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Changing paradigms in *Aedes* control: considering the spatial heterogeneity of dengue transmission

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ABSTRACT *Current dengue vector control strategies, focusing on reactive implementation of insecticide-based interventions in response to clinically apparent disease manifestations, tend to be inefficient, short-lived, and unsustainable within the worldwide epidemiological scenario of virus epidemic recrudescence. As a result of a series of expert meetings and deliberations, a paradigm shift is occurring and a new strategy, using risk stratification at the city level in order to concentrate proactive, sustained efforts in areas at high risk for transmission, has emerged. In this article, the authors 1) outline this targeted, proactive intervention strategy, within the context of dengue epidemiology, the dynamics of its transmission, and current* Aedes *control strategies, and 2) provide support from published literature for the need to empirically test its impact on dengue transmission as well as on the size of disease outbreaks. As chikungunya and Zika viruses continue to expand their range, the need for a science-based, proactive approach for control of urban* Aedes *spp. mosquitoes will become a central focus of integrated disease management planning.*

Key words Dengue; epidemiology; *Aedes*; vector control; Belgium; Brazil; Colombia; Cuba; Mexico; Peru; Caribbean region; Latin America.

Dengue, the most rapidly spreading vector-transmitted virus, yields a significant public health, economic, and social burden in Asia and Latin America. The importance of dengue as a public health threat is demonstrated in the exponentially growing incidence within endemic countries (1) together with a recent spreading to previously "transmission-free" areas, such as the United States (2), Croatia and France (3), and Portugal (4), following the geographic distribution of its vectors. Cases are also increasingly reported from the African continent (5). This remarkable global range expansion, reaching a global burden of 390 million infections per year, of which 96 million are symptomatic (6) and about 24 000 are fatal (7), is closely tied to global trends in population growth, unplanned urbanization, widespread travel, and globalization (8). Based on the disability-adjusted life years (DALYs) metric, dengue is responsible for an average annual loss of 658 DALYs per million population in Latin America and the Caribbean, the same

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order of magnitude as tuberculosis in this region (9, 10). The costs of treating clinical and severe (hospitalized) cases, the economic and social costs of loss of productive time, and the costs for controlling epidemics are exploding (9, 11).

The main mosquito vectors *Aedes aegypti* and *Ae. albopictus* can be found in the tropical and subtropical region, predominantly in urban environments, although recent empiric evidence has documented their expansion into rural areas (12–14). The four distinct but closely related dengue virus serotypes cause a wide range of disease manifestations. Dengue infection frequently remains asymptomatic but can cause classical dengue fever (an acute systemic disease characterized by fever, headache, and arthralgia/myalgia lasting for 5–7 days) or appear as a potentially lethal, severe disease with plasma leakage, with or without haemorrhagic signs. Serotype-specific immunity is lifelong but progression to more serious disease is frequently albeit not exclusively associated with secondary infection by heterologous dengue serotypes (15). Recent experimental feeding trials have documented the ability of individuals with asymptomatic infections to infect *Ae. aegypti* mosquitoes (16), leading to a new public health challenge in the surveillance and control of urban dengue.

Limitations of current dengue control strategies

The control of dengue is mainly based on the control of its vectors at different life stages, as prevention by immunization is not yet programmatically available (but foreseeable in the future). The Phase III trials in Asia and Latin America of a leading life-attenuated candidate vaccine (yellow fever vaccine backbone) yielded efficacy rates for symptomatic dengue of 44.6% and 65.6% in people < 9 years old and ≥ 9 years old respectively (17). Unlike the vaccine for yellow fever, the development of a dengue vaccine is challenged by the need for a balanced immune response in order to address the theoretical risk of immune enhancement (18). Other vaccines are in the pipeline, such as the life-attenuated candidate that uses a DENV4 backbone, which has shown promising results in a Phase II study (18, 19). There is a growing consensus that eliminating dengue as a public health burden can only be achieved by integrating effective vector control with selective vaccination (once the vaccine is available), given the complementarity of the two approaches, and the expectation of a synergistic effect (20). The recent spread of other arboviruses transmitted by *Aedes*, such as chikungunya and Zika (21, 22), for which no vaccine is available, underscores the importance of controlling this vector within the umbrella of an integrated disease management plan.

