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

Yong-Dae Gwon (kwon.yongdae@umu.se)
Umea Universitet
https://orcid.org/0000-0002-0703-4188

Magnus Evander
Umea Universitet Medicinska fakulteten

Research

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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
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 (zikv) 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-Barré
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**

| Year | Publication | Citations |
|------|-------------|-----------|
| 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       |
|   | Authors          | Title                                                                 | Journal                  | Page |
|---|------------------|----------------------------------------------------------------------|--------------------------|------|
| 18| MA et al.        | Composition And Relative Abundance Entomology                        |                         |      |
| 19| 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 |
|--------|---------------|--------|----------|
| MUSSO D et al., | Potential Sexual Transmission Of Zika Virus | Emerging Infectious Diseases | 603 |
| ZANLUCA C et al., | First Report Of Autochthonous Transmission Of Zika Virus In Brazil | Memorias Do Instituto Oswaldo Cruz | 518 |
| HAMEL R et al., | Biology Of Zika Virus Infection In Human Skin Cells | Journal Of Virology | 439 |
| GOURINAT AC et al., | Detection Of Zika Virus In Urine | Emerging Infectious Diseases | 375 |
| MUSSO D et al., | Detection Of Zika Virus In Saliva | Journal Of Clinical Virology | 287 |
| BUATHONG R et al., | Detection Of Zika Virus Infection In Thailand, 2012-2014 | American Journal Of Tropical Medicine And Hygiene | 139 |
| ZAMMARCHI L et al., | Zika Virus Infections Imported To Italy: Clinical, Immunological And Virological Findings, And Public Health Implications | Journal Of Clinical Virology | 114 |
| DIAGNE CT et al., | Potential Of Selected Senegalese Aedes Spp. Mosquitoes (Diptera: Culicidae) To Transmit Zika Virus | Bmc Infectious Diseases | 105 |
| ZAMMARCHI L et al., | Zika Virus Infection In A Traveller Returning To Europe From Brazil, March 2015 | Eurosurveillance | 84 |
| RODRIGUEZ-MORALES AJ | Zika: The New Arbovirus Threat For Latin America | Journal Of Infection In Developing Countries | 77 |
| 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 |
| AUBRY M et al., | Seroprevalence Of Arboviruses Among Blood Donors In French Polynesia, 2011-2013 | International Journal Of Infectious Diseases | 70 |
| 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 |
| SUMMERS DJ et al., | Zika Virus In An American Recreational Traveler | Journal Of Travel Medicine | 32 |
| BRITO C | Zika Virus: A New Chapter In The History Of Medicine | Acta Medica Portuguesa | 31 |
| ZNDORF I et al., | Brazil In Health Emergency: Zika - Once Again A New Viral Infection | Deutsche Apotheker Zeitung | 28 |
| ZWIZWAI R | Infectious Disease Surveillance Update | The Lancet. Infectious Diseases | 28 |
| WILSON ME et al., | Dengue: Update On Epidemiology | Current Infectious Disease Reports | 24 |
| COX BD et al., | Predicting Zika Virus Structural Biology: Challenges And Opportunities For Intervention | Antiviral Chemistry And Chemotherapy | 23 |
| KEIGHLEY CL et al., | Viral Exanthems | Current Opinion In Infectious Diseases | 23 |
| 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      |
2017
| Author          | Article title                                                                 | Source                                         | Cited by |
|-----------------|-------------------------------------------------------------------------------|------------------------------------------------|----------|
| 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      |
| MOORE CA et al. | Characterizing The Pattern Of Anomalies In Congenital Zika Syndrome For Pediatric Clinicians | Jama Pediatrics                                | 173      |
| 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      |
| GOOTENBERG JS et al. | Nucleic Acid Detection With Crispr-Cas13a/C2c2 | Science                                        | 164      |
| PARDI N et al. | Zika Virus Protection By A Single Low-Dose Nucleoside-Modified Mrna Vaccination | Nature                                         | 155      |
| BARDINA SV et al. | Enhancement Of Zika Virus Pathogenesis By Preexisting Antiflavivirus Immunity | Science                                        | 145      |
| RICHNER JM et al. | Modified Mrna Vaccines Protect Against Zika Virus Infection | Cell                                           | 134      |
| FARIA NR et al. | Establishment And Cryptic Transmission Of Zika Virus In Brazil And The Americas | Nature                                         | 115      |
| KRAUER F et al. | Zika Virus Infection As A Cause Of Congenital Brain Abnormalities And Guillainbarr Syndrome: Systematic Review | Plos Medicine                                  | 110      |
| LIU Y et al. | Evolutionary Enhancement Of Zika Virus Infectivity In Aedes Aegypti Mosquitoes | Nature                                         | 104      |
| YUAN L et al. | A Single Mutation In The Prm Protein Of Zika Virus Contributes To Fetal Microcephaly | Science                                        | 103      |
| MEERTENS L et al. | Axl Mediates Zika Virus Entry In Human Glial Cells And Modulates Innate Immune Responses | Cell Reports                                    | 95       |
| SHAN C et al. | A Live-Attenuated Zika Virus Vaccine Candidate Induces Sterilizing Immunity In Mouse Models | Nature Medicine                                | 95       |
| MURRAY KO et al. | Prolonged Detection Of Zika Virus In Vaginal Secretions And Whole Blood | Emerging Infectious Diseases                   | 94       |
| BAUD D et al. | An Update On Zika Virus Infection | The Lancet                                      | 92       |
| MOREIRA J et al. | Sexually Acquired Zika Virus: A Systematic Review | Clinical Microbiology And Infection            | 92       |
| MINER JJ et al. | Zika Virus Pathogenesis And Tissue Tropism | Cell Host And Microbe                          | 91       |
| 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       |
| 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       |
| 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 |
|-------------------|-------------------------------------------------------------------------------|--------------------------------|----------|
| PAZ-BAILEY G et al., | Persistence Of Zika Virus In Body Fluids-Final Report                        | New England Journal Of Medicine | 113      |
| GOOTENBERG JS et al., | Multiplexed And Portable Nucleic Acid Detection Platform With Cas13, Cas12a And Csm6 | Science                         | 85       |
| 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       |
| 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       |
| GARDY JL et al., | Towards A Genomics-Informed, Real-Time, Global Pathogen Surveillance System | Nature Reviews Genetics          | 36       |
| MYHRVOLD C et al., | Field-Deployable Viral Diagnostics Using Crispr-Cas13                         | Science                         | 36       |
| 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       |
| BENELLI G et al., | Management Of Arthropod Vector Data Social And Ecological Dynamics Facing The One Health Perspective | Acta Tropica                    | 33       |
| AFSAHI S et al., | Novel Graphene-Based Biosensor For Early Detection Of Zika Virus Infection | Biosensors And Bioelectronics   | 32       |
| HOEN B et al., | Pregnancy Outcomes After Zikv Infection In French Territories In The Americas | New England Journal Of Medicine | 30       |
| MEAD PS et al., | Zika Virus Shedding In Semen Of Symptomatic Infected Men                      | New England Journal Of Medicine | 30       |
| ABRAMOV DM et al., | Auditory Brainstem Function In Microcephaly Related To Zika Virus Infection   | Neurology                       | 28       |
| ADACHI K et al., | Zika Clinical Updates: Implications For Pediatrics                           | Current Opinion In Pediatrics    | 28       |
| 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       |
| 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       |
| ALAM MK et al., | Zika Virus: Raising Awareness To Prevent A Pandemic                           | Bangladesh Journal Of Medical Science | 28       |
| ALAYED MS et al., | Seroprevalence Of Zika Virus Among Asymptomatic Pregnant                       | Annals Of Saudi                 | 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

