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THE RISE OF ZIKA VIRUS: A HISTORICAL ANALYSIS OF ITS EMERGENCE, SPREAD, AND GLOBAL HEALTH CHALLENGES

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1.Introduction

After the Zika virus was initially formally described in 1952, only a small number of specialized researchers were interested in it for the majority of the next 60 years. The WHO has declared a public health emergency of international concern for the Zika virus, which is currently generating headlines worldwide.2. This significant shift has been brought about by the Zika virus's growing global identification and correlation with progressively larger illness outbreaks. Prior to 2007, virological and immunological data indicated that, despite the Zika virus's widespread distribution in Africa and Asia, only 14 cases of Zika fever—13 from natural infections and one from a laboratory infection—were reported globally, making it a disease of little concern to humans Yap State, a region in the western Pacific Ocean that is a component of the Federated States of Micronesia, experienced the first significant Zika fever outbreak outside of Africa and Asia in 2007. 49 confirmed and 59 probable cases of Zika virus infection were found in this outbreak, compared to an estimated 440 000–1300 000 cases recorded in the most recent outbreak in Brazil. Awareness of this new mosquito-transmitted disease has increased due to the concerning scope of the current outbreak and the possibility of autochthonous spread of this virus in North America and other regions3, 4, 14. Yellow fever and chikungunya fever Additionally, the virus can spread from mother to child during pregnancy, through sexual contact, and through blood transfusions The incubation period for ZIKV normally lasts between three to fourteen days, according to research that is currently available and clinical findings. Global travel patterns, urbanization, and climate conditions all have an impact on the geographic expansion of these mosquitoes and, consequently, the virus. Particularly at risk are areas with tropical and subtropical climates, including portions of Africa, Southeast Asia, and Latin America. There is currently no authorized vaccine or particular therapy for the ZIKV that the general population can get as of 2024. This is because vector control is complicated, many infections are asymptomatic, and social and economic issues impact access to healthcare. Although they are uncommon, consequences from ZIKV infections can be serious and even fatal, but the majority are asymptomatic or moderate. However, depending on when the infection occurs during gestation, a woman who contracts it during pregnancy may experience a variety of serious negative consequences, making it a serious health risk for women of reproductive age. Congenital Zika syndrome (CZS), which includes a variety of abnormalities like microcephaly, parenchymal or cerebellar calcifications, ventriculomegaly, central nervous system (CNS) hypoplasia or atrophy, arthrogryposis, ophthalmic abnormalities, and low birthweight for gestational age, is significantly associated with infections during the first and second trimesters and is significantly associated with an increased risk of severe congenital defects in offspring. Research has indicated that the incidence of CZS in infants delivered to The percentage of pregnant women infected with ZIKV ranged from 5% to 14%. The virus's direct assault on the growing central nervous system is the main pathogenic mechanism of CZS, resulting in significant brain damage and anomalies in development. Long-term developmental delays, intellectual disabilities, and other health problems that put a strain on families and healthcare systems can result from these illnesses. Further aggravating the public health impact, ZIKV may also result in unfavorable pregnancy outcomes such miscarriage, abortion because of a serious congenital deformity, fetal death, and neonatal and post-neonatal fatalities.

1.1 ZIKV's epidemiology and history

ZIKV is a member of the Flaviviridae family and is transmitted by the Aedes genus. Japanese encephalitis viruses, dengue viruses, and arboviruses are further members of this family. Animal species, particularly non-human primates, have also been found to have ZIKV antibodies. Aedes africanus, an arboreal mosquito, and Aedes aegypti and albopictus, two mosquitoes with a wide tropical and subtropical distribution, respectively, were among the mosquito species from Africa and Asia from which ZIKV was also recovered. According to studies, ZIKV has three primary lineages: two African and one Asian. East and West African clusters represent the divide of the African ancestry. Asian ancestry has a wider geographic range because it originated in South America and the Pacific Ocean . The epidemic that struck America in 2015–16 was due to strain of the Asian lineage generally known as the American strain. However, some consider the American outbreak strain as its own lineage. Epidemiology studies revealed distribution of ZIKV in half of the north African continent, Vietnam, Malaysia, Indonesia, Philippines, India, Thailand and Pakistan (Fig. 1) When neutralizing antibodies to ZIKV were found in serum during a study conducted in Uganda in 1952, the first human case was discovered. Prior to the 2007 epidemic of ZIKV infection in humans in Yap, Federated States of Micronesia, in the Pacific, there were very few documented cases of infection in people. From 2013 to 2014, the biggest ZIKV outbreak in French Polynesia spread to neighboring Pacific Islands, including Solomon Islands, Easter Island, Vanuatu, Cook Islands, and New Caledonia [5]. In 55 nations and territories, ZIKV transmission is known to occur. However, only in 2015–2016 were 41 of them confirmed to have indigenous transmission, with six nations indirectly confirming the virus's circulation, five countries reporting that outbreaks had ended, and three countries Five nations reported ending epidemics, while three countries experienced local infections.

1.2 Virology and molecular biology

Hepacivirus (one species, the hepatitis C virus), Pestivirus (four species), Pegivirus (two species), and Flavivirus (53 species) are among the four genera of clinically significant arboviruses in the Flaviviridae family. The majority of clinically significant pathogens, aside from the hepatitis C virus, are members of the genus Flavivirus. Hemorrhagic fever, encephalitis, fever, rashes, and visceral involvement are the most common clinical signs of flaviviruses. The 10,794 kb ZIKV genome is made up of a large open reading frame that codes for a polyprotein and a positive sense single-stranded RNA molecule with two noncoding regions (NCR)—39 and 59 NCR. NS1-NS2A-NS2BNS3-NS4A-NS4B-NS5-39 59-C-prM-E. The protein is broken down into seven non-structural proteins (NS1-NS2A-NS2BNS3-NS4A-NS4B-NS5), capsid (C), envelope (E), and precursor of membrane (prM) (Fig. 2). E protein is the main virion surface protein. This protein plays a role in facilitating binding, membrane fusion, and several aspects of the viral cycle. The biggest viral protein, NS5, possesses RNA-dependent RNA polymerase (RdRP) activity in its C-terminal part. Its N-terminus processes RNA through methyl transferase activity, which results in RNA capping. There are 27 folding patterns and 428 nucleotides in the 39 NCR of of the genome of ZIKV These nucleotides and folding patterns could be involved in translation, cyclization, RNA packaging, viral recognition, cellular recognition, and genomic stabilization.
The amino acids that surround a glycosylation site in the virus's shell, which is made up of two different proteins with 180 copies, differ in all known flavivirus structures. ZIKV differs from other flaviviruses in that it has a glycosylation patch on its surface. Many sugars are attached to the viral protein's surface at this location via a carbohydrate molecule. The ZIKV's glycosylation site and surrounding residues may be what allow the virus to adhere to human cells. changes in the amino acids of different flaviviruses may indicate changes in the types of human cells to which they can adhere and infect. An antiviral substance may be appropriate to target the glycosylation site if its function is comparable to that of DENV (attachment to the human body's cell receptor).
accompanied by anorexia, maculopapular rash, fever, malaise, headache, dizziness, and stomachache Additionally, it may result in oedema, diarrhea, lymph adenopathy, and retroorbital eye pain. Additional symptoms that have been described include sweating, aphthous ulcers, photophobia, back discomfort, cough malaise, gastrointestinal disorders, and edema of the limbs. Particularly in regions where ZIKV infection is common, it might be mistaken for other arboviruses and bacterial illnesses. There are severe neurological issues in French Polynesia with ZIKV sickness has an incubation period of two to seven days and manifests as influenza syndrome. During the outbreak, Guillain-Barré syndrome surged 20-fold.

