History, Epidemiology, and Clinical Manifestations of Zika: A Systematic Review

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Objectives. To describe salient epidemiological characteristics of Zika virus outbreaks across the world and to examine the clinical presentations, complications, and atypical manifestations related to their occurrence in recent history.

Methods. We conducted a systematic review of the literature by searching through MEDLINE, Embase, and Global Health Library, as well as the epidemiological bulletins and alerts from the World Health Organization, the Pan American Health Organization, and the European Centre for Disease Prevention and Control over the period 1954 to 2016.

Results. The search yielded 547 records. We retained 333 for further analysis, to which we added 11 epidemiological bulletins from various sources. Of these, we systematically reviewed 52 articles and reports, revealing some epidemiological features and patterns of spread of the Zika virus worldwide, as well as pathological outcomes suspected to be linked to Zika outbreaks. Neurologic disorders among zika patients were similar in Brazil and French Polynesia but a causal link is not established. Incidence of zika infection in pregnant women is not known. In Brazil, during the zika outbreak the incidence of microcephaly increased more than 20 times. Among 35 infants with microcephaly, born from women suspected to have Zika infection during pregnancy in northeast Brazil, 74% of the mothers reported rash during the first and second trimester.

Conclusions. On February 1, 2016, The World Health Organization declared the ongoing Zika crisis an emergency and that, although not yet scientifically proven, the link between the virus and growing numbers of microcephaly cases was "strongly suspected." However, the causal relationship between zika and microcephaly is not universally accepted.

Public Health Implications. The current situation with regard to Zika is not encouraging, because there is no vaccine, no treatment, and no good serological test, and vector control remains a challenge. (*Am J Public Health.* 2016;106:606–612. doi:10.2105/AJPH.2016.303112)

Among diseases emerging in the 21st century, Zika is raising one of the greatest amounts of concern for public health globally. Zika virus (ZIKV) has presented as outbreaks since 2007; however, more recently, it has become the main suspected cause of an unusual and completely unexpected microcephaly epidemic, exposing the urgent needs for knowledge about this disease.

Zika fever is an exanthematous disease, related to dengue fever, West Nile, and yellow fever.[1] This infection is characterized by symptoms that can last 1 week, with a clinical presentation similar to that of other arbovirus infections such as chikungunya and dengue, including mild fever, rash, arthralgia, arthritis, myalgia, headache, conjunctivitis, and edema. Severe cases involving hospitalization are uncommon, and deaths are rare.[2] This disease is caused by a flavivirus, isolated for the first time in 1947 from the blood of a sentinel rhesus monkey (*Macacamulatta*) in the Zika forest near Entebbe, Uganda.[3]

Zika virus has been isolated from *Aedes africanus*,[4] *Aedes luteocephalus*,[5] *Aedes aegypti*,[6] *Aedes albopictus*,[7,8] *Aedes furcifer,*[9] and *Aedes vittatus*[5,9] mosquitos and, therefore, although *A aegypti* is the main vector in the Brazil epidemic, all of these *Aedes* species are probably involved in the transmission of ZIKV to humans. Zika was the predominant virus identified during the Yap Island outbreak, even though it was not isolated from *Aedes hensilli*. The evidence that this species was the most likely vector of dengue made this the suspected vector of ZIKV in Micronesia.[10] *Aedes* species present special difficulty to vector control agencies, mainly because they can reproduce in extremely small amounts of water (e.g., the water in a bottle cap) and their eggs are extremely hardy (e.g., the eggs can survive drying for more than a year).

Recently, a large increase was observed in the circulation of ZIKV worldwide, which initially was endemic only in Africa and Asia. Cases have been reported in countries of Europe, Oceania, and the Americas, particularly in Latin America where it is rapidly spreading to new areas.[11] From places with established autochthonous transmission, such as Brazil, viremic travelers have the capacity to introduce ZIKV into new countries, where *Aedes* mosquitoes would become infected and perpetuate local transmission cycles. In South America, Brazil had large concentration of cases of Zika, especially in the Northeast region, and serious complications occurred simultaneously with the outbreak of this arbovirus. Until this moment, only 1 review on Zika has been published,[12] and that

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was before the virus's introduction in the American region. Thus, we decided to produce another review with the newly available information, and to identify gaps in the available knowledge about this disease.

