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Fatal Zika virus infection in the Americas: A systematic review★

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ABSTRACT

Introduction: While death due to Zika virus (ZIKV) infection has been described, reports of fatal cases have been infrequent and no systematic reviews on the subject have been published.
Methods: A systematic review of the literature in four databases was performed to assess fatal outcomes of postnatal ZIKV infection and the available evidence that links ZIKV infection to death.
Results: Three hundred and eleven articles were retrieved; 20 of them were epidemiological reports from surveillance agencies and ministries of health. After screening by abstract and title, 59 articles were selected for full-text assessment. Of these, 35 were excluded (with reasons) and 24 were finally included for qualitative analysis. A total of 51 reported deaths associated with ZIKV infection in nine countries were identified. The majority of cases (56.9%) were not related to Guillain–Barré syndrome. Cases from three countries accounted for 67.6% of the deaths. ZIKV infection was laboratory-confirmed in the majority of cases (64.7%).
Discussion: ZIKV was not considered to be a dangerous, and much less a lethal pathogen, until very recently. However, an increasing number of fatalities have been published in the literature since the first death was reported in 2016. Additional research is needed to elucidate factors that may mediate the pathogenesis of severe, atypical, and fatal disease.

Introduction

Rationale

Zika virus (ZIKV) was first isolated in 1947 from the blood of a sentinel monkey during studies of sylvatic yellow fever transmission in Uganda (Azevedo et al., 2016; Martinez-Pulgarin et al., 2016; Rodriguez-Morales, 2015). During the next 60 years, ZIKV was sporadically isolated from mosquitoes and from humans in various countries in Sub-Saharan Africa and Southeast Asia.

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Starting in 2007, when ZIKV was associated with an outbreak on the island of Yap in Micronesia (Azevedo et al., 2016; Duffy et al., 2009; Lanciotti et al., 2008; Martinez-Pulgarin et al., 2016; Rodriguez-Morales, 2015), outbreaks became more common, spreading through Oceania and eventually reaching Latin America by 2013 (Faria et al., 2016a).

At this time, ZIKV had long been considered a benign flavivirus infection, not responsible for severe or fatal outcomes. Reports of human cases of ZIKV infection prior to 2013 indicated relatively mild clinical manifestations of a self-limited illness lasting 3–5 days, characterized by fever, myalgia, headache, conjunctivitis, and rash (Azevedo et al., 2016; Duffy et al., 2009; Lanciotti et al., 2008; Paniz-Mondolfi et al., 2016; Rodriguez-Morales, 2015). However, ZIKV transmission, including severe or fatal cases, could easily have gone unrecognized, given the clinical similarity of Zika to other acute viral illnesses, particularly dengue fever. Moreover, basic serological assays have lacked specificity in discriminating closely related flaviviruses, and ZIKV infection could have been misdiagnosed as dengue, Japanese encephalitis, or others (Azevedo et al., 2016; Duffy et al., 2009; Lanciotti et al., 2008; Paniz-Mondolfi et al., 2016; Rodriguez-Morales, 2015).

An increase in cases of Guillain–Barré syndrome (GBS) and other neurological diseases, as well as cases of microcephaly and other birth defects (Martinez-Pulgarin et al., 2016; Mlakar et al., 2016; Rodriguez-Morales et al., 2019; Villamil-Gomez et al., 2016), began to be reported in 2015, as ZIKV spread rapidly from Brazil to other countries in the Americas (Faria et al., 2016b; Rodriguez-Morales et al., 2016). Notably, there were fatalities among early reported cases (Soares et al., 2016). In addition, patients with comorbidities, such as diabetes, hypertension, and sickle cell disease, among others, were reported to have developed severe disease and a fatal outcome (Arzuza-Ortega et al., 2016; Sarmiento-Ospina et al., 2016). Severe manifestations of ZIKV infection have raised many questions regarding the determinants of disease, ranging from immunological, host or viral genetic, environmental, etc. Since the onset of the epidemic, additional reports of Zika-associated deaths have accumulated. However, a systematic effort to consolidate what has been learned from each individual reported case is lacking, as is a rigorous evaluation of causality linkage between infection and outcome.

Objectives

The objectives were (1) to systematically review the published literature on fatal outcomes of ZIKV infection in the Americas; (2) to assess the available evidence that causally links ZIKV and fatal cases; and (3) to examine the clinical context and spectrum of disease in Zika cases that progress to death.

Methods

Protocol and registration

The review protocol followed the recommendations established in the PRISMA statement (Moher et al., 2009), and it has been registered in the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017059347).

Information sources

This systematic review was conducted using the MEDLINE/PubMed, Scopus, LILACS, and SciELO databases, the official web pages of the ministries of health of countries included in the World Health Organization (WHO) list of the Americas region, and information from the following international surveillance agencies: the US Centers for Disease Control and Prevention (CDC; https://www.cdc.gov), European Centers for Disease Control and Prevention (ECDC; https://ecdc.europa.eu/en/home), the WHO (https://www.who.int), and the Pan American Health Organization (PAHO; https://www.paho.org/).

Search strategy

The following search terms were used: “Zika AND Fatal”, “Zika AND Death”, and “Zika AND Severe.” No limit was set on article language or time of publication. The official web pages of surveillance agencies and ministries of health were checked to identify epidemiological reports and bulletins reporting deaths associated with ZIKV infection. The searches were concluded by January 1, 2018, and search results were independently evaluated by five different researchers. Studies in English, Spanish, Portuguese, and French were included.

Eligibility criteria

Eligible articles were required to meet the following criteria: published peer-reviewed articles that reported cases with a fatal outcome linked with ZIKV infection. Eligible study designs were case–control, cohort studies, case reports, and series of cases. Information published in epidemiological reports and bulletins by the CDC, ECDC, WHO, PAHO, and national governments through their surveillance systems or ministries of health were also included.

