Emerging and Reemerging *Aedes*-Transmitted Arbovirus Infections in the Region of the Americas: Implications for Health Policy

The increasing geographical spread and disease incidence of arboviral infections are among the greatest public health concerns in the Americas. The region has observed an increasing trend in dengue incidence in the last decades, evolving from low to hyperendemicity. Yellow fever incidence has also intensified in this period, expanding from sylvatic-restricted activity to urban outbreaks. Chikungunya started spreading pandemically in 2005 at an unprecedented pace, reaching the Americas in 2013. The following year, Zika also emerged in the region with an explosive outbreak, carrying devastating congenital abnormalities and neurologic disorders and becoming one of the greatest global health crises in years.

The inadequate arbovirus surveillance in the region and the lack of serologic tests to differentiate among viruses poses substantial challenges. The evidence for vector control interventions remains weak. Clinical management remains the mainstay of arboviral disease control. Currently, only yellow fever and dengue vaccines are licensed in the Americas, with several candidate vaccines in clinical trials.

The Global Arbovirus Group of Experts provides in this article an overview of progress, challenges, and recommendations on arboviral prevention and control for countries of the Americas. (*Am J Public Health*. 2019;109:387–392. doi:10.2105/AJPH.2018.304849)

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The ever-increasing geographical spread and rising disease incidence of arboviral (arthropod-borne virus) infections are among the most significant public health concerns in the Americas.[1,2] In addition to the reemergence of dengue virus (DENV) and yellow fever virus (YFV), new arboviral pathogens once confined to specific regions of the world, such as chikungunya virus (CHIKV) and Zika virus (ZIKV), recently resulted in pandemics associated with significant morbidity.[3–6]

Dengue infection is an *Aedes*-borne disease caused by flaviviruses and is second only to malaria as a cause of vector-borne disease mortality and morbidity. For several decades, the Americas have observed an increasing trend in dengue incidence, evolving from low to hyperendemicity, with epidemics recurring approximately every 3 to 5 years.[3] In 2010, 1.7 million dengue cases were reported to the Pan American Health Organization (PAHO), an incidence rate of 174.6 cases per 100 000 population.[7] In 2016, 2.2 million cases were reported (220.0 cases per 100 000 population),[8] though rates were trending lower in 2017.[8] These rates are likely a significant underestimate; modeling studies estimate as many as 53.8 million DENV infections in Latin America and the Caribbean in 2010, including 13.3 million symptomatic infections—way above the numbers reported to PAHO.[9]

In 2005, CHIKV caused an outbreak on the island of Comoros, followed by a large outbreak in India, resulting in more than 1 million cases and significant postinfectious musculoskeletal sequelae. Subsequently, CHIKV spread pandemically at an unprecedented pace, reaching the Americas in 2013, rapidly resulting in more than 1.3 million infections reported in more than 43 countries.[2,10] Incidence rates climbed as high as 137.1 infections per 1000 person-years among Nicaraguan children during the peak of the epidemic.[11]

ZIKV, like CHIKV, had not previously circulated within the Western Hemisphere, and resulted in an explosive outbreak in the Americas, with its identification first on Easter Island, Chile, in 2014, followed by northeast Brazil in 2015, and then spreading throughout the Americas. By late 2015, Zika had become one of the greatest global health crises in years and was associated with devastating congenital abnormalities including microcephaly (Figure 1), Guillain-Barré syndrome, and other neurologic disorders, and with the ability to spread by sexual contact.[6,12–16] By late 2016, ZIKV transmission had extended to 48 countries and territories in the Americas, with a

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Source. Photo courtesy of the Pan American Health Organization. Printed with permission.

FIGURE 1—Brazilian Mother With Her Baby With Microcephaly, a Consequence of an Intrauterine Zika Virus Infection: Recife, Brazil, 2016

total of 707 133 reported cases. These estimates are also likely a significant underestimate as reporting is passive and, therefore, they do not capture asymptomatic cases.[17,18]

For decades, YFV persisted in the Americas as sylvatic cycles of transmission. Beginning in 1997, YFV circulation in Brazil and neighboring countries intensified. In 2008, Asunción, Paraguay, experienced its first urban yellow fever outbreak, which accounted for almost 50% of all yellow fever cases reported that year in the Americas.[19] Over the past 30 years, YFV activity had been restricted to an enzootic area shared by Bolivia, Brazil, Colombia, Ecuador, French Guyana, Guyana, Panama, Peru, Suriname, Trinidad and Tobago, and Venezuela. Since late 2007, the region has experienced intense circulation of YFV, with extensive epizootics and spillover outbreaks in humans. The endemic area has extended to include Paraguay and northern Argentina, with human cases and epizootics detected in 2008.[4] Yellow fever continues to be a significant public health concern for these 13 countries of the Americas.[19]

