Future VIROLOGY

Review

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Zika outbreak aftermath: status, progress, concerns and new insights

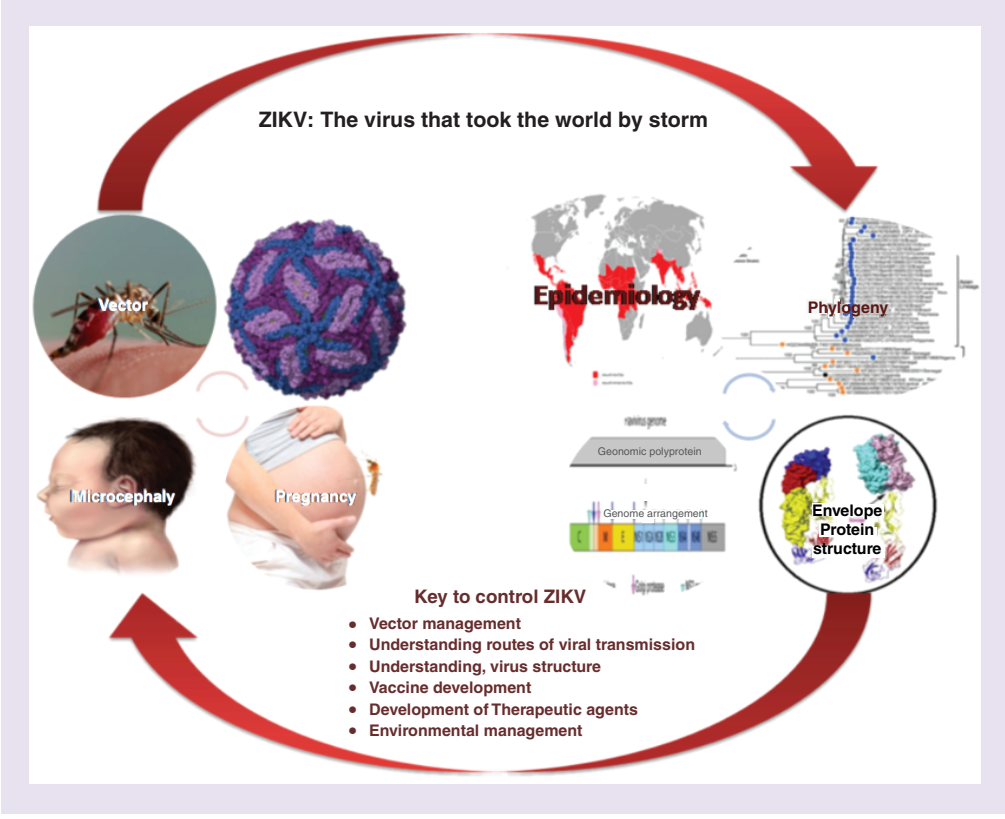
Neelima Arora*[,1], Amit K Banerjee[2] & Mangamoori L Narasu[1]

[1]Centre for Biotechnology, Institute of Science & Technology (Autonomous), Jawaharlal Nehru Technological University-Hyderabad, Kukatpally, Hyderabad 500085, Telangana, India

[2]Biology Division, CSIR-Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad 500007, Telangana, India

*Author for correspondence: Tel.: +91 402 789 1230; neelimaiict@gmail.com

Zika, a neurotrophic virus belonging to *Flaviviridae* family of viruses and transmitted by vector mosquitoes of *Aedes* species, took the world by storm during its recent outbreak. Its spread to newer territories, unprecedented pace of transmission, lack of existing therapeutic agents and vaccines and an empty drug pipeline raised an alarm. Uncertainty about full spectrum of diseases and its long-term consequences, newly discovered modes of transmission and controversies over vector status of mosquito species like *Culex quinquefasciatus* led to layers of complexity and presented new hurdles and challenges in Zika virus research. This review summarizes the progress and updates of efforts, concerns, financial burden and available resources in light of newly acquired knowledge in Zika virus research.



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Future Medicine

From being an unknown virus to a public health threat, Zika virus (ZIKV) succeeded in reminding us of the persistent need to search for strengthening our arsenal against emerging pathogens. ZIKV, an arbovirus belonging to the Spondweni serocomplex of the family *Flaviviridae* and transmitted primarily by *Aedes* mosquitoes has been making headlines for the past 2 years. ZIKV was first isolated from a Rhesus monkey in 1947 in Uganda and then from a mosquito in 1948 [1]. ZIKV, which was reported to have two lineages, African lineage and Asian lineage, was mainly restricted to African and south Asian regions [2]. After the outbreak of ZIKV in 2007 in Yap Island, several ZIKV outbreaks were reported outside its geographical range (Asia and Africa), but these outbreaks were sporadic and none received much attention. ZIKV infection leads to self-limiting mild illness and 80% of the Zika infections are asymptomatic [3,4]. The concern over ZIKV was raised due to upsurge in microcephaly cases in infants born and increased incidence of Guillain–Barré syndrome (GBS) in the affected regions [5]. ZIKV spread in 84 countries and territories affecting 559,721 individuals raising an alarm. The worst hit country was Brazil which received a lot of media attention. The scale and impact of ZIKV outbreak jolted researchers and medical practitioners across the world. Such was the gravity of situation that WHO declared Zika as Public Health Emergency of International Concern on 1 February 2016 [6]. WHO also issued a ZIKV geographical risk classification scheme in 2017. Pregnant women and women of child bearing age were advised against traveling to areas with active ZIKV transmission. Several nations cautioned women in reproductive age bracket and suggested considering delayed pregnancy.

Researchers are currently trying to understand transmission dynamics, alternative transmission routes and long-term effects of ZIKV. Therefore, we are yet to understand the disease spectrum, thus formulating proper control and treatment strategies can be challenging. Though a vast array of data about virus, symptoms, epidemics and preventive measures is available, there are still many uncertainties and fears that surround the ZIKV [7]. The panic and the concerns surrounding ZIKV all reflect poorly on our preparedness of tackling new emerging pathogens and the delay in onset of outbreak and response marks the big implementation gap in research and practice. Like any other new pathogen, ZIKV outbreak spurred many studies and efforts but we need to reminisce over the outcomes, existing knowledge and what new insights have been gained due to this outbreak. Whether this renewed interest in ZIKV research will translate into meaningful results in terms of prevention, diagnosis and therapeutics need to be seen. Though a lot of knowledge about molecular biology and transmission cycle of ZIKV was available earlier yet most of the structural data were derived after the recent outbreak. Various agencies are working on several high-priority areas in ZIKV research [8]. This may enable us to orient our efforts in a proper direction to deal with any future outbreak. We need to tread the path of ZIKV control with caution. Major focus after the recent outbreak has been the knowledge acquisition but implementation gap in dissemination of acquired knowledge in scientific community and general public and clinicians has become a major setback in ZIKV control [9–15]. A much neglected link in implementation remains proper coordination between obstetricians and pediatricians, which can be instrumental in ensuring proper screening, maintenance of electronic health records, development of better decision support systems and setting timely reminders for the subjects [16]. Strengthening of surveillance systems and laboratory diagnostics capabilities and development of accurate and sensitive diagnostic techniques will aid in ZIKV control in nations prone to ZIKV risk with high population density and vector presence due to geographical conditions and settings. Brazil and other countries with active ZIKV transmission are adopting integrated vector management for vector control. Some of the affected countries are promoting the use of mosquito-driven dissemination of small particles of juvenile-killing insecticides like pyriproxyfen to breeding sites [17]. Brazil has adopted both medium to long-term active measures for ZIKV control ranging from scaling up diagnostics to environmental management. Brazil employed all conventional measures to control ZIKV outbreak by conducting massive fumigation, release of genetically modified sterile mosquitoes and introduction of bacterium *Wolbachia* in the mosquito-breeding sites. Conventional vector control measures have shown limited success in the past during Dengue and other mosquito-borne diseases outbreaks. It has been established time and again that knowledge gaps and lack of awareness about a disease often mar the progress of its control. So, the countries are focusing and channelizing their funds and resources toward increasing public awareness and societal involvement. As there is a dire need to strengthen the surveillance and monitoring of ZIKV for effectively tackling the ZIKV spread, many researchers are now exploring and harnessing the telecommunication systems and mobile technology. An ongoing pilot study combining geolocation and mobile data for ovitrap monitoring seems promising in providing clues for community-based surveillance in Columbia. Priye *et al.* described a nucleic acid amplification tests device that combines quenching of unincorporated amplification signal reporters and multiplexed reverse

transcription-loop mediated isothermal amplification assay that diagnose Zika, Chikungunya and Dengue virus with a novel smartphone-based detection system, eliminating the complex sample preparation routine and cold-chain requirement and providing accurate diagnosis at the point of care [18]. Affordability, portability, high sensitivity and accuracy make this a promising technique for rapid diagnosis of ZIKV. Kelvin *et al.* developed ZIKATracker (zikatracker.net), a multilingual mobile app for reporting ZIKV cases will help in ZIKV surveillance [19]. Use of digital platforms and mobile applications and their impact on ZIKV and Ebola outbreaks has been reviewed recently and it is emphasized that Information and communication technologies can pave a way for effective accumulation and dissemination of knowledge related to the present outbreak [20].