Study selection

Articles identified through the initial search strategy were first screened by title and abstract. The full texts of appropriate articles were examined against the inclusion and exclusion criteria (Figure 1). Studies reporting antenatal deaths, cases without a laboratory confirmation test, and reports with incomplete information were excluded, as were studies about severe cases not associated with ZIKV infection. Letters to the editor and reviews that did not report severe cases related to ZIKV were also excluded. When a bulletin or article reported duplicate information related to the same patient, the information in both reports was combined in order to obtain the most complete data, but only counted as a single case.

Data collection process and data items

Data extraction forms including information on the type of publication, the publishing institution, country, year of publication, the number of reported deaths, laboratory tests used, and the cause of death were completed independently by five investigators. A sixth researcher checked the article list and data extraction to ensure that there were no duplicate articles or duplicate information of the same patient; this researcher also resolved discrepancies about study inclusion.

Assessment of methodological quality and risk of bias

For the quality assessment, the Quality Appraisal of Case Series Studies Checklist of the Institute of Health Economics (IHE) (Institute of Health Economics, 2014) was used. In order to assess the causality linkage between ZIKV and the evolution to severe or fatal outcomes, as well as the risk of bias regarding the definition of the exposure and the outcome, the WHO Zika Causality Working Group Causality Framework was used (Krauer et al., 2017). This framework evaluates causality in 10 dimensions (temporality, biological plausibility, strength of association, exclusion of alternative explanations, cessation, dose–response relationship, animal experiments, analogy, specificity, and consistency). The

questions in each category were adapted from the previously published framework, and defined and addressed by two investigators in order to assess the linkage between ZIKV and severe and fatal cases.

Results

Study selection and characteristics

A total of 311 articles were retrieved using the search strategy. Of these, 20 were epidemiological reports or bulletins from surveillance agencies and ministries of health. After screening by abstract and title, 59 articles were selected for full-text assessment, of which 35 were excluded (with reasons) and 24 were finally included for qualitative analysis (Figure 1). The following articles were included: 13 epidemiological bulletins from national ministries of health that reported deaths attributable to ZIKV, eight case reports, and three Morbidity and Mortality Weekly Reports from the CDC (Table 1).

There were 50 reported deaths associated with postnatal ZIKV infection in nine countries, of which 56.9% were not related to GBS. The Dominican Republic, Brazil, and Puerto Rico reported 67.6% of the deaths (33.3%, 18.6%, and 15.7%, respectively). Of the reported cases, 64.7% were confirmed either by RT-PCR, IgM antibody capture ELISA (MAC-ELISA), or immunohistochemistry (Table 1). The remaining cases (35.3%) were not laboratory-confirmed, but were diagnosed by the clinical definition of fever, rash, conjunctivitis, and arthralgias in a location with previous ZIKV circulation (with at least one case confirmed by RT-PCR in the same area) (Pan American Health Organization/World Health Organization, 2017a, f). Sixteen records were used to evaluate the causality linkage according to the Zika Causality Group Framework (Krauer et al., 2017) (Table 2). The quality assessment of each study using the IHE instrument is summarized in Table 3.

Due to the lack of population-based studies assessing ZIKV and the risk of death, only nine of the 20 studies examined here directly addressed the questions of the Zika Causality Group Framework (Table 2). The retrieved answer to each question is shown in Table 3. Hence, for the assessment of strength of association, cessation, and consistency, the findings of the included case reports and epidemiological bulletins were taken together in order to summarize the available evidence in each dimension, as described later. For the assessment of animal experiments, the evidence derived from references of the included articles, as well as experiments in animal models published by January 1, 2018, were summarized.