Common approaches to control *Aedes* (i.e., those used by the disease control programs of dengue-endemic countries (23)) are directed at the insect's larval stages and include the application of chemical larvicides or biological tools in water storage containers and mechanical destruction of non-useful containers filled with rainwater (environmental management), accompanied, or not, by community participation and a communication for behavioral impact (COMBI) strategy. These approaches can also target the adult mosquito, using methods such as outdoor and/or (less frequently) indoor insecticide space-spraying or fogging. Indoor residual spraying, when performed properly, has shown significant impacts in preventing dengue disease when applied in a top-down, regimented way (24). Some new tools, such as insecticide-treated materials, and lethal ovitraps (a device partly submerged in a cup of water that mimics container-breeding mosquitos' breeding habitats) have recently become available (25–28). Other strategies still under evaluation are designed to reduce the *Aedes* population through the release of genetically modified mosquitoes (the Release of Insects with Dominant Lethality (RIDL) approach) or *Wolbachia*-infected mosquitoes (20). As an alternative option for dengue control, efforts can be made to decrease human–vector contact through the application of repellents at the individual level and screening doors/windows at the household level (26).

Most of the vector control measures have shown some degree of effectiveness (29) when intensive and standardized application processes are used, high coverage is reached, and sustained uptake is secured (7). However, under routine conditions, none of these measures has shown potential to halt transmission, due to, at least in part, the above-mentioned implementation challenges, as well as the increasing levels of resistance of local vectors to both larvicides and adulticides (30–32).

Current dengue control strategies in dengue-endemic countries mainly comprise dispersed and irregular control actions carried out in response to detected clinical cases, and/or massive insecticide application designed to mitigate outbreaks. These "response measures" are usually carried out several days or weeks after infection occurred, and are directed toward case houses, which may not be the major site of infection (33). The spraying of adulticide is often implemented after the peak of the epidemic (34). In contrast, a few countries conduct proactive vector control operations on a regular basis, and at nationwide scale, but the high costs (up to US$ 24 per inhabitant per year (35)) make them difficult to sustain.

The way forward

In order to design a more rational and appropriate approach (i.e., suitable for countries where dengue is endemic or epidemic), current control strategies need to be re-thought, taking into consideration, as a starting point, the various demographic, environmental, and social conditions that drive dengue transmission dynamics. Even if it does not immediately address the distal determinants of the problem, the new paradigm in dengue control should not be designed with the assumption that transmission intensity is the same everywhere. It should consider the spatially heterogeneous character of dengue transmission risk at the city level and hence stratify geographic areas. Whenever possible the different strata should be defined and control efforts differentiated by the risk conditions that make them more or less exposed/vulnerable to dengue transmission. The research team revisited evidence on dengue epidemiology to support this new paradigm in dengue control, keeping in mind the need for a strategy that is more effective and efficient.

In the sections below, the authors 1) outline this targeted, proactive intervention strategy, within the context of dengue epidemiology, the dynamics of its transmission, and current *Aedes* control strategies, and 2) provide support from published literature for the need to empirically test its impact on dengue transmission as well as on the size of disease outbreaks.

Identifying areas with high risk for dengue transmission. Transmission of infectious diseases in general and vector-borne diseases specifically is known to be highly heterogeneous in terms of space and time (36–38). Mathematical models indicate that infectious disease interventions that are targeted spatially (and/or temporally) can be more effective than those applied evenly across different locations and time periods (39). Transmission of dengue has also shown spatial and temporal heterogeneity. Spatial areas of elevated risk for dengue were identified at the sub-city level in Peru and at the district level in Vietnam (40, 41). The stability of spatial patterns of dengue incidence was highlighted in research carried out by Barrera et al. (42) in a hyperendemic city in Venezuela, where 70% of reported cases over a five-year period occurred in 35% of all neighborhoods (where 55% of the city inhabitants lived). In Cairns, a non-endemic city in Australia, an analysis of the spatio-temporal dimension of dengue virus transmission demonstrated that 18 space–time clusters involved 65% of cases, and most dengue introductions leading to epidemic propagation occurred within the coastal (and much older) neighborhoods of the city (24).