Sudden interest in forgotten virus

Very few articles on Zika were published prior to the recent outbreak and majority of them were case reports. A quick search on PubMed on 29 April 2018 using the term 'Zika' showed that the number of articles published thus far as 4515 proving there has been an astonishing rise in number of articles after the Zika outbreak. Out of these, only eight articles were clinical trials reports, three each from 2016 and 2017 and two from 2018. Out of the 573 review articles, only a fraction was published before 2015 but the number increased exponentially after the recent outbreak in Brazil (208 in 2016, 270 in 2017 and 82 in 2018). A glimpse into the recent literature available in PubMed and keywords or search terms gave a clue regarding the focus/priority areas (Figure 1). The prominent search terms defining the research directions found were: 'Zika virus epidemiology,' 'Zika virus transmission,' 'transmission Zika virus,' 'Zika microcephaly,' 'Zika virus microcephaly,' 'Zika dengue,' 'Zika virus brazil,' 'Zika pregnancy,' 'Zika review,' 'Zika vaccine,' 'Zika virus review,' 'Zika virus vaccine,' 'Zikaguillain,' 'Zikaguillainbarre,' 'Zika virus guillain,' 'Zika sexual' and 'Zika virus genome.' Before the recent outbreak, as the focus was mainly on transmission and general biology of ZIKV, not much information was available on Zika macromolecules. There has been a sudden interest in structural biology of Zika after the publication of cryoEM structure of ZIKV in 2016 and now the count of macromolecule structures of Zika in Protein Data Bank has reached 73 within a short span of time. Studies before the recent ZIKV outbreak mainly illustrated the transmission routes and geographical ranges and case reports of sporadic events of ZIKV but the association of microcephaly cases in Brazil made the researchers to shift focus to Congenital Zika syndrome (CZS) and other implications [21]. A number of studies focused on presenting an overview of Zika prevention and related advices. Reports of hitherto unknown sexual transmission route of ZIKV also generated a lot of interest and publications and speculations and hypothesis related to its impact on local transmission of ZIKV were abounding thereafter. Many studies tried to assess the risk in specific regions or zones/countries based on presence and abundance of vectors and seasonality. Several systematic reviews provided overall view for general readers about various aspects after the outbreak for providing information to general public but there was a clear lack of literature that highlights the importance of sanitation and planning in urban dwellings, which started emerging after the current outbreak. A huge proportion of media reports focused on impeding effects and danger due to a mass event, Olympic in this case, on ZIKV outbreaks. Sequencing of ZIKV genome in 2016 gave much needed impetus to the studies focusing on genetic aspects and signatures and its evolution. More reports about hurdles in vaccine development were published instead of more initiatives. Another issue that reflected in publication was the possibility of co-morbidity of Dengue and Zika and how the control of one disease could have prevented outbreak of another disease. The lessons learnt from Dengue control program were being shared and extrapolated for ZIKV.

Hallmarks of CZS

A sharp increase in cases of microcephaly was observed in Brazil in the late 2015 that reached to epidemic scale soon after. Though microcephaly and congenital abnormalities could arise due to any insult that disturbs early brain growth and can be seen in association with hundreds of genetic syndromes and infectious agents, spatiotemporal association of cases of microcephaly and ZIKV infection led to the hypothesis associating ZIKV infection and unique set of congenital abnormalities in neonates, supported by evidences emerging from case studies and epidemiological reports. ZIKV infection was linked to microcephaly and GBS and triggered a wave of panic. A marked feature for CZS is congenital microcephaly that is defined as occipital–frontal circumference or head circumference at least two standard deviations smaller than the mean for a particular age and sex. There has been a perplexity and lack of consensus for definition of microcephaly in cases of preterm delivery. A case–control study carried out in the metropolitan region of Recife in Pernambuco state in Brazil, between January and May 2016 confirmed the

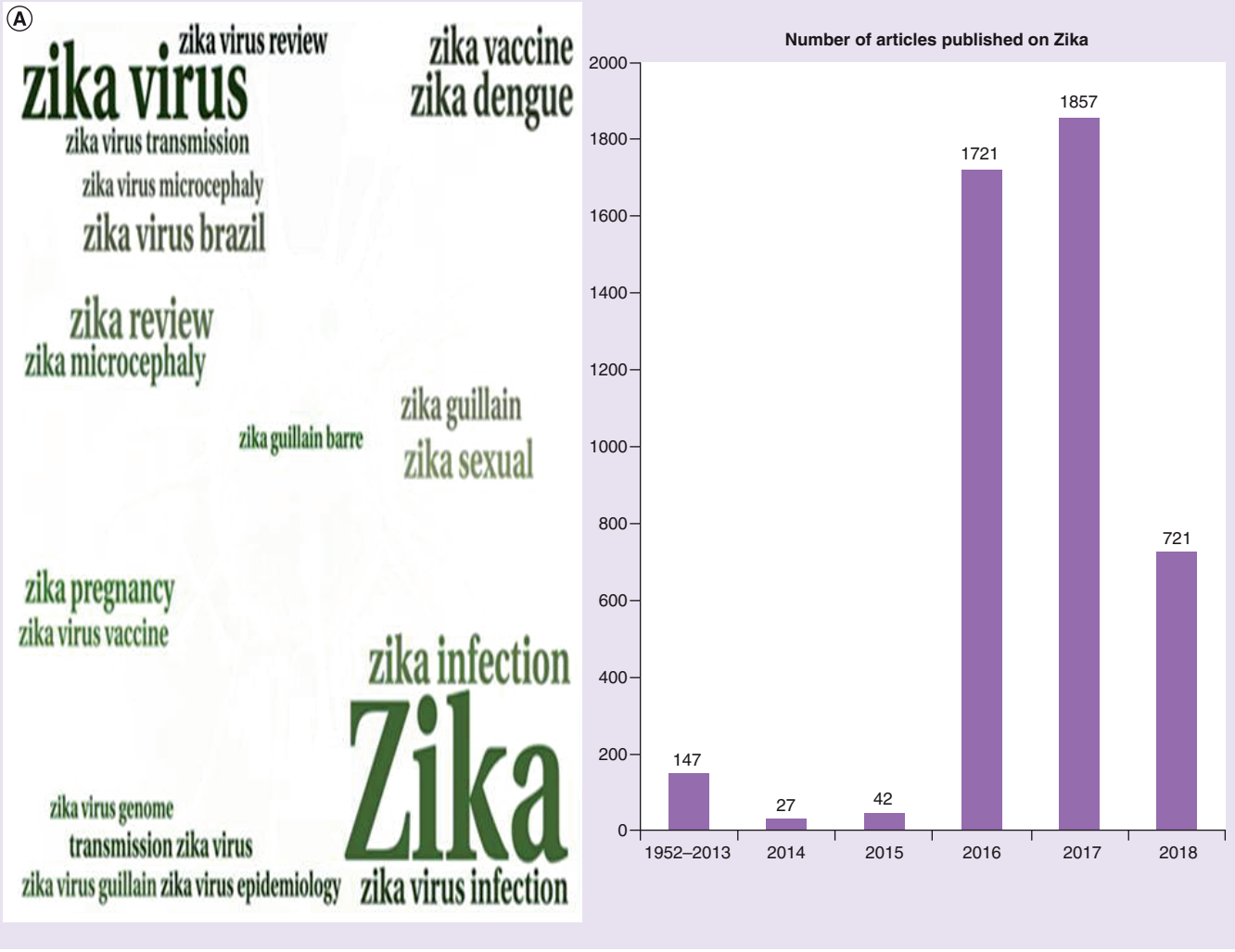

Figure 1. Research trends and global interest in Zika virus and epidemiology. (A) Popular search terms related to ZIKV. The represented size of the search term with relation to Zika is proportionate to number of articles found in PubMed (number of articles on ZIKV published in a year).
ZIKV: Zika virus.

association between ZIKV infection and microcephaly in Brazil [22]. It is suggested to consider ZIKV as an emerging TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus and herpes simplex) infection owing to striking similarities between other TORCH agents and devise future research strategies accordingly [23,24]. CZS demonstrates a distinctive and unique pattern of anomalies in fetuses and infants and can be differentiated characteristically by five features from other neurological implications involving cognitive, sensory and motor disabilities, in other words, 'severe microcephaly with partially collapsed skull; thin cerebral cortices with subcortical calcifications; macular scarring and focal pigmentary retinal mottling; congenital contractures; and marked early hypertonia and symptoms of extrapyramidal involvement' [25]. It is suggested that the most vulnerable period for infection is during the late first trimester and early second trimester. Cauchemez *et al.* assessed the risk of microcephaly with maternal ZIKV infection and concluded that highest risk lies in the first trimester [26]. Recognition of phenotypical features and full spectrum of CZS symptoms and availability of this knowledge will aid the clinicians in resolving the perplexity and charting a proper course of action for evaluation, follow-up, treatment and care.

Forecasting ZIKV: a step toward prevention

Availability of a model that can predict ZIKV transmission pattern and its spread in advance can help in devising public health interventions and strategies for prevention of its outbreak. Forecasting the onset and trends of mosquito-borne diseases is gaining traction owing to several epidemics like Chikungunya, Dengue and the most recent ZIKV episodes. Last decade witnessed the emergence and reemergence of various mosquito-borne viral diseases primarily those caused by members of *Alphaviridae* and *Flaviviridae* families. The attempts to predict the outbreaks of Yellow fever, Dengue, Chikungunya have met with limited success.

Internet can be used as a reliable source for obtaining disease surveillance data without any significant lag period, thus enabling policy makers in tracking disease incidence and transmission pattern for chalking out effective strategies to prevent epidemics. The data may be derived from various electronic social media sources such as search engines, news reports, online surveillance systems, electronic health records, Twitter and satellite data [27,28]. Digital epidemiology has come a long way since its conception in mid-1990s and proved its worth in early outbreak situational awareness. Pollett *et al.* recently reviewed the pros and cons of utilizing Internet-based surveillance methods and highlighted their potential in biosurveillance of vector-borne diseases [29]. Simultaneously, it is also important to mention that proper data curation and validation is mandatory while using online data resources for the studies. Proper filtering is the key for the achieving accuracy.

