the possibility that climate change could increase transmission in temperate areas (88), there is justifiable concern that areas such as Europe, China, Australia, and the United States might be at risk of further dengue expansion.

At least four separate attempts have been made to predict future change in the global distribution of dengue; they consider various projected climatic and socioeconomic changes (88). Future predictions are limited by the availability of future global projections of key drivers of dengue spread but also by a lack of mechanistic understanding of how these drivers affect the distribution of dengue (102). The effects of temperature on two important determinants of transmission [mosquito survival (17, 18) and DENV incubation period (24)] have been well characterized, and detailed future projections of temperature increases have been assembled for a variety of purposes (60). As a result, many projections of dengue assume that temperature will be the principle or sole determinant of future changes. However, these projections do not predict the current distribution of dengue accurately, omit factors that we know have been important for the historical spread of dengue (such as spread of *Ae. aegypti*), and underestimate uncertainty in future projections (88). There is, therefore, a lack of consensus on the magnitude of the threat of future potential spread of dengue but some agreement that areas at the fringe of the current distribution of dengue in the southern United States, the Mediterranean basin, and southern China are likely to be most at risk.

HOW EXPANSION OF *AEDES AEGYPTI* ENABLED EXPANSION OF DENGUE

A critical question is how dengue has been able to undertake such a rapid, sustained, and robust global expansion. In this section, we explore how the spread of DENV's primary vector species, *Ae. aegypti*, enabled and perhaps even drove the expansion of dengue.

Up until approximately 500 years ago, ancestral *Ae. aegypti* was thought to be a forest-dwelling sub-Saharan mosquito species that laid its eggs in tree holes and fed on nonhuman mammal hosts (99). It has been hypothesized that, as human settlement expanded at the forest edge, human water storage containers provided an ideal alternative larval habitat to avoid the effects of harsh seasonal droughts (99). With closer proximity to humans came increasing potential for alternative blood meal sources, and it is likely that the domestication of *Ae. aegypti* occurred in situ in West Africa with frequent backcrossing with forest-dwelling species (41).

Genetic evidence points to a monophyletic split between African and New World *Ae. aegypti* between 300 and 550 years ago (28, 41, 99, 119). This time coincides with the arrival of the slave-trading period among Europe, West Africa, and the New World, and it is likely that *Ae. aegypti* larvae were transported in drinking water containers between Africa and the New World (99). It did not take long for *Aedes*-borne viruses to follow, with the first yellow fever outbreaks in the New World confirmed in 1648 (85). A transatlantic crossing would have taken 2–4 months, providing evidence of full domestication of *Ae. aegypti* by this time given the need to go through

multiple transmission cycles to maintain YFV during the crossing (141). The modern *Ae. aegypti* was then introduced into Asia later (140–230 years ago), either from the New World or via a now-extinct Mediterranean ancestral form of *Ae. aegypti* (99). It is possible that many of these early translocations were soon followed by the kinds of sporadic port-city dengue outbreaks observed from the eighteenth to the early twentieth century.

A lack of comprehensive historical *Ae. aegypti* sampling limits our ability to understand how the mosquito spread after these transcontinental jumps. Resurgence of the mosquito following the *Ae. aegypti* eradication program in the Americas presents a unique opportunity to understand some historical aspects of spread. Reconstructing genetic relationships using microsatellite loci has shown that reinvasion into Brazil likely occurred both overland and by sea, with northern populations being closely related to those in neighboring Venezuela, while *Ae. aegypti* in the urban, highly connected southeast were more closely related to populations in the Caribbean (68, 90). Studies such as these have been instrumental in shaping the theory that the rapid spread and maintenance of geographically disparate *Ae. aegypti* populations are supported by the utilization of human trade and transport systems (54, 77). This process has only been directly observed in a few circumstances, such as the incrimination of river boats in transporting *Ae. aegypti* outside Iquitos, Peru (45), but it is likely that a wide variety of transportation methods are involved, with the probability of establishment being proportional to frequency and timing of introduction, as well as the size of the introduced population (77). This has resulted in the pattern that we observe today of frequent gene exchange among cities at the regional and international level even among smaller, less well-connected areas (42).