Based on the malaria hotspot definition provided by Bousema (43), areas with a high risk for dengue transmission could be defined as geographic sites where transmission intensity exceeds the average level. But unlike malaria, average transmission for dengue must be framed within temporal scales because it is dependent on the amount of time that has elapsed since the dengue or a specific serotype was introduced to the area, the level of immunity to a specific serotype within the population, and the transmission intensity within an epidemic/endemic period. Various approaches can be used to assign different levels of risk to specific geographic areas, such as neighborhoods. Two of those approaches are described below. The first approach is based on measures of disease incidence; the second approach is based on measures of vulnerability.

One advantage of the approach based on disease incidence is that data on dengue cases at the population level are routinely available. However, the incidence measure approach has several drawbacks, such as only capturing data from people who have visited public health services and for whom dengue was reported as the main diagnosis (44), and the variability of symptom presentation, which is partly dependent on previous dengue exposure. In addition, these types of data are associated with the residential address of each case, rather than the actual point of transmission, which limits estimations of true location-specific incidence, given that transmission could have occurred outside the neighborhood/city where individuals live (45). In addition, a significant proportion of dengue infections are asymptomatic, even though they can still play an important role in maintaining disease transmission (16, 46). A better measure of past transmission would be dengue serotype–specific seroprevalence, which includes asymptomatic infections. Unfortunately, such data are rarely available at the population level due to the high cost of the diagnostic procedures (47). However, incidence and/or seroprevalence information can be modeled afterward, looking at space–time correlations and taking into account possible covariates.

The second approach, based on measures of vulnerability, is designed to capture multiple dimensions of risk for dengue transmission, beyond the limited predictive ability for actual transmission of one determinant used in isolation. Therefore, models based on this approach incorporate variables characterizing dengue transmission risk: entomologic (48), epidemiologic (49), demographic (50), behavioral (33), and environmental (51, 52) factors. This multifactorial approach is in line with the Mesoamerican plan for integrated dengue prevention and control (53). In a multidisciplinary meeting with dengue experts from academia and national control program managers (Havana, 2014), specific factors within these determinant groups were identified ~~by~~ municipality or city (the level at which control programs are organized). Epidemiologic risk per neighborhood can be characterized based on several indicators: cumulative incidence of dengue cases over a 5–10 year period, the neighborhoods where the first cases usually appear, the persistence of case incidence in/between epidemics, and the serotype(s) that are circulating. The entomologic risk per neighborhood can be explained by two main indicators: the persistence of high indices over time, and cumulative infestation levels (over a period of 2–5 years). These indicators will need to be adapted for the local context of each country, as available entomologic information differs across countries in terms of the methods used, the frequency, and the geographic coverage of surveys. As detailed information on entomologic infestation levels is often lacking or incomplete, the model should also include environmental factors that enhance the probability of vector presence. Environmental and behavioral characteristics could include local risk behaviors or risk spots for *Aedes* infestation (e.g., cemeteries, tire storage areas). For demographic factors, it was found that, along with population density (or, if more appropriate, urbanization characteristics from satellite imagery), it was important to take into account intensive human movement (54, 55). Factors such as temperature, rainfall, and altitude were not retained, as they hardly vary at the municipal or city level. However, in cases where they are deemed important, they could be added to the list of variables.

Criteria that must be defined and questions that must be answered before adapting the control paradigm to a targeted intervention. Before designing an intervention strategy, based on the identification of high-risk areas, certain criteria must be defined and certain research questions answered. One major criterion to define is the geographic scale at which the disease transmission areas need to be defined. To date, appraisal of heterogeneity has mainly been used operationally to identify vast subnational geographic entities (e.g., provinces) to direct dengue control actions (56). However, some researchers have observed that heterogeneity of transmission is better exploited on a smaller scale, because vector infestation levels and risk for dengue transmission can differ markedly from one neighborhood to another within the same city (57). For example, in Peru, it has been shown that neighborhoods (aggregated spatial units) have a higher level of stability as transmission-risk units than individual households (58). Based on these findings, and on the operationalization of routine programs, neighborhoods could be a better target for focusing control efforts than the household or the entire city.