2. ZIKV vector-borne Transmission

The possible vectors that spread ZIKV infection through biting are Aedes aegypti, Aedes polynesiensis, and Aedes albopictus. The primary vector of CHIKV and DENV is Aedes aegypti. In French Polynesia, Aedes polynesiensis is the primary vector that spreads lymphatic filariasis. These mosquito species were gathered and examined for ZIKV infection using RT-PCR following the outbreak in French Polynesia. Only one Aedes aegypti mosquito was found to have ZIKV RNA; experimental studies revealed that the French Polynesian strain of Aedes aegypti is capable of replicating the French Polynesian ZIKV strain (Additional file 1: Figure S1).

61 nations and territories across six WHO regions have confirmed the presence of conventionally competent Aedes aegypti vectors, but ZIKV transmission has not yet been reported. Therefore, there is still a chance that ZIKV will spread to other nations. Perhaps fewer nations did not report transmission because of a lack of detection. Additionally, the re-emergence or reintroduction was documented in every region where ZIKV transmission had previously been documented.

Eight mosquitoes in total were isolated from the African lineage, but P6-740 was the lone mosquito recovered from the Asian lineage (Malaysia/1966). ZIKV was discovered in people infected with West African Aedes aldopictus mosquitoes in 2007. Nonetheless, the Aedes (stregomyia) hensilli was shown to be the most likely primary vector responsible for the Micronesia outbreak.

. The ZIKV mostly shared characteristics with Aedes aegypti and Aedes aldopictus species until spreading to French Polynesia in 2013 and then to Oceanian islands (New Caledonia, Cook Islands, and Easter Island). Eleven percent of the population had the main symptoms, which included rash, low-grade fever, arthralgia, conjunctivitis, and Guillain-Barré syndrome (GBS). Additionally, Aedes aegypti is thought to be the most prevalent DENV vector in Central-South America. Chouin-Carneiro later stated in 2006 that the Asian lineage continues to diverge as a result of the New World strains of Aedes aegypti and Aedes albopictus, which were shown to be poor ZIKV transmitters. These strains switched to a direct human-to-human transmission method, which eliminates the need for a vector.

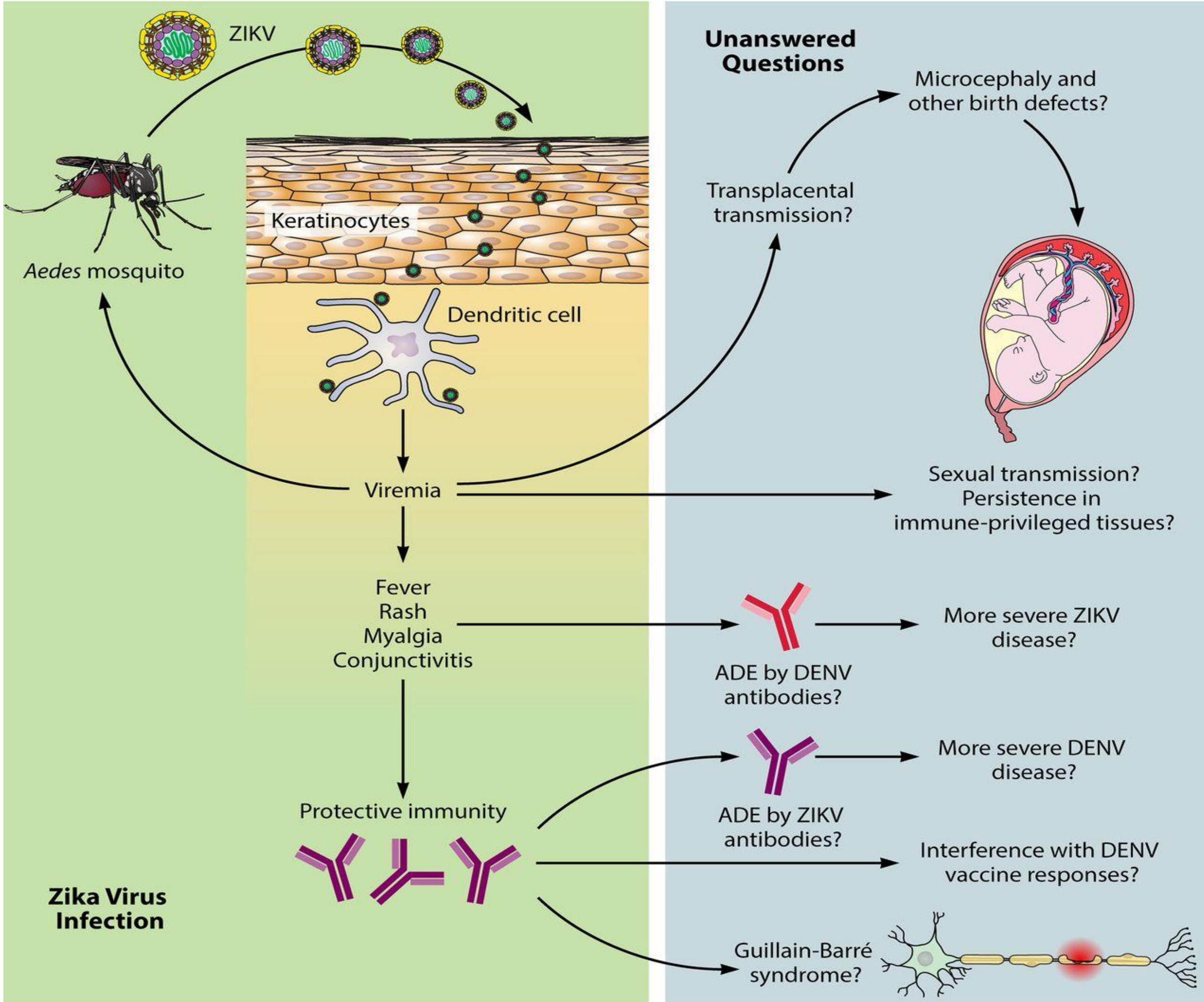

Fig:1 The transplantation transmission of Zika virus

Although it is commonly believed that Aedes is the vector of ZIKV, Guedes et al. have shown that ZIKV can infect and multiply in the midgut, salivary glands, and even in the saliva of Culex species. All things considered; this research raises the possibility that the transmission vector range for ZIKV may be greater than anticipated (albeit this is still a contentious issue that requires further investigation).

2.1 Transfers that are not vector-borne

Sexual intercourse, organ transplants, blood transfusions, and childbirth are all non-vector-borne ways that ZIKV infections might spread.