Despite frequent genetic mixing at the macro scale, within cities, there is genetic and even morphological diversity among *Ae. aegypti* populations in different neighborhoods that result in some epidemiologically important phenotypes (113, 135). With a limited (typically <250m) flight range (49) and ample food and egg-laying habitat locally (54), *Ae. aegypti* populations rarely spread and can often be limited by simple urban features such as highways (113). Given the diverse range of urban habitats and different selective pressures imposed by varying insecticide exposures, local-scale variation in *Ae. aegypti* populations is perhaps unsurprising. Our ability to detect and understand these local variations is improving with the first wide-scale releases of modified mosquitoes (21, 94, 95, 113). These novel vector control strategies aim to either replace the wild-type mosquito population with individuals infected with an intracellular bacterium (*Wolbachia*) that reduces their competence for DENV or suppress the population through inviable mating [release of insects carrying a dominant lethal (RIDL) or male-only *Wolbachia* release]. With researchers having control over the number of these laboratory-reared modified mosquitoes that are released and conducting intensive follow-up using ovitraps that can differentiate modified from wild-type mosquitoes, such releases can give important insights into mosquito bionomics. Longitudinal measurements of population size, relative fitness, mating competitiveness, insecticide resistance, and dispersal can be obtained through simple dose-response measurements and made at a spatial scale orders of magnitude larger (4) than existing mark-release-recapture studies (49). The ability to profile key mosquito bionomics across an entire city adds a powerful tool to characterize the heterogeneity in *Ae. aegypti* ecology that has limited existing vector control strategies. Identifying where and why these interventions do not work as expected can build an understanding of how to combine different vector control tools and give longer-term insights into the robustness of population replacement strategies to reinvasion and adaptation. One early example of this is the discovery of diverse insecticide resistance profiles within Rio de Janeiro that prevented early establishment of *Wolbachia*-infected mosquitoes in some neighborhoods (37).

The unique spatial ecology of *Ae. aegypti* therefore presents a considerable challenge: needing tools that are simultaneously tailored to the bionomics of local mosquito populations and robust

to reintroduction from any one of many possible long-distance sources. Unsurprisingly, this challenge has not yet been overcome, but it will be essential to solve it in a new era of vector-based (36, 107) arbovirus control strategies.

WHY IS *AEDES AEGYPTI* SUCH AN EFFECTIVE VECTOR SPECIES?

Above, we describe and discuss why *Ae. aegypti* as a species was able to spread across the globe; however, what makes *Ae. aegypti* such a successful vector species for DENV and other arboviral pathogens extends beyond its ability as an invasive species. In this section, we briefly review the particular bionomics of *Ae. aegypti* that optimize it for DENV transmission and allow it to evade current vector control practices (**Figure 3**). For a more extensive review, we refer readers to Ritchie (106).