A second criterion that needs to be defined/verified is the stability/persistence of dengue transmission risk within the selected geographic units. The evidence on geographic consistency of clinical dengue incidence and *Aedes* infestation is scarce, uses different geographic scales, and is mainly based on retrospective data analysis. Study results demonstrate highly variable findings on the stability of risk (40–42; 58–61). The best way to validate the spatial consistency of transmission risk in specified operational settings is to use prospective data for evaluating the consistency of an analysis in real time, or current data for evaluating the consistency of an analysis over a retrospective period.

Finally, the following question should be posed: "Do areas with elevated risk for transmission seed/fuel transmission outside these areas?" Albeit not absolutely necessary, intervention impact would increase considerably if dengue control interventions in high-risk areas led to decreased dengue transmission in the surrounding areas. Therefore, the level of control achieved should be evaluated (as "cases averted" or "reduction of transmission"), along with the benefits of the cost-effectiveness of the "targeting" interventions (described below) compared to the more expensive blanket control measures.

Dentarget research network

DENTARGET is a multidisciplinary research network that brings together decision-makers and academics with extensive experience in dengue from five Latin American countries (Brazil, Colombia, Cuba, Mexico, and Peru) and the Institute of Tropical Medicine (Antwerp, Belgium) to develop effective and efficient novel dengue control strategies. Network members[10] have elaborated a research plan consisting of three steps. First, they plan an investigation to identify and validate areas at high risk of dengue transmission in several municipalities per country. Once the group is confident the most appropriate neighborhoods have been identified, it designs a "targeting" intervention (proactive vector control activities in high-risk neighborhoods) to complement routine dengue control activities. The effectiveness of the intervention is assessed in terms of 1) dengue transmission (which could be expressed as averted cases), and 2) the ratio of incremental cost-effectiveness (i.e., from the perspective of the vector control program) of the "targeting" strategy versus the "routine" strategy. In the final step, the group assesses the scope and barriers for possible scaling up of the "targeting" intervention. Given the recent expansion of chikungunya and Zika viruses in the Americas, this approach will also allow for testing of the hypothesis that proactively targeting dengue hotspots could limit the transmission of other *Ae. aegypti*–transmitted arboviruses with similar eco-epidemiologic determinants. Studies in Acapulco, Mexico, found mosquito pools coinfected with both dengue and chikungunya, suggesting co-circulation of dengue (different serotypes) and chikungunya viruses within small geographic units (62). Targeting control can thus improve the cost-effectiveness of interventions in the current scenario of multiple co-circulating viruses.

Expected breakthrough if successful

If successful, the methodologies used and the results of the identification of areas at high risk for dengue transmission could be useful for 1) the organization of health services for case management (i.e., preparation for high-transmission season); 2) the selection of sites for sentinel surveillance (a system proposed by PAHO[11]); and 3) the development of a strategy for scaling up control efforts and/or the deployment of a future dengue vaccine. If proven effective, the targeting strategy could also benefit efforts to control the recently spreading viruses, chikungunya and Zika.

Conclusions

An alternative dengue control strategy was identified based on the spatial heterogeneity characteristic of disease transmission. Implementation studies are under way and will provide evidence on its effectiveness and cost-effectiveness.

Conflicts of interest. None.

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[11] Pan American Health Organization (http://www.paho.org/pan/index.php?option=com_content&view=article&id=782:paises-americas-implementaran-un-sistema-vigilancia-integrada-dengue&Itemid=303).

