The trends of Zika virus-related research from 2014 to 2018: a systematic review and meta-analysis

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Research

Keywords: Zika virus, bibliometrics, systematic review, research trends, emerging infectious disease

Posted Date: January 21st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-47737/v2>

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Abstract

Background

Zika virus (ZIKV) is a mosquito-borne disease discovered in 1947, but with no reports of serious disease for almost 60 years. The first large ZIKV outbreak was reported from Yap island in 2007, then in 2015, the emergence of ZIKV in the Americas highlighted clinical manifestations such as microcephaly and Guillain-Barré syndrome. On February 1, 2016, WHO declared a Public Health Emergency of International Concern due to the magnitude of the outbreak, which then officially ended in November 2016.

Methods

Ever since the Brazilian authority released the first report of autochthonous transmission of ZIKV in 2015, it became the object of interdisciplinary investigation and global research collaboration. To follow and understand the trend of ZIKV research, we performed a systematic review and meta-analysis of ZIKV publications during 2014-2018, by using the scientific database Scopus.

Results

We found that the number of ZIKV related publications increased in 2016, 2017, and 2018 (39.2, 56.5, and 58.5 times, respectively) compared to an average number of publications (23.5) in 2014-2015. During the five years, there was not only an increment of publication numbers but also the area of research was expanded. In 2014-2015, the majority in the research area was epidemiological research with the aims to report the consequence of the ZIKV outbreak, and the trend was shifted to the development of diagnostic methods, antiviral treatment, and vaccine in the following three years. In addition, the number of countries involved in ZIKV research increased from 11 and 13 in 2014-2015 to 59, 67, and 66 in 2016-2018, showing that ZIKV research was changed from a low-level stage to active and globalized in the coming five years.

Conclusions

Our results highlight the importance of gathering public interest when the world is facing the phase of global health alert, and how it can drive the research field from inactive to active. However, despite this enormous progress in ongoing ZIKV research, many questions are yet to be answered and should be addressed to accelerate the development of effective ZIKV countermeasures. Nevertheless, our systematic review and meta-analysis emphasized the importance of a worldwide multidisciplinary effort to combat outbreaks or unknown infectious disease threats in the future.

Background

Zika virus (ZIKV) is a mosquito-borne zoonotic virus in the family *Flaviviridae*, genus *Flavivirus*. Mainly *Aedes* mosquitoes are primary vectors of ZIKV transmission (1, 2). Since the first discovery in the Zika

forest of Uganda in 1947, ZIKV has circulated in Africa and Asia and did not appear to cause serious disease for almost 60 years (3-5).

The epidemiology of ZIKV changed in 2007 when the first outbreak outside of Africa or Asia was reported on Yap Island (5, 6). Later, in 2013-2014, the ZIKV epidemic spread eastward in the Pacific Ocean, and eventually, in 2015, it reached the Americas and caused the first report of autochthonous transmission of ZIKV in Brazil (7, 8). During the outbreaks from 2007 to the present, reports confirmed that ZIKV infection had a strong association with microcephaly in newborns, neurological disorders in adults (such as Guillain–Barré syndrome), as well as a potential for sexual transmission. Thus, ZIKV became a major concern for public health (5, 9-12).

Due to the accumulation of reports that showed the significant consequences of the ZIKV outbreak in the Americas, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) on 1st February 2016 and agreed on the urgent need to coordinate international efforts to close the knowledge gaps associated with ZIKV potential to cause birth defects, mainly microcephaly (13-15).

Since 2015, interdisciplinary investigation and intersectoral cooperation regarding ZIKV have increased rapidly (16, 17). This has resulted in a better understanding of the transmission, pathogenesis, and control of the previously little-known ZIKV (17). To characterize and visualize the rapid growth of global, multidisciplinary action against ZIKV, we decided to perform a bibliometric analysis of ZIKV research from 2014 to 2018.

Bibliometrics is a powerful tool that uses statistical analysis of publications to measure the “output” of individuals/research teams, institutions, and countries, to identify national and international networks (18). Bibliometrics has been widely used in the library and information science, especially for collection management and resource access (19). To date, four bibliometric studies on ZIKV have been identified (5, 20-22). All these previous studies were performed up to 2016 and pointed to the importance of bibliometric study in global emergencies to provide an accurate overview of scientific output over time and its future impact. As a methodological tool, scientific publication databases (e.g. Pubmed, Scopus, and Web of Science, etc) have been widely used for bibliometric analysis to assess the value of published scientific output worldwide (23).

Therefore, we chose a systematic review and meta-analysis method by using scientific publication databases to follow the trend of ZIKV research. For analysis, we have collected publications for 2014-2018 and examined the trends of ZIKV research to observe the impact of the ZIKV outbreak in 2015 on the research area during the following five years.

Methods

This review was performed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines, and the PRISMA flow diagram of this study was compiled in Additional

file 1 (24).