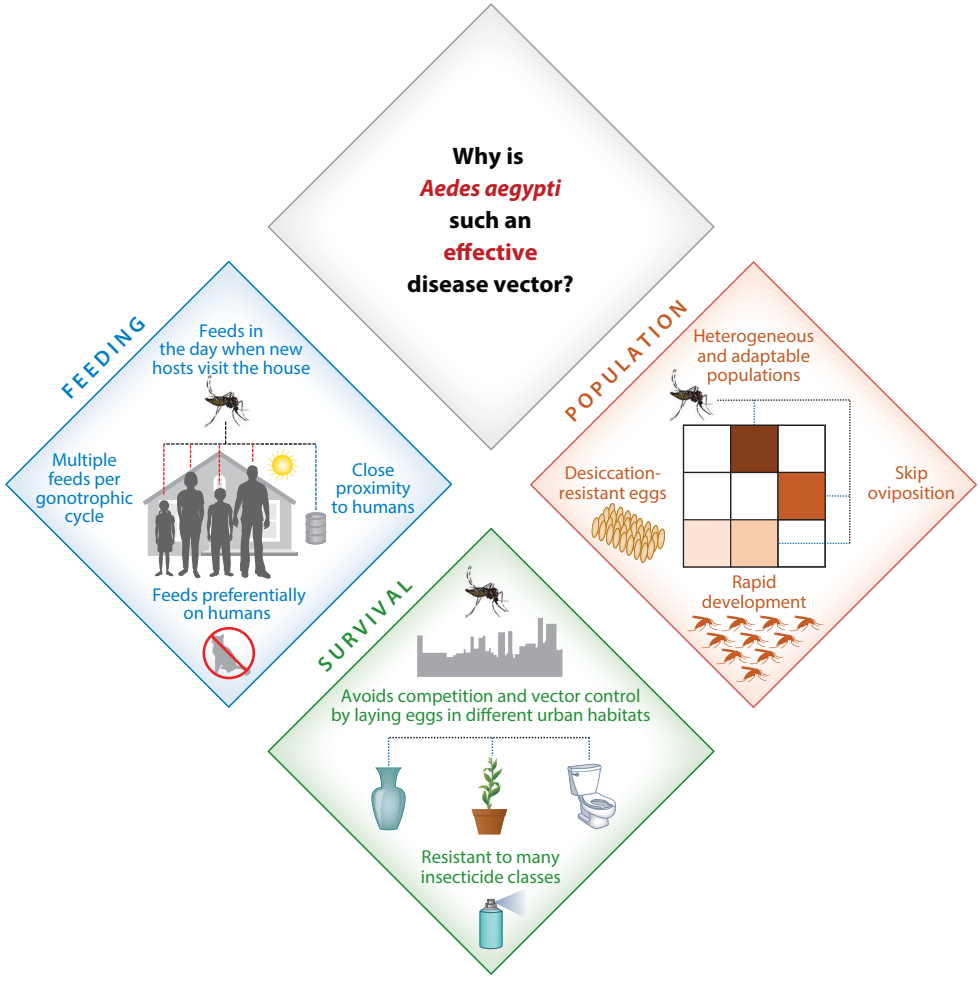


Figure 3

Schematic of the main factors making *Aedes aegypti* a highly effective vector for dengue and other arboviruses.

Ae. aegypti exhibits dynamic, heterogeneous, adaptable, and unpredictable population dynamics. Adult females skip oviposit, i.e., distribute their eggs heterogeneously across many different water-holding container habitats (26, 103). Container preference balances the need to identify habitats that contain adequate resources for development while avoiding intraspecific competition and is therefore often a complex combination of the size and shape of the container, the cleanliness of the water within it, and the number of existing *Ae. aegypti* larvae, all of which help to increase heterogeneity and adaptability (23, 103). Deposited eggs can survive long periods (up to four months) of desiccation, enabling them to persist through seasonal dry periods and be transported over long distances (65, 109). Larval populations also exhibit a behavior known as stacking, where cohorts of larvae will delay progression to pupal stages until sufficient resources become available (106). When such resources do become available, rapid pupal production follows, and large numbers of adult mosquitoes can emerge in a short period of time. It is thought that, historically, these were adaptations that enabled *Ae. aegypti* to survive in areas with long periods of drought (99), but with human habitation providing year-round habitat, they now ensure that *Ae. aegypti* can generate large population sizes in a short amount of time and recover from vector control efforts using just a small number of small, inaccessible containers.

The feeding habits of *Ae. aegypti* also contribute to its efficiency as a vector. There is evidence of both genetic and neural changes underlying female *Ae. aegypti* preference for human biting (for a review, see 84) and blood meal analysis from wild-caught specimens suggests that 70–99% of blood meals originate from human hosts (35, 53, 98, 115, 117). High-protein blood meals are good for egg production, but to sustain metabolism without the fructose that many other mosquitoes access through plant feeding requires nearly daily human blood meals, increasing the number of DENV transmission opportunities (20). Unlike other highly human-adapted mosquito species, such as *Anopheles gambiae* (40), *Ae. aegypti* bite predominantly during daylight hours (53). The elevated risk of mortality that comes from biting during daylight hours means that feedings are usually brief but frequent, with multiple feeds required per gonotrophic cycle, sometimes on different hosts (29, 116). Daytime biting also increases the chance that mosquitoes bite visitors to the house, which is a key mechanism that allows dengue to spread rapidly through urban areas despite limited mosquito dispersal (125). Finally, day biting renders one of the most effective vector control tools, insecticide-treated bed nets (10), ineffectual, and alternatives such as insecticide-treated curtains (74) or clothing (6) have proven to be inadequate replacements.