Utility of Google Trends in prediction of various infectious diseases such as Dengue and Influenza has been proved and this paved a way for developing forecasting methods and tools using Web-based surveillance data [30,31]. As such systems employ nearly real-time data from surveillance, it may provide a means to bypass the delay caused between monitoring, communication and action and help public health workers in implementation of appropriate strategies for prevention of outbreak. Teng *et al.* recently developed an efficient dynamic forecasting method for predicting the pattern of ZIKV transmission using AutoRegressive Integrated Moving Average model by utilizing the correlation data derived from Zika-related online searches using Google Trends [32]. Another study assessed the utility of nontraditional data sources *viz.* HealthMap and Google Trends for near real-time estimation of transmission dynamics in Colombian ZIKV disease outbreak [33]. McGough *et al.* utilized digital data derived from an array of Web-based sources for predicting the ZIKV incidence ahead of time [27]. Manore *et al.* employed a mathematical model that considered parameters derived from field data like vector density and competencies and human host use and seasonality to assess the conditions conducive for local transmission of ZIKV [34]. They concluded that even one of every two travelers carrying the infection could initiate local transmission under the suitable conditions. Munoz *et al.* used two vectors one host model (for *Aedes aegypti* and *Aedes albopictus*) to predict the suitability of conditions for the outbreak of Aedes-borne diseases like Dengue and Zika and developed a new probabilistic forecast system for predicting such outbreaks [35]. Major issue in development of successful predictive models is the complexity arising due to nonlinear interactions between various parameters influencing the disease transmission like effects of population immunity and susceptibility and immunological interactions occurring because of co-morbidity apart from meteorological conditions [36–38]. Teng *et al.* assessed the risk of Zika outbreak in Asia–Pacific regions using gradient boosted regression tree (BRT) models including a vast array of information arising from socioeconomic, ecological and meteorological data and combing the existing and new knowledge for elucidating the most influencing parameters leading to outbreak [39]. They found that increase in vapor pressure, Dengue virus infection and population density led to probability of Zika outbreaks while economic factors like health expenses and high gross domestic product (GDP) brought down the chances of outbreaks. A simple prediction model based on airline transportation network data and country-wise data of ZIKV incidence was also successful in estimating risks of importation and local transmission of ZIKV with significant specificity [40]. Chowells *et al.* used 'Phenomenological Models' for determining the transmission pattern of ZIKV and forecasting the temporal evolution of Zika epidemic in a province of Colombia [41]. Hsieh used phenomenological model to study the temporal patterns and transmission potential of ZIKV in various nations and found significant differences in transmission pattern in island- and land-based populations and pointed toward the important role played by geographic heterogeneity in the spread of vector-borne diseases [42]. Dinh *et al.* assessed the risk of ZIKV transmission in Florida and generated a short-term forecast for ZIKV cases using the bootstrap method along with the logistic and renewal equations [43]. Messina *et al.* employed an ensemble BRT-based method using data from South American outbreak for determining vulnerable population [44]. Samy *et al.* employed maximum entropy ecological niche modeling available in Maxent version 3.3 [45] and developed four models using diverse set of parameters including meteorological, socioeconomic, vector density and behavior, land-usage pattern to successfully

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predict the epidemics but failed at levels with transmission routes other than vector-based transmission [46]. As year round, ZIKV transmission in temperate regions seems highly improbable, time-specific ecological niche models are being used for predicting the Zika outbreak in effective manner [47] but they are constrained with the lack of framework and adaptability to incorporate near real-time data [48,49]. Carlson *et al.* adopted and combined as many as seven different methods incorporating climatic factors and normalized difference vegetation index to derive a mathematical model and also pointed toward the limitations and reasons for conflict in earlier models and provided spatially explicit database of Zika incidences from the existing knowledge base and an assembly of ecological niche models for mapping the potential geographical distribution of the virus [49]. Evans *et al.* collected a number of derived parameters like mosquito traits and virus traits and used BRT implemented in generalized boosted regression models package in R for determining the ZIKV transmission potential of various mosquito species and predicted 35 species of mosquitoes as potential vectors including seven prevalent in the continental USA [50]. Perkins *et al.* derived projections of Zika cases in pregnant women using a number of variables such as climate and spatial data while taking into account factors like economic index and host–vector contact for a more realistic model [51]. Kucharski *et al.* used a compartmental mathematical model to study the transmission dynamics of ZIKV on six archipelagos in French Polynesia during the 2013–2014 outbreak using a susceptible-exposed-infectious-removed (SEIR) framework for modeling people and mosquitoes and determined the basic reproduction number, magnitude of the outbreak and population vulnerable to infection in the future [52]. Agusto *et al.* developed a compartmental model to investigate ZIKV transmission dynamics considering sexual route of transmission along with vector-based transmission using both mosquito and host population [53]. Dantas *et al.* developed an SEIR-based model where population was segregated in susceptible, exposed, infected and recovered groups to describe the ZIKV transmission dynamics during the recent outbreak in Brazil [54]. Wiratsudakul *et al.* reviewed and summarized five common types of mathematical models for vector borne diseases *viz.* compartmental, spatial, metapopulation, network and individual-based models and their architecture and explained their crucial role in ZIKV import risk estimation and planning of intervention strategies [55]. They stressed that with changing dynamics of disease, there has been a marked shift from simple-to-complex mathematical models that are adaptable and analyze near real-time data for more accurate predictions.

These forecasts can help policy makers, researchers and public health workers in devising timely intervention and prioritizing resource allocation to the most vulnerable regions, thereby curbing the outbreak. As the predictive variables like vector density, temperature, precipitation, stagnant water and population density remain same for ZIKV transmission as other mosquito-borne diseases, the problem of development of accurate forecasting models is also compounded because of unique capacity of ZIKV for sexual transmission thus, increasing its dependence on demographic features and migration pattern.

Controversy over vectors & vector control

In the wake of recent outbreak, many research groups attempted to explore the possibility of involvement of vectors other than *A. aegypti* and other *Aedes* species in Zika transmission. As *Culex* species are known vectors for many viruses belonging to *Flaviviridae*, studies exploring the vectorial capacity and competence of Culex mosquitoes gained impetus. Only one study conducted in Brazil demonstrated the ZIKV replication in *C. quinquefasciatus* [56] but other studies conducted across various geographical regions ruled out *C. quinquefasciatus* as ZIKV vector owing to low infection rates [57]. In a study that aimed at determining spatiotemporal pattern of ZIKV transmission in Senegal, many mosquito species including *Ae. furcifer, Ae. luteocephalus, Ae. africanus, Ae. vittatus, Ae. tailor, Ae. dalzieli, Ae. hirsutus, Ae. metallicus, Ae. aegypti, Ae. unilinaetus, Mansonia uniformis, Cx. perfuscus* and *An. coustani* were found to be infected with ZIKV but only *Ae. vittatus* and *Ae. furcifer* were identified to be potentially capable of ZIKV transmission [58,59]. *C. quinquefasciatus* has been implicated as a ZIKV vector in Hainan province in China where viral transmission was observed but the results could not be replicated using *C. quinquefasciatus* from Singapore in another study [60]. Report of ZIKV competence of *C. quinquefasciatus* in experimental conditions warrants the need of more such studies before establishing its vector status [60]. Numerous studies confirmed the incompetence of *C. quinquefasciatus* and *C. pipiens* in transmission of ZIKV [61–67]. Different studies focusing on vector competence and behavior of mosquito species were reviewed recently [68]. As the controversy over the role of other mosquitoes as Zika vectors lurks, it is imperative to assess their role in transmission of ZIKV. Keeping in mind the difference in habit and habitats of *Aedes* and *Culex*, vector control strategies need to be made exhaustive and scaled up accordingly. Considering domiciliary nature of *Aedes* mosquito, awareness about habitats and breeding places of *Aedes* and hygienic practices can play a crucial role in Zika prevention. As prevention is considered better

than cure, we need to concentrate on comprehensive program that includes source reduction, contact avoidance using mosquito nets and repellants and elimination of vectors. As the chemical means of vector control are losing their sheen owing to nonspecificity, resistance in vectors and environmental problems, alternative methods for vector control like manual methods and biological control should also be included. Biological control methods for *Aedes* mosquitoes like use of biopesticides derived from *Bacillus thuringiensis* subsp. *Israelensis, Bacillus sphaericus* and introduction of *Wolbachia*, fungi, copepods, fish, tadpoles and other mosquito species have been reviewed recently [69].

Concerns over other routes of Zika transmission

Nonvector-borne routes did not gain much attention in the past outbreaks but as the other modes of Zika transmission like sexual transmission, through blood transfusion, mother-to-child transmission came into light, there are other concerns and areas that need to be explored. It is argued that cases of sexual transmission of Zika do not constitute a significant proportion of total cases and hence, is unlikely to cause an outbreak [70]. There is evidence of sexual transmission of Zika in male-to-female, male-to-male and female-to-male sexual contact but not much is known about female-to-female transmission either because of clear gender disparity or under-reporting [71]. ZIKV has been detected in semen [72], vaginal fluids [73], saliva [74], urine [75] and breast milk [76]. Further detection of ZIKV in semen for extensive period even while evading the detection in blood invigorates the need for detection of Zika in other body fluids and saliva.