REFERENCES

1. San Martin JL, Brathwaite O, Zambrano B, Solórzano JO, Bouckenooghe A, Dayan GH, et al. The epidemiology of dengue in the Americas over the last three decades: a worrisome reality. Am J Trop Med Hyg. 2010;82(1):128–35.
2. U.S. Centers for Disease Control and Prevention. Locally acquired Dengue—Key West, Florida, 2009–2010. MMWR Morb Mortal Wkly Rep. 2010;59(19):577–81.
3. Medlock JM, Hansford KM, Schaffner F, Versteirt V, Hendrickx G, Zeller H, et al. A review of the invasive mosquitoes in Europe: ecology, public health risks, and control options. Vector Borne Zoonotic Dis. 2012;12(6):435–47.
4. Tomasello D, Schlagenhauf P. Chikungunya and dengue autochthonous cases in Europe, 2007–2012. Travel Med Infect Dis. 2013;11(5):274–84.
5. Amarasinghe A, Kuritsk JN, Letson GW, Margolis HS. Dengue virus infection in Africa. Emerg Infect Dis. 2011;17(8):1349–54.
6. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504–7. doi: 10.1038/nature12060. Epub 2013 Apr 7.
7. World Health Organization. Global strategy for dengue prevention and control. 2012–2020. Geneva: WHO; 2012.
8. Gubler DJ. Dengue, urbanization and globalization: the unholy trinity of the 21st century. Trop Med Health. 2011;39(4 Suppl):3–11.
9. Shepard DS, Coudeville L, Halasa YA, Zambrano B, Dayan GH. Economic impact of dengue illness in the Americas. Am J Trop Med Hyg. 2011;84(2):200–7.