The recent emergences of ZIKV and CHIKV in 2016 created an unprecedented situation: the cocirculation of 4 important human arboviruses transmitted by the same mosquito, primarily *Aedes aegypti*, in the same time and place. Intense and prolonged rainy seasons and an increase of 2 degrees centigrade in average temperature probably also contributed to an abundance of vectors.[4,20] Deforestation has been associated with yellow fever and Zika outbreaks. Migration of unvaccinated populations to endemic areas has also been a key factor in yellow fever occurrence in South America.[4,20]

SURVEILLANCE

Currently, the inconsistent and inadequate surveillance in the region along with the lack of laboratory serologic testing that can consistently differentiate between closely related flaviviruses poses substantial challenges to respond adequately to these diseases.[21]

Limitations of Existing Systems and Rationale

Existing arbovirus surveillance systems have several limitations, including problems intrinsic to passive surveillance, lack of organizational structure and integration within existing systems, and inadequate laboratory capacity.

Triggered by syndromic fever and rash reporting, most countries in the Americas collect clinical and laboratory data for arboviral diseases through voluntary passive case reporting within health care systems. Most national laboratories have access to serologic and molecular diagnostic testing for existing arboviral pathogens, but fewer laboratories have sequencing and genotyping capability for identifying novel emerging pathogens, genotypes, and outbreaks. Regional laboratory networks exist to facilitate logistical support, technical expertise, and data sharing such as PAHO's Arbovirus Diagnosis Laboratories Network of the Americas.[22]

Data analysis, reporting, and data sharing systems also vary. Although many countries require mandatory reporting of all arboviral diseases, case reporting is often not performed, especially within the private sector. Many countries publish routine case counts of suspected and confirmed arboviral disease cases, though the quality and timeliness of reporting varies. The PAHO Health Information Platform for the Americas is a real-time, voluntary, electronic reporting system that facilitates rapid reporting of data in the region.[23]

Existing surveillance systems, including syndromic, laboratory-based, and other (e.g., postmortem, clinician-based, event-based) systems are often not integrated, which limits their ability to link relevant data and leverage existing resources. Given limited resources, surveillance systems may place a large focus on current arboviral diseases and not dedicate sufficient resources to identify new or emerging arboviral pathogens.

Cross-reactivity of serologic testing between flaviviruses (particularly DENV and ZIKV) makes interpretation difficult. Numerous rapid diagnostic tests of varying quality make laboratory interpretation difficult, especially in the context of changing arboviral epidemiology. Inadequate attention to logistics of sample transport and subsequent testing leads to delays in the availability and reporting of results. Many laboratories do not perform postmortem testing. These limitations in the performance of existing laboratory systems became even more evident during the introduction of new pathogens in the region such as ZIKV.

Surveillance Diagnostics

Given the challenge in clinical differential diagnosis among DENV, ZIKV, and CHIKV, in 2016, the PAHO Directing Council proposed to its member states a strategy for comprehensive surveillance of arboviral diseases. This strategy is based on the coordination and strengthening of epidemiological surveillance, integrated vector control, and laboratory diagnosis.[24]

The clinical differential diagnosis of DENV, ZIKV, and CHIKV is challenging and underscores the importance of laboratory diagnostic tests. Antibody detection tests can distinguish among the alphaviruses (e.g., CHIKV, Venezuelan equine encephalitis, Mayaro, and Ross River viruses) and the flaviviruses (e.g., DENV, ZIKV, YFV, West Nile, and Japanese encephalitis viruses). However, because of previous exposure to related flaviviruses and extensive cross-reactions among flaviviruses, serological tests such as immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) and neutralization assays are not reliable in many situations for distinguishing among flaviviruses.