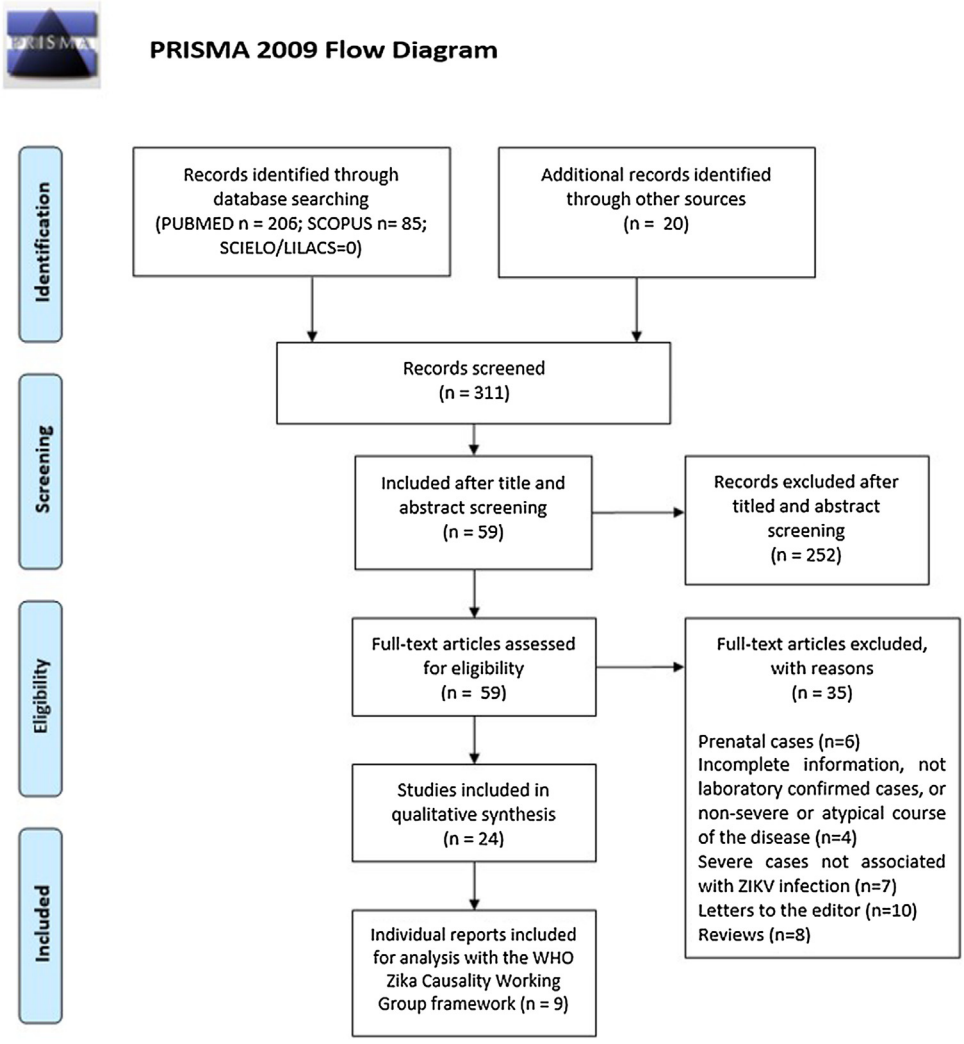

Figure 1. Study selection and characteristics.

Table 1
Characteristics of the studies.

Studies	Type of publication	Institution	Country	Total Zika cases (country)	Reported deaths	Infection assessment	Number (total deaths)	GBS-related deaths	Non-GBS-related deaths	CFR (country)	Year
Walker (2016)	MMWR	CDC	USA	4969	1	RT-PCR, MAC-ELISA, PNRT	1	0	1	0.020	2016
Brent (2016)	MMWR	CDC			1						
Pan American Health Organization/World Health Organization (2017a,b,c,d,e,f,g,h)	Epidemiological Bulletin	WHO			1						
Swaminathan et al. (2016)	Case report	University of Utah School of Medicine			1						
Pan American Health Organization/World Health Organization (2017a,b,c,d,e,f,g,h)	Epidemiological Bulletin	WHO	Puerto Rico	39 339	8	RT-PCR	8	2	6	0.020	2016
Dirlikov et al. (2016)	MMWR	CDC			1	MAC-ELISA					
Sharp et al. (2016)	Case report	CDC			1	RT-PCR, ELISA					
Pan American Health Organization/World Health Organization (2017a,b,c,d,e,f,g,h)	Epidemiological Bulletin	WHO	Brazil	346 475	11	RT-PCR	11	0	11	0.003	2015–2016
Ministério da Saúde - Brasil (2016)	Epidemiological Bulletin	Secretaria de Vigilância em Saúde – Ministério da Saúde									
Ministério da Saúde - Brasil (2016)	Epidemiological Bulletin	Secretaria de Vigilância em Saúde – Ministério da Saúde									
Soares et al. (2016)	Case report	Hospital Federal dos Servidores do Estado			1	RT-PCR, ELISA					
Azevedo et al. (2016)	Case report	Instituto Evandro Chagas			3	RT-PCR, Immuno-histochemistry					
Schwartzmann et al. (2017)	Case report	Clinic Hospital of Ribeirão Preto			1	RT-PCR					
Pan American Health Organization/World Health Organization (2017a,b,c,d,e,f,g,h)	Epidemiological Bulletin	WHO	Suriname	3490	4	RT-PCR/ELISA	4	0	4	0.115	2016–2017
Zonneveld et al. (2016)	Case report	Academic Hospital Paramaribo			3	RT-PCR					
Sarmiento-Ospina et al. (2016)	Case report	Hospital del Tolima	Colombia	107 206	4	RT-PCR	5	0	5	0.005	2015
Arzuza-Ortega et al. (2016)	Case report	Empresa Social del Estado Hospital de Malambo			1	RT-PCR					
Ministerio de Salud Pública de República Dominicana (2017)	Epidemiological Bulletin	WHO	Dominican Republic	5241	17	Unknown	17	17	0	0.324	2016
Ministerio de Salud Pública de República Dominicana (2017)	Epidemiological Bulletin	Ministerio de Salud Pública			17	Unknown					
Pan American Health Organization/World Health Organization (2017a,b,c,d,e,f,g,h)	Epidemiological Bulletin	WHO	Guadeloupe	31 227	3	RT-PCR	3	1	2	0.010	2016–2017
Agence Régionale de Santé (2017)	Epidemiological Bulletin	Agence Régionale de Santé			2	RT-PCR					
Pan American Health Organization/World Health Organization (2017a,b,c,d,e,f,g,h)	Epidemiological Bulletin	WHO	Martinique	36 701	1	RT-PCR	1	1	0	0.003	2016
Agence Régionale de Santé (2016)	Epidemiological Bulletin	Agence Régionale de Santé			1	RT-PCR					
Pan American Health Organization/World	Epidemiological Bulletin	WHO	Bolivia	1029	1	Unknown	1	1	0	0.097	2016

Table 1 (*Continued*)

Studies	Type of publication	Institution	Country	Total Zika cases (country)	Reported deaths	Infection assessment	Number (total deaths)	GBS-related deaths	Non-GBS-related deaths	CFR (country)	Year
Health Organization (2017a,b,c,d,e,f,g,h)											

CDC, US Centers for Disease Control and Prevention; CFR, case fatality rate; GBS, Guillain–Barré syndrome; MMWR, Morbidity and Mortality Weekly Report; PAHO, Pan American Health Organization; WHO, World Health Organization. For this table, and subsequents part of the article, Puerto Rico is an unincorporated territory of the United States of America (*Free Associated State of Puerto Rico*).

Table 2
Reference framework for the assessment of Zika death.