Literature search

We designed a search strategy to access the literature related to ZIKV research from 2014 to 2018. The search strings were selected by referring to previous systematic reviews on ZIKV (20, 21, 25). A literature search was conducted in Scopus using the search string ((TITLE-ABS-KEY (zika) OR TITLE-ABS-KEY (zika) OR KEY (zika AND virus) OR KEY (zika AND virus AND infection))).

Eligibility criteria

This systematic review was designed to follow the trend of ZIKV research in 2014-2018 using quantitative methods. Titles and abstracts were scrutinized to determine whether the articles addressed our review objectives and fulfilled the inclusion and exclusion criteria. Differences between the reviewers were resolved through discussions.

- All studies reported on ZIKV research in the natural science field.
- Studies were published between 2014 and 2018.
- Studies were published as research articles, peer-reviewed, written in English.

Studies were excluded:

- Neither title nor abstract is presented.
- Type of publication - commentaries, letters, notes, short surveys, conference papers/reviews, articles in press, erratum, and retractions.
- The author's name is not available.
- The publication is not relevant to ZIKV related research.

Screening of the articles

All papers obtained from the search were imported to Endnote (EndNote version X9 Clarivate Analytics) for storage and subsequent screening. Initially, duplicates were removed from the database. To remove the potential for selection bias, two authors also independently completed the screening of papers. The inclusion and exclusion criteria mentioned above were used for publication selection by reviewing abstracts and titles.

Data extraction and visualization

Following the screening of titles and abstracts, eligible studies were analyzed and the following details were extracted and summarized.

To extract data from selected articles, we used R programming language (Rstudio, Version 1.1.463) with the open-source tool “Bibliometrix” which is a unique R package for quantitative research in

scientometrics and bibliometrics that includes all the main bibliometric methods of analysis (26). Based on the extracted data, we performed tabulation and visualization. Briefly, we designed the tables containing specific information of the articles which were sorted annually or numeric order (authors, title, journal source, institute, year, citation, country of the corresponding author). We assumed that the corresponding author is usually the author who provides the intellectual input and approves protocols in the study. The corresponding author's country was noted, extracted from the publications, and sorted to generate the geographical distribution and number of publications in different countries during 2014-2018.

The visual graphic is useful to present such data with easy to catch at a glance. Therefore, we chose a geographic information system (GIS) to display the distribution of the publication and number of publications in a different country (27). To generate and illustrate the GIS maps, we used Rstudio with "rworldmap" plug-in which is a package for visualizing global-scale data, concentrating on data referenced by country codes or gridded at half-degree resolution (28).

Graph data visualization was performed by using GraphPad 7.0 (CA, USA) and Adobe Illustrator CC 2017 (CA, USA).

Statistical analysis

We compared the retrieved result from 2014-2015 (low active stage) with the result from 2016-2018 (high active stage) with the unpaired t-test (parametric continuous variables). Statistical significance was set at 2-tailed $P < 0.05$. Statistical analyses were performed using GraphPad 7.0 (CA, USA).

Results

The ZIKV research field was driven by public interest

The comparison of publication numbers is a way to observe an active/inactive stage of the research area. So, we compared the number of ZIKV related publications to follow the movement of research in the last five years.

In 2014-2015, the average number of ZIKV related publications was 23.5 and the number then increased rapidly in 2016, 2017, and 2018 (39.2, 56.5, and 58.5 times, respectively). The conceivable reason behind this rapid increment of publication is an accumulation of the public interest after the Brazilian authority publicized the first report of autochthonous transmission of ZIKV in 2015 and the association with new clinical manifestations such as congenital Zika syndrome and Guillain-Barré syndrome. That propelled ZIKV research to a subject of international concern and led to efforts to better understand ZIKV and suggest measures to liberate the world from the ZIKV emergency declared by WHO (Fig 1).

Martinez-Pulgarin et al, (2016) previously showed that only 325 ZIKV related publications were found over six decades, inferring that research on ZIKV was at a very low level until 2015 (29). We could see that the publication number was increased tremendously in the consecutive three years (average number = 1209.3 publications/year). When comparing 2014-2015 (low active stage) vs 2016-2018 (high active stage) there was a P value = 0.0078, 95% confidence interval = 594.9 – 1777, and difference between means = 1186 ± 185.7 , $R^2 = 0.9315$.

This result showed how the research on ZIKV was changed to a highly active stage after the emergence of ZIKV in the Americas (Fig 1). In addition, the declaration of a public health emergency by WHO did not only bring public interest to ZIKV research but also increment funding opportunities for researchers (described in the timeline of ZIKV in Figure 1). We could observe that the public interest in emerging diseases leads to increased funding, which then results in a surge of publications in the research field.

The ZIKV research field moved from epidemiological research to the development of clinical applications

We decided to categorize ZIKV related publications into eight different research fields (antiviral research, vaccine development, fundamental research, diagnostic research, experimental models and tools, vector research, epidemiological research, clinical management/public communication) to follow the trend of ZIKV research fields in the last five years.