Serosurvey investigations found antibodies against ZIKV in sheep, bats, goats, and rodents (Meriones hurrianae and Tatera indica). According to these investigations, ZIKV and a particular animal species are not clearly associated. Infected Aedes aegypti mosquitoes, which are typically found in tropical and sub-tropical areas in household water-holding containers close to homes, bite humans to spread the disease. As a result, when a mosquito bites someone who has already contracted ZIKV, the virus-infected blood enters the midgut and spreads. into the bloodstream. ZIKV can also be spread by Aedes albopictus, a mosquito that is identical to this one. Sexual interaction may also be a factor in the spread of this virus in humans. Since a high ZIKV RNA load has been found in breast milk, breastfeeding may spread the virus, and blood transfusions may also spread it, as was the case in Brazil in December 2015, which was the first instance of ZIKV blood transfusion transmission. Enzootic and sub-urban cycles are used to spread ZIKV (Fig. 4); in enzootic settings, this is done by Aedes species mosquitoes and non-human primates; in urban settings, human beings and Aedes species mosquitoes show both vector and non-vector borne transmission of ZIKV.

2.1 Pathophysiology and diagnosis

Initially, dengue infection was mistaken for ZIKV illness. For the laboratory diagnosis evaluation of ZIKV, virus isolation and serological techniques are used (Table 1) [48]. While convalescent and acute sampling, as well as flavivirus cross-reactions, are the limitations of serological approaches, virus isolation takes several days, or 1-2 weeks. Although it can be done in specialized labs, cell culture can be used to isolate ZIKV [5, 16]. ZIKV infections are confirmed by reverse transcription PCR (RT-PCR), while ELISA can identify IgM against ZIKV. Time-saving, sensitive, and specific, RT-PCR can identify ZIKV in serum or cell culture. Saliva used during the acute phase of sickness, especially in children, boosted the molecular identification of ZIKV. Fig. 5 displays the PAHO diagnosis of ZIKV fever. Saliva or blood samples are used for RT-PCR for ZIKV. If RT-PCR yields positive results, sequencing is carried out. ZIKV IgM serology includes immunofluorescence or ELISA detection, followed by plaque reduction neutralization test (PRNT) confirmation if results are positive or unclear.

2.2 Transmission of the Zika virus

The Zika virus is a spherical, enveloped particle that belongs to the genus Flavivirus and family Flaviviridae. The virus is classified in the Spondweni virus serogroup and is a member of the mosquito-borne cluster of the genus Flavivirus. The virus's genome, like that of other flaviviruses, is a positive-sense, 11 kb single-stranded RNA molecule that codes for three structural proteins and seven non-structural proteins.

3.Identification of the Zika virus and early epidemiology

A sentinel monkey that had been set up on a platform in the Zika Forest close to Entebbe, Uganda, was the first source of the Zika virus. One The initial sample from which the Zika virus was obtained was taken in 1947. The virus was then isolated from a pool of Aedes africanus mosquitoes taken from the same woodland another time in 1948.The Zika virus was neurotropic in mice, according to later research on the virus's pathogenicity in animals.

3.1 Yap State's Zika virus epidemiology

Using a combination of genetic and serological investigation, 49 individuals in Yap State were found to have a confirmed Zika virus infection and 59 to have a probable infection in 2007, marking the first known transmission of the virus outside of Africa and Asia.12, 13 Five of the additional 72 individuals classified as suspected cases were not infected with the Zika virus.12 However, preliminary laboratory testing using a commercially available dengue IgM assay revealed that the dengue virus was the pathogen that caused the illness.

Fig:2 Structural-morphology and symptoms of Zika virus infected patients.

Epidemiology of the Zika virus in French Polynesia and adjacent Pacific islands

Reports of a Zika virus outbreak in French Polynesia began to surface in October 2013, affecting a number of islands, including Tahiti, Moorea, Raiatea, Taha'a, Bora Bora, Nuku Hiva, and Arutua.67 The Zika virus genome was detected by RT-PCR in molecular and virological investigation of patient samples, and in certain instances, the virus was recovered by inoculating Vero cells.68 around a year following the initial Zika virus infection cases.

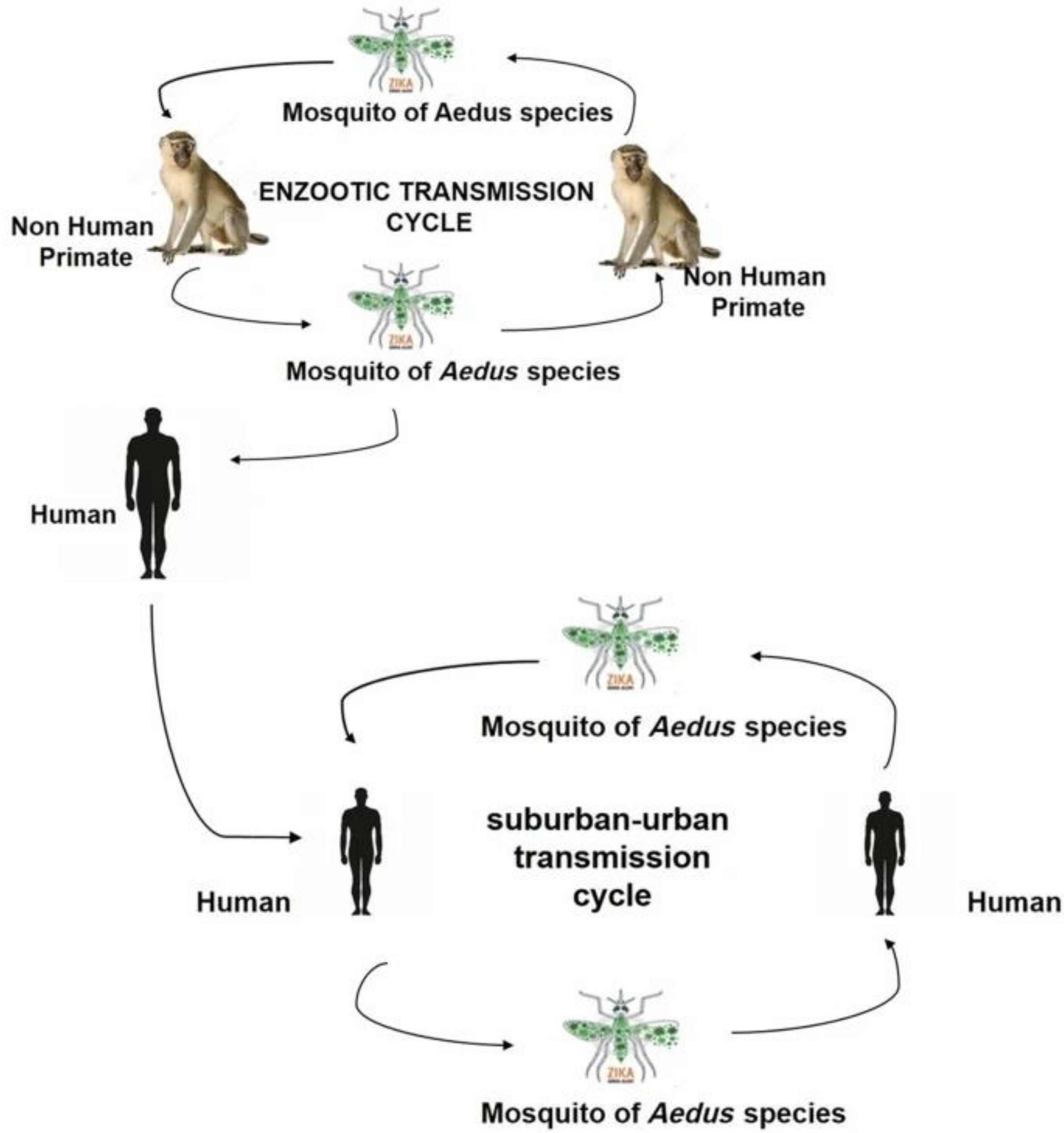

Fig:3 Aedus species mosquito transmission cycle from monkey to human.