	Dimension	Number of linked cases	Linked items
1	Temporality		
1.1	Does ZIKV infection precede the evolution to death in individuals?	14	(Arzuza-Ortega et al., 2016; Azevedo et al., 2016; Sarmiento-Ospina et al., 2016; Schwartzmann et al., 2017; Swaminathan et al., 2016; Zonneveld et al., 2016)
1.2	Is there a consistent time-dependent relationship between the occurrence of ZIKV cases and cases that evolve to death at the population level?	0	
1.3	Is the interval between exposure to ZIKV and occurrence of related symptoms typical for post-infectious death?	15	(Arzuza-Ortega et al., 2016; Azevedo et al., 2016; Dirlikov et al., 2016; Sarmiento-Ospina et al., 2016; Schwartzmann et al., 2017; Sharp et al., 2016; Swaminathan et al., 2016; Zonneveld et al., 2016)
2	Biological plausibility		
2.1	Are there biologically plausible mechanisms that explain how ZIKV can evolve to death?	–	
3	Strength of association		
3.1	How strong is the association between ZIKV infection and death at the individual level?	–	
3.2	How strong is the association between ZIKV infection and death at the population level?	–	
4	Exclusion of alternative explanations		
4.1	Have other explanations/confounders of the association between ZIKV infection and death been excluded, such as other infections?	11	(Azevedo et al., 2016; Sarmiento-Ospina et al., 2016; Schwartzmann et al., 2017; Sharp et al., 2016; Zonneveld et al., 2016)
4.2	Have other explanations/confounders of the association between ZIKV infection and fatal cases been excluded, such as underlying systemic disease?	4	(Azevedo et al., 2016; Sarmiento-Ospina et al., 2016; Zonneveld et al., 2016)
4.3	Have other explanations/confounders of the association between ZIKV infection and death been excluded, such as inappropriate treatment?	13	(Arzuza-Ortega et al., 2016; Azevedo et al., 2016; Dirlikov et al., 2016; Schwartzmann et al., 2017; Soares et al., 2016; Zonneveld et al., 2016)
5	Cessation		
5.1	Does the intentional prevention/removal/elimination of ZIKV infection in individuals, e.g. by insect repellents, lead to a reduction in fatal cases?	–	
5.2	Does the intentional removal/elimination/prevention of ZIKV at the population-level, e.g. by vector control, lead to a reduction in fatal cases?	–	
5.3	Does a natural removal/elimination/prevention of ZIKV at the population level, e.g. increase in immune individuals or decrease in vector abundance, lead to a reduction in fatal cases?	–	
6	Dose–response relationship		
6.1	Are the risk of death and the clinical severity of ZIKV infection associated with higher viral titers or viral load in biological samples?	1	(Zonneveld et al., 2016)
7	Animal experiments		
7.1	Do animal experiments support the association of ZIKV infection and fatal cases?	–	
8	Analogy		
8.1	Do other flaviviruses or arboviruses cause death and by similar mechanism(s)?	16	(Arzuza-Ortega et al., 2016; Azevedo et al., 2016; Dirlikov et al., 2016; Sarmiento-Ospina et al., 2016; Schwartzmann et al., 2017; Swaminathan et al., 2016)
9	Specificity		
9.1	Are there pathological findings in fatal cases specific for ZIKV infection?	2	(Azevedo et al., 2016; Schwartzmann et al., 2017)
10	Consistency		
10.1	Is the association between ZIKV infection and fatal cases consistently found across different geographical regions?	–	
10.2	Is the association between ZIKV infection and fatal cases consistently found across different populations/subpopulations?	–	
10.3	Is the association between ZIKV infection and fatal cases consistently found across different ZIKV lineages/strains?	–	
10.4	Is the association between ZIKV infection and fatal cases consistently found across different study designs?	–	

ZIKV, Zika virus.

Table 3
Quality assessment of the studies.

Case	Quality criteria[a]																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Swaminathan S, Schlaberg R, Lewis J, Hanson KE, Couturier MR. Fatal Zika virus infection with secondary nonsexual transmission. N Engl J Med 2016;375:1907–9.	Y	Y	N	Y	P	P	Y	P	N	Y	U	Y	U	N	Y	N	Y	Y	Y	Y
Dirlikov E, Major CG, Mayshack M, et al. Guillain–Barré syndrome during ongoing Zika virus transmission—Puerto Rico, January 1–July 31, 2016. MMWR Morb Mortal Wkly Rep 2016;65:910–4.	N	Y	Y	Y	Y	Y	Y	Y	P	P	N	Y	Y	Y	Y	N	Y	Y	Y	Y
Soares CN, Brasil P, Carrera RM, Sequeira P, de Filippis AB, Borges VA, et al. Fatal encephalitis associated with Zika virus infection in an adult. J Clin Virol 2016;83:63–5.	Y	Y	N	N	Y	Y	N	Y	Y	Y	N	Y	Y	N	Y	N	N	Y	Y	Y
Azevedo RS, Araujo MT, Martins Filho AJ, Oliveira CS, Nunes BT, Cruz AC, et al. Zika virus epidemic in Brazil. I. Fatal disease in adults: clinical and laboratorial aspects. J Clin Virol 2016;85:56–64.	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y
Schwartzmann PV, Ramalho LN, Neder L, Vilar FC, Ayub-Ferreira SM, Romeiro MF, et al. Zika virus meningoencephalitis in an immunocompromised patient. Mayo Clin Proc 2017;92:460–6.	Y	Y	N	Y	Y	P	N	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Sharp TM, Munoz-Jordan J, Perez-Padilla J, Bello-Pagan MI, Rivera A, Pastula DM, et al. Zika virus infection associated with severe thrombocytopenia. Clin Infect Dis 2016;63:1198–201.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y
Zonneveld R, Roosblad J, Staveren JW, Wilschut JC, Vreden SG, Codrington J. Three atypical lethal cases associated with acute Zika virus infection in Suriname. IDCases 2016;5:49–53.	Y	Y	Y	N	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	U	N	Y	Y	Y	Y
Sarmiento-Ospina A, Vasquez-Serna H, Jimenez-Canizales CE, Villamil-Gomez WE, Rodriguez-Morales AJ. Zika virus associated deaths in Colombia. Lancet Infect Dis 2016;16:523–4.	P	Y	N	Y	Y	P	Y	Y	N	Y	Y	P	U	N	Y	N	Y	N	Y	Y
Arzuza-Ortega L, Polo A, Perez-Tatis G, Lopez-Garcia H, Parra E, Pardo-Herrera LC, et al. Fatal sickle cell disease and Zika virus infection in girl from Colombia. Emerg Infect Dis 2016;22:925–7.	P	Y	Y	N	Y	P	N	Y	P	Y	N	Y	Y	N	Y	N	N	Y	Y	Y