In antiviral and vaccine research, the first publications appeared in 2016 and increased thereafter. Research regarding diagnostic research and experimental models/tools started to expand from 2015 and increased every year. Vector research and epidemiology research was present for the five years studied, but the number of publications increased dramatically from 2016. The publications regarding fundamental research and clinical management/public communication also increased during the five years, except in 2018 (Fig 2A).

Next, we generated pie charts to follow the change in frequency between the different fields of research. Vaccine development appeared in 2016 (3.8%) and steadily increased until 2018 (6.5%). Antiviral research almost doubled from 2016 (4.1%) to 2017-2018 (8.2% and 7.8%). Vector research was the second-largest field of ZIKV research in 2014 (17.6%), decreased in 2015 (4.55%), but then increased continuously until 2018 (12.2%). The frequency of fundamental research was above 20% in most years, except 2015 (18.2%). On the other hand, epidemiological research was the major field in 2014 (58.8%), but it decreased gradually to 24.2% in 2018. The clinical management and public communications research fields also gradually decreased from 2016 (24.7%) to 2018 (12.3%) (Fig 2B).

Also, we extracted the 20 most cited articles in an attempt to determine which articles were influential in ZIKV research, based on the respective research field. The result showed that mainly case reports were the most cited in 2014. In 2015, case reports, diagnostic methods, epidemiological studies, and potential sexual transmission of ZIKV were the most cited. In 2016, the articles regarding the association between ZIKV infection and new clinical manifestations (such as microcephaly, Guillain-Barre

Syndrome), and the development of ZIKV animal models were highly cited. Studies of the ZIKV vaccine, ZIKV antiviral treatment, and understanding of ZIKV pathogenicity and tropism were most cited in 2017. In 2018, articles regarding viral persistence, and diagnostic approaches using advanced techniques such as CRISPR-Cas9 (Clustered regularly interspaced short palindromic repeats-CRISPR associated protein 9) and graphene, as well as vaccine development, and real-time surveillance system were most cited (Table 1).

Table 1. Top 20 most cited Zika virus-related publications 2014 to 2018

2014

	Author	Article title	Source	Cited by
1	OEHLER E et al.,	Zika Virus Infection Complicated By Guillain-Barr Syndrome "Case Report, French Polynesia, December 2013	Eurosurveillance	492
2	BESNARD M et al.,	Evidence Of Perinatal Transmission Of Zika Virus, French Polynesia, December 2013 And February 2014	Eurosurveillance	385
3	FAYE O et al.,	Molecular Evolution Of Zika Virus During Its Emergence In The 20th Century	Plos Neglected Tropical Diseases	365
4	MUSSO D et al.,	Potential For Zika Virus Transmission Through Blood Transfusion Demonstrated During An Outbreak In French Polynesia, November 2013 To February 2014	Eurosurveillance	346
5	GRARD G et al.,	Zika Virus In Gabon (Central Africa) - 2007: A New Threat From Aedes Albopictus?	Plos Neglected Tropical Diseases	324
6	MUSSO D et al.,	Rapid Spread Of Emerging Zika Virus In The Pacific Area	Clinical Microbiology And Infection	306
7	IOOS S et al.,	Current Zika Virus Epidemiology And Recent Epidemics	Medecine Et Maladies Infectieuses	304
8	ROTH A et al.,	Concurrent Outbreaks Of Dengue, Chikungunya And Zika Virus Infections An Unprecedented Epidemic Wave Of Mosquito-Borne Viruses In The Pacific 20122014	Eurosurveillance	230
9	DIALLO D et al.,	Zika Virus Emergence In Mosquitoes In Southeastern Senegal, 2011	Plos One	150
10	BARONTI C et al.,	Complete Coding Sequence Of Zika Virus From A French Polynesia Outbreak In 2013	Genome Announcements	139
11	FONSECA K et al.,	Case Report: First Case Of Zika Virus Infection In A Returning Canadian Traveler	American Journal Of Tropical Medicine And Hygiene	137
12	TAPPE D et al.,	First Case Of Laboratory-Confirmed Zika Virus Infection Imported Into Europe, November 2013	Eurosurveillance	130
13	LEDERMANN JP et al.,	Aedes Hensilli As A Potential Vector Of Chikungunya And Zika Viruses	Plos Neglected Tropical Diseases	108
14	KUTSUNA S et al.,	Two Cases Of Zika Fever Imported From French Polynesia To Japan, December To January 2013	Eurosurveillance	88
15	BERTHET N et al.,	Molecular Characterization Of Three Zika Flaviviruses Obtained From Sylvatic Mosquitoes In The Central African Republic	Vector-Borne And Zoonotic Diseases	66
16	HEALY K et al.,	Integrating The Public In Mosquito Management: Active Education By Community Peers Can Lead To Significant Reduction In Peridomestic Container Mosquit	Plos One	21
17	KADDUMUKASA	Mosquitoes Of Zika Forest, Uganda: Species	Journal Of Medical	11