3.2 Southeast Asian epidemiology of the Zika virus

A toddler who was attending a health clinic in Kampong Speu Province, Cambodia, in 2010 had specimens taken from him (figure 2), which later tests revealed were positive for the Zika virus.58 The child did not require hospitalization because of their modest symptoms, which included fever, headache, cough, and sore throat without any maculopapular rash. This was the sole positive Flavivirus infection that was not dengue or Japanese encephalitis, and no other Zika virus infections were documented during this period.

3.3 South American Zika virus epidemiology

As a result of a persistent outbreak of a disease marked by fever, maculopapular rash, muscle and joint pain, and conjunctivitis, blood samples were taken from 24 patients at Santa Helena Hospital in Camaçari, Bahia, Brazil, in March 2015.Seven individuals had Zika virus and three had chikungunya virus, according to 80 RT-PCR analysis; no co-infection was found.Sequence study of 80 Zika virus envelope protein domains revealed 99% similarity with French sequences.

3.4 Is the clinical presentation of Zika virus infection evolving?

Early symptoms of a spontaneous human Zika virus infection included a maculopapular rash and a brief, self-limiting, moderate feverish sickness.10. Yap State saw the first significant Zika virus infection outbreak in 2007. The illness was linked to rash, fever, arthralgia, and conjunctivitis, however there were no documented hospitalizations or fatalities. Twelve In the same way, the cases in the Philippines in 201259 and Cambodia in 201058 were settled without the need for a hospital.

The Institute of Health Metrics and Evaluation coordinates and implements the Global Burden of Diseases, Injuries, and Risk Factors Study 2021 (GBD 2021) which provides the baseline data for this investigation. The GBD database is one of the most popular health data sources in the world since it uses a variety of data sources, strict statistical techniques, and models to guarantee data trustworthiness. It covers 204 nations and territories and 371 illnesses and injuries. This study retrieved annual incidence counts and rates of ZIKV infection in women of reproductive age (15–49 years) from 2011 to 2021, by global, GBD regions, countries, SDI levels, and age categories, using the GBD 2021 database, which was updated on May 17, 2024. Comprehensive calculation methods for GBD ZIKV infection The Supplementary Methods provide more information on the precise estimation processes for ZIKV infection in GBD 2021. In summary, official reports, mainly from the Pan American Health Organization (PAHO), are the main source of information on acute Zika cases and CZS [18]. By performing a meta-analysis, the GBD group calculated that 41% of Zika infections were symptomatic (14–68%), while 59% were asymptomatic. Then, using location as a random effect, they used the Integrated Nested Laplace Approximation (INLA) approach, as implemented in R-INLA with negative binomial likelihood, to predict incidence and estimate the incidence of ZIKV infection by adjusting reported cases using expansion factors [19]. The incidence of symptomatic Zika was then estimated by location, year, age, and sex by dividing the overall incidence according to the age/sex-distribution model.

3.5 Data extraction

Women of reproductive age (15–49 years) were the subject of this investigation, which looked at the prevalence of ZIKV infection in 204 nations and territories, including 21 GBD regions that were distinguished by their geographic continuity and epidemiological homogeneity (Table S1) Using the 25th and 975th values from a thousand iterations of the posterior distribution, the 95% uncertainty intervals (UIs) were utilized to evaluate the uncertainty of each measure, which included the number of infection cases and incidence rates per 100,000 population. The socio-demographic index (SDI), which ranges from 0 to 1, is determined by three factors: the distribution of per capita income, the average education of individuals over 15, and the fertility rate for those under 25. The SDI is strongly correlated with the level of economic development. Additionally, we have extracted region-specific incidence statistics. by SDI quintile: low, low-middle, middle, high-middle, and high SDI levels.

Furthermore, this study separated the age groups into the following: 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, and 45–49 years.

4.Analysis of statistics

We determined the worldwide and regional absolute numbers of ZIKV infection cases and incidence rates (per 100,000 population). The temporal trends were quantified using the expected annual percentage change (EAPC) of incidence rates and the relative percent change in cases from 2011 to 2016 and from 2016 to 2021. For instance, the relative percent change for the 2011–2016 timeframe was calculated as (Numbers2011 - Numbers2016)/Numbers2011 × 100.

4.1 Variations in the incidence of ZIKV infection between the five SDI regions

The incidence rates and cases of ZIKV infection varied significantly throughout the five SDI zones (Table 1). Both in 2016 (1663,147 cases) and 2021 (38,593 cases), the middle SDI region had the most infections, followed by the low-middle SDI region (1463,036 cases in 2016; 20,619 cases in 2021). The patterns seen at the worldwide level were reflected in the trends in the number of ZIKV infection cases in each of the five SDI areas between 2011 and 2021. In terms of incidence rates, the middle SDI area had the highest rate in 2021 (6.24 per 100,000). population), which was in contrast to the trends seen in 2016 and 2011, and then the low-middle SDI zone (4.07 per 100,000 population). Between 2011 and 2021, the incidence rates of ZIKV infection in the five SDI regions showed a significant increase and then a drop, peaking in 2016. While the low SDI (EAPC = -75.05%) and high SDI (EAPC = -74.1%) regions showed the fastest reductions between 2016 and 2021, the high SDI region saw the largest rise in incidence rate from 2011 to 2016 (EAPC = 414.4%).

4.2 Variations per country in the prevalence of ZIKV infection

ZIKV infection posed a danger to 30, 51, and 33 nations and territories in 2011, 2016, and 2021, respectively (Table S2). Among all nations and territories, Brazil had the most cases in 2016 (902,873 cases), followed by Colombia (537,048 cases) and Venezuela (396,580 cases). In 2021, 48.60 percent of ZIKV infection cases worldwide were in Brazil (29,003 cases), followed by Peru (10,221 cases) and Mexico (9383 cases). Fig. 4 shows the incidence rates for 2021, with El Salvador having the highest rate at 203.47 per 100,000 population, followed by Belize at 136.89 per 100,000 and Peru at 106.26 per 100,000. Almost one out of five women who were of reproductive age in 2016 were were infected in Saint Kitts and Nevis, Dominica, and Jamaica. Mexico (EAPC = 504.97%), Jamaica (EAPC = 466.00%), and Puerto Rico (EAPC = 424.29%) saw the fastest increases in ZIKV infection incidence rates between 2011 and 2016 (Table S3). Nonetheless, all countries saw a significant drop in incidence rates between 2016 and 2021.