Ethical concerns about Zika

Concerns are raised about the risk minimization, adequate compensation, rights of subjects and ethical justification of the infection challenge program [77]. Being the first mosquito-borne virus known to cause congenital malformations and neurological disorders, it is also the first to raise ethical concerns and moral obligations to provide free access to contraception as in Zika Contraception Access. Network [78]. Lathrop *et al.* update about Zika consequences and need of providing freedom and support system for women of child-bearing age for making well-informed decisions.

Current status & problems in Zika vaccine development

At present, there are no vaccines available for preventing ZIKV. The road to development of an effective vaccine is full of challenges, some of them are: vaccine should be effective against various Zika strains, safe for use in pregnancy, able to evade antibody-dependent enhancement of infection caused by anti-Dengue virus monoclonal antibodies in view of licensing of Dengue vaccine in countries where Dengue and Zika coexist, and capable of leading a systemic immune response and not elicit neurological side effects [79]. Immunity provided by vaccine should pass from mother to fetus and new born [80]. It is also very difficult to gauge the clinical efficacy of such vaccine as majority of Zika cases are asymptomatic. It should provide immunity to a wide range of subjects ranging from new born to adults who may require different level of protection [80]. Absence of an animal model for GBS prevents us from exploring neurological effects and immune responses [81]. Though these complexities mar the enthusiasm for vaccine development, success of vaccines against other *Flaviviruses* like Yellow fever and Japanese encephalitis virus raises hopes. Still, there is a light at the end of tunnel as many vaccine candidates are in preclinical development stage and different phases of clinical trials [82]. DNA and RNA vaccines for Zika have generated a great deal of interest owing to the advantages over conventional vaccines as they: eliminate the risk of exposure; do not require chemicals, preservatives or adjuvants; and do not require refrigeration. But the method of delivery poses a problem due to the cost factor and scaling up. Inovio's DNA-based Zika vaccine GLS-5700 containing a single plasmid coding for the prME antigen has entered Phase II trials following 100% success rate in Phase I trial [83]. After being granted Fast Track designation by the US FDA, purified, inactivated, alum-adjuvanted, whole ZIKV vaccine candidate TAK-426 from Japanese Company Takeda has entered Phase I trial (ZIK-101) under a US Investigational New Drug application [84]. Two other nucleic-acid-based vaccines that have entered Phase II trials are mRNA-1325(mRNA-based) developed by Moderna Therapeutics and VRC-ZKADNA090-00-VP (DNA-based) developed by NIAID [85,86]. Many vaccine candidates from various platforms like peptide, recombinant viral vaccine, DNA, mRNA, inactivated whole target organism sponsored by industry, government and academia are in different stages of clinical trials according to WHO Vaccine Pipeline Tracker [87]. With the uncertainty about market demand of ZIKV in wake of sharp decline in Zika cases, it is to be seen that how many of these vaccines see daylight.

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Race for antivirals

Sudden outbreak of Zika spurred many studies and a maddening rush for discovering potent drugs and lead compounds against ZIKV. Sofosuvir [88], 7-deaza-2′-*C*-methyladenosine [89], NITD008 [90], favipiravir and ribavirin [91], T-1105 [92], 2′-C-methylcytidine [88], nanchangmycin [93], BCX4430 [94], obatoclax, saliphenylhalamide and gemcitabine [95], nordihydroguaiaretic acid, tetramethyl nordihydroguaiaretic acid [96], PHA-690509 and emricasan [97] are some of the compounds that have shown promising results against ZIKV. The accelerated pace of drug discovery for combating Zika has brought drug repurposing at the forefront and broad-spectrum antiviral compounds are being explored for their efficacy against ZIKV. Some of the attractive drug targets for Zika are envelope glycoprotein, proteases NS2B3 and NS3, NS3 helicase, NS5 methyltransferase, NS5 RNA-dependent RNA polymerase. A quick way to boost the drug discovery pace will be testing existing approved drugs and use of *in silico* methods.

Alternative medicines for ZIKV

Studies exploring the efficacy of herbal drugs and formulations against ZIKV have shown promising results. It is proposed that many bioactive compounds from *Azadirachta indica* and *Tinospora cordifolia* showing broad-spectrum antiviral activities can be used against ZIKV [98–100]. Utility of homeopathic medicines and ayurvedic prescriptions in ZIKV has been recently reviewed [100]. Some of the natural compounds showing anti-ZIKV activity are listed in Table 1.

Money matters: economic burden of Zika

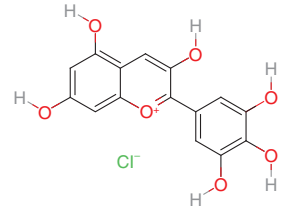
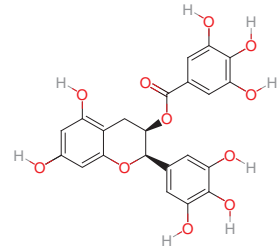
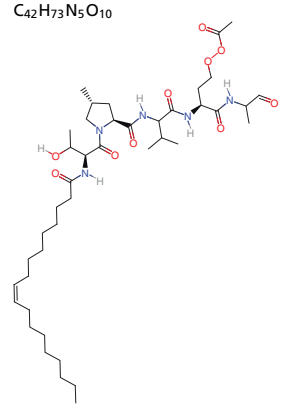
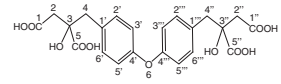
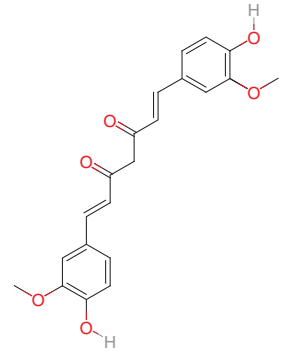
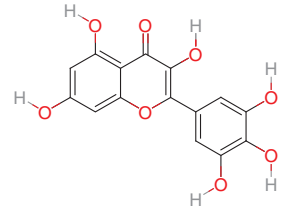
Like any other mosquito-borne disease, it is difficult to estimate the economic burden of ZIKV. Being a new disease, not much information about productivity loss, disease avoidance and treatment costs in the literature is available for ZIKV. Several studies focused on quantifying the economic burden of ZIKV [110]. Lee *et al.* developed a computational model for predicting the potential economic burden of ZIKV across six states in the USA at varying attack rates [111]. An important measure of indirect cost incurred due to a disease, disability-adjusted life years (DALYs) were calculated for ZIKV for the first time in 2016. All-age DALYs (in thousands) and age-standardized DALY (per 1,000,000) rates were reported to be 5.1 and 0.1, respectively [112]. The impact of ZIKV was illustrated by striking figures that showed loss of 29.95 DALYs and medical expenditure amounting to $91,102 per lifetime by microcephaly and 1.25 DALYs per case and direct treatment cost of $28,818 per case due to GBD [113]. It is imperative to find the cost–effectiveness of intervention measures to curb ZIKV with losses incurred both in terms of DALYs and out of pocket cost. Another study predicted that increased access to contraceptive measures could lower the ZIKV cost by $65.2 million in Puerto Rico during a ZIKV epidemic [114]. There is a huge gap between estimated ZIKV-related losses and funds raised for curbing Zika. Encounter with ZIKV means a lifetime care for the affected newborns leading to staggering social and economic costs for the family. The projected amount of ZIKV-related economic losses in Latin America is $3·5 billion by World Bank does not even include loss of life or severe impairment. Massive economic downturn in affected countries is expected to be observed not only because of plummeting productivity but also reduced trade and tourism. Escalating medical costs for providing lifelong healthcare and support systems to the newborns may push the families further into vicious cycle of poverty. It is to be seen that how far the sum of US$150 million sanctioned by World Bank for ZIKV-affected countries will meet the need when the projected burden is estimated to be US$3.5 billions [115].

ZIKV resources on web

Various resources touching different aspects related to genomics, proteomics and transmission dynamics of ZIKV are freely available for public, clinicians, researchers and policy makers to understand it better (Table 2). Whole new database on ZIKV (www.ncbi.nlm.nih.gov/genomes/VirusVariation/Database/nph-select.cgi?taxid=64320) has been added to National Center for Biotechnology Information (NCBI) virus variation database with useful searchable options. Virus pathogen Resource has also provided a platform for cataloging, searching and sharing information on various aspects of ZIKV (www.fludb.org/brc/home.spg?decorator=flavi_zika). Links to relevant literature related to ZIKV sorted by publishers and type are available at ZIKV home at CDC (www.cdc.gov/zika/resources/index.html).

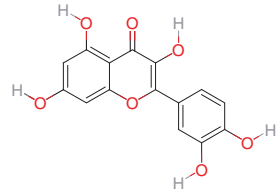
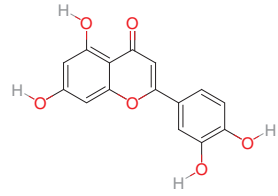
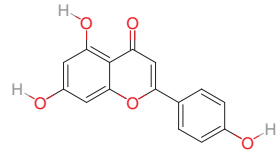
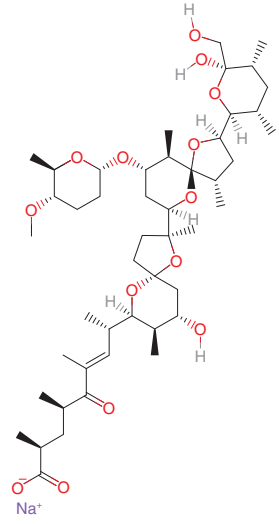
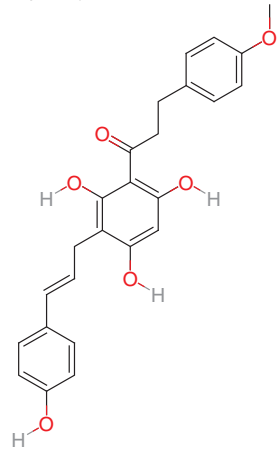
Global concerted efforts are mandatory for addressing the problem of infectious diseases as diseases transcend borders. Global warming, fast paced travel and trade aggravated the fast spread of the disease and bring forth the problem of quarantine for checking the epidemic within a specific geographical region. As the needs and capacities

Table 1. Natural compounds active against Zika virus.