	MA et al,.	Composition And Relative Abundance	Entomology	
18	BRUST KB et al,.	Trouble In Paradise	Idcases	3
19	THOMAS SJ et al,.	Flaviviruses (Dengue, Yellow Fever, Japanese Encephalitis, West Nile Encephalitis, St. Louis Encephalitis, Tick-Borne Encephalitis, Kyasanur Forest Di	Mandell, Douglas, And Bennett's Principles And Practice Of Infectious Diseases	2
20	KUANG L et al,.	Expression Profiles Of Myostatin, Myogenin, And Myosin Heavy Chain In Skeletal Muscles Of Two Rabbit Breeds Differing In Growth Rate	Animal Biotechnology	1

2015

	Author	Article title	Source	Cited by
1	MUSSO D et al.,	Potential Sexual Transmission Of Zika Virus	Emerging Infectious Diseases	603
2	ZANLUCA C et al.,	First Report Of Autochthonous Transmission Of Zika Virus In Brazil	Memorias Do Instituto Oswaldo Cruz	518
3	HAMEL R et al.,	Biology Of Zika Virus Infection In Human Skin Cells	Journal Of Virology	439
4	GOURINAT AC et al.,	Detection Of Zika Virus In Urine	Emerging Infectious Diseases	375
5	MUSSO D et al.,	Detection Of Zika Virus In Saliva	Journal Of Clinical Virology	287
6	BUATHONG R et al.,	Detection Of Zika Virus Infection In Thailand, 2012-2014	American Journal Of Tropical Medicine And Hygiene	139
7	ZAMMARCHI L et al.,	Zika Virus Infections Imported To Italy: Clinical, Immunological And Virological Findings, And Public Health Implications	Journal Of Clinical Virology	114
8	DIAGNE CT et al.,	Potential Of Selected Senegalese Aedes Spp. Mosquitoes (Diptera: Culicidae) To Transmit Zika Virus	Bmc Infectious Diseases	105
9	ZAMMARCHI L et al.,	Zika Virus Infection In A Traveller Returning To Europe From Brazil, March 2015	Eurosurveillance	84
10	RODRGUEZ-MORALES AJ	Zika: The New Arbovirus Threat For Latin America	Journal Of Infection In Developing Countries	77
11	LEUNG GHY et al.,	Zika Virus Infection In Australia Following A Monkey Bite In Indonesia	Southeast Asian Journal Of Tropical Medicine And Public Health	72
12	AUBRY M et al.,	Seroprevalence Of Arboviruses Among Blood Donors In French Polynesia, 2011-2013	International Journal Of Infectious Diseases	70
13	ALTHOUSE BM et al.,	Impact Of Climate And Mosquito Vector Abundance On Sylvatic Arbovirus Circulation Dynamics In Senegal	American Journal Of Tropical Medicine And Hygiene	40
14	SUMMERS DJ et al.,	Zika Virus In An American Recreational Traveler	Journal Of Travel Medicine	32
15	BRITO C	Zika Virus: A New Chapter In The History Of Medicine	Acta Medica Portuguesa	31
16	ZNDORF I et al.,	Brazil In Health Emergency: Zika - Once Again A New Viral Infection	Deutsche Apotheker Zeitung	28
17	ZWIZWAI R	Infectious Disease Surveillance Update	The Lancet. Infectious Diseases	28
18	WILSON ME et al.,	Dengue: Update On Epidemiology	Current Infectious Disease Reports	24
19	COX BD et al.,	Predicting Zika Virus Structural Biology: Challenges And Opportunities For Intervention	Antiviral Chemistry And Chemotherapy	23
20	KEIGHLEY CL et al.,	Viral Exanthems	Current Opinion In Infectious Diseases	23