Y, yes; N, no; P, partial; U, unclear.
[a] 1: Was the hypothesis/aim/objective of the study clearly stated? 2: Was the study conducted prospectively? 3: Were the cases collected in more than one centre? 4: Were patients recruited consecutively? 5: Were the characteristics of the patients included in the study described? 6: Were the eligibility criteria (i.e., inclusion and exclusion criteria) for entry into the study clearly stated? 7: Did patients enter the study at a similar point in the disease? 8: Was the intervention of interest clearly described? 9: Were additional interventions (co-interventions) clearly described? 10: Were relevant outcome measures established a priori? 11: Were outcome assessors blinded to the intervention that patients received? 12: Were the relevant outcomes measured using appropriate objective/subjective methods? 13: Were the relevant outcome measures made before and after the intervention? 14: Were the statistical tests used to assess the relevant outcomes appropriate? 15: Was follow-up long enough for important events and outcomes to occur? 16: Were losses to follow-up reported? 17: Did the study provide estimates of random variability in the data analysis of relevant outcomes? 18: Were the adverse events reported? 19: Were the conclusions of the study supported by results? 20: Were both competing interests and sources of support for the study reported?

Causality linkage assessment by dimension

The characteristics of the individual case reports by dimension are summarized in Table 4.

Temporality

Fifteen cases, reported in eight articles, addressed questions related to the temporality dimension (Arzuza-Ortega et al., 2016; Azevedo et al., 2016; Dirlikov et al., 2016; Sarmiento-Ospina et al., 2016; Schwartzmann et al., 2017; Sharp et al., 2016; Swaminathan et al., 2016; Zonneveld et al., 2016). In most of these cases, ZIKV infection was confirmed before the evolution to death, and the interval between exposure to ZIKV and the occurrence of related symptoms was typical for arbovirus infections (Arzuza-Ortega et al., 2016; Azevedo et al., 2016; Dirlikov et al., 2016; MM et al., 2018; Sarmiento-Ospina et al., 2016; Schwartzmann et al., 2017; Sharp et al., 2016; Swaminathan et al., 2016; Zonneveld et al., 2016). Remarkably, one of the patients, a 73-year-old man from the USA, developed the clinical picture after a 3-week travel to a ZIKV endemic area. When he returned to his home country, a non-arboviral endemic area, he developed a febrile illness lasting a few days, with an RT-PCR test confirmatory for ZIKV. Following this, he presented hypotension and dyspnea, and died (Brent, 2016; Swaminathan et al., 2016; Walker, 2016). In two cases (Dirlikov et al., 2016; Soares et al., 2016), the infection was not documented before the complication, and in one of them the patient quickly developed neurological symptoms and signs leading to death (Soares et al., 2016). There were no studies addressing a time-dependent relationship between the occurrence of ZIKV cases and cases that evolved to death at the population level.

Biological plausibility

The reported cases support evolution to death after ZIKV infection through a disseminated viral infection. ZIKV antigens and RNA were found in tissues of three cases reported in two studies, suggesting spread of the virus to the injured organs (Azevedo et al., 2016; Schwartzmann et al., 2017). In one case, the autopsy revealed features of a viral encephalitis, characterized by neuronal necrosis of basal nuclei in the brain with intense edema in the white matter, focal gliosis, neuronophagia, and perivascular hemorrhages, with an inflammatory infiltrate mainly of mononuclear cells in the cortex (Azevedo et al., 2016). On the other hand, features suggestive of a viral hepatitis were found with necrotic lesions and acidophilic bodies generally accompanied by multifocal steatosis, inflammatory infiltrates, and vascular congestion in the portal space in another report (Azevedo et al., 2016). Nevertheless, information regarding particular features of the innate and adaptive immune response of the patients that could facilitate the dissemination and infiltration of tissues and evolution to death in the reported cases is lacking, although animal experiments are in support of this, as will be discussed further.

Strength of association

Since no studies assessing the risk of death during acute ZIKV infection at the population level were found, data derived from epidemiological bulletins and reports were evaluated for the assessment of this dimension. Twelve epidemiological bulletins reported deaths associated with ZIKV infection occurring in several countries (Agence Régionale de Santé, 2016; Ministério da

Table 4
Characteristics of the individual cases of Zika death.