10. United Nations Development Programme/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases; Scientific Working Group on Dengue. Report of the Scientific Working Group meeting on Dengue. Geneva, 1–5 October 2006. Geneva: WHO; 2007. (TDR/SWG/08).
11. Beatty ME, Beutels P, Meltzer MI, Shepard DS, Hombach J, Hutubessy R, et al. Health economics of dengue: a systematic literature review and expert panel's assessment. Am J Trop Med Hyg. 2011;84(3):473–88.
12. Brady OJ, Golding N, Pigott DM, Kraemer MU, Messina JP, Reiner RC Jr, et al. Global temperature constraints on Aedes aegypti and Ae. albopictus persistence and competence for dengue virus transmission. Parasit Vectors. 2014;7:338.
13. Campbell LP, Luther C, Moo-Llanes D, Ramsey JM, Danis-Lozano R, Peterson AT. Climate change influences on global distributions of dengue and chikungunya virus vectors. Philos Trans R Soc Lond B Biol Sci. 2015;370(1665). pii: 20140135. doi: 10.1098/rstb.2014.0135.
14. Guagliardo SA, Barboza JL, Morrison AC, Astete H, Vazquez-Prokopec G, Kitron U. Patterns of geographic expansion of Aedes aegypti in the Peruvian Amazon. PLoS Negl Trop Dis. 2014;8(8):e3033.
15. Rothman AL. Dengue: defining protective versus pathologic immunity. J Clin Invest. 2004;113(7):946–51.
16. Duong V, Lambrechts L, Paul RE, Ly S, Lay RS, Long KC, et al. Asymptomatic humans transmit dengue virus to mosquitoes. Proc Natl Acad Sci U S A. 2015;112(47):14688–93.
17. Hadinegoro SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, Dietze R, et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. N Engl J Med. 2015;373(13):1195–206. doi: 10.1056/NEJMoa1506223. Epub 2015 Jul 27.
18. Vannice KS, Durbin A, Hombach J. Status of vaccine research and development of vaccines for dengue. Vaccine. 2016;34(26):2934–8. doi: 10.1016/j.vaccine.2015.12.073. Epub 2016 Mar 11.
19. Kirkpatrick BD, Whitehead SS, Pierce KK, Tibery CM, Grier PL, Hynes NA, et al. The live attenuated dengue vaccine TV003 elicits complete protection against dengue in a human challenge model. Sci Transl Med. 2016;8(330):330ra36.
20. Achee NL, Gould F, Perkins TA, Reiner RC Jr, Morrison AC, Ritchie SA, et al. A critical assessment of vector control for dengue prevention. PLoS Negl Trop Dis. 2015;9(5):e0003655.
21. Fischer M, Staples JE; Arboviral Diseases Branch, National Center for Emerging and Zoonotic Infectious Diseases, U.S. Centers for Disease Control and Prevention. Notes from the field: chikungunya virus spreads in the Americas—Caribbean and South America, 2013–2014. MMWR Morb Mortal Wkly Rep. 2014;63(22):500–1.
22. Zanluca C, Melo VC, Mosimann AL, Santos GI, Santos CN, Luz K. First report of autochthonous transmission of Zika virus in Brazil. Mem Inst Oswaldo Cruz. 2015;110(4):569–72.
23. Horstick O, Runge-Ranzinger S, Nathan MB, Kroeger A. Dengue vector-control services: how do they work? A systematic literature review and country case studies. Trans R Soc Trop Med Hyg. 2010;104(6):379–86.
24. Vazquez-Prokopec GM, Kitron U, Montgomery B, Horne P, Ritchie SA. Quantifying the spatial dimension of dengue virus epidemic spread within a tropical urban environment. PLoS Negl Trop Dis. 2010;4(12):e920.
25. Degener CM, Azara TM, Roque RA, Rosner S, Rocha ES, Kroon EG, et al. Mass trapping with MosquiTRAPs does not reduce Aedes aegypti abundance. Mem Inst Oswaldo Cruz. 2015;110(4):517–27. doi: 10.1590/0074-02760140374. Epub 2015 Apr 28.
26. Manrique-Saide P, Che-Mendoza A, Barrera-Perez M, Guillermo-May G, Herrera-Bojorquez J, Dzul-Manzanilla F, et al. Use of insecticide-treated house screens to reduce infestations of dengue virus vectors, Mexico. Emerg Infect Dis. 2015;21(2):308–11.
27. Rapley LP, Johnson PH, Williams CR, Silcock RM, Larkman M, Long SA, et al. A lethal ovitrap-based mass trapping scheme for dengue control in Australia: II. Impact on populations of the mosquito Aedes aegypti. Med Vet Entomol. 2009;23(4):303–16.
28. Vanlerberghe V, Villegas E, Oviedo M, Baly A, Lenhart A, McCall PJ, et al. Evaluation of the effectiveness of insecticide treated materials for household level dengue vector control. PLoS Negl Trop Dis. 2011;5(3):e994.
29. Bowman LR, Donegan S, McCall PJ. Is dengue vector control deficient in effectiveness or evidence?: Systematic review and meta-analysis. PLoS Negl Trop Dis. 2016;10(3):e0004551.
30. Cattand P, Desjeux P, Guzmán MG, Jannin J, Kroeger A, Medici A, et al. Tropical diseases lacking adequate control measures: dengue, leishmaniasis, and African trypanosomiasis. In: Jamison DT, Breman JG, Measham AR, Alleyne D, Claeson M, Evans DB, et al., editors. Disease control priorities in developing countries. 2nd ed. New York: Oxford University Press; 2006. Pp. 451–66.
31. Morrison AC, Zielinski-Gutierrez E, Scott TW, Rosenberg R. Defining challenges and proposing solutions for control of the virus vector Aedes aegypti. PLoS Med. 2008;5(3):e68.
32. Ranson H, Burhani J, Lumjuan N, Black WC. Insecticide resistance in dengue vectors. TropIKA.net [online]. 2010;1(1). Available from: http://journal.tropika.net/scielo.php?script=sci_arttext&pid=s2078-86062010000100003&lng=en.
33. Stoddard ST, Morrison AC, Vazquez-Prokopec GM, Paz Soldan V, Kochel TJ, Kitron U, et al. The role of human movement in the transmission of vector-borne pathogens. PLoS Negl Trop Dis. 2009;3(7):e481.
34. Eisen L, Beaty BJ, Morrison AC, Scott TW. Proactive vector control strategies and improved monitoring and evaluation practices for dengue prevention. J Med Entomol. 2009;46(6):1245–55.
35. Baly A, Toledo ME, Vanlerberghe V, Ceballos E, Reyes A, Sanchez I, et al. Cost-effectiveness of a community-based approach intertwined with a vertical Aedes control program. Am J Trop Med Hyg. 2009;81(1):88–93.
36. Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM. Superspreading and the effect of individual variation on disease emergence. Nature. 2005;438(7066):355–9.
37. Reisen WK. Landscape epidemiology of vector-borne diseases. Annu Rev Entomol. 2010;55:461–83.
38. Woolhouse ME, Dye C, Etard JF, Smith T, Charlwood JD, Garnett GP, et al. Heterogeneities in the transmission of infectious agents: implications for the design of control programs. Proc Natl Acad Sci U S A. 1997;94(1):338–42.
39. Vazquez-Prokopec GM, Spillmann C, Zaidenberg M, Gürtler RE, Kitron U. Spatial heterogeneity and risk maps of community infestation by Triatoma infestans in rural northwestern Argentina. PLoS Negl Trop Dis. 2012;6(8):e1788.
40. Cuong HQ, Vu NT, Cazelles B, Boni MF, Thai KT, Rabaa MA, et al. Spatiotemporal dynamics of dengue epidemics, southern Vietnam. Emerg Infect Dis. 2013;19(6):945–53.
41. Morrison AC, Minnick SL, Rocha C, Forshey BM, Stoddard ST, Getis A, et al. Epidemiology of dengue virus in Iquitos, Peru 1999 to 2005: interepidemic and epidemic patterns of transmission. PLoS Negl Trop Dis. 2010;4(5):e670.
42. Barrera R, Delgado N, Jiménez M, Villalobos I, Romero I. Estratificacion de una ciudad hiperendemica en dengue hemorragico. Rev Panam Salud Publica. 2000;8(4):225–33.
43. Bousema T, Griffin JT, Sauerwein RW, Smith DL, Churcher TS, Takken W, et al. Hitting hotspots: spatial targeting of malaria for control and elimination. PLoS Med. 2012;9(1):e1001165.
44. Gómez-Dantés H, Willoquet JR. Dengue in the Americas: challenges for prevention and control. Cad Saude Publica. 2009;25 Suppl 1:S19–31.
45. Kraemer MU, Perkins TA, Cummings DA, Zakar R, Hay SI, Smith DL, et al. Big city, small world: density, contact rates, and transmission of dengue across Pakistan. J R Soc Interface. 2015;12(111):20150468.
46. Teixeira Mda G, Barreto ML, Costa Mda C, Ferreira LD, Vasconcelos PF, Cairncross S. Dynamics of dengue virus circulation: a silent epidemic in a complex urban area. Trop Med Int Health. 2002;7(9):757–62.
47. Imai N, Dorigatti I, Cauchemez S, Ferguson NM. Estimating dengue transmission intensity from sero-prevalence surveys in multiple countries. PLoS Negl Trop Dis. 2015;9(4):e0003719.
48. Sanchez L, Cortinas J, Pelaez O, Gutierrez H, Concepción D, Van der Stuyft P. Breteau Index threshold levels indicating risk for dengue transmission in areas with low Aedes infestation. Trop Med Int Health. 2010;15(2):173–5.