The aim of our systematic review was to describe the current knowledge on the epidemiological characteristics, frequency, spatial distribution, clinical presentation, and complications or atypical manifestations related to the occurrence of Zika outbreaks.

METHODS

This study is being reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol was registered on PROSPERO, an international database of prospectively registered systematic reviews in health and social care. The registration number is CRD42016033168.

We searched MEDLINE, Embase, and Global Health Library to identify studies reporting epidemiological aspects of Zika disease worldwide (age, sex, prevalence, attack rates), clinical presentation, atypical manifestations, and negative fetal outcomes. We searched databases in January 2016 with the following approach: (1) Zika terms "Zika" and "Zika infections," and (2) "epidemic," "epidemiology," "outbreak," "seroprevalence," "attack rates," "clinical presentation," "clinical manifestation," "clinical symptoms," "clinical features," "atypical manifestations," "neurological symptoms," "cardiovascular symptoms," "eye disease," "kidney disease," "ocular symptoms," and "vertical transmission." We supplemented database searches by screening bibliographies of the articles. We also included epidemiology bulletins from World Health Organization (WHO), Pan American Health Organization (PAHO), European Centre for Disease Prevention and Control (ECDC), and ministries of health from countries affected by Zika virus. We included studies published in English, Portuguese, French, and Spanish. We reviewed all titles and abstracts of publications identified in the course of the primary search for relevance and eligibility after we removed the duplicate articles. (Full electronic search strategy for MEDLINE can be found in Table A, available as a supplement to the online version of this article at http://www.ajph.org.)

Eligibility criteria were original studies that reported cases of Zika infections, and epidemiology bulletins from the WHO, PAHO, ECDC, and ministries of health from countries affected by Zika virus. Eligible study designs were case–control, cohort, cross-sectional case series, case reports, and ecological studies. We excluded reviews, in vitro studies, animal studies, studies of disease vectors, and studies examining Zika and other exanthematous diseases together or without the epidemiological aspects or clinical presentation.

Two independent reviewers (ESP, FB) screened article titles and abstracts to select articles for full-text screening. The reviewers assessed full texts independently; in case of disagreement, they consulted a third author (MNC), and agreed upon a decision by consensus.

We used a uniform tool to extract data from eligible articles and bulletins: study design, year of publication, study location, period of study, authors, and population characteristics such as age, sex, ethnicity, clinical symptoms, frequency of outcomes, and laboratory confirmation.

The epidemiological characteristics of the patients with Zika (mean age, sex) and clinical presentation are presented and the attack rate and proportion of complications calculated.

RESULTS

Results of the search are presented in Figure 1. The primary search identified 547 papers. We removed 217 duplicates. We screened 333 articles to assess eligibility, and excluded 292 that did not meet the inclusion criteria. We included 41 articles in the synthesis (30 case reports or case series and 11 surveillance or cross-sectional studies). We also included 11 epidemiological bulletins and alerts from WHO, PAHO, ECDC, and ministries of health from Brazil and French Polynesia.

Study Characteristics

The case report, case series surveillance, and cross-sectional study characteristics are described in Table A. The studies were published from 1954 to 2016. The majority were case reports describing clinical symptoms of patients with laboratory-confirmed illness. These cases presented as a mild nonspecific disease; the most common symptoms reported were rash, fever, arthralgia, conjunctivitis, myalgia, and headache; 55% of the case reports described Zika in travelers.[13–29] Coinfection occurred with dengue,[30] chikungunya,[31] and HIV,[32] but the patients recovered without complications. Although Zika is a vector-borne disease, there is some evidence of sexual[27,33] and perinatal[34] transmission, and a theoretical possibility of transmission via blood transfusion.[35] The virus was found in blood,[35] semen,[33] urine,[14,36] and saliva samples,[37] and 1 study proposed the bite of a monkey as a plausible route of transmission.[15]