| No | Author(s)                  | Title                                                        | Journal                                      | Publication Year |
|----|----------------------------|--------------------------------------------------------------|----------------------------------------------|------------------|
| 18 | ALCENDOR DJ                | Zika Virus Infection And Implications For Kidney Disease     | Journal Of Molecular Medicine                | 2018             |
| 19 | ALFONSO-PARRA C et al.     | Molecular Responses To The Zika Virus In Mosquitoes          | Pathogens                                   | 2018             |
| 20 | ALLEN MP                   | Chronicling The Risk And Risk Communication By Governmental Officials During The Zika Threat | Risk Analysis                                | 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

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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.

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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, R² = 0.9315.
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. Technique development consists of the publications related to the scope of the development of the animal model and experimental tools (e.g., infectious clone DNA). Vector research consists of the publication related to the scope of vector competence, vector control approaches. Epidemiological research consists of the publication related to the scope of case study, surveillance, and transmission. Public 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, R² = 0.7136; (2) Vaccine development: P value = 0.0598, 95% confidence interval = -5.006 – 135, difference between means = 65 ± 22, R² = 0.7443; (3) Fundamental research: P value = 0.0139, 95% confidence interval = -116.1 – 484.6, difference between means = 300.3 ± 57.9, R² = 0.8997; (4) Diagnostic research: P value = 0.0688, 95% confidence interval = -13.14 – 196.8, difference between means = 91.83 ± 32.99, R² = 0.7209; (5) Technique development: P value = 0.0492, 95% confidence interval = 0.3579 – 108, difference between means = 54.17 ± 16.91, R² = 0.7738; (6) Vector research: P value = 0.0551, 95% confidence interval = -4.742 – 237.4, difference between means = 116.3 ± 38.04, R² = 0.7571; (7) Epidemiological research: P value = 0.0039, 95% confidence interval = 183.3 – 419.7, difference between means = 301.5 ± 37.13, R² = 0.9565; (8) Public health related: P value = 0.0025, 95% confidence interval = 136.9 – 275.4, difference between means = 206.2 ± 21.76, R² = 0.9677.
Figure 3

Geographic distribution and number of Zika virus-related publications 2014-2018. Corresponding author's country and numbers were used to generate geographic information systems by using Rstudio with open source plug-in “Rworldmap”. Statistical analysis was performed by unpaired, two-tailed t-test, 2014-2015 (low active stage) vs 2016-2018 (high active stage); P value = 0.0104, 95% confidence interval = 466.2 – 1620, difference between means = 1043 ± 181.3, R2 = 0.9169. Note: The designations employed and
the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

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