Case	Age (years)	Sex	Co-morbidities	Cause of death	Causality dimension																			
					1. Temporality			2. Biological plausibility	3. Strength of association		4. Exclusion of alternative explanations			5. Cessation			6. Dose–response relationship	7. Animal experiments	8. Analogy	9. Specificity	10. Consistency			
					1.1	1.2	1.3	2.1	3.1	3.2	4.1	4.2	4.3	5.1	5.2	5.3	6.1	7.1	8.1	9.1	10.1	10.2	10.3	10.4
Swaminathan S, Schlaberg R, Lewis J, Hanson KE, Couturier MR. Fatal Zika virus infection with secondary nonsexual transmission. N Engl J Med 2016;375:1907–9.	73	M	Y	Respiratory and renal failure, hepatitis, and shock	Y	–	Y	–	–	–	N	N	N	–	–	–	Y	–	Y	N	–	–	–	–
Dirlikov E, Major CG, Mayshack M, et al. Guillain–Barré syndrome during ongoing Zika virus transmission—Puerto Rico, January 1–July 31, 2016. MMWR Morb Mortal Wkly Rep 2016;65:910–4.	NA	NA	NA	GBS-related septic shock	N	–	Y	–	–	–	N	N	Y	–	–	–	N	–	Y	N	–	–	–	–
Soares CN, Brasil P, Carrera RM, Sequeira P, de Filippis AB, Borges VA, et al. Fatal encephalitis associated with Zika virus infection in an adult. J Clin Virol 2016;83:63–5.	47	F	N	Respiratory failure associated to a neurological syndrome	N	–	N	–	–	–	N	N	Y	–	–	–	N	–	Y	N	–	–	–	–
Azevedo RS, Araujo MT,	36	M	Y	Respiratory failure	Y	–	Y	Y	–	–	Y	N	N	–	–	–	N	–	Y	Y	–	–	–	–
Martins Filho AJ, Oliveira CS, Nunes BT, Cruz AC, et al. Zika virus epidemic in Brazil. I. Fatal disease in adults: clinical and	16	F	N	Severe thrombocytopenia related with jaundice and severe hemorrhage	Y	–	Y	Y	–	–	Y	Y	Y	–	–	–	N	–	Y	N	–	–	–	–
laboratorial aspects. J Clin Virol 2016;85:56–64.	20	F	N	Pancytopenia with hemorrhage and pulmonary abscess	Y	–	Y	Y	–	–	Y	Y	Y	–	–	–	N	–	Y	Y	–	–	–	–
Schwartzmann PV, Ramalho LN, Neder L, Vilar FC, Ayub-Ferreira SM, Romeiro MF, et al. Zika virus meningoencephalitis in an immunocompromised patient. Mayo Clin Proc 2017;92:460–6.	36	M	Y	Encephalitis, lymphopenia and cardiogenic shock due to acute cardiac allograft rejection	Y	–	Y	–	–	–	Y	N	Y	–	–	–	N	–	Y	Y	–	–	–	–
Sharp TM, Munoz-Jordan J, Perez-Padilla J, Bello-Pagan MI, Rivera A, Pastula DM, et al. Zika virus infection associated with severe thrombocytopenia. Clin	72	M	Y	Severe thrombocytopenia related with severe hemorrhage	Y	–	Y	–	–	–	Y	N	N	–	–	–	N	–	Y	N	–	–	–	–

Table 4 (*Continued*)

Case	Age (years)	Sex	Co-morbidities	Cause of death	Causality dimension																			
					1. Temporality			2. Biological plausibility	3. Strength of association		4. Exclusion of alternative explanations			5. Cessation			6. Dose–response relationship	7. Animal experiments	8. Analogy	9. Specificity	10. Consistency			
					1.1	1.2	1.3	2.1	3.1	3.2	4.1	4.2	4.3	5.1	5.2	5.3	6.1	7.1	8.1	9.1	10.1	10.2	10.3	10.4
Infect Dis 2016;63:1198–201.																								
Zonneveld R, Roosblad J, Staveren JW, Wilschut JC, Vreden SG, Codrington J. Three atypical lethal cases associated with acute Zika virus infection in Suriname. IDCases 2016;5:49–53.	61	M	Y	Septic shock	Y	–	Y	–	–	–	Y	Y	Y	–	–	–	Y	–	Y	N	–	–	–	–
	64	M	Y	Thrombocytopenia and septic shock	Y	–	Y	–	–	–	Y	N	Y	–	–	–	N	–	Y	N	–	–	–	-
	59	M	Y	Septic shock	Y	–	Y	–	–	–	Y	Y	Y	–	–	–	N	–	Y	N	–	–	–	–
Sarmiento-Ospina A, Vasquez-Serna H, Jimenez-Canizales CE, Villamil-Gomez WE, Rodriguez-Morales AJ. Zika virus associated deaths in Colombia. Lancet Infect Dis 2016;16:523–4.	2	F	N	Respiratory failure and shock	Y	–	Y	–	–	–	Y	N	Y	–	–	–	N	–	Y	N	–	–	–	–
	30	F	N	Severe thrombocytopenia, severe hemorrhage, respiratory failure, seizures and shock	Y	–	Y	–	–	–	Y	N	Y	–	–	–	N	–	Y	N	–	–	–	–
	61	M	Y	Respiratory failure, acute myocardial infarction, shock	Y	–	Y	–	–	-	N	N	Y	–	–	–	N	–	Y	N	–	–	–	–
	72	F	Y	Respiratory failure and shock	Y	–	Y	–	–	–	Y	N	Y	–	–	–	N	–	Y	N	–	–	–	–
Arzuza-Ortega L, Polo A, Perez-Tatis G, Lopez-Garcia H, Parra E, Pardo-Herrera LC, et al. Fatal sickle cell disease and Zika virus infection in girl from Colombia. Emerg Infect Dis 2016;22:925–7.	15	F	Y	Respiratory failure	Y	–	Y	–	–	–	N	N	Y	–	–	–	N	–	Y	N	–	–	–	–
Surveillance du virus Zika aux Antilles Guyane, Situation épidémiologique, Point épidémiologique du 22 décembre 2016 - N° 42/ 2016.	NA	NA	NA	GBS-related	NA	–	NA	–	–	–	NA	NA	NA	–	–	–	NA	–	NA	NA	–	–	–	–
Pan American Health Organization/World Health Organization. Zika – Epidemiological Report Bolivia. March 2017. Washington, DC: PAHO/ WHO; 2017.	NA	NA	NA	GBS-related	NA	–	NA	–	–	–	NA	NA	NA	–	–	–	NA	–	NA	NA	–	–	–	–

Y, yes; N, no; NA, not available/not applicable; M, male; F, female; GBS, Guillain–Barré syndrome; PAHO, Pan American Health Organization; WHO, World Health Organization.