Epidemiology

After the first evidence of human infection in 1952,[38] sporadic cases and serological evidence of Zika were reported in surveys and case reports, showing that Zika was active in several countries in Africa and Asia[39–42] before spreading to the Pacific region and more recently to the Americas. In 1954, a serological surveillance in French Equatorial Africa showed only 0.5% were positive for Zika antibodies.[39] In Nigeria (1971–1975), 38% of the individuals had neutralizing antibodies to Zika in sera,[38] and this disease was serologically confirmed in 3.1% of febrile patients in an hospital in Java, Indonesia (1977–1978).[42]

From 1983 until 2006, there were no publications on Zika, until the Yap Island outbreak when it was detected for the first time in Oceania. The overall attack rate (of Zika illness presenting to a health care facility) was 14.6 per 1000 inhabitants. It was higher among women and the mean age was 36 years.[43] A household survey conducted in this area estimated a Zika infection rate (positive immunoglobulin M) of 73% (95% confidence interval = 68%, 77%), and clinical manifestations in approximately 1 in every 5 infected people. Males were more likely to have Zika infection than females; this result did not differ across age groups. No hospitalizations or deaths attributable to Zika were detected, but the population was small (fewer than 10 000 people).[43]

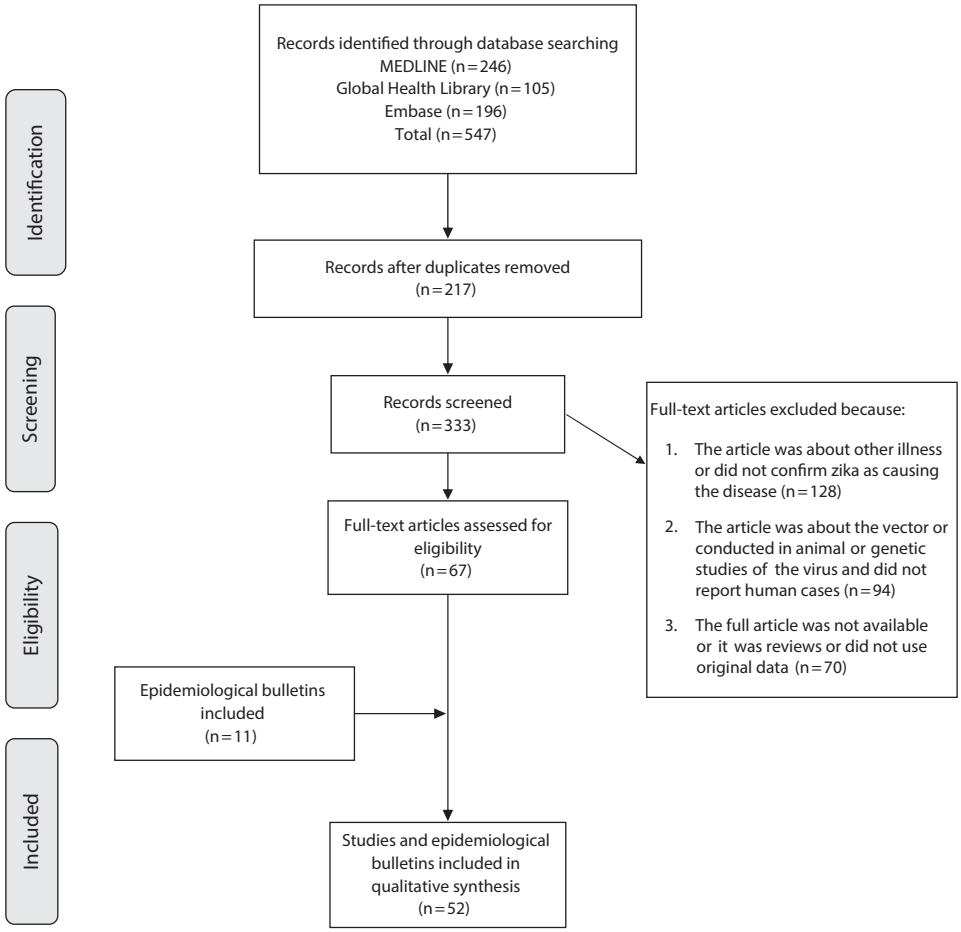

FIGURE 1—Process of Selection of the Studies for a Systematic Review on Epidemiology and Atypical Manifestations of Zika Virus Outbreaks