Adult female *Ae. aegypti* also have several features that allow them to increase their longevity, a parameter that disproportionately amplifies the abundance and vectorial capacity of the species (16). By residing in dark, humid, and warm areas of households, *Ae. aegypti* minimize their exposure to variable and harsh environmental conditions, which allows them to survive at times when and in places where less anthropophilic species would not (114). By living most of their lives either indoors or in shaded outdoor areas in close proximity to the household when more open building structures are present (30, 54, 140), female *Ae. aegypti* only rarely have to undertake inter-household dispersal. This allows them to minimize their chances of mortality due to harsh environmental conditions, inability to find resources, and predation. A lack of dispersal would ordinarily have the disadvantage of limited variety and quantity of egg-laying containers; however, so diverse is the urban habitat, and so adaptable is *Ae. aegypti* as a species, that it is able to lay its eggs in a wide variety of containers. These can include containers as small as plant pots and as inaccessible as rain gutters (7), and the diversity of containers presents a barrier to the effectiveness of community-led clear-up campaigns (138). Finally, *Ae. aegypti* has developed resistance to many known classes of insecticides, and efforts to contain the spread of insecticide-resistance genes have been largely futile given the high long-distance mobility of the species, as discussed above (93).

ALTERNATIVE VECTOR SPECIES OF DENGUE

While there is a consensus that *Ae. aegypti* is the primary urban vector of DENV, several alternative species play a role in transmission in specific geographies and environments. Members of the *Aedes scutellaris* group, and in particular *Aedes polynesiensis*, have been shown to be competent and abundant on various Pacific island nations (58, 80, 91, 108), including those that see dengue transmission in the absence of *Ae. aegypti*. *Ae. polynesiensis* presents a unique vector control challenge in these settings due to its use of both man-made and natural containers (including sea shells) that are not reached by traditional community-based clear-up campaigns (19). In the Caribbean, *Aedes mediovittatus* may also play a role in maintaining DENV transmission (48), although it rarely occurs separately from *Ae. aegypti*, making its epidemiological contribution difficult to measure (76).

In contrast, a large amount of research effort has been expended to understand how much risk *Ae. albopictus* poses for DENV transmission. This is due to three main factors. First, like *Ae. aegypti*, *Ae. albopictus* has undergone a rapid and extensive recent global expansion that now includes much of the tropical and temperate world, spreading as far north as the southern United States, Europe, and China (71). This spread has also been aided by increasing human trade, in particular shipping of used tires that form an ideal egg-laying habitat for the species (56, 127). Second, in addition to demonstrating competence for DENV transmission in the laboratory (12), under certain circumstances, *Ae. albopictus* has proven capable of sustaining outbreaks in the absence of *Ae. aegypti*, as in Guangzhou, China (79). Third, *Ae. albopictus* is a proven competitor of *Ae. aegypti* in peridomestic environments; it largely outcompetes *Ae. aegypti* larvae and pupae and can also outcompete *Ae. aegypti* in adult mating competitiveness (64). Finally, in 2005, Chikungunya virus underwent a single-point E1-A226V mutation that increased its ability to be transmitted by *Ae. albopictus* and resulted in one of the highest-prevalence arboviral outbreaks ever observed (39, 131). Given these concerns, accurately assessing the threat that this vector poses is essential in predicting whether dengue will continue to expand (69).

There are also several good reasons, reviewed extensively in Lambrechts et al. (73), to think that the risk posed by *Ae. albopictus* may be overestimated. *Ae. albopictus*, on average, exhibits lower vector competence for disseminated DENV infection when compared to *Ae. aegypti* (73). *Ae. albopictus* also typically inhabits more rural environments, at least in areas in which the two species coexist, such as southern Europe and Florida (55, 132), and has a broader host range than the human-only *Ae. aegypti* (78). While the two species do compete, they also coexist in many places, particularly within the native range of *Ae. albopictus* in Asia (70), and it is not widely known what limits competition between the two species. Finally, and perhaps most critically, the significant outbreaks of dengue that have occurred in Europe and the United States have been confined to the much more geographically restricted areas where *Ae. aegypti* is present. Outbreaks in southern Florida in 2009–2010 (13) and Madeira in 2012 (123) caused hundreds and thousands of cases, respectively. With the notable exception of the 2001 Hawaii outbreak (122 confirmed cases), outbreaks in *Ae. albopictus*–predominating areas have been limited to <20 cases (130). More research is needed outside of temperate Europe and the United States, particularly from the species' native range in Asia (72), to better understand the threat that *Ae. albopictus* poses for dengue expansion, especially if the investments in *Ae. albopictus* surveillance and research are to be justified and sustained.