Saúde - Brasil, 2016, 2017; Ministerio de Salud Pública de República Dominicana, 2017; Pan American Health Organization/World Health Organization, 2017a,b,c,d,e,f,g,h). Case fatality rates (CFR) were calculated using the total reported deaths and the laboratory confirmed cases by March 2017 when the epidemic was ending. The CFR was calculated by country using the following formula: (fatal cases/WHO cumulative reported cases until March 2017) × 100. A median CFR of 0.02% among countries was estimated (range 0.002% in Martinique to 0.324% in the Dominican Republic). The lack of prospective cohort studies makes it difficult to properly estimate the individual risk of progression to death following ZIKV infection.

Exclusion of alternative explanations

In 11 cases from five articles, infectious diseases other than ZIKV were excluded as alternative explanations for the cause of death (Azevedo et al., 2016; Sarmiento-Ospina et al., 2016; Schwartzmann et al., 2017; Sharp et al., 2016; Zonneveld et al., 2016). The assessment of co-infections or an alternative infectious explanation for the outcome varied across different reports, as expected because of the different epidemiological backgrounds and clinical pictures. It included a wide variety of arboviral diseases like dengue, chikungunya, St. Louis encephalitis, West Nile, and yellow fever, as well as other viral diseases like rotavirus infection, viral hepatitis A, B, and C, HIV-1 and 2, human T-lymphotropic virus (HTLV) I/II, herpes virus types 1, 2, and 6, polyomavirus, Epstein–Barr virus, cytomegalovirus, and varicella zoster (Azevedo et al., 2016; Schwartzmann et al., 2017), among others. Bacterial diseases like syphilis, leptospirosis, bacterial meningitis, and bacteremia, and parasitic infections like Chagas disease, malaria, and toxoplasmosis were also assessed (Azevedo et al., 2016; Sharp et al., 2016; Swaminathan et al., 2016; Zonneveld et al., 2016).

Ten of the 16 cases reported at least one co-morbidity (Arzuza-Ortega et al., 2016; Azevedo et al., 2016; Sarmiento-Ospina et al., 2016; Schwartzmann et al., 2017; Sharp et al., 2016; Swaminathan et al., 2016; Zonneveld et al., 2016). However, in some of these, the co-morbidity was not directly related to the cause of death; for example, hyperlipidemia or high blood pressure with severe thrombocytopenia (Sharp et al., 2016) or arterial hypotension with septic shock and respiratory failure (Sarmiento-Ospina et al., 2016; Zonneveld et al., 2016) (Table 4). According to the information reported in the articles, there is no evidence pointing to inappropriate treatment as the cause of death. Notably, in four cases, the researchers were able to exclude an infection other than ZIKV, co-morbidities, and inappropriate treatment as alternative associated factors with the evolution to death (Azevedo et al., 2016; Zonneveld et al., 2016).

Cessation

Although no specific item specifically assessed this dimension, no reports of ZIKV-associated deaths were found after the reduction of ZIKV infection cases during the first half of 2017.

Dose–response relationship

For viral infections, a dose–response relationship would be present if a greater degree of viremia correlated with disease manifestations and/or death. Only four cases reported quantification of the viral load (Swaminathan et al., 2016; Zonneveld et al., 2016), although some of them reported qualitative results with quantitative RT-PCR. Since we did not find assessment of ZIKV infection and its relationship with viral load at the population level, it is not possible to conclude whether higher viral copy numbers confer an increased risk of complications and death. The present search revealed cases of death with viral loads at both the high and low end of the spectrum: two cases with a viral load lower than 1×10^4 copies/ml (Zonneveld et al., 2016) and two cases with a viral load higher than 1×10^8 copies/ml (Swaminathan et al., 2016; Zonneveld et al., 2016). Animal experiments as well as analogy are explained in the Supplementary material.

Specificity

Three out of the 16 individual cases showed pathological findings specific for ZIKV infection, as demonstrated by RT-PCR and immunohistochemistry in damaged tissues (Azevedo et al., 2016; Schwartzmann et al., 2017). One of them was a 36-year-old man with a history of a heart transplant 8 months before the onset of fever and a clinical picture compatible with a viral meningoencephalitis. During treatment, immunosuppressive drugs were withdrawn except methylprednisolone, and the patient died because of cardiogenic shock due to acute cardiac allograft rejection. ZIKV antigens were detected in inflammatory cells within the central nervous system, as well as in the heart, liver, and lung (Schwartzmann et al., 2017).

Another of the patients was a 36-year-old man with erythematous lupus who presented with a clinical picture similar to severe dengue and evolved to acute respiratory failure. Intra-cardiac blood, as well as fragments of brain, spleen, and liver, and a pool of heart, lung, and kidney were obtained at autopsy for examination. RT-qPCR for ZIKV was positive in all specimens, and ZIKV antigen was found in the brain, liver, kidney, heart, and lung, mainly in apoptotic cells. Viral isolation was possible in pooled viscera (Azevedo et al., 2016).

The last patient was a 20-year-old woman who presented with a febrile illness, pancytopenia, and bilateral pulmonary abscesses. During the autopsy, specimens of lung, kidney, and liver were collected, and these tested positive for ZIKV RNA by RT-qPCR and for ZIKV antigens by immunohistochemistry, although viral isolation was not possible in this case (Azevedo et al., 2016). Consequently, the evidence suggests that tissue injuries could be related specifically to the presence of the virus or its components in tissues and organs demonstrated through immunological and molecular tools.