From 2008 to 2013, 4 studies were published on Zika—3 case reports and 1 surveillance study. Three cases of Zika occurred in Senegal and Colorado (possible non–vector-borne transmission: 2 scientists acquired Zika in Senegal and returned home to Colorado, and 1 transmitted Zika to his wife via semen),[27] and 2 in Cambodia[44,45]; the surveillance study was conducted in Cameroon.[46] No further transmission was reported in the Pacific region until 2013, when French Polynesia identified its first case. Statistics of the country estimated that 11.5% (32 000) of the population used the health facilities with Zika-like symptoms. A total of 383 cases were serologically confirmed; the mean age of those patients was 28 years.[47] A serological surveillance conducted in 2013 to 2014 among blood donors found that 2.8% were reverse-transcription polymerase chain reaction (RT-PCR) positive for Zika. Out of the 42 positive donors, 26.2% reported Zika fever–like disease from 3 to 10 days after blood donation.[35]

During the Zika outbreak in French Polynesia, an unusual increase in the number of neurological and autoimmune complications was identified. Among patients that visited health care facilities with Zika-like symptoms, 2.3 per 1000 had neurological complications and 1.3 per 1000 (42 cases) had Guillain–Barré Syndrome (GBS). Among the GBS cases, 88% reported a viral syndrome up to 23 days before the onset of the neurological syndrome. Only 1 case was laboratory-confirmed during the infection by RT-PCR[48] and several other cases were found to be immunoglobulin G–positive against Zika after the neurological signs; the average age was 46 years and 74% were men.[47] Fifteen cases required intensive care, and 9 needed mechanical ventilation; however, no deaths were reported.[49,50]

After the report of the Brazilian epidemic of microcephaly in 2013, French Polynesia authorities looked back and reported central nervous system malformations in fetuses and newborns to women who were pregnant during the Zika outbreak on the island. They identified 17 cases of malformations.[51] None of the pregnant women reported clinical signs of Zika; however, a serological test was performed in 4 women and they were immunoglobulin G–positive for flavivirus, suggesting a possible asymptomatic Zika infection.[51] Perinatal Zika transmission was reported in 2 cases in French Polynesia in 2013 to 2014.[34]

The French Polynesian outbreak spread to other Pacific islands and autochthonous cases have been reported in New Caledonia (1400 confirmed cases),[52] Cook Islands (932 suspected cases, 50 confirmed),[52] Fiji, Samoa, and Solomon Island.[53] Countries such as

Philippines[54] and Thailand[55] have been reporting cases of Zika. Imported cases (without autochthonous transmission) were reported in Japan,[14,18] Australia,[15,16] Italy,[24] Germany,[26] Norway,[25] Canada,[20] United States,[19,29,27] and United Kingdom[28] in persons who visited countries with local transmission.

The autochthonous circulation of Zika in the Americas was first confirmed on Easter Island (Chile) in 2014. A total of 51 of 89 samples from cases suspected of Zika were positive by RT-PCR and the majority of the positive patients were women.[56] In early 2015, Zika infection was laboratory-confirmed in Brazil and autochthonous transmission established.[57,58] According to preliminary estimates from the Brazilian Ministry of Health, between 440 000 and 1 300 000 cases of Zika occurred in Brazil in 2015.[59] In Bahia (northeast state of Brazil), the attack rate in 2015, detected among reported cases, was approximately 4.4 per 1000 inhabitants. In some cities of Bahia, such as Camaçari, Itabuna, Senhor do Bomfim, and Monte Santo, the attack rate was greater than 25 per 1000 inhabitants.[60]

As in French Polynesia, an unusual increase in the number of neurological manifestations and GBS occurred in Brazil. In Bahia, the proportion of neurological complications temporally associated with Zika was 2.3 per 1000 (proportion estimated with reported cases)[60]; GBS was diagnosed in 1 of every 1000 reported cases. Laboratory testing was performed in 224 samples of suspected Zika cases; this virus was confirmed in 10 patients, and 7 of those with viral confirmation had a neurological syndrome.[61] In Brazil, 2 deaths of adults were attributed to Zika and 7 are under investigation by the Ministry of Health.[59]