Compound	Class	Source	Molecular formula and structure	Ref.
Delphinidin	Polyphenol	Berries, red grapes, purple sweet potatoes, red cabbages and other pigmented foods, plants and vegetables	$C_{15}H_{11}ClO_7$ 	[101]
EGCG	Polyphenol	Green tea	$C_{22}H_{18}O_{11}$ 	[102]
Cavinafungin	Cyclic depsilipopeptide	*Colispora cavincola*	$C_{42}H_{73}N_5O_{10}$ 	[103]
Crispoic acid		*Leila marinate*	$C_{22}H_{22}O_{11}$ 	[104]
Curcumin	Phytopolylphenol	*Curcuma longa*	$C_{21}H_{20}O_6$ 	[105,106]
Myricetin	Flavonoid	Grapes, berries, fruits, vegetables, herbs, as well as other plants	$C_{15}H_{10}O_8$ 	[106]

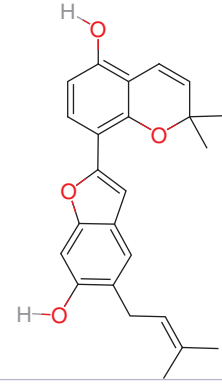
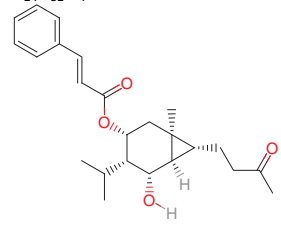
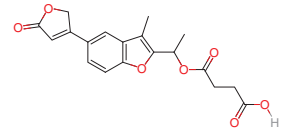
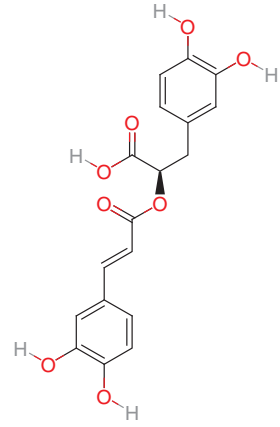
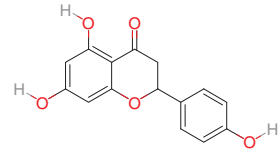
EGCG: Epigallocatechingallate.

Table 1. Natural compounds active against Zika virus (cont.).

Compound	Class	Source	Molecular formula and structure	Ref.
Quercetin	Flavonoid	Grapes, citrus fruit, tomato, broccoli and other leafy green vegetables and many berries	$C_{15}H_{10}O_7$ 	[106,107]
Luteolin	Flavonoid	Flowering plants	$C_{15}H_{10}O_6$ 	[106]
Apigenin	Flavonoid	German chamomile (*Matricaria recutita*) and Roman or English chamomile (*Chamaemelum nobile*)	$C_{15}H_{10}O_5$ 	[106]
Nanchangmycin	Polyether	*Streptomyces nanchangensis* NS3226	$C_{47}H_{77}NaO_{14}$ 	[93]
Balsacone B	Chalcones	*Populus balsamifera*	$C_{25}H_{24}O_6$ 	[108]

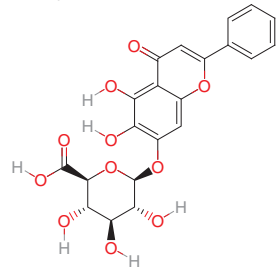
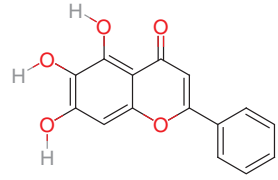
EGCG: Epigallocatechingallate.

Table 1. Natural compounds active against Zika virus (cont.).

Compound	Class	Source	Molecular formula and structure	Ref.
Kanzonol	Benzopyrans	*Glycyrrhiza glabra*	$C_{24}H_{24}O_4$ 	[108]
Cinnamoylechinaxanthol	Sesquiterpenoids	*Echinacea*	$C_{24}H_{32}O_4$ 	[108]
Cimiphenol	Phenolics	*Actaea racemosa*	$C_{19}H_{18}O_7$ 	[108]
Rosmarinic acid	Coumaric acids and derivatives	*Rosmarinus officinalis*	$C_{18}H_{16}O_8$ 	[108]
Naringenin	Flavanone, a type of flavonoid	Grapefruit, many herbs and fruits	$C_{15}H_{12}O_5$ 	[109]

EGCG: Epigallocatechingallate.

Table 1. Natural compounds active against Zika virus (cont.).

Compound	Class	Source	Molecular formula and structure	Ref.
Baicalin	Flavone glycoside	Roots of *Scutellaria baicalensis* and *Scutellaria lateriflora*, bark of *Oroxylum indicum*	$C_{21}H_{18}O_{11}$ 	[109]
Baicalein	Flavone	Roots of *Scutellaria baicalensis* and *Scutellaria lateriflora*	$C_{15}H_{10}O_5$ 	[109]

EGCG: Epigallocatechingallate.

Table 2. Important resources for Zika virus.

Database	URL	Type of information		Ref.
Zukav	http://bioinfo.imtech.res.in/manojk/zikavr/	Information on whole genome sequences, proteins, genes and structural content, whole-genome alignments, conservation and variation, Cog islands, cordon context, usage bias and phylogenetic inferences, glycosylation sites, molecular diagnostic primers, vaccine epitopes, siRNAs, miRNAs, sgRNAs and repurposing drug candidates		[116]
ZikaBase	http://test5.bicpu.edu.in	Information on genes involved in ZIKV infection obtained from literature, DEGs identified through the analysis of transcriptome data for ZIKV-infected human brain sample and direct and associated genes between ZIKV and human as protein–protein interaction network		[117]
ZIKV-CDB	http://zikadb.cpqrr.fiocruz.br	miRNAs predicted for all complete ZIKV genomes		[118]
Zika Research Projects List	www.paho.org/zika-research/	Information on all scientific studies on ZIKV worldwide	PAHO/WHO	
Zika Virus Resource Center	www.ama-assn.org/delivering-care/zika-virus-resource-center	A general comprehensive resource for public, physicians and researchers	American Medical Association	
ZiBRA	http://zibraproject.github.io	Sequencing data, protocols and materials	Zika Real-time Sequencing Consortium	
CIDMA	http://zika.cidma.us/	Tool for identifying the cost effectiveness of policies and intervention measures on Zika control		[113]

CDB: Collaborative Database; CIDMA: Center for Research & Development in Mathematics and Applications; DEG: Differentially expressed genes; PAHO: The Pan American Health Organization; ZiBRA: Zika in Brazil real-time analysis; ZIKV: Zika virus.

of different nations for curbing an outbreak vary based on their respective geographical social, political, economic condition and policies, the global efforts in response to ZIKV need to be strengthened.

The fundamental question is, whether we are ready to face any emergency situation after all these research efforts? The ultimate goal of research and development is to search out some plausible solution to the present problem as well as finding some possible preventive measures for the future outbreaks. Every time a new pathogen attacks, our lack of preparedness costs us several lives. In several practical situations, it was observed that apart from lack of awareness and resources; cost remained an important barrier for immediate quarantine and response. Moreover, the initial symptoms of the infection are often similar to other general infections which often result in delays or neglect in seeking the treatment and underreporting. Similar concern is recently reported in developed countries such as the USA [16].

Conclusion & future perspective

Time and again, emergence of new pathogens and subsequent epidemics have taken a toll on mankind. Continuous endeavors in scientific research have led to innovative solutions that made victory marches against deadly diseases and pathogens possible. We cannot afford to live continuously in fear of another outbreak. ZIKV posed new challenges in terms of complexity, impact on long-term effects on life; hence, we need to notch up our efforts to confront it. It is imperative to predict the outbreaks by strengthening the forecasting systems, develop new mathematical models including impact of different routes of transmission and fueling the drug pipelines that can be eventually exploited in event of such outbreak. Combinatorial approaches using *in silico* methods, drug repurposing and repositioning and high-throughput screening methods can aid in finding effective therapeutics

Executive summary

Zika virus is an emerging pathogen

- Emergence of Zika virus (ZIKV) and its spread to new territories outside its known geographical range has raised an alarm.
- ZIKV is associated with microcephaly and neurological sequelae and responsible for congenital Zika syndrome in newborns and infants.
- There is no specific drug available for ZIKV infection and only symptomatic relief can be provided.
- No vaccine against ZIKV infection is available to provide protection against the disease.
- Several vaccine candidates have entered different phases of clinical trials.
- Effective and safe therapeutic agents and vaccines are urgently required.

New routes of ZIKV transmission & new challenges

- ZIKV is the first mosquito-borne virus with sexual transmission route.
- ZIKV can also be transmitted through blood transfusion and from mother to child.
- Persistence of ZIKV in semen for extended period of time warrants the need for detection of Zika in other body fluids.

ZIKV & pregnancy outcomes

- ZIKV has emerged as a new TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus and herpes simplex) agent.
- Being the first mosquito-borne virus known to cause congenital malformations and neurological disorders, ZIKV has raised several ethical concerns.
- Women in the reproductive age bracket in countries with active ZIKV transmission should be provided free access to medical advice and contraceptive measures.
- Pregnant women and new mothers should have access to support system for diagnosis, counseling and care.