2016

	Author	Article title	Source	Cited by
1	MLAKAR J et al.,	Zika Virus Associated With Microcephaly	New England Journal Of Medicine	1105
2	CAO-LORMEAU VM et al.,	Guillain-Barr Syndrome Outbreak Associated With Zika Virus Infection In French Polynesia: A Case-Control Study	The Lancet	946
3	RASMUSSEN SA et al.,	Zika Virus And Birth Defects - Reviewing The Evidence For Causality	New England Journal Of Medicine	803
4	BRASIL P et al.,	Zika Virus Infection In Pregnant Women In Rio De Janeiro	New England Journal Of Medicine	686
5	TANG H et al.,	Zika Virus Infects Human Cortical Neural Progenitors And Attenuates Their Growth	Cell Stem Cell	520
6	SCHULER-FACCINI L et al.,	Possible Association Between Zika Virus Infection And Microcephaly Brazil, 2015	Morbidity And Mortality Weekly Report	500
7	CALVET G;AGUIAR RS et al.,	Detection And Sequencing Of Zika Virus From Amniotic Fluid Of Fetuses With Microcephaly In Brazil: A Case Study	The Lancet Infectious Diseases	495
8	CUGOLA FR et al.,	The Brazilian Zika Virus Strain Causes Birth Defects In Experimental Models	Nature	486
9	PETERSEN LR et al.,	Zika Virus	New England Journal Of Medicine	483
10	FAUCI AS et al.,	Zika Virus In The Americas-Yet Another Arbovirus Threat	New England Journal Of Medicine	474
11	MUSSO D et al.,	Zika Virus	Clinical Microbiology Reviews	469
12	FARIA NR et al	Zika Virus In The Americas: Early Epidemiological And Genetic Findings	Science	430
13	CAUCHEMEZ S et al.,	Association Between Zika Virus And Microcephaly In French Polynesia, 2013-15: A Retrospective Study	The Lancet	421
14	QIAN X et al.,	Brain-Region-Specific Organoids Using Mini-Bioreactors For Modeling Zikv Exposure	Cell	416
15	DRIGGERS RW et al.,	Zika Virus Infection With Prolonged Maternal Viremia And Fetal Brain Abnormalities	New England Journal Of Medicine	408
16	GARCEZ PP et al.,	Zika Virus: Zika Virus Impairs Growth In Human Neurospheres And Brain Organoids	Science	398
17	LAZEAR HM et al.,	A Mouse Model Of Zika Virus Pathogenesis	Cell Host And Microbe	374
18	DEJNIRATTISAI W et al.,	Dengue Virus Sero-Cross-Reactivity Drives Antibody-Dependent Enhancement Of Infection With Zika Virus	Nature Immunology	358
19	MINER JJ et al.,	Zika Virus Infection During Pregnancy In Mice Causes Placental Damage And Fetal Demise	Cell	358

20	SIROHI D et al.,	The 3.8 Resolution Cryo-Em Structure Of Zika Virus	Science	296
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2017

	Author	Article title	Source	Cited by
1	NAGHAVI M et al.,	Global, Regional, And National Age-Sex Specific Mortality For 264 Causes Of Death, 1980-2016: A Systematic Analysis For The Global Burden Of Disease St	The Lancet	549
2	MOORE CA et al.,	Characterizing The Pattern Of Anomalies In Congenital Zika Syndrome For Pediatric Clinicians	Jama Pediatrics	173
3	HONEIN MA et al.,	Birth Defects Among Fetuses And Infants Of Us Women With Evidence Of Possible Zika Virus Infection During Pregnancy	Jama - Journal Of The American Medical Association	172
4	GOOTENBERG JS et al.,	Nucleic Acid Detection With Crispr-Cas13a/C2c2	Science	164
5	PARDIN et al.,	Zika Virus Protection By A Single Low-Dose Nucleoside-Modified Mrna Vaccination	Nature	155
6	BARDINA SV et al.,	Enhancement Of Zika Virus Pathogenesis By Preexisting Antiflavivirus Immunity	Science	145
7	RICHTNER JM et al.,	Modified Mrna Vaccines Protect Against Zika Virus Infection	Cell	134
8	FARIA NR et al.,	Establishment And Cryptic Transmission Of Zika Virus In Brazil And The Americas	Nature	115
9	KRAUER F et al.,	Zika Virus Infection As A Cause Of Congenital Brain Abnormalities And Guillainbarr Syndrome: Systematic Review	Plos Medicine	110
10	LIU Y et al.,	Evolutionary Enhancement Of Zika Virus Infectivity In Aedes Aegypti Mosquitoes	Nature	104
11	YUAN L et al.,	A Single Mutation In The Prm Protein Of Zika Virus Contributes To Fetal Microcephaly	Science	103
12	MEERTENS L et al.,	Axl Mediates Zika Virus Entry In Human Glial Cells And Modulates Innate Immune Responses	Cell Reports	95
13	SHAN C et al.,	A Live-Attenuated Zika Virus Vaccine Candidate Induces Sterilizing Immunity In Mouse Models	Nature Medicine	95
14	MURRAY KO et al.,	Prolonged Detection Of Zika Virus In Vaginal Secretions And Whole Blood	Emerging Infectious Diseases	94
15	BAUD D et al.,	An Update On Zika Virus Infection	The Lancet	92
16	MOREIRA J et al.,	Sexually Acquired Zika Virus: A Systematic Review	Clinical Microbiology And Infection	92
17	MINER JJ et al.,	Zika Virus Pathogenesis And Tissue Tropism	Cell Host And Microbe	91
18	REYNOLDS MR et al.,	Vital Signs: Update On Zika Virus-associated Birth Defects And Evaluation Of All U.S. Infants With Congenital Zika Virus Exposure U.S. Zika Pregnancy R	Morbidity And Mortality Weekly Report	87
19	ELONG NGONO A et	Mapping And Role Of The Cd8+ T Cell Response During Primary Zika Virus Infection In Mice	Cell Host And Microbe	81

	al,.			
20	HIRSCH AJ et al,.	Zika Virus Infection Of Rhesus Macaques Leads To Viral Persistence In Multiple Tissues	Plos Pathogens	81