49. Barbazan P, Yoksan S, Gonzalez JP. Dengue hemorrhagic fever epidemiology in Thailand: description and forecasting of epidemics. Microbes Infect. 2002;4(7):699–705.
50. Hagenlocher M, Delmelle E, Casas I, Kienberger S. Assessing socioeconomic vulnerability to dengue fever in Cali, Colombia: statistical vs expert-based modeling. Int J Health Geogr. 2013;12(1):36.
51. Toledo ME, Rodriguez A, Valdés L, Carrión R, Cabrera G, Banderas D, et al. Evidence on impact of community-based environmental management on dengue transmission in Santiago de Cuba. Trop Med Int Health. 2011;16(6):744–7.
52. Vanwambeke SO, Bennett SN, Kapan DD. Spatially disaggregated disease transmission risk: land cover, land use and risk of dengue transmission on the island of Oahu. Trop Med Int Health. 2010;16(2): 174–85. doi: 10.1111/j.1365-3156.2010.02671.x. Epub 2010 Nov 14.
53. Gómez-Dantés H, San Martin JL, Danis-Lozano R, Manrique-Saide P. La estrategia para la prevención y el control integrado del dengue en Mesoamérica. Salud Publica Mex. 2011;53 Suppl 3:S349–57.
54. Honório NA, Nogueira RM, Codeço CT, Carvalho MS, Cruz OG, Magalhäes Mda A, et al. Spatial evaluation and modeling of Dengue seroprevalence and vector density in Rio de Janeiro, Brazil. PLoS Negl Trop Dis. 2009;3(11):e545.
55. Stoddard ST, Forshey BM, Morrison AC, Paz-Soldan VA, Vazquez-Prokopec GM, Astete H, et al. House-to-house human movement drives dengue virus transmission. Proc Natl Acad Sci U S A. 2013;110(3):994–9.
56. Hernández-Avila JE, Rodríguez MH, Santos-Luna R, Sánchez-Castañeda V, Román-Pérez S, Ríos-Salgado VH, et al. Nation-wide, web-based, geographic information system for the integrated surveillance and control of dengue fever in Mexico. PLoS One. 2013;8(8):e70231.
57. Sanchez L, Vanlerberghe V, Alfonso L, Marquetti Mdel C, Guzman MG, Bisset J, et al. Aedes aegypti larval indices and risk for dengue epidemics. Emerg Infect Dis. 2006;12(5):800–6.
58. LaCon G, Morrison AC, Astete H, Stoddard ST, Paz-Soldan VA, Elder JP, et al. Shifting patterns of Aedes aegypti fine scale spatial clustering in Iquitos, Peru. PLoS Negl Trop Dis. 2014;8(8):e3038.
59. Barrera R. Spatial stability of adult Aedes aegypti populations. Am J Trop Med Hyg. 2011;85(6):1087–92.
60. Dom NC, Ahmad AH, Latif ZA, Ismail R. Measurement of dengue epidemic spreading pattern using density analysis method: retrospective spatial statistical study of dengue in Subang Jaya, Malaysia, 2006–2010. Trans R Soc Trop Med Hyg. 2013;107 (11):715–22.
61. Bhoomiboonchoo P, Gibbons RV, Huang A, Yoon IK, Buddhari D, Nisalak A, et al. The spatial dynamics of dengue virus in Kamphaeng Phet, Thailand. PLoS Negl Trop Dis. 2014;8(9):e3138.
62. Dzul-Manzanilla F, Martinez N, Cruz-Nolasco M, Gutierrez-Castro C, Lopez-Damian L, Ibarra-Lopez J, et al. Evidence of vertical transmission and co-circulation of chikungunya and dengue viruses in field populations of Aedes aegypti (L.) from Guerrero, Mexico. Trans R Soc Trop Med Hyg. 2016;110(2):141–4. doi: 10.1093/trstmh/trv106. Epub 2015 Dec 28.