Forecasting ZIKV & digital technology can help in winning the battle against Zika

- Accurate mathematical models and early warning forecast systems for ZIKV outbreak can help in devising effective and timely strategies for adopting suitable intervention measures and channelizing resources and funds on priority basis to vulnerable regions.
- Harnessing of big data originating from social media, online trends and other digital platforms can provide insight about knowledge, attitude and practices of public about ZIKV.
- Digital platforms and mobile technology can effectively complement the conventional programs in dissemination of knowledge and increasing public awareness for societal participation.

Controversy over vectors & vector control

- ZIKV is mainly transmitted by mosquito vector *Aedes aegypti*.
- *Culex* mosquitoes cannot be considered ZIKV vectors.
- More competence studies are needed to identify potential ZIKV vectors.
- Integrated vector management should be adopted.

Natural products

- Herbal medicines and natural products can be exploited for ZIKV infection.
- Bioactive compounds from natural plant sources can also be used for vector control or avoidance.

Future perspective

- There is a need to explore combinatorial approaches using *in silico* methods, drug repurposing/repositioning and high-throughput screening methods for accelerating our efforts for developing new chemotherapeutic agents and vaccines.
- Economic equality, knowledge and awareness about the role of hygiene in environmental management and disease prevention and access to healthcare can go a long way in avoiding such outbreaks in the future.
- Recent outbreak of ZIKV after several other outbreaks of Dengue, Chikungunya warrants the need for invigorating our preparedness for other flaviviruses pandemics in wake of conducive settings, wide geographical range of vector mosquitoes and climatic conditions.

10.2217/fvl-2018-0040

measures for ZIKV. Recent retreat of ZIKV virus globally may extinguish the new-found interest in search for ZIKV therapeutics in academia and industry but we need to continuously and relentlessly search for long-term solutions instead of looking for momentary gains. Apart from the well-known route of ZIKV transmission by mosquito, we need to focus on other modes of transmission also as we lack a knowledge base or reference from the past. We need to prioritize our research plans and strategize for harnessing the knowledge acquired after this ZIKV outbreak to prevent any such outbreak in the future. Time has come for policy makers, researchers, medical practitioners, funding agencies and pharma majors in both public and private sectors to join hands for finding solutions for ZIKV.

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References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Dick GW, Kitchen SF, Haddow AJ. Zika virus. I. Isolations and serological specificity. *Trans. R. Soc. Trop. Med. Hyg.* 46, 509–520 (1952).
2. Haddow AD, Schuh AJ, Yasuda CY *et al.* Genetic characterization of Zika virus strains: geographic expansion of the Asian lineage. *PLoS Negl. Trop. Dis.* 6(2), e1477 (2012).
3. CDC. Zika virus. US Department of Health and Human Services, CDC, Atlanta, GA, USA (2016). http://www.cdc.gov/zika/index.html.
4. Duffy MR, Chen TH, Hancock WT *et al.* Zika virus outbreak on Yap Island, Federated States of Micronesia. *N. Engl. J. Med.* 360, 2536–2543 (2009).
5. Butler D. Zika virus: Brazil's surge in small-headed babies questioned by report. *Nature* 530, 13–14 (2016).
6. WHO. WHO Director-General summarizes the outcome of the Emergency Committee regarding clusters of microcephaly and Guillain–Barré syndrome. http://www.who.int/mediacentre/news/statements/2016/emergency-committee-zika-microcephaly/en/
7. Arora N, Banerjee AK, Narasu ML. Zika virus: an emerging arboviral disease. *Future Virol.* 11(6), 395–399 (2016).
8 . WHO. Zika virus research agenda. (2016). http://origin.who.int/reproductivehealth/zika/zika-virus-research-agenda/en/
9. Kitson A, Straus SE. The knowledge-to-action cycle: identifying the gaps. *CMAJ* 182(2), E73–E77 (2010).
10. Freedman LP. Implementation and aspiration gaps: whose view counts? *Lancet* 388(10056), 2068–2069 (2016).
11. Delaunay S, Kahn P, Tatay M, Liu J. Knowledge sharing during public health emergencies: from global call to effective implementation. *Bull. World Health Organ.* 94(4), 236–236A (2016).
12. Garcia Serpa Osorio-de-Castro C, Silva Miranda E, Machado de Freitas C, Rochel de Camargo Jr K, Cranmer HH. The Zika virus outbreak in Brazil: knowledge gaps and challenges for risk reduction. *Am. J. Public Health* 107(6), 960–965 (2017).
13. Kapogiannis BG, Chakhtoura N, Hazra R, Spong CY. Bridging knowledge gaps to understand how Zika virus exposure and infection affect child development. *JAMA Pediatr.* 171(5), 478–485 (2017).

• **An excellent article that describes the issue of child care in relation to Zika virus (ZIKV) infection and emphasizes on the significance of monitoring the development trajectory of the ZIKV affected children, especially those who do not show any symptoms at birth.**

14. Tambo E, Khayeka-Wandabwa C, Oluwasogo OA, Adedeji AA, Ngogang JY, Khater EI. Addressing knowledge gaps in molecular, sero-surveillance and monitoring approaches on Zika epidemics and other arbovirus co-infections: a structured review. *Parasite Epidemiol. Control.* 2(2), 50–60 (2017).
15. Erbelding E, Cassetti C. Zika virus and future research directions. *J. Infect. Dis.* 216(Suppl. 10), S991–S994 (2017).
16. Morain SR, Wootton SH, Eppes C. A devastating delay-Zika and the implementation gap. *N. Engl. J. Med.* 377(16), 1505–1507 (2017).
17. Lloyd AM, Farooq M, Estep AS, Xue RD, Kline DL. Evaluation of pyriproxyfen dissemination via *Aedes albopictus* from a point-source larvicide application in northeast Florida. *J. Am. Mosq. Control Assoc.* 33(2), 151–155 (2017).
18. Priye A, Bird SW, Light YK, Ball CS, Negrete OA, Meagher RJ. A smart phone-based diagnostic platform for rapid detection of Zika, Chikungunya, and Dengue viruses. *Sci. Rep.* 7, 44778 (2017).

19. Kelvin AA, Banner D, Pamplona L, Alencar C, Rubino S, Heukelbach J. ZIKATracker: a mobile app for reporting cases of ZIKV worldwide. *J. Infect. Dev. Ctries.* 10, 113–115 (2016).
20. Tambo E, Kazienga A, Talla M, Chengho CF, Fotsing C. Digital technology and mobile applications impact on Zika and Ebola epidemics data sharing and emergency response. *J. Health Med. Informat.* 8, 254 (2017).
21. Kindhauser MK, Allen T, Frank V, Santhana RS, Dye C. Zika: the origin and spread of a mosquito-borne virus. *Bull. World Health Organ.* 94(9), 675–686 (2016).
22 . De Araújo TVB, Rodrigues LC, de Alencar Ximenes RA *et al.* Association between Zika virus infection and microcephaly in Brazil, January to May, 2016: preliminary report of a case–control study. *Lancet Infect. Dis.* 16, 1356–1363 (2016).
23 . Coyne CB, Lazear HM. Zika virus – reigniting the TORCH. *Nat. Rev. Microbiol.* (11), 707–715 (2016).
24. Mehrjardi MZ. Is Zika virus an emerging TORCH agent? An invited commentary. *Virology (Auckl.)* 8, 1178122X17708993 (2017).
•• **Discusses the importance of inclusion of ZIKV as another TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus and herpes simplex) agent along with Toxoplasmosis, other agents, rubella, cytomegalovirus and herpes simplex for screening infections in newborns.**
25. Moore CA, Staples JE, Dobyns WB *et al.* Congenital Zika syndrome: characterizing the pattern of anomalies for pediatric healthcare providers. *JAMA Pediatr.* 171(3), 288–295 (2017).
26. Cauchemez S, Besnard M, Bompard P *et al.* Association between Zika virus and microcephaly in French Polynesia 2013-15: a retrospective study. *Lancet* 387, 2125–2132 (2016).
27. McGough SF, Brownstein JS, Hawkins JB, Santillana M. Forecasting Zika Incidence in the 2016 Latin America outbreak combining traditional disease surveillance with search, social media, and news report data. Althouse B (Ed.). *PLoS Negl. Trop. Dis.* 11(1), e0005295 (2017).
28. Brownstein JS, Freifeld CC, Reis BY, Mandl KD. Surveillance sans frontières: internet-based emerging infectious disease intelligence and the HealthMap project. *PLoS Med.* 5, e151 (2008).
29. Pollett S, Althouse BM, Forshey B, Rutherford GW, Jarman RG. Internet-based biosurveillance methods for vector-borne diseases: are they novel public health tools or just novelties? Reiner RC (Ed.). *PLoS Negl. Trop. Dis.* 11(11), e0005871 (2017).
30. Gluskin RT, Johansson MA, Santillana M, Brownstein JS. Evaluation of Internet-based dengue query data: Google dengue trends. *PLoS Negl. Trop. Dis.* 8, e2713 (2014).
31. Yang S, Santillana M, Kou SC. Accurate estimation of influenza epidemics using Google search data via ARGO. *Proc. Natl Acad. Sci. USA* 112(47), 14473–14478 (2015).
32. Teng Y, Bi D, Xie G *et al.* Dynamic forecasting of Zika epidemics using Google trends. *PLoS ONE* 12(1), e0165085 (2017).
33. Majumder MS, Santillana M, Mekaru SR, McGinnis DP, Khan K, Brownstein JS. Utilizing nontraditional data sources for near real-time estimation of transmission dynamics during the 2015 ± 2016 Colombian Zika virus disease outbreak. *JMIR Public Health Surveill.* 2, e30 (2016).
34. Manore CA, Ostfeld RS, Agusto FB, Gaff H, LaDeau SL. Defining the risk of Zika and Chikungunya virus transmission in human population centers of the eastern United States. *PLoS Negl. Trop. Dis.* 11(1), e0005255 (2017).
35. Muñoz ÁG, Thomson MC, Stewart-Ibarra AM *et al*. Could the recent Zika epidemic have been predicted? *Front. Microbiol.* 8, 1291 (2017).
36. Ferguson NM, Cucunubá ZM, Dorigatti I *et al.* Countering the Zika epidemic in Latin America. *Science* 353, 353–354 (2016).
37. Perkins TA. Retracing Zika's footsteps across the Americas with computational modeling. *Proc. Natl Acad. Sci. USA* 114, 5558–5560 (2017).
38. Lourenço J, Maia de Lima M, Faria NR *et al.* Epidemiological and ecological determinants of Zika virus transmission in an urban setting. *eLife* 6, e29820 (2017).
39 . Teng Y, Bi D, Xie G *et al*. Model-informed risk assessment for Zika virus outbreaks in the Asia–Pacific regions. *J. Infect.* 74(5), 484–491 (2017).
40. Nah K, Mizumoto K, Miyamatsu Y, Yasuda Y, Kinoshita R, Nishiura H. Estimating risks of importation and local transmission of Zika virus infection. Benelli G (Ed.). *Peer J.* 4, e1904 (2016).
41. Chowell G, Hincapie-Palacio D, Ospina J *et al.* Using phenomenological models to characterize transmissibility and forecast patterns and final burden of Zika epidemics. *PLoS Curr.* 8, pii: ecurrents.outbreaks.f14b2217c902f453d9320a43a35b9583 (2016).
42. Hsieh Y-H. Temporal patterns and geographic heterogeneity of Zika virus (ZIKV) outbreaks in French Polynesia and Central America. *Peer J.* 5, e3015 (2017).
43. Dinh L, Chowell G, Mizumoto K, Nishiura H. Estimating the subcritical transmissibility of the Zika outbreak in the State of Florida, USA, 2016. *Theor. Biol. Med. Model* 13, 20 (2016).
44. Messina JP, Kraemer MU, Brady OJ *et al.* Mapping global environmental suitability for Zika virus. *eLife* 5, e15272 (2016).
45. Warren DL, Seifert SN. Ecological niche modeling in maxent: the importance of model complexity and the performance of model selection criteria. *Ecol. Appl.* 21, 335–342 (2011).