The most reliable diagnostic tests include nucleic acid tests such as reverse-transcription polymerase chain reaction, and the nonstructural glycoprotein-1 ELISA. The latter detects acute-phase infections. Only the nonstructural glycoprotein-1 ELISA is currently commercially available, and only for DENV.[25]

Until a decade ago, IgM ELISA was the diagnostic method of choice for yellow fever diagnosis. However, the cross-reactivity among flaviviruses again is a major limitation. In endemic areas, immunity to other flaviviruses is very common, and some severe dengue patients present with the clinical manifestations of yellow fever. In addition, IgM may persist for months and is therefore not a reliable marker of a recent YFV infection. The development of molecular diagnostic tools has significantly advanced the diagnosis of yellow fever and the ability to distinguish severe infections caused by wild-type virus versus the 17D vaccine strain.[26]

INTEGRATED CASE MANAGEMENT AND VECTOR CONTROL

Response to *Aedes*-transmitted arboviral infections can benefit from integrated approaches to case management and vector control, which can improve the response to *Aedes*-transmitted arboviral infections. A combination of resources and efforts such as water, sanitation, and hygiene; maternal, newborn, and child health; and integrated management of childhood illness, among others, are needed for more effective and timely solutions.[27,28]

Case Management

Asymptomatic arbovirus infections are common. Symptomatic cases are often mild and resolve spontaneously after 1 to 2 weeks. However, some arboviral infections result in high fever, hemorrhage, meningitis, encephalitis, hepatitis, and other serious clinical outcomes and even death, causing a significant clinical and socioeconomic burden.[29] Clinical diagnosis is challenging, initial prodromes are similar, and sensitivity and specificity of clinical algorithms to distinguish CHIKV, DENV, YFV, and ZIKV have not been estimated.[30] As noted, serologic diagnosis may be impeded by cross-reactivity among related viruses.

In the absence of specific antiviral agents, case management of arboviral disease is symptomatic and supportive. The aim is to prevent mortality by monitoring for shock and hemorrhage and managing exacerbated underlying medical conditions. In areas where *Aedes*-transmitted arboviral disease is endemic, cases should be monitored until clinically stable.[31]

Several recent studies have addressed possible therapeutic options, including the use of traditional antiviral compounds, the synthesis of designer compounds, high-throughput and in silico screening for existing products with possible efficacy, and the use of nucleic acid compounds, therapeutic monoclonal antibodies, and drugs that target host cell proteins.[2] However, none are routinely recommended, and they essentially need further research.

Vector Control

The number of arthropod species potentially capable of transmitting arboviruses is enormous, though 2 mosquito species, *A aegypti* and *Aedes albopictus*, are the primary and most important vectors for arboviruses that infect humans in the Americas. *A aegypti* is primarily an urban, peridomestic, and indoor mosquito and is the main vector for DENV, CHIKV, ZIKV, and YFV. *A albopictus* is a secondary vector for these pathogens but has a more extended geographical range than *A aegypti* and, thus, may play a significant role in arboviral transmission in some regions.[32,33]

Early results of genome sequencing indicate that mosquitoes carry large numbers of known and unknown viruses that infect humans and, because of their high mutation rates, many new pathogenic arboviruses may potentially emerge. In accordance, vector control has a potentially predominant role in the context of arboviral control, as is the case with the integrated vector management strategy of the World Health Organization (WHO).[34]

Vector-control methods for *Aedes* control can be broadly divided into biological, chemical, and environmental.[35] Biological methods include *Bacillus thuringiensis israelensis* (Bti), larvivorous fish, and copepods for the control of larval stages. The use of the bacteria *Wolbachia*, genetically modified mosquitoes, and mosquitoes modified by sterile insect technique are currently being evaluated for public health use.[36] Chemical methods include insecticides for residual sprayings, such as peridomestic or intradomiciliary spraying (including indoor residual spraying); long-lasting insecticide treated materials or insecticide-treated nets or insecticide-treated curtains, mostly targeting adult mosquitoes; and larvicides to control larval stages. Environmental methods target productive breeding sites, such as emptying of water containers, waste management, provision of piped water or physical barriers, window screens, and water container covers. Community involvement is considered a crucial element for any vector-control strategy.[37]

Recently a WHO handbook recommended the use of contingency planning, including an algorithm to predict and detect dengue outbreaks.[38] Although global eradication of mosquito vectors is not possible, routine vector control and emergency operations can significantly reduce vector populations.[35] However, in many countries, integrated vector control is poorly implemented.[39,40] For an integrated approach, combining different vector-control methods following the integrated vector management concept requires an assessment of the specific diseases and vectors to be targeted.[41,42] However, the use of chemical methods is almost always included, particularly indoor residual spraying, insecticide-treated nets, and insecticide-treated materials. Biological methods and environmental methods may also be used. In general, the effectiveness of vector control, in terms of primary prevention of transmission, has been assessed for dengue but remains controversial.[36,43]

VACCINES AGAINST *AEDES*-TRANSMITTED ARBOVIRUS

Because of the challenges related to vector control described previously, vaccines may well emerge as the most efficient tools for controlling and preventing *Aedes*-transmitted arbovirus infections. Currently, there are only 2 licensed vaccines against emerging and reemerging arboviruses in the Americas: the live attenuated yellow fever 17D vaccine and a recently licensed live attenuated chimeric yellow fever–derived tetravalent dengue vaccine (CYD-TVD). Although no vaccines are yet licensed against ZIKV or CHIKV, several candidate vaccines are in different phases of clinical trials.