Consistency

ZIKV infection-related deaths were found across different countries in the Americas region, across a wide range of ages, and in both sexes (Table 2). However, the reports were limited to case reports, case series, and epidemiological bulletins, and in some of these, the ZIKV lineage was not necessarily determined. No population-based studies assessing the risk of death across different populations were found, but the retrieved reports came from nine different countries in the Americas.

Discussion

The existing literature on clinical outcomes in ZIKV infection includes several reports of severe manifestations, as well as fatal cases (Rajahram et al., 2019; Rodriguez-Morales et al., 2019). We found 51 deaths reported during the 2016–2017 epidemic, with a mean CFR of 0.02% in the Americas. Assessment of the causality link through the WHO Zika Causality Working Group Framework, allowed it to be established that these clinical varieties of the disease occur within a period of time similar to that of other arboviruses, with a clinical picture analogous to other arboviruses, and through mechanisms that are possibly similar to those found in lethal animal models implicating a disseminated viral disease (Arzuza-Ortega et al., 2016; Azevedo et al., 2016; Rodriguez-Morales

et al., 2019; Soares et al., 2016; Swaminathan et al., 2016). These lethal cases have been reported in different territories in the Americas, and the pathological changes have been proved to be specifically related to ZIKV infection by immunohistochemistry and RT-PCR (Sarmiento-Ospina et al., 2016).

The role of co-morbidities, age, and viral load could not be definitively established. An argument against ZIKV infection per se being causative in lethal cases is that most deaths occurred either in elderly patients or in those with significant medical co-morbidities (Sarmiento-Ospina et al., 2016). However, cases of healthy young patients evolving to death have also been reported (Azevedo et al., 2016; Sarmiento-Ospina et al., 2016). Of note in these cases, the time of the evolution and the clinical picture were similar to those of other arboviruses, particularly dengue, and alternative explanations like other infections, co-morbidities, and treatment errors were excluded. However, because no population-level studies have been conducted assessing co-morbidities, age, and viral load as risks factors, the weight of these variables in the evolution to death could not be established.

The role of the immune response is still incompletely understood. ZIKV infection is lethal in animal models deficient in certain innate immune responses. Features of the adaptive immune response have also been associated with protection from ZIKV-induced neurological disease, viral replication (Aliota et al., 2016; Dowall et al., 2016; Hassert et al., 2018; Kawiecki et al., 2017; Lazear et al., 2013, 2016; Rossi et al., 2016), and viral tissue burden. However, ZIKV is also able to disseminate to multiple tissues even in immunocompetent non-human primates, which is likely a necessary step along the evolution to death in fatal Zika cases. It is possible that, for example, asymptomatic humans shed live virus in semen, but this is not necessarily enough evidence to conclude that dissemination is a defining feature of fatal cases. It can be assumed that ZIKV disseminates to a lot of tissues in asymptomatic and self-limiting cases as well, thus this is not an explanation for the difference in the associated outcome. The role of specific features of the immune response, like interferon polymorphisms, in the evolution to disseminated and complicated infections by ZIKV is unknown, but these have proven to be important in other viral infections (Lazear et al., 2019; Lindqvist et al., 2016).

Limitations

Although individual cases have been reported, and epidemiological data from epidemiological bulletins were used for the estimation of the CFR, the lack of properly conducted population-based studies for the assessment of the study outcome of interest limits the strength of the evidence for definitive conclusions. Based on the individual assessment of the reported cases, certain dimensions of the WHO Zika Causality Working Group Framework were assessed by compiling data from individual case reports or case series; however, other elements like consistency, cessation, and the dose–response relationship were addressed based on observations derived from epidemiological bulletins – although these are not the most robust source of data for answering population-level questions. This systematic review highlights the need for case–control and cohort studies to thoroughly assess ZIKV infection as a cause of death and to understand common features of Zika cases with adverse outcomes in order to inform optimal clinical management.

Conclusions

The results of this systematic review suggest that ZIKV infection can evolve to severe forms of disease, including death. However, severe outcomes appear to be rare, and it would be difficult to confidently attribute severe outcomes to ZIKV infection alone (ie., exclude other contributing causes) in the absence of large population-based studies. Certain co-morbidities could increase the risk of severe ZIKV infection, but it should also be considered whether previous infection by a heterologous flavivirus such as dengue virus contributed to the pathogenesis of severe Zika. Clinicians should be aware that ZIKV infection can present with a clinical picture similar to dengue and other arboviruses, including with thrombocytopenia and bleeding, shock, or severe neurological disease including encephalitis, although these severe manifestations have very rarely been reported. Most arbovirus infections are subclinical, and symptomatic illness usually manifests in three primary clinical syndromes: (1) a systemic febrile illness, (2) neuro-invasive disease, or (3) hemorrhagic fever. ZIKV infection manifests mainly as a systemic febrile illness and neuro-invasive disease. Thrombocytopenia and bleeding in ZIKV infection may be due to a non-specific systemic inflammatory response in rare cases rather than a hemorrhagic fever syndrome as seen with other flavivirus infections such as dengue virus and yellow fever.

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Ethical approval

Approval was not required.

Conflict of interest

All authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Author contributions

AJRM and JACO formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript. WFAM, KMNP, and DFMP refined the search strategy by conducting iterative database queries and incorporating novel search terms. WFAM, KMNP, and DFMP searched and collected the articles. JACO and VGV conducted the quality assessment. All authors critically reviewed the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript.

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inmune adaptativa de memoria específica durante el embarazo, contra arbovirus endémicos, en un grupo de pacientes embarazadas de La Virginia, Risaralda, Colombia", Código 5-19-3 [2019-2021]).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.08.033.

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