46. Samy AM, Thomas SM, Wahed AAE, Cohoon KP, Peterson AT. Mapping the global geographic potential of Zika virus spread. *Mem. Inst. Oswaldo Cruz.* 111(9), 559–560 (2016).

47. Bogoch II, Brady OJ, Kraemer MUG *et al.* Potential for Zika virus introduction and transmission in resource-limited countries in Africa and the Asia–Pacific region: a modelling study. *Lancet Infect. Dis.* 16, 1237–1245 (2016).

48. Castro LA, Fox SJ, Chen X, Liu K, Bellan SE, Dimitrov NB. Assessing real-time Zika risk in the United States. *BMC Infect. Dis.* 17, 284 (2017).

49. Carlson CJ, Dougherty E, Boots M, Getz W, Ryan SJ. Consensus and conflict among ecological forecasts of Zika virus outbreaks in the United States. *Sci. Rep.* 8, 4921 (2018).

- **It claims high importance as it suggests a way of considering consensus stochastic values to resolve the issue of ecological predictions of Zika infections in the USA.**

50. Evans MV, Dallas TA, Han BA, Murdock CC, Drake JM. Data-driven identification of potential Zika virus vectors. *eLife* 6, e22053 (2017).

51. Perkins TA, Siraj AS, Ruktanonchai CW, Kraemer MU, Tatem AJ. Model-based projections of Zika virus infections in childbearing women in the Americas. *Nat. Microbiol.* 1(9), 16126 (2016).

52. Kucharski AJ, Funk S, Eggo RM, Mallet H-P, Edmunds WJ, Nilles EJ. Transmission dynamics of Zika virus in island populations: a modelling analysis of the 2013–14 French polynesia outbreak. Barker CM (Ed.). *PLoS Negl. Trop. Dis.* 10(5), e0004726 (2016).

53. Agusto FB, Bewick S, Fagan WF. Mathematical model for Zika virus dynamics with sexual transmission route. *Ecol. Complex.* 29, 61–81 (2017).

54. Dantas E, Tosin M, Cunha A. Zika virus in Brazil: calibration of an epidemic model for 2016 outbreak. *Proceeding Series of the Brazilian Society of Computational and Applied Mathematics*. SP, Brazil, September 2017.

55. Wiratsudakul A, Suparit P, Modchang C. Dynamics of Zika virus outbreaks: an overview of mathematical modeling approaches. *Peer J.* e4526 (2018).

56. Guedes DR, Paiva MH, Donato MM *et al.* Zika virus replication in the mosquito *Culex quinquefasciatus* in Brazil. *Emerg. Microbes Infect.* 6(8), e69 (2017).

57. Epelboin Y, Talaga S, Epelboin L, Dusfour I. Zika virus: an updated review of competent or naturally infected mosquitoes. Ebel GD (Ed.). *PLoS Negl. Trop. Dis.* 11(11), e0005933 (2017).

58. Diallo D, Sall AA, Diagne CT *et al.* Zika virus emergence in mosquitoes in southeastern Senegal, 2011. *PLoS ONE* 9(10), e109442 (2014).

59. Vorou R. Zika virus, vectors, reservoirs, amplifying hosts, and their potential to spread worldwide: what we know and what we should investigate urgently. *Int. J. Infect. Dis.* 48, 85–90 (2016).

60. Guo XX, Li CX, Deng YQ *et al. Culex pipiens quinquefasciatus*: a potential vector to transmit Zika virus. *Emerg. Microbes Infect.* 5, e102 (2016).

61. Fernandes RS, Campos SS, Ferreira-de-Brito A *et al.* Culex quinquefasciatus from Rio de Janeiro is not competent to transmit the local Zika virus. *PLoS Negl. Trop. Dis.* 10, e0004993 (2016).

62. Liu Z, Zhou T, Lai Z *et al.* Competence of *Aedes aegypti*, *Ae. albopictus*, and *Culex quinquefasciatus* mosquitoes as Zika virus vectors, China. *Emerg. Infect. Dis.* 23, 1085–1091 (2017).

63. Weger-Lucarelli J, Rückert C, Chotiwan N *et al.* Vector competence of American mosquitoes for three strains of Zika virus. *PLoS Negl. Trop. Dis.* 10, e0005101 (2016).

64. Boccolini D, Toma L, Di Luca M *et al.* Experimental investigation of the susceptibility of Italian *Culex pipiens* mosquitoes to Zika virus infection. *Euro. Surveill.* 21, 1–3 (2016).

65. Aliota MT, Peinado SA, Osorio JE, Bartholomay LC. *Culex pipiens* and *Aedes triseriatus* mosquito susceptibility to Zika virus. *Emerg. Infect. Dis.* 22, 1857–1859 (2016).

66. Kenney JL, Romo H, Duggal NK *et al.* Transmission incompetence of *Culex quinquefasciatus* and *Culex pipiens pipiens* from North America for Zika Virus. *Am. J. Trop. Med. Hyg.* 96, 1235–1240 (2017).

67. Lourenço-de-Oliveira R, Marques JT, Sreenu VB *et al. Culex quinquefasciatus* mosquitoes do not support replication of Zika virus. *J. Gen. Virol.* 99(2), 258–264 (2018).

68. Waddell LA, Greig JD. Scoping review of the Zika virus literature. *PLoS ONE* 11(5), e0156376 (2016).

- **An excellent review that captures the essence of 233 studies and identifies existing knowledge gaps in Zika research.**

69. Singh RK, Dhama K, Khandia R *et al*. Prevention and control strategies to counter Zika virus, a special focus on intervention approaches against vector mosquitoes-current updates. *Front Microbiol.* 9, 87 (2018).

70. Althaus CL, Nicola LO. How relevant is sexual transmission of Zika virus? *PLoS Med.* 13(10), e1002157 (2016).

- **Discusses the importance of increasing awareness about sexual route of ZIKV transmission.**

71. Maxian O, Neufeld A, Talis EJ, Childs LM, Blackwood JC. Zika virus dynamics: when does sexual transmission matter? *Epidemics* 21, 48–55 (2017).

72. Mansuy JM, Suberbielle E, Chapuy-Regaud S *et al*. Zika virus in semen and spermatozoa. *Lancet Infect. Dis.* 16(10), 1106–1107 (2016).

73. Murray KO, Gorchakov R, Carlson AR *et al*. Prolonged detection of Zika virus in vaginal secretions and whole blood. *Emerg. Infect. Dis.* 23(1), 99–101 (2017).

74. Musso D, Roche C, Nhan TX, Robin E, Teissier A, Cao-Lormeau VM. Detection of Zika virus in saliva. *J. Clin. Virol.* 68, 53–55 (2015).

75. Gourinat AC, O'Connor O, Calvez E, Goarant C, Dupont-Rouzeyrol M. Detection of Zika virus in urine. *Emerg. Infect. Dis.* 21(1), 84–86 (2015).

76. Sotelo JR, Sotelo AB, Sotelo FJB *et al.* Persistence of Zika virus in breast milk after infection in late stage of pregnancy. *Emerg. Infect. Dis.* 23(5), 854–856 (2017).