***Table*: 1** Geological information of zika virus infected countries.

GBD Region	Countries and Territories
Australasia	Australia, , New Zealand
High-income Asia Pacific	Japan, South Korea, Singapore, Brunei Darussalam
Central Asia	Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, Uzbekistan
East Asia	China, Democratic People's Republic of Korea, Taiwan (Province of China)
Southeast Asia	Cambodia, Indonesia, Laos, Malaysia, Maldives, Mauritius, Myanmar, Philippines, Seychelles, Sri Lanka, Thailand, Timor-Leste, Viet Nam.
South Asia	Bangladesh, Bhutan, India, Nepal, Pakistan
Caribbean	Antigua and Barbuda, Bahamas, Barbados, Belize, Bermuda, Cuba, Dominica, Dominican Republic, Grenada, Guyana, Haiti, Jamaica, Puerto Rico, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, United states Virgin Islands
Andean Latin America	Bolivia, Ecuador, Peru
Central Latin America	Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Venezuela
Southern Latin America	Argentina, Chile, Uruguay
Tropical Latin America	Brazil, Paraguay
Western Sub-Saharan Africa	Benin, Burkina Faso, Cape Verde, Cameroon, Chad, Cote d'lvoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Sao Tome and Principe, Senegal, Sierra Leone, Togo
Central Sub-Saharan Africa	Angola, Cameroon, Central African Republic, Congo, Democratic Republic of the Congo, Equatorial Guinea, Gabon
Eastern Sub-Saharan Africa	Burundi, Comoros, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mozambique, Rwanda, Somalia, South Sudan, Uganda, United Republic of Tanzania, Zambia.
Southern Sub-Saharan Africa	Botswana, Eswatini, Lesotho, Namibia, South Africa, Zimbabwe.
North Africa and Middle East	Afghanistan, Algeria, Bahrain, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Palestine, Qatar, Saudi Arabia,

	Sudan, Syrian Arab Republic, Tunisia, Tükiye, United Arab Emirates, Yemen
Central Europe	Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czechia, Hungary, Montenegro, North Macedonia, Poland, Romania, Serbia, Slovakia, Slovenia
Eastern Europe	Belarus, Estonia, Latvia, Lithuania, Republic of Moldova, Ukraine, Russian Federation
Western Europe	Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Israel, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Spain, Sweden, Switzerland, United Kingdom.
Oceania	American Samoa, Cook Islands, Fiji, Guam, Kiribati, Marshall Islands, Micronesia, Nauru, Niue, Northern Mariana Islands, Palau,Papua New Guinea, Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, Vanuatu.
High-income North America	Canada, Greenland, United States of America

5. Overview of GBD

Data on global descriptive epidemiology that has been published, made available to the public, and contributed to is systematically evaluated scientifically by the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD). Using 100,983 data sources, GBD 2021 estimated the incidence, point prevalence (henceforth referred to as prevalence), years lived with disability (YLDs), years of life lost (YLLs), and disability-adjusted life-years (DALYs) for 371 diseases and injuries. It also estimated the healthy life expectancy (HALE). Vital registration systems, verbal autopsies, household surveys, censuses, disease-specific registries, health service contact information, and other sources were used to collect data. Prevalence and incidence for the majority of illnesses and injuries were calculated using Disease Modeling Meta-Regression, or DisMod-MR 2.1, version 2.1. Internally consistent estimates of prevalence, incidence, remission, and mortality by sex, location, year, and age group are produced by the Bayesian disease modeling meta-regression tool DisMod-MR 2.1. The Socio-demographic Index (SDI), a composite measure of per capita income, years of education, and fertility rate among females under 25, was taken into consideration by the GBD 2021 group while analyzing the results. The posterior distribution's 25th and 975th sorted 1000 draw values were used to create uncertainty intervals (UIs) for each metric.

5.1 Estimation of Zika virus infection in GBD 2021

Modelling strategy

The GBD group estimate the all-age incidence of symptomatic Zika as the product of reported Zika cases and country-specific expansion factors that adjust for underreporting. Those expansion factors are derived from our dengue model, and the methods used for their estimation are detailed in the dengue model documentation and by Stanaway and colleagues. (ref a).The GBD group employs a comprehensive approach to adjust for underreporting by incorporating multiple data sources, including surveillance data, household surveys, and other relevant datasets. Since Zika disease is often under-reported due to health system capacity or misdiagnosed as other febrile illnesses, they conducted a systematic literature review to identify sources that compared incidence rates reported via active versus passive surveillance. Then they included comparisons using enhanced surveillance compared to passive surveillance, to generate an adjustment factor to correct for under-reporting. The under-reporting adjustment factors were estimated using MR-BRT (meta-regression—Bayesian, regularized, trimmed) and included Sociodemographic Index (SDI) and reported incidence rate, trimming 10% of the input data. The uncertainty from the MR-BRT meta-regression was applied to the adjustment.

First, the GBD group use the expansion factor to inflate the raw data. Then, the GBD group used the Integrated Nested Laplace Approximation (INLA) method, as implemented in R-INLA (ref b) with negative binomial likelihood, using location as a random effect, to predict incidence. These random effects consisted of i.i.d. effects by most-detailed locations (including sub-nationals where appropriate), country, and GBD region. The GBD group used the Healthcare Access and Quality (HAQ) Index, proportion of the population living above 1500m of elevation, Enhanced Vegetation Index long term average 2000–2012, and population-weighted mean temperature as random effects covariates, using second-order random walk (RW2) models to accommodate non-linearity. As fixed effects covariates, the GBD group used rainfall, sanitation, and solar radiation. The model also included a single-order random walk (RW1) model on years since the peak of the initial outbreak in a given location. The GBD group used age-specific data to estimate age- and sex-specific incidence curves, using the INLA method, with a single-order random walk (RW1) model on the midpoint of each age bin, replicated by sex. The GBD group then split total incidence based on the age/sex-distribution model to estimate the incidence of symptomatic Zika by location, year, age, and sex.

The GBD group conducted a meta-analysis of three studies(ref c–e) to estimate the proportion of all Zika infections that are symptomatic. The GBD group estimate that 41% of Zika infections are symptomatic (14–68%), with 59% being asymptomatic.

5.2 Changes from GBD 2019 to GBD 2021

The major change from GBD 2019 was the implementation of the INLA method to estimate the incidence of Zika virus as described above, instead of a mixed-effects negative binomial model as was used in previous GBD cycles. In addition, the GBD group switched to using the negative binomial model described above to estimate the proportion of at-risk births resulting in CZS; in GBD 2019, an intercept-only mixed-effects Poisson regression with random effects on location and year was used instead. The GBD group did not apply any adjustments for the COVID-19 pandemic to Zika due to a lack of available data quantifying the impacts of the pandemic on NTD epidemiology.