At the end of 2015, Brazilian authorities reported possible links between Zika infection during pregnancy and microcephaly.[62] Over the past 5 years, an annual average of 163 (5.6 per 100 000 live births) cases of microcephaly were routinely identified each year, according to routine birth reports. In 2015, there were 3530 (121.7 per 100 000 live births) suspected cases of microcephaly reported including 46 deaths, mainly in Pernambuco, a state that concentrated 35% of the total of suspected cases of microcephaly.[63] ZIKV RNA was found in amniotic fluid samples from 2 pregnant women with fetal microcephaly.[64] The 2 women had Zika-like symptoms at gestation weeks 18 and 19.

Currently, autochthonous Zika transmission has occurred in 27 counties in the Americas including Colombia (16 419 reported cases; 66.4% were female; 798 laboratory-confirmed cases); Guatemala (17 suspected cases); Mexico (confirmed local transmission); Panama (3 cases); Paraguay (6 laboratory-confirmed cases); Venezuela (4 laboratory-confirmed cases, 15 GBS cases); El Salvador (240 cases, 46 GBS cases, 54% of them male, and 2 deaths); Honduras, and Martinique. Bolivia, Guyana, Ecuador, Guadeloupe, Guatemala, Puerto Rico, Barbados, Saint Martin, and Haiti have reported sporadic transmission following recent introduction.[65]

DISCUSSION

We systematically reviewed 52 studies and epidemiology bulletins reporting epidemiological aspects of Zika disease worldwide (age, sex, seroprevalence, attack rates), clinical presentation, atypical manifestations, and negative fetal outcomes. On the basis of the data published in these documents, it is possible to know some epidemiological characteristics of Zika outbreaks and to have some idea where this illness has been circulating worldwide. In addition, we report some complications that have occurred during Zika outbreaks.

Epidemiological Patterns of Emergence and Spread

Zika infection is an acute exanthematous disease that for many years circulated silently in Africa and Asia. During this period, data about cases of Zika were restricted to case reports and serological surveys; the clinical presentation was similar to that of nonspecific viral illness. There were a few epidemiological characteristics of the patients reported, and atypical presentations were not reported.

The highest attack rate estimated among patients that presented to health care facilities was documented in French Polynesia. In Brazil, the true attack rate of the epidemic is not known; however, a study conducted in 1 city of Bahia showed that, from February to June 2015, an outbreak of indeterminate acute exanthematous disease occurred, in which 14 835 cases were reported. It was suggested that this outbreak was caused by ZIKV and the overall attack rate was 5.5 per 1000 inhabitants,[66] almost 3 and 20 times lower than in Micronesia and French Polynesia, respectively. The overall attack rate, estimated by reported cases, greatly varied between the countries. We suggest 3 possible reasons for this: (1) the competence of mosquito vector (the predominant vector in Yap was *A hensilli* whereas in French Polynesia and Brazil it was *A aegypti*), (2) The multiplicity of analogous diseases circulating simultaneously (dengue and Zika in Yap and French Polynesia and Zika, dengue and chikungunya in Brazil) increase the probability of misdiagnosis and consequently undernotification, and (3) the recent introduction in Brazil which did not allow the outbreak to reach its peak.

In places where gender information was available (Yap, Brazil, Thailand, and Easter Island) among patients who had access to health care facilities, the disease was more frequently seen in women,[43,55,56,66] possibly because women attended health services more often than did men. The mean age of the patients was slightly different, but all outbreaks reached all age groups, which is the classic pattern of an introduction of new disease in a susceptible population.

The estimated rate of asymptomatic Zika infection, as was described for other arboviruses such as West Nile virus[67] and dengue,[68] is high. If we use the ratio of 1 to 5 clinical cases observed in Micronesia to estimate the attack rate of Zika infection in French Polynesia and Brazil, we estimate that 55% of the French Polynesian and 2.5% of Brazilian inhabitants have been infected. Challenges for accurate estimates include a high rate of unapparent infections and the cross-reactivity of the serologic test of zika and dengue.