77. Shah SK, Kimmelman J, Lyerly AD *et al*. Ethical considerations for zika virus human challenge trials: report and recommendations. (2017). https://www.niaid.nih.gov/sites/default/files/EthicsZikaHumanChallengeStudiesReport2017.pdf

78. Lathrop E, Romero L, Hurst S *et al*. The Zika contraception access network: a feasibility programme to increase access to contraception in Puerto Rico during the 2016-17 Zika virus outbreak. *Lancet Public Health* 3(2), e91–e99 (2018)

79. Basu R, Tumban E. Zika virus on a spreading spree: what we now know that was unknown in the 1950's. *Virol. J.* 13(1), 165 (2016).

80. Poland GA, Kennedy RB, Ovsyannikova IG, Palacios R, Ho PL, Kalil J. Development of vaccines against Zika virus. *Lancet Infect. Dis.* S1473–S3099(18), 30063-X (2018).

•• **This up-to-date review gives a detailed account of vaccine development efforts for Zika virus and research gaps and challenges in the development of candidate vaccines.**

81. Thomas SJ, L'Azou M, Jackson NAC. Fast-track Zika vaccine development: is it possible? *N. Engl. J. Med.* 375, 1212–1216 (2016).

82. Blackman MA, Kim IJ, Lin JS, Thomas SJ. Challenges of vaccine development for Zika virus. *Viral Immunol.* 31(2), 117–123 (2017).

83. Muthumani K, Griffin BD, Agarwal S *et al. In vivo* protection against ZIKV infection and pathogenesis through passive antibody transfer and active immunisation with a prM Env DNA vaccine. *NPJ Vaccines* 16021 (2016)

84 . Asian Scientist. Takeda's Zika vaccine moves into the fast lane read more from Asian Scientist Magazine. www.asianscientist.com/2018/02/pharma/takeda-zika-vaccine-fast-track

85. National Institute of Allergy and Infectious Diseases. Safety and immunogenicity of a Zika virus DNA vaccine, VRC-ZKADNA085-00-VP, in healthy adults. NLM identifier: NCT02840487; https://clinicaltrials.gov/ct2/show/NCT02840487

86. Moderna Therapeutics, Biomedical Advanced Research and Development Authority. Safety, tolerability, and immunogenicity of mRNA-1325 in healthy adult subjects. NLM identifier: NCT03014089; https://clinicaltrials.gov/ct2/show/NCT03014089

87 . WHO vaccine pipeline. www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/

88. Bullard-Feibelman KM, Govero J, Zhu Z *et al.* The FDA-approved Drug Sofosbuvir Inhibits Zika Virus Infection. *Antiviral Res.* 137, 134–140 (2017).

89. Zmurko J, Marques RE, Schols D, Verbeken E, Kaptein SJF, Neyts J. The viral polymerase inhibitor 7-deaza-2'-*C*-methyladenosine is a potent inhibitor of *in vitro* Zika virus replication and delays disease progression in a robust mouse infection model. *PLoS Negl. Trop. Dis.* 10(5), e0004695 (2016).

90 . Deng YQ, Zhang NN, Li CF *et al.* Adenosine analog NITD008 is a potent inhibitor of Zika virus. *Open Forum Infect. Dis.* 3(4), ofw175 (2016).

91. Kim JA, Seong RK, Kumar M, Shin OS. Favipiravir and ribavirin inhibit replication of Asian and African strains of Zika virus in different cell models. *Viruses* 10(2), p ii, E72 (2018).

92. Cai L, Sun Y, Song Y *et al*. Viral polymerase inhibitors T-705 and T-1105 are potential inhibitors of Zika virus replication. *Arch. Virol.* 162(9), 2847–2853 (2017).

93. Rausch K, Hackett B, Weinbren N *et al.* Screening bioactives reveals nanchangmycin as a broad spectrum antiviral active against Zika virus. *Cell Rep.* 18(3), 804–815 (2017).

94. Julander JG, Siddharthan V, Evans J *et al*. Efficacy of the broad-spectrum antiviral compound BCX4430 against Zika virus in cell culture and in a mouse model. *Antiviral Res.* 137, 14–22 (2017).

95. Kuivanen S, Bespalov MM, Nandania J *et al*. Obatoclax, saliphenylhalamide and gemcitabine inhibit Zika virus infection *in vitro* and differentially affect cellular signaling, transcription and metabolism. *Antiviral Res.* 139, 117–128 (2017).

96. Merino-Ramos T, Jiménez de Oya N, Saiz J-C, Martín-Acebes MA. Antiviral activity of nordihydroguaiaretic acid and its derivative tetra-o-methyl nordihydroguaiaretic acid against west Nile virus and Zika virus. *Antimicrob. Agents Chemother.* 61(8), e00376–e00417 (2017.)

97. Xu M, Lee EM, Wen Z *et al*. Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen. *Nat. Med.* 22(10), 1101–1107 (2016).

98. Munjal A, Khandia R, Dhama K *et al*. Advances in developing therapies to combat Zika virus: current knowledge and future perspectives. *Front. Microbiol.* 8, 1469 (2017).

•• **Provides glimpse of progress, knowledge gaps and lacunae in ZIKV research.**

99. Parida MM, Upadhyay C, Pandya G, Jana AM. Inhibitory potential of neem (Azadirachta indica Juss) leaves on dengue virus type 2 replication. *J .Ethnopharmacol.* 79, 273–278 (2002).

100. Saxena SK, Elahi A, Gadugu S, Prasad AK. Zika virus outbreak: an overview of the experimental therapeutics and treatment. *Virusdisease* 27(2), 111–115 (2016).

101. Vázquez-Calvo Á, Jiménez de Oya N, Martín-Acebes MA, Garcia-Moruno E, Saiz JC. Antiviral properties of the natural polyphenols Delphinidin and Epigallocatechin Gallate against the flaviviruses west Nile virus, Zika virus, and Dengue virus. *Front. Microbiol.* 8, 1314 (2017).

102. Carneiro BM, Batista MN, Braga ACS, Nogueira ML, Rahal P. The green tea molecule EGCG inhibits Zika virus entry. *Virology* 496, 215–218 (2016).

103. Estoppey D, Lee CM, Janoschke M *et al*. The natural product Cavinafungin selectively interferes with Zika and Dengue virus replication by inhibition of the host signal peptidase. *Cell Rep.* 19(3), 451–460 (2017).

104. Belloto AC, Souza GK, Perin PC *et al*. Crispoic acid, a new compound from Laeliamarginata (*Orchidaceae*), and biological evaluations against parasites, human cancer cell lines and Zika virus. *Nat. Prod. Res.* 1–6 (2017) (Epub ahead of print).

105. Mounce BC, Cesaro T, Carrau L, Vallet T, Vignuzzi M. Curcumin inhibits Zika and chikungunya virus infection by inhibiting cell binding. *Antiviral Res.* 142, 148–157 (2017).

106. Roy A, Lim L, Srivastava S, Lu Y, Song J. Solution conformations of Zika NS2B-NS3pro and its inhibition by natural products from edible plants. *PLoS ONE* 12(7), e0180632 (2017).

107. Wong G, He S, Siragam V *et al*. Antiviral activity of quercetin-3-β-O-D-glucoside against Zika virus infection. *Virol. Sin.* 32(6), 545–547 (2017).

108. Byler KG, Ogungbe IV, Setzer WN. *In-silico* screening for anti-Zika virus phytochemicals. *J. Mol. Graph. Model.* 69, 78–91 (2016).

109. Suroengrit A, Yuttithamnon W, Srivarangkul P *et al*. Halogenated Chrysins inhibit Dengue and Zika virus infectivity. *Sci. Rep.* 7(1), 13696 (2017).

110. Macciocchi D, Lanini S, Vairo F *et al*. Short-term economic impact of the Zika virus outbreak. *New Microbiol.* 39(4), 287–289 (2016).

111. Lee BY, Alfaro-Murillo JA, Parpia AS *et al.* The potential economic burden of Zika in the continental United States. *PLoS Negl. Trop. Dis.* 11(4), e0005531 (2017).

112. GBD 2016. DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 390(10100), 1260–1344 (2017)

113 . Alfaro-Murillo JA, Parpia AS, Fitzpatrick MC *et al.* A cost–effectiveness tool for informing policies on Zika virus control. *PLoS Negl. Trop. Dis.* 10(5), e0004743 (2016).

•• **Describes an excellent method that can determine the viability and cost–benefit ratio of policies targeting Zika. This tool can help policy makers in devising appropriate strategies after evaluating their cost and effectiveness in tackling Zika.**

114. Li R, Simmons KB, Bertolli J *et al*. Cost–effectiveness of increasing access to contraception during the Zika virus outbreak, Puerto Rico, 2016. *Emerg. Infect. Dis.* 23(1), 74–82 (2017).

115. Durrani Z, Waheed Y, Durrani TZ. Zika virus, a pathway to new challenges. *Asian Pac. J. Trop. Med.* 9(7), 626–629 (2016).

116. Gupta AK, Kaur K, Rajput A *et al.* ZikaVR: an integrated Zika virus resource for genomics, proteomics, phylogenetic and therapeutic analysis. *Sci. Rep.* 6, 32713 (2016).

117. Gurumayum S, Brahma R, Naorem LD, Muthaiyan M, Gopal J, Venkatesan A. ZikaBase: an integrated ZIKV- Human Interactome Map database. *Virology* 514, 203–210 (2018).

118. Pylro VS, Oliveira FS, Morais DK *et al.* ZIKV-CDB: a collaborative database to guide research linking SncRNAs and ZIKA virus disease symptoms. *PLoS Negl. Trop. Dis.* 10(6), e0004817 (2016).