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RESUMEN

Cambio de paradigma en el control de *Aedes*: consideración de la heterogeneidad espacial de la transmisión del dengue

Las estrategias actuales de control de vectores del dengue, centradas en la ejecución reactiva de intervenciones con insecticidas en respuesta a la aparición de cuadros clínicos evidentes de la enfermedad, suelen ser ineficientes, de duración limitada e insostenibles en el contexto epidemiológico mundial, caracterizado por la recrudescencia de las epidemias virales. Como resultado de una serie de reuniones y deliberaciones entre expertos, está en proceso un cambio de paradigma y ha surgido una nueva estrategia, que consiste en estratificar el riesgo de cada ciudad para concentrar y mantener los esfuerzos proactivos donde hay un alto riesgo de transmisión. En este artículo, los autores 1) describen esta estrategia de intervención específica y proactiva dentro del contexto de las características epidemiológicas del dengue, la dinámica de su transmisión y las estrategias actuales de control de *Aedes* y 2) fundamentan con fuentes bibliográficas la necesidad de demostrar empíricamente las repercusiones de esta estrategia sobre la transmisión del dengue y el tamaño de los brotes. Dado que los virus del chikunguña y el Zika siguen ampliando su alcance, uno de los objetivos primordiales de la planificación de la atención integrada de estas enfermedades estará determinado por la necesidad de adoptar un enfoque científico y proactivo del control urbano de los mosquitos del género *Aedes*.

Palabras clave Dengue; epidemiología; *Aedes*; control de vectores; Bélgica; Brasil; Colombia; Cuba; México; Perú; Región del Caribe; América Latina.