5.3 Interactions between ZIKV and DENV.

One of the characteristic features of DENV pathogenesis is that whereas infection with one serotype provides durable immunity to that same serotype, antibodies to one DENV serotype can exacerbate infection with different serotypes via antibody-dependent enhancement (ADE) (). ADE occurs when cross-reactive nonneutralizing antibodies bind to a heterologous DENV serotype. Antibody-opsonized but nonneutralized virus can infect myeloid cells (e.g., monocytes or macrophages) expressing Fc-gamma receptors at a higher rate, allowing enhanced infection and yield. Because of this, secondary DENV infections (or primary infections in infants with circulating maternal antibodies) can produce severe disease manifestations, including plasma leakage, hemorrhage, and circulatory collapse. ADE can be demonstrated for many flaviviruses in cell culture, but the phenomenon appears to be biologically relevant only in the context of DENV, possibly due to the degree of antigenic relatedness between different DENV serotypes or because of the unique biology of the DENV NS1 protein Given the relatedness between DENV and ZIKV, and the high cross-reactivity demonstrated in serological assays, ADE between DENV and ZIKV and altered disease pathogenesis warrant further evaluation. The severity of disease seen in recent outbreaks of ZIKV has been greater than that seen in earlier outbreaks. While explanations for this include changes in the virus and an enhanced ability to detect rare presentations in larger outbreaks, one feature that distinguishes the most recent ZIKV outbreaks is that they occurred in regions of DENV hyperendemicity, where multiple strains of DENV cocirculate and where most people have been infected previously by one or more DENV serotypes. This raises the possibility

6. Vaccine development.

Successful vaccination programs have reduced the global health burden of many flavivirus infections. More than 500 million doses of vaccine to prevent YFV infection have been administered since the vaccine was developed in 1937, and effective vaccines have blunted the impact of JEV and TBEV. Recently, after decades of study, the first live-attenuated tetravalent DENV vaccine (Dengvaxia) completed phase III human trials and is being deployed in Brazil, Philippines, and Mexico.

As no ZIKV vaccines have been tested even at the preclinical stage, we are likely years away from the introduction of a ZIKV vaccine. It is expected that at least some groups with existing flavivirus vaccine platforms (e.g., chimeric live attenuated strains, passaged or genetically engineered live attenuated strains, E protein subunit, subviral particles, inactivated virions, or DNA plasmid) will apply these strategies toward ZIKV vaccine development in an expedited manner. A major issue remains as to whether it will be easy or difficult to generate an immunogenic and safe vaccine against ZIKV. Given the relatively low variation between ZIKV strains (approximately 94% amino acid identity across the viral genome) and the lack of different genotypes or serotypes, it is plausible that an effective vaccine against one strain would function broadly against all circulating ZIKV strains. ZIKV outbreaks are occurring in areas with high seroprevalence rates for DENV infection and vaccination with YFV. Thus, at least some fraction of candidates for ZIKV vaccines would have preexisting cross-reactive antibodies derived from natural or vaccine-induced flavivirus immunity. This could impact ZIKV responses in one of three ways: (i) by boosting cross-reactivity immunity, conferring protection against ZIKV; (ii) by boosting cross-reactive immunity at the expense of generating protective ZIKV-specific responses ("original antigenic sin"); (iii) by neutralizing live-attenuated ZIKV without appreciably affecting cross-reactive immunity (sterilizing immunity).

6.1 Treatment of ZIKV

In ZIKV infection, individuals should have adequate water intake, ample rest and treat pain and fever with liquid solutions. If the symptoms aggravate, they should look for counselling and therapeutic consideration (Fig. 6). There are no specific medications or vaccine available to treat or prevent ZIKV infections until now; only medications for symptomatic relief can be considered such as paracetamol to relieve pain and fever associated with this infection . Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided and individuals should seek medical advice before taking additional medication if they are already taking medicines for another medical condition . Homeopathy is a worthy treatment option in ZIKV infection as it proved to be effective in Japanese encephalitis virus which is included in the same genus like Zika virus . Treatment with belladonna efficaciously reduced the severity of Japanese encephalitis virus infection Atropa belladonna plant belongs to family Solanaceae It has been effective in numerous medical conditions having great commercial significance as a major source of alkaloids, mainly scopolamine and hyoscyamine that are pharmaceutical bioactive compounds Belladonna is native to North Africa, Western Asia and Europe. In Atropa belladonna majority of alkaloidal contents are present in ripe fruit and green leaves. It has been used from ancient times in order to treat various human ailments including menstrual disorders, headache, peptic ulcer, inflammation and histaminic reaction . Ultra-diluted belladonna concentrations like 1:10 or 1:100 are used in homeopathy and they are recommended for management of all the infectious diseases and illnesses

Eupatorium is a naturally occurring pharmaceutical homeopathic compound effective against the symptoms of ZIKV disease, so it can be utilized as prophylactic treatment against ZIKV infection [63]. Eupatorium perfoliatum, Rhustox and Atropa belladonna are the homeopathic prescriptions that may be utilized for ZIKV infection treatment. These medicinal agents are effective against the symptoms of ZIKV infection . During epidemics homeopathic pharmaceuticals are more effective in reduction of mortality and morbidity as compare to conventional system of medicine

One of the utmost momentous features of ayurvedic structure is that they are natural substances and free from side effects and there is no scientific evidence of danger for human use . It is a primordial medical science that contains herbal medicines of natural origin with minimal side effects. Tinospora cordifolia is a herb and utilized for years as potential immunomodulator and effective natural remedy for viral disease of any nature. It boosts up the immune system and make body resistant enough to fight against infections. Theses herbs potentiate phagocytic abilities of macrophages . Intestinal sickness, urinary tract infections, dengue and swine influenza are effectively treated by the astringent characteristics of these ayurvedic plants so they might also be effective for ZIKV .

Beside homeopathic and ayurveda medicines, engineering approaches were also applied to develop peptide therapeutics and support the potential of a brain-penetrating peptide to treat neurotropic viral infections. Therapeutic treatment protected against mortality and evidently lessened symptoms, neuroinflammation and viral loads, furthermore mitigated microgliosis, neurodegeneration and brain damage

Current medical recommendations are directed towards resolving symptoms and not the actual infection; however, ZIKV treatments and vaccines are in development. In 2016, WHO enlist all publicly affirmed commercial, government and academic-led projects focused at ZIKV interventions, together with vaccines . The list encompasses numerous approaches, comprising vaccines via purified inactivated virus, Virus-like particles (VLP), protein subunits, DNA and live recombinant attenuated viruses. Since April 2019, no vaccines have been permitted for clinical usage, though utmost were in the clinical stages of development

Suggested workflow for prompt discovery of drug counter to ZIKV is presented in Fig. 7; whole process is proposed to initiate from screening moderate or high-throughput in vitro analysis development following with testing of approved drugs or other antiviral agents. Virtual screening based on docking could be selected for testing further compounds by means of advanced model of homology or phenotypic and genotypic analyses if drug repurposing will be unsuccessful. Priority can be given to the compounds resulting from docking for in vitro analysis in parallel. Consequent steps are typical as a pipeline in the discovery of any drug including developing the models of animals, clinical trial and if getting optimistic results, manufacturing the drug against ZIKV by scale up process, advertising and dissemination of drug