2018

	Author	Article title	Source	Cited by
1	PAZ-BAILEY G et al.,	Persistence Of Zika Virus In Body Fluids-Final Report	New England Journal Of Medicine	113
2	GOOTENBERG JS et al.,	Multiplexed And Portable Nucleic Acid Detection Platform With Cas13, Cas12a And Csm6	Science	85
3	GAUDINSKI MR et al.,	Safety, Tolerability, And Immunogenicity Of Two Zika Virus Dna Vaccine Candidates In Healthy Adults: Randomised, Open-Label, Phase 1 Clinical Trials	The Lancet	45
4	MODJARRAD K et al.,	Preliminary Aggregate Safety And Immunogenicity Results From Three Trials Of A Purified Inactivated Zika Virus Vaccine Candidate: Phase 1, Randomised,	The Lancet	41
5	GARDY JL et al.,	Towards A Genomics-Informed, Real-Time, Global Pathogen Surveillance System	Nature Reviews Genetics	36
6	MYHRVOLD C et al.,	Field-Deployable Viral Diagnostics Using Crispr-Cas13	Science	36
7	BENELLI G et al.,	Mosquito Control with Green Nanopesticides: Towards The One Health Approach? A Review Of Non-Target Effects	Environmental Science And Pollution Research	34
8	BENELLI G et al.,	Management Of Arthropod Vector Data Social And Ecological Dynamics Facing The One Health Perspective	Acta Tropica	33
9	AFSAHI S et al.,	Novel Graphene-Based Biosensor For Early Detection Of Zika Virus Infection	Biosensors And Bioelectronics	32
10	HOEN B et al.,	Pregnancy Outcomes After Zikv Infection In French Territories In The Americas	New England Journal Of Medicine	30
11	MEAD PS et al.,	Zika Virus Shedding In Semen Of Symptomatic Infected Men	New England Journal Of Medicine	30
12	ABRAMOV DM et al.,	Auditory Brainstem Function In Microcephaly Related To Zika Virus Infection	Neurology	28
13	ADACHI K et al.,	Zika Clinical Updates: Implications For Pediatrics	Current Opinion In Pediatrics	28
14	ADAM A et al.,	Multiplexed Fluorospot For The Analysis Of Dengue Virus- And Zika Virus-Specific And Cross-Reactive Memory B Cells	Journal Of Immunology	28
15	ADAMS Z et al.,	Risk Of Exposure To Zika Virus And Impact On Cord Blood Banking And Adult Unrelated Donors In Hematopoietic Cell Transplantation: The Canadian Blood S	Biology Of Blood And Marrow Transplantation	28
16	ALAM MK et al.,	Zika Virus: Raising Awareness To Prevent A Pandemic	Bangladesh Journal Of Medical Science	28
17	ALAYED MS et	Seroprevalence Of Zika Virus Among Asymptomatic Pregnant	Annals Of Saudi	28

	al,.	Mothers And Their Newborns In The Najran Region Of Southwest Saudi Arabia	Medicine	
18	ALCENDOR DJ	Zika Virus Infection And Implications For Kidney Disease	Journal Of Molecular Medicine	28
19	ALFONSO-PARRA C et al,.	Molecular Responses To The Zika Virus In Mosquitoes	Pathogens	28
20	ALLEN MP	Chronicling The Risk And Risk Communication By Governmental Officials During The Zika Threat	Risk Analysis	28

Overall, the trend of ZIKV research was shifted from epidemiological research to the development of clinical applications (e.g. advanced diagnostic techniques, antiviral treatment, vaccine) during the five years.

The geographic distribution of ZIKV publications points to the globalization of ZIKV research.

In 2014 and 2015, we retrieved ZIKV publications from 11 and 13 different countries, respectively. The number of countries with ZIKV publications increased to 59, 67, and 66 in the consecutive three years. The result showed that ZIKV research became global after 2015. USA showed the highest number of corresponding authors in ZIKV research publications for the whole period 2014-2018. The next countries were Brazil, China, France, and the United Kingdom, making up the top 5 countries in ZIKV research publications from 2016 to 2018 (Fig 3). We found a similar pattern for the top 20 authors for ZIKV related publications, where the USA showed the highest number of authors (13/20), followed by Brazil, China, France (all 2/20), and Germany (1/20) (Table 2). The average number of publication numbers from the top 20 relevant authors was 28.65 (rank no.1 was 41 articles by Weaver SC, University of Texas Medical Branch, USA).