Potential Pathological Outcomes Linked to Zika Outbreaks

Hospitalizations for Zika were not reported until the French Polynesia outbreak, when neurological complications were identified temporally and spatially connected with Zika. In Brazil, Venezuela, and El

Salvador, GBS cases correlating with Zika outbreaks were also reported. The proportions of neurological disorders including GBS among Zika patients were very similar in Brazil and French Polynesia. In mice, ZIKV has a brain tropism, suggesting that the virus can cross the blood–brain barrier and cause negative outcomes[3]; however, more investigations are required to prove that this complication was caused by ZIKV. The literature comprises cases of neurological disorders including GBS caused by other flaviviruses such as West Nile virus[69] and dengue.[70]

Authorities of French Polynesia and Brazil reported possible links between Zika infection during pregnancy and microcephaly, and perinatal transmission of Zika was confirmed in 2 reported cases.[34] The incidence of Zika infection in pregnant women is not known, and data on pregnant women infected with ZIKV are scarce. In Brazil, during the Zika outbreak, the incidence of microcephaly increased more than 20 times. Among 35 infants with microcephaly born from women suspected to have Zika infection during pregnancy in northeast Brazil, 74% of the mothers reported having a rash during the first and second trimester.[71]

The causal relationship between Zika and microcephaly, although sufficiently established for public health actions, is not universally accepted. Experts agree that the reported number is likely inflated because of the search for cases and because of misdiagnosis; so far, out of the cases of microcephaly investigated with neuroimaging, 270 cases were confirmed and 462 were rejected as false diagnoses. According to the Latin American Collaborative Study of Congenital Malformations, the number of suspected cases of microcephaly is too high to be plausible.[72] Epidemiological research including case–control studies and prospective studies of pregnant women with rash will finally establish the causal association between Zika infection and the microcephaly outcomes.

Limitations of the Study

This literature review has some limitations. Zika is an emerging disease, and so there is a small number of studies that address this infection, the majority of which are case reports and a small number of serological surveys mainly conducted before the spreading of Zika to the American region. We also included in this review data provided by the passive surveillance systems, which can vary with the quality and coverage of the local surveillance system, and over time, and may underrepresent the real number of cases. Another limitation is the lack of epidemiological studies about this disease and the potential complications that occurred during the outbreaks. We did not carry out an assessment of quality of the studies and we did not exclude studies with potential weaknesses; as a consequence, any limitations of the original studies are pointed out in this review. The inclusion of publications in 4 languages reduced selection bias.

Perspectives

The rapid spread of Zika infection raises new challenges for the health authorities and researchers about the magnitude and possible complications in future outbreaks. Cases of Zika in travelers also raise concerns among unaffected countries since nonautochthonous cases have been diagnosed in Europe; ZIKV has the potential to rapidly spread across Latin America and the Caribbean.[73] It has been suggested that global warming may have favored the reemergence, emergence, and rapid spread of arboviruses worldwide.[74] With regard to Zika outbreaks, there are more questions than answers, and further studies are required to address questions about competence of the vector, proportion of asymptomatic and symptomatic cases, long-lasting natural immunity, and whether the relationship with Zika and microcephaly and neurologic disorders is causal.

The current situation with regard to Zika is not encouraging, because there is no vaccine, no treatment, and no good serological test, and vector control remains a challenge. There is no information about the burden caused by the cocirculation with other arboviruses such as dengue and chikungunya, both endemic diseases in countries where Zika recently has been introduced. In Brazil, for example, in 2015, more than 1 649 008 cases of dengue and more than 20 000 cases of chikungunya have been reported.[75] Zika is transmitted by the same vectors as dengue; thus, the prospect of Zika spreading to more than a hundred countries where dengue is endemic–epidemic is concrete. However, if it is confirmed that Zika is causing complications such as GBS and congenital malformations, the future scenario presented will be much more worrisome than it was for dengue, and this illness can be considered one of the greatest challenges and problems of our time for global public health. AJPH

CONTRIBUTORS

All authors participated in the study design and in writing the final article.

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HUMAN PARTICIPANT PROTECTION

For this systematic review, we used data already published from other studies, so ethics approval was not required.

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