Yellow Fever Vaccines

The live, attenuated yellow fever 17D vaccine developed in 1936 is one of the oldest live attenuated vaccines in current use.[44] The vaccine is widely used for the prevention of yellow fever in travelers, for routine immunization of infants in endemic areas, and for emergency response during outbreaks. Twenty to 60 million doses are distributed annually.[26]

Yellow fever 17D vaccine elicits a rapid, exceptionally strong, and essentially lifelong adaptive immune response. Vaccinologists have harnessed 17D as a vector for foreign genes,[26] a promising area for continued research.

Two types of severe adverse events are temporally associated with the yellow fever 17D vaccine: neurotropic and viscerotropic disease. Both are fortunately rare. Yellow fever vaccine–associated neurotropic disease is manifest in more than half of the cases by meningitis or encephalitis, and the remainder have clinical or radiological evidence for Guillain-Barré or acute disseminated encephalomyelitis. Neurotropic adverse events occur between 0.2 (Europe) and 0.8 (United States) per 100 000 population vaccinated. Most cases are in infants aged younger than 7 months. In 1960, recommendations were made contraindicating vaccine use in infants up to 6 months of age.[26] Recent reports have documented yellow fever 17D virus transmission, with resulting yellow fever vaccine–associated neurotropic disease, in 3 breastfed newborn babies from mothers who had been recently vaccinated.[26]

In 2001, 7 cases (6 fatal) of viscerotropic disease were reported with acute multiorgan failure. Such cases are caused by the 17D virus and resemble cases caused by wild-type YFV. Over the next 10 years, a total of 65 cases have been recorded, with a high case fatality rate of 63%. Fortunately, yellow fever vaccine–associated neurotropic disease remains rare. The risk is higher with advancing age, reaching 1.0 to 2.3 per 100 000 in persons aged older than 60 years, and is associated with impaired immunity. Despite the higher reporting rate in the elderly, severe disease and deaths have also occurred in young persons and in women of childbearing age.[26]

Countries in the Americas follow PAHO's Technical Advisory Group's recommendations to prevent and control yellow fever in the region, which include (1) universal introduction of the yellow fever vaccine in national immunization programs for children aged 1 year in countries with endemic transmission, (2) preventive vaccination campaigns for populations aged younger than 2 years living in enzootic areas during interepidemic periods, (3) vaccination campaigns in response to outbreaks or epizootics, and (4) vaccination of travelers to areas with a risk of YFV transmission.[45]

Unfortunately, the limited vaccine availability does not allow countries to fully implement these recommendations. The vaccination coverage in children at 1 year of age is approximately 70% in the region. Recent outbreaks of yellow fever in Angola and the Democratic Republic of Congo depleted the global vaccine stockpile, highlighting the challenges to maintaining supply. To address the shortage, on the basis of existing published data, experts have recommended fractional doses to administer reduced volumes of the vaccines.[46,47]

Dengue Vaccines

Vaccine development against DENV infections is among the most complex challenges in vaccinology, complicated by 2 major issues. First, DENV comprises 4 antigenically distinct serotypes with several genotypes within each serotype. Infection with 1 serotype generally confers lifelong immunity to the infecting serotype and only transient cross-protection to heterologous serotypes. Secondary infection expands the cross-reactive immunity, making symptomatic infections by a third DENV serotype unusual. However, inducing protection to all 4 DENV serotypes by 1 vaccine has been difficult. Second, severe manifestations of dengue occur at a higher rate in secondary infections. Antibody-dependent enhancement has been proposed as a mechanism to explain the more severe presentation of dengue in a secondary infection. During antibody-dependent enhancement, cross-reactive but nonneutralizing antibodies from primary infection by a heterologous DENV serotype enhance entry and replication of virus particles in immune cells, especially macrophages, resulting in high titers of virus in blood and consequently severe disease during the second DENV infection. Thus, a DENV vaccine carries the potential for increasing the risk of severe disease in DENV-naïve individuals unless the vaccine gives rise to lasting, protective immunity to all serotypes.[48]

Currently, multiple candidate vaccines are in clinical development and 1 vaccine, CYD-TDV (Dengvaxia), has recently been licensed in 19 countries, including Mexico, Brazil, El Salvador, and Paraguay. Dengvaxia is a tetravalent combination of 4 monovalent chimeric attenuated viruses with adequate protection against DENV3 and DENV4, modest protection against DENV1, and inadequate protection against DENV2.[49–51]