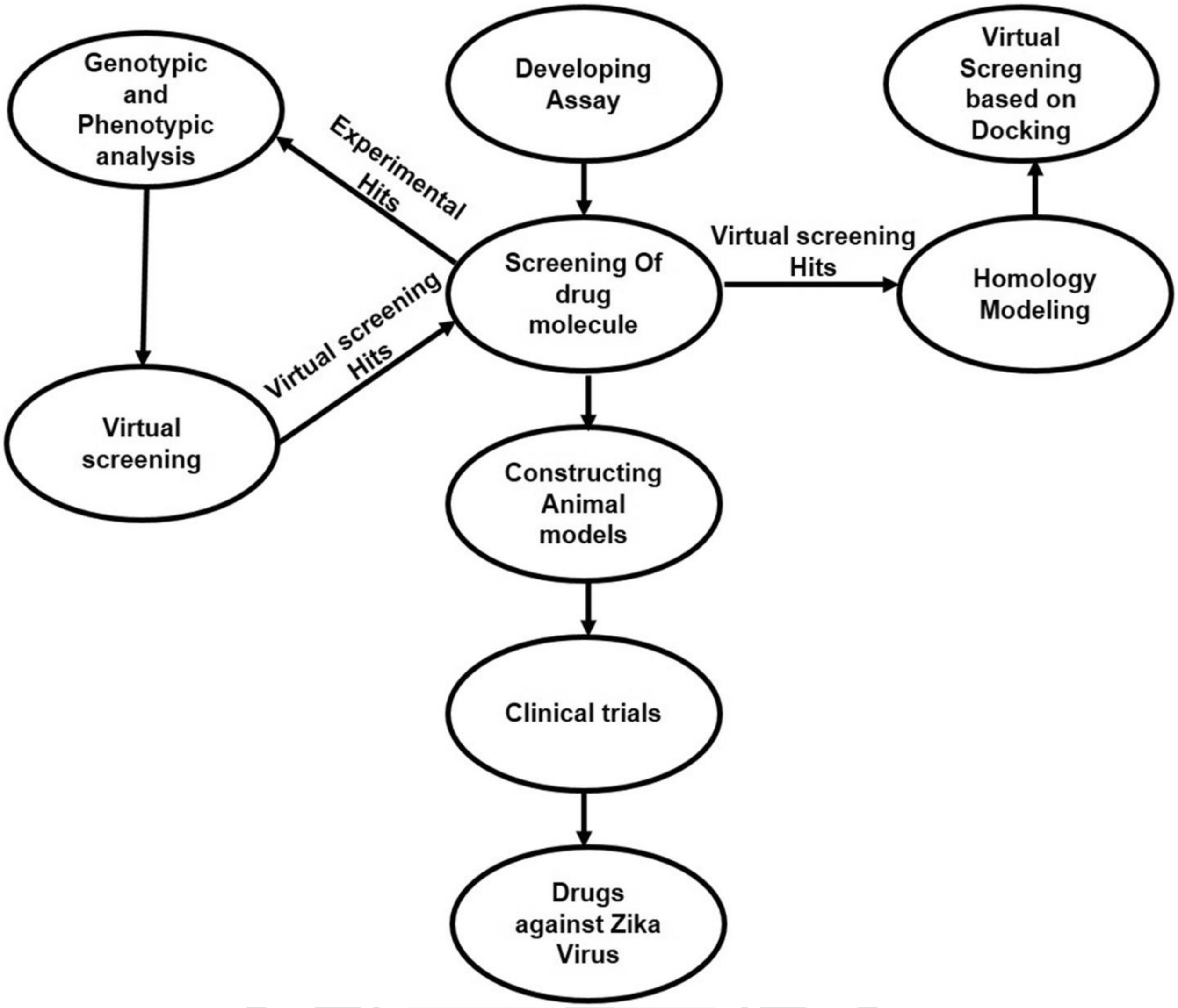

Fig:4 Flowchart of zika virus treatment and drug development

6.2 Prevention and control of ZIKV

Most precarious threats for ZIKV infection are mosquitoes including their reproducing localities. Their encounter with humans must be reduced in order to control and prevent their outspread. This can be employed by using mosquito repellents, mosquito nettings and closing the entrances and openings. Insect killing sprays recommended by the WHO Pesticide Evaluation Scheme should be used as larvicides . Insect repellents should not be used for babies under two months, mosquito nets should be used to protect babies from insect bite. Centre of disease control recommends mosquito repellents with active ingredients picaridin, DEET, eucalyptus oil, IR3535, oil of lemon and para-menthane-diol. These are safe for pregnant and lactating mothers . Repellants containing eucalyptus oil, lemon oil and para-menthane-diol should be avoided for children below 3 years of age. Mosquitoes should be killed using indoor mosquito killing sprays which contain active ingredient Imidacloprid and β-Cyfluthrin available in market Flying insect fogger can also be used against the mosquitoes containing active ingredients Tetramethrin and Cypermethrin Tests against ZIKV infection should be performed before blood transfusions to prevent transfusion related transmission. Pregnancy must be avoided in the high risk ZIKV infection prone areas before complete eradication or extra care must be exercised as microcephaly is associated with ZIKV infection .

Besides, different vector control strategies for averting Zika virus spread can be employed. Subjugation of mosquito population can be accomplished by a bacterium that can infect mosquitoes. Other strategies include the use of intracellular bacteria Wolbachia, which acts as a biopesticide to control mosquito population. Larvae of Toxorhynchites splendens mosquito species does not feed on blood. They feed on the larvae of other mosquito species, while the adults feed on honeydew, fruit, and nectar . Hence, the spread of ZIKV can be encountered by utilizing these species. Aedes species mosquitoes populations can also be suppressed by the strategy of using sterile males to induce sterility in wild fertile females.

6.3 Chemical control measures

Chemical treatment includes the use of pyrethroids, organochloride, and organophosphorus, which primarily act on the nervous system of the vector (van den Berg et al., Imidacloprid, thiacloprid, and thiamethoxam have larvicidal and adulticidal efficacies in different mosquito species. The use of fogging with insecticides is adopted in the outdoor environment to control the vector population though this can lead to development of resistance among the vector population (Maciel-de-Freitas et al., von Seidlein et al., The development of resistance and bioaccumulation are major problems associated with the use of chemicals to control mosquitoes (Uragayala et al., . Moreover, most of these chemical products have other environmental problems because of their wide range of toxic action for several organisms, such as being non-specific insecticides and negatively affecting in some cases to all arthropods or even the rest of aquatic fauna as well as mammals and birds. Consequently, although these chemicals are currently necessary to reduce adult mosquito populations in concrete epidemiological scenarios, however a deep analysis of benefits-costs balance should be addressed before implementing a large-scale use of these insecticides for mosquito control. Repellents can be used at household to prevent mosquito nuissance at home thus preventing major mosquito borne diseases like ZIKV. Recently, a study compared the efficacy of repellet sprays with devices that repell mosquitoes, where N,N-Diethyl-meta-toluamide (DEET) and p-menthane-3,8-diol were found better effective repellent among the 11 different mosquito repellent sprays used (Rodriguez et al., Similarly, devices with metofluthrin were found more effective in attracting mosquito among the five devices compared (Rodriguez et al., Of note, DEET and picaridin-containing insect repellents have been found safe for the pregnant women (Kline and Schutze, Permethrin treated mosquito repellent apparels are available to prevent from mosquito bites (Richards et al.. To note further, unwashed clothes and those which were not exposed to light showed highest repelling activity (Richards et al.,