THE IMPORTANCE OF MAPPING THE BIONOMICS OF *AEDES AEGYPTI* FOR FUTURE RESEARCH PRIORITIES

One open question of global importance remains ascertaining the true burden of dengue in Africa. Following growing amounts of evidence, particularly from returning infected travelers, it is now

widely accepted that dengue is present across broad areas of sub-Saharan Africa (3, 15, 62). We also know that the same kinds of multiserotype, urban, *Ae. aegypti*–vectored outbreaks do occur, for example, in Ouagadougou (105) and Luanda (22) in 2013. Despite this, no African countries routinely report case numbers in official health statistics (15, 138). The leading hypothesis for the apparent absence of dengue from Africa is ascertainment bias on a vast scale brought about by clinical misdiagnosis of dengue as one of many other causes of febrile illness present on the continent and a near-complete lack of laboratory resources for DENV-infection confirmation (61). Contrastingly, it seems unlikely that DENV transmission intensity in Africa is as high as in South America or Asia, where millions of cases are reported each year (138). Given that Africa is the ancestral source of the modern domesticated form of *Ae. aegypti* (99) and possibly of DENV as well (52), it is difficult to explain why dengue would have such differing epidemiology in Africa.

Ae. aegypti has been historically characterized into two subspecies, a fully domesticated *Ae. aegypti aegypti* present largely outside Africa and a more ancestral *Ae. aegypti formosus* within Africa that retains many non-domesticated traits (25). It has been shown that *Ae. aegypti formosus* does have lower vector competence for DENV (11) and has a lower preference for human blood meals (83). However, others have argued that dividing *Ae. aegypti* into subspecies creates a false dichotomy due to the broad genetic, bionomic, and phenotypic overlap between the suggested groupings (100). Given the increasing frequent movement of humans and mosquitoes between Africa and the rest of the world, there is also probably little reason why more domesticated forms could not return to invade African cities (69, 127).

Understanding whether Africa already has a considerable unrecognized dengue burden and whether it is vulnerable to dengue re-emergence is of critical importance for a continent that has made important recent gains against vector-borne diseases (9) and infectious diseases in general (38). Efforts to improve surveillance and surveillance policy for dengue in Africa are underway (75, 139), but without thorough entomological studies, we will not know why the epidemiology of dengue is so different in Africa, nor how risk will change for the continent in the future.

Improving our understanding of the geographic complexity of *Ae. aegypti* bionomics in Africa could have global implications for dengue control. With the latest dengue vaccine exhibiting complex efficacy (124), and with the emergence of Zika and Chikungunya as global threats, there has been a return in emphasis on integrated control strategies that include different combinations of vector control methods in different places (97, 139). Understanding geographic variation in mosquito survival, biting behavior, connectedness, and population dynamics is essential for understanding why new and existing vector control tools work in some places but not others (14).

This understanding will prove pivotal in designing effective and robust national arbovirus control strategies. While taking such measurements across whole countries or continents seems a daunting task, the advent of modified mosquito approaches offers the hope of a new era of intervention-driven entomological sampling and understanding (113). While this may mean that many of the newest and most promising vector control tools suffer initial local failures (37), the gain in understanding will ultimately lead to more effective and sustainable dengue control.

CONCLUSION

In this review, we describe how dengue emerged to become a pathogen of global importance and explain how it was enabled by the domestication and then spread of the *Ae. aegypti* mosquito. While we understand many of the fundamental reasons why *Ae. aegypti* is such an effective disease vector and why it is so hard to control, complexity and geographic heterogeneity undermine our efforts to design effective and sustainable control strategies. The arrival of new control methods and sampling techniques that can measure mosquito bionomics in much greater volumes offers

the hope of novel insights at the scale needed to control and even reverse the global spread of dengue.

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