In 2011, the vaccine underwent phase III clinical trials, including more than 30 000 individuals in 10 endemic countries throughout Asia and Latin America. Pooled data indicated a 59.2% efficacy against all clinically diagnosed dengue cases, and 76.9% efficacy against severe dengue 1 year after a 3-dose vaccine regimen. In May 2016, the PAHO Technical Advisory Group stated that there was insufficient safety and effectiveness evidence to recommend the introduction of the DENV vaccine into routine national immunization programs of the region.[52] In November 2017, the vaccine manufacturer announced study results that showed increased hospitalized cases with severe dengue observed in young children from 2 to 5 years of age who were DENV-naïve.[53–55] On the basis of these findings, in April 2018, the WHO Scientific Advisory Group of Experts recommended conducting serologic testing of DENV immune status before vaccine administration and avoiding vaccinating DENV-naïve individuals.[56]

Two other live-attenuated DENV vaccines are in phase III trials, whereas still others, such as a purified inactivated vaccine, are in phase I trials. In addition, attenuated strains are being used as challenge strains in the human DENV infection model and have great promise for moving to phase III clinical trials.[53] DENV E protein is being pursued as the main antigen in several subunit-based vaccines.[53] Research on plant-based vaccines will potentially revolutionize the way vaccine can be produced, if proven successful.[57]

Other Arboviral Vaccines

Zika vaccines in the pipeline. ZIKV vaccine development has benefited from the head start that DENV research has provided. As with DENV, ZIKV also presents some human immunologic challenges for vaccine development. In many areas affected by ZIKV, seropositivity for DENV is very high. Although ZIKV differs from DENV by 41% to 46% in the genetic sequence of its envelope protein, some experts argue that the data suggest that cross-reactivity between DENV with ZIKV may drive antibody-dependent enhancement of infection in people previously exposed to DENV who are later infected with ZIKV.[58] Several vaccine platforms are being investigated for ZIKV vaccine development. Leading vaccine candidates, some of which are in phase I and II human trials, have produced promising results in preclinical studies.[59] Future challenges for ZIKV vaccine development include having sufficient cases to enable successful phase III trials.

Chikungunya vaccines in the pipeline. After the reemergence of CHIKV in 2004, there was renewed interest in developing a vaccine. Options including virus-like particles, subunit vaccines, vectored or chimeric vaccines, nucleic acid vaccines, and live attenuated vaccines have all been explored as possibilities. One significant challenge is that there are numerous different virus strains used, different animal models with different routes of both vaccination and challenge, and different methods for evaluating efficacy.[2]

RECOMMENDATIONS

In June 2018, the George Washington University Milken Institute of Public Health convened a Global Arbovirus Group of Experts, including leading international and regional experts from PAHO, the Centers for Disease Control and Prevention, the National Institutes of Health, and the Center for Global Health at the University of Colorado, among others, to discuss current challenges for *Aedes*-transmitted arbovirus infections in the Americas. The Global Arbovirus Group of Experts issued the following technical recommendations with the overriding priority to prevent unnecessary morbidity and mortality of arbovirus infections: Cases need to be detected earlier so essential clinical and public health interventions can be implemented in a more timely fashion. To that end, efforts to improve the following will be critical: laboratory capacity and diagnostics, case reporting and management, integrated surveillance system with an emphasis on data quality, and community communication to minimize exposures. Research, including that for vaccine development, improved diagnostics, and operational research for best practices such as vector control within an integrated approach and vaccination achieving high coverage rates among communities most at risk will also be essential. A more detailed list of recommendations is included as Appendix A (available as a supplement to the online version of this article at http://www.ajph.org). AJPH

CONTRIBUTORS

M. A. Espinal and J. K. Andrus jointly conceptualized the review and co-led the writing. B. Jauregui compiled the recommended references and supported the preparation of the draft. D. Olson contributed substantial content and provided extensive revisions and additional references. S. H. Waterman, D. M. Morens, J. I. Santos, and L. A. Francis contributed additional content and revisions and provided references. O. Horstick was the primary expert and contributor to vector control.

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CONFLICTS OF INTEREST

D. Olson served as a consultant in an advisory meeting to Sanofi Pasteur regarding its CYD-TDV (Dengvaxia) dengue vaccine in 2018. All other authors have no potential conflicts of interest to declare.

HUMAN PARTICIPANT PROTECTION

No protocol approval was necessary because no research involving human participants was conducted.

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