Table 2. Top 20 most authors for Zika virus-related publications 2014 to 2018

	Author	Institutes	Publications
1	WEAVER SC	University of Texas Medical Branch, USA	41
2	DIAMOND MS	Washington University School of Medicine, USA	40
3	SHI PY	University of Texas Medical Branch, USA	37
4	QIN CF	Beijing Institute of Microbiology and Epidemiology, China	33
5	HONEIN MA	Centers for Disease Control and Prevention, USA	32
6	MUSSO D	Institut Louis Malardé, French Polynesia; Aix Marseille Univ, France	32
7	VASILAKIS N	University of Texas Medical Branch, USA.	32
8	JAMIESON DJ	Emory University, USA	31
9	LI Y	Emory University, USA	31
10	GAO GF	Chinese Center for Disease Control and Prevention (China CDC), China	26
11	SHAN C	University of Texas Medical Branch, USA.	26
12	BRASIL P	Instituto Nacional de Infectologia Evandro Chagas, Brazil	25
13	FISCHER M	Centers for Disease Control and Prevention, USA	25
14	HARRIS E	University of California, USA	25
15	VENTURA CV	Altino Ventura Foundation, Brazil; HOPE Eye Hospital, Brazil	25
16	LEPARC-GOFFART I	French Armed Forces Biomedical Research Institute, France	24
17	SCHMIDT-CHANASIT J	Bernhard-Nocht-Institut für Tropenmedizin, Germany; German Centre for Infection Research (DZIF), Germany	24
18	MEANEY-DELMAN D	Centers for Disease Control and Prevention, USA	22
19	ROSSI SL	University of Texas Medical Branch, USA	21
20	STAPLES JE	Centers for Disease Control and Prevention, USA	21

Discussion

In this study, we retrieved data to follow the ZIKV research trends by using a bibliometric analysis of ZIKV related publications during 2014-2018. Our results highlighted the importance of gathering public interest in global health issues, and how public interest can act as a powerful catalyzer to trigger the research field (30, 31). Likewise, we found that the efforts to overcome the global emergency caused by the ZIKV outbreak in the Americas led to globalization in the research field (32).

Although the connection between ZIKV and more severe clinical manifestations had been suggested already in 2007 and the following years. ZIKV research was still at a low activity stage until the outbreak in the Americas occurred, with microcephaly in newborn infants that alerted public attention (16, 33, 34). For example, photographs of a mother holding her newborn baby with microcephaly, most likely caused by ZIKV infection during pregnancy, prompted sympathy and concerned authorities (35). Once the public interest was gathered, it led to global awareness and actions to combat the outbreak, and various research fields were fuelled to investigate and better understand all aspects of ZIKV.

During 2014-2015, the ZIKV research trend mainly focused on epidemiological aspects and public health, such as source and spread of ZIKV, case reports, and diagnostic methods. Then it shifted to the development of clinical applications to counteract ZIKV (e.g. advanced diagnostic techniques, antiviral treatment, vaccine) based on the accumulated knowledge in ZIKV publications. According to the WHO vaccine pipeline tracker, several ZIKV vaccine candidates are currently in clinical phase 1 or 2 (36).

The geographic distribution of ZIKV research showed that ZIKV research became a global issue after 2015, with an increase in investigations by the international research community (16). Besides, the change from a low to a high active stage in ZIKV research was accelerated by an increase in ZIKV research funding. When WHO declared ZIKV as a PHEIC, the budget for Ebola virus research was shifted to ZIKV research in the USA (37); the European Union launched fundings in three research consortia: ZikaPLAN, ZIKAction, ZikAlliance (38); Brazil, the first country reported autochthonous transmission of ZIKV infection in the Americas and the host of the Fédération Internationale de Football Association (FIFA) World Cup in 2016, was financially supported from the Brazilian Development Bank (39). These global supports for ZIKV research resulted in the increment of funding opportunities to the researchers and eventually, these supports led to the increment of research outcomes globally.

However, despite the progress in ZIKV research many questions remain to be addressed to continue the development of effective ZIKV countermeasures. For instance: how long-lasting is the immune response in a ZIKV exposed patient; could pre-existing immunity against ZIKV lead the antibody-dependent enhancement of new ZIKV variants, or other flaviviruses (such as dengue fever); what treatment options are there for the babies born with a neurological disorder caused by ZIKV infection during pregnancy; and ZIKV re-emergence could potentially occur in naïve regions, and global efforts should be directed towards surveillance, vaccines, and antiviral drug development.

Limitations

There are also some limitations to the study. Although we used Scopus for our bibliometric analysis (we believe that no scientific literature database is considered better), there are other public and commercially available scientific literature databases, such as PubMed. The decision to use Scopus was based on three reasons

1. The retrieved data from Scopus has compatibility to R programming language, particularly open-source R package “Bibliometrix”, while the data from PubMed has not.
2. There are wide variations in citation data in each database (40, 41).
3. For searching for ZIKV related publications from 2014-2018, Scopus showed more extended results than PubMed (42).

Because this study was limited to articles that were published only in English, we missed articles published in Portuguese and Spanish which were native languages in most of the outbreak area.