Insect growth regulators (IGRs) are promising alternatives with high degrees of insecticidal efficacy and environmentally safe compared to conventional chemical larvicides (Mulla et al., World Health Organization,. Analogs of juvenile hormone like methoprene or pyriproxyfen, and chitin synthesis inhibitors such as diflubenzuron and triflumuron are some examples of efficient mosquito larvicides. Some of these IGRs like pyriproxyfen are good candidates for autodisemination strategies, having positive results in recent trials conducted against ZIKV vectors (Unlu et al., von Seidlein et al., Since essential endocrine pathways for the activity of pyriproxyfen are lacking in human, there is no negative effect in human population (Hirano et al., . Notingly, the judictive usage of appropriate chemicals could prevent the growing mosquito population and spread of several diseases inclduing ZIKV infection.

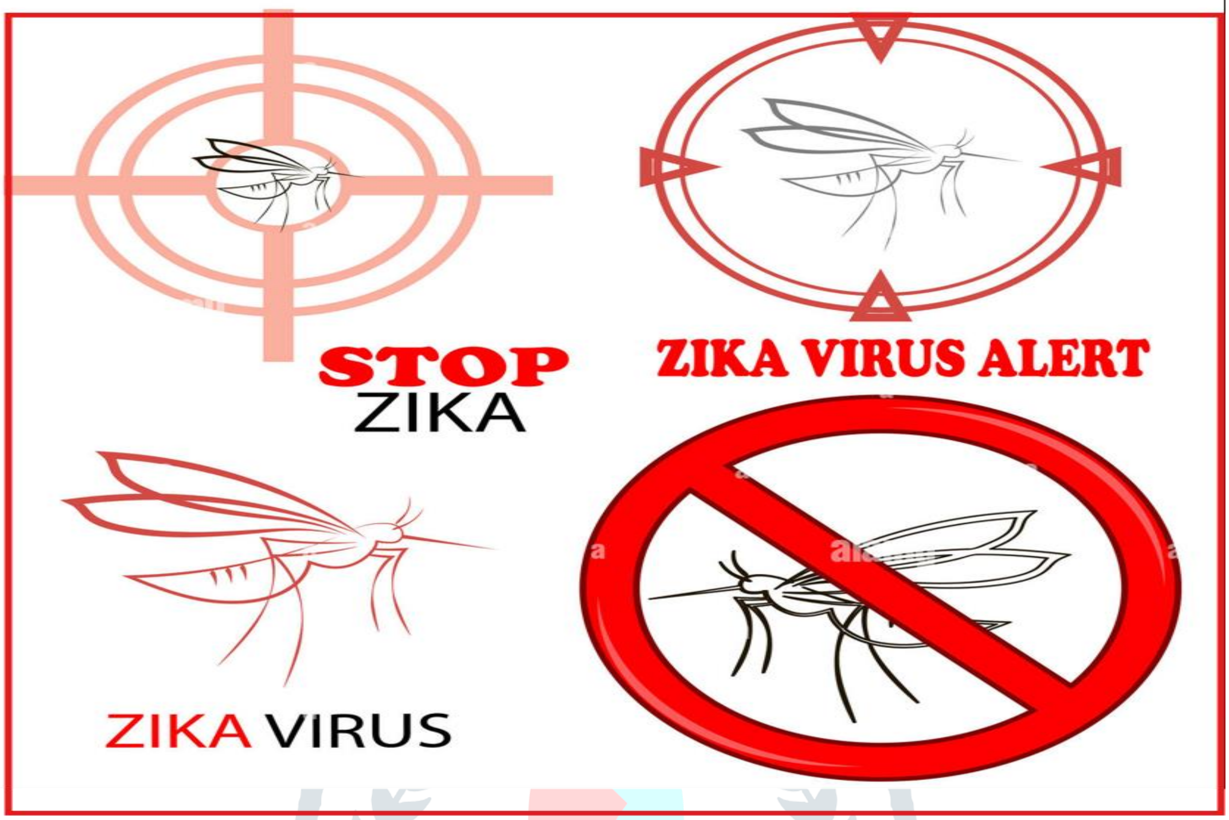

Fig:5 Alert and prevention of Zika virus transmission

7. Future directions

Mosquito-borne epidemics are critically aggravating the pre-existing burden that the primary healthcare systems face. Work force will be affected and the societies may be threatened by the epidemic wave if they are not prepared well. Improved investigation and actions against response are required to alleviate the substantial burden on health systems and control promoting it worldwide. At present there is no vaccine available for ZIKV infection. Vaccines against flaviviral infections available for use of human are yellow fever vaccine, Japanese encephalitis vaccine, tick-borne encephalitis vaccines and dengue vaccine, so the rules for the vector borne infections must be followed in order to prevent ZIKV infection, as well as avoiding mosquito bite and control of vector is the only available options. Animal models of the ZIKV disease are immediately required not only for exhibiting the materno-fetal transmission and confirmation of its neurologic manifestations but also to report the influence of virus on host's immunity and reproductive health throughout the life. ZIKV infection is increasing dramatically, so it is the need of hour to take some necessary steps to eliminate this lethal infection and to constrain its future entrance as well. ZIKV specific rapid molecular diagnosis should be done urgently in order to detect the infection in less time before it aggravates. Modern techniques of molecular biology should be utilized to make vaccine specific to ZIKV. Research gaps should be addressed promptly and systematically. This can be accomplished by understanding the occurrence of broad spectrum clinical consequences that are resulting from fetal ZIKV infection and the environmental influences that effect their emergence. This also require the advancement of flaviviruses selective investigative tools, models of animals to detect developing effects of fetus resulting from viral septicity [79, 80], novel products to control vector and strategies, effective medications and the vaccines to shield humans counter to ZIKV disease.

8.Conclusion

With expanding global outbreaks, Zika infection has emerged as a significant threat to public health, and epidemiological similarities of ZIKV with chikungunya and dengue make it a suitable candidate for becoming a global health problem. The explosive outbreak in Brazil and the recent Indian outbreak have already highlighted ZIKV's potential for rapid population spread. Public health authorities should make effective policies to prevent non-vector-borne transmissions along with conventional vector control measures. Detailed research using animal models is greatly needed to clearly understand the pathogenesis and association of ZIKV with neurological and autoimmune complexities. Factors such as climate change, increasing urbanization, global travel, and growth in the human population are behind the increase in the geographical range of mosquitoes and leading burden of various arboviral diseases. It is difficult to predict the next ZIKV epidemic, but with the help of effective surveillance studies integrated with accurate and rapid diagnosis and the development of specific antivirals and vaccines, we could prepare ourselves for better management and control of this emerging infection.

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