We showed the trend of ZIKV related research based on publication number, citation number, and geographic information. However, a limitation of our study is that we could not correlate between the shifting of trends in ZIKV research and the size of research funding. It would be interesting to merge the actual ZIKV research budget of each country for 2014-2018 into our GIS (Fig 3) to investigate whether the ZIKV research field has been driven by not only public interest but also actual financial support to each researcher in different countries.

Conclusions

Bibliometric assessments in infectious diseases are of utmost importance, not only to correlate the needs for research in a global emergency but also, as shown here, to provide an accurate overview of scientific output over time and its future impact (43, 44). Through this study, we have provided an analysis of the ZIKV research trends for 2014-2018. Particularly, the publication number was tremendously increased from 2016-2018 and geographic distribution showed that publications from the USA, Brazil, China, and Europe led the scientific production on ZIKV research.

During the publication process, Covid-19 has emerged from late 2019, and it is, at the time of writing, a pandemic with devastating effects. The silver lining is the unprecedented fast development of Covid-19 vaccines from several companies, and vaccine administration program has started in many countries. This rapid development of Covid-19 research and development of counter-acting measures is probably even more pronounced than for ZIKV, and it would be interesting to follow the speed of research, the shift in research areas, and the effect of directed research funding on Covid-19 from 2019 and forward, and we believe that the present study on ZIKV bibliography contains fruitful insights and useful information.

To conclude, we have to remember the importance of support and multidisciplinary collaboration against the ZIKV outbreak (also against the current Covid-19 pandemic) to be better prepared for the next infectious disease threat.

Abbreviations

ZIKV: Zika virus

WHO: World Health Organization

PHEIC: Public Health Emergency of International Concern

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

GIS: geographic information system

CRISPR-Cas9: Clustered regularly interspaced short palindromic repeats-CRISPR associated protein 9

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests

Funding

This work was supported by the Umeå Centre for Microbial Research (UCMR).

Authors' contributions

GYD designed and performed the experiments; analyzed, compiled, and interpreted the data; and wrote the manuscript. ME designed, interpreted, and compiled the data; wrote the manuscript; and provided funding. All authors read and approved the final manuscript.

Acknowledgments

Not applicable

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Figures

Figure 1

The number of Zika virus-related publications and major events in Zika virus history during 2014-2018. (1) The major events in the figure were selected from “WHO - The History of Zika Virus” (30). Statistical analysis was performed by unpaired, two-tailed t-test, 2014-2015 (low active stage) vs 2016-2018 (high active stage); P value = 0.0078, 95% confidence interval = 594.9 – 1777, difference between means = 1186 ± 185.7 , $R^2 = 0.9315$.

Figure 2

Categorized Zika virus-related publications to eight different research fields, 2014-2018. The publications were categorized into eight different research fields (antiviral research, vaccine development, fundamental research, diagnostic research, experimental models and tools, vector research, epidemiological research, clinical management/public communication) to follow the trend of Zika virus research in the last five years. 1Fundamental research consists of publications related to the scope of

genomics, immunology, pathogenesis, or virology. 2Technique development consists of the publications related to the scope of the development of the animal model and experimental tools (e.g. infectious clone DNA). 3Vector research consists of the publication related to the scope of vector competence, vector control approaches. 4Epidemiological research consists of the publication related to the scope of case study, surveillance, and transmission. 5Public health-related category consists of the publication related to clinical management and public communication. Some publications were categorized into multiple fields. Statistical analysis was performed by unpaired, two-tailed t-test; 2014-2015 (low active stage) vs 2016-2018 (high active stage) of each different research fields, respectively. (1) Antiviral research: P value = 0.0717, 95% confidence interval = -14.37 – 189.7, difference between means = 87.67 ± 32.06 , $R^2 = 0.7136$; (2) Vaccine development: P value = 0.0598, 95% confidence interval = -5.006 – 135, difference between means = 65 ± 22 , $R^2 = 0.7443$; (3) Fundamental research: P value = 0.0139, 95% confidence interval = -116.1 – 484.6, difference between means = 300.3 ± 57.9 , $R^2 = 0.8997$; (4) Diagnostic research; P value = 0.0688, 95% confidence interval = -13.14 – 196.8, difference between means = 91.83 ± 32.99 , $R^2 = 0.7209$; (5) Technique development: P value = 0.0492, 95% confidence interval = 0.3579 – 108, difference between means = 54.17 ± 16.91 , $R^2 = 0.7738$; (6) Vector research: P value = 0.0551, 95% confidence interval = -4.742 – 237.4, difference between means = 116.3 ± 38.04 , $R^2 = 0.7571$; (7) Epidemiological research: P value = 0.0039, 95% confidence interval = 183.3 – 419.7, difference between means = 301.5 ± 37.13 , $R^2 = 0.9565$; (8) Public health related: P value = 0.0025, 95% confidence interval = 136.9 – 275.4, difference between means = 206.2 ± 21.76 , $R^2 = 0.9677$.

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