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Ten Years of Congenital Zika Syndrome: From Outbreak to a Decade of Clinical, Therapeutic, and Preventive Advances in a Tropical Disease Context

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Abstract

A decade has elapsed since the first recognized cluster of congenital anomalies associated with Zika virus (ZIKV) was reported in Brazil in 2015, culminating in the formal delineation of Congenital Zika Syndrome (CZS) as a specific pattern of birth defects. This narrative review examines the ten-year trajectory of CZS as a tropical infectious disease, from its initial emergence and public health emergency declaration by the World Health Organization (WHO) in February 2016, through evolving epidemiological, clinical, and scientific understanding. CZS is characterized by a spectrum of severe neurological manifestations—including microcephaly, subcortical calcifications, malformations of cortical development, ventriculomegaly, and corpus callosum abnormalities—alongside ophthalmic, auditory, and musculoskeletal complications. Transmitted primarily by Aedes aegypti mosquitoes in tropical and subtropical regions, ZIKV disproportionately affects low- and middle-income countries in Latin America, Africa, and Southeast Asia, underscoring its nature as a quintessential tropical disease linked to poverty, inadequate vector control, and health inequity. Over ten years, substantial advances have been made in understanding ZIKV pathogenesis, neurodevelopmental outcomes, diagnostic criteria, and multidisciplinary clinical management of affected children. In the therapeutic and preventive domain, over 45 vaccine candidates have been identified, with 16 reaching Phase 1 or 2 clinical trials by late 2025, though no licensed vaccine or specific antiviral therapy yet exists. This review contextualizes CZS within the broader framework of neglected tropical diseases, evaluates its global and family-level burden, and critically appraises progress and remaining gaps in clinical care, vaccination, and vector control over the past ten years.

Keywords: Zika virus; congenital Zika syndrome; microcephaly; flavivirus; tropical disease; neurodevelopment; ZIKV vaccine; Aedes aegypti; arbovirus; neglected tropical diseases

1. Introduction

The emergence of Zika virus (ZIKV) as a major teratogen represents one of the most significant and unexpected events in modern tropical medicine. Although ZIKV was first isolated in 1947 from a rhesus monkey in the Zika Forest of Uganda and subsequently identified in humans in Nigeria in 1952, it remained a pathogen of modest clinical concern for decades, associated with mild, self-limited febrile illness. The first recognized human outbreak occurred in the Yap Islands of Micronesia in 2007, followed by a larger epidemic in French Polynesia in 2013–2014. It was during the 2015–2016 epidemic in Brazil, however, that ZIKV revealed its devastating teratogenic potential.

In May 2015, Brazilian health authorities reported the first confirmed autochthonous ZIKV cases. By late 2015, an unprecedented and alarming surge in microcephaly cases—predominantly in the northeastern states of Brazil—prompted an intensive scientific and public health response. On

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November 28, 2015, Brazil declared a national public health emergency; on February 1, 2016, the World Health Organization (WHO) declared ZIKV infection a Public Health Emergency of International Concern (PHEIC), a designation reserved for extraordinary events constituting a risk to international public health.

The constellation of congenital anomalies associated with prenatal ZIKV exposure was subsequently named Congenital Zika Syndrome (CZS), formally characterized in 2017 as a specific pattern including severe microcephaly with a partially collapsed skull, thin cerebral cortex with subcortical calcifications, macular scarring and focal pigmentary retinal mottling, congenital contractures of varying severity, and early-onset hypertonia with extrapyramidal symptoms. These features distinguish CZS from other congenital infections and define it as a novel teratogenic syndrome.

Ten years after the identification of the first CZS cases, this review provides a comprehensive synthesis of the epidemiological, clinical, neurodevelopmental, therapeutic, and preventive advances achieved during this period. It also contextualizes CZS within the framework of tropical infectious diseases, emphasizing the social determinants—including poverty, inadequate sanitation, and limited vector control—that render populations in tropical regions disproportionately vulnerable to ZIKV infection and its congenital consequences.

2. Background: Zika Virus as a Tropical Pathogen

2.1. Virology and Transmission

Zika virus is a single-stranded, positive-sense RNA virus belonging to the genus Flavivirus within the family Flaviviridae, phylogenetically related to dengue, West Nile, yellow fever, and Japanese encephalitis viruses. The ZIKV genome encodes three structural proteins—capsid (C), precursor membrane (prM), and envelope (E)—and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5). Two major lineages are recognized: the African lineage and the Asian lineage, with the Asian lineage being responsible for the Pacific and American epidemics associated with congenital disease.

The predominant route of transmission is through the bite of infected Aedes mosquitoes, principally Aedes aegypti and, to a lesser extent, Aedes albopictus. Both species thrive in tropical and subtropical environments characterized by warm temperatures, high humidity, and standing water—conditions frequently associated with rapid urbanization, inadequate infrastructure, and limited waste management. This ecological dependency firmly places ZIKV among the quintessential arboviruses of tropical medicine.

Beyond vector-borne transmission, ZIKV is unique among flaviviruses for its documented non-vectorial routes of spread, including sexual transmission (both male-to-female and female-to-male), vertical (mother-to-fetus) transmission—the primary mechanism underlying CZS—and probable transmission through blood transfusion and, in limited reports, breastfeeding. Sexual transmission and the virus's capacity to persist in seminal fluid for extended periods have added complexity to preventive strategies.

2.2. Epidemiology and Global Burden

From 2015 to 2016, ZIKV spread rapidly across the Americas, with local transmission documented in over 48 countries and territories. Brazil bore the heaviest burden; between November 2015 and October 2018, approximately 3,420 CZS cases were confirmed. The total number of children affected by CZS across 27 countries has been estimated at approximately 4,000. Epidemiological surveillance demonstrated that first-trimester maternal infection carries the highest risk for severe fetal neurological compromise, with reported risks of microcephaly ranging from 1% to 13% following confirmed maternal infection.

Since 2017, ZIKV incidence has markedly declined in the Americas, attributed to the combination of herd immunity in heavily affected populations and seasonal fluctuations in vector

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activity. Nonetheless, serological evidence demonstrates continued low-level circulation in Brazil, Colombia, and parts of the Caribbean. Internationally, localized outbreaks have continued in India, Angola, and Southeast Asian nations. The low but persistent global circulation, coupled with large susceptible populations in tropical regions, maintains the threat of future large-scale outbreaks.

ZIKV disproportionately affects populations living in poverty, in areas with high vector density, limited access to healthcare, and inadequate reproductive health services. This epidemiological profile mirrors that of neglected tropical diseases (NTDs), with which ZIKV shares determinants including vector dependence, geographic concentration in tropical low- and middle-income countries, and the compounding effects of poverty and health inequity.

3. Clinical Profile of Congenital Zika Syndrome

3.1. Neurological Manifestations

The neurological phenotype of CZS is its defining and most severe dimension. Systematic reviews and case series have characterized a spectrum of brain abnormalities in CZS-affected children. The cardinal finding is microcephaly—defined as head circumference more than two standard deviations below the mean for gestational age and sex—often with a distinctive partially collapsed skull, resulting in a furrowed scalp appearance. Severe microcephaly (more than three standard deviations below the mean) is particularly common when maternal infection occurs in the first trimester.

Neuroimaging studies, including computed tomography (CT) and magnetic resonance imaging (MRI), have revealed a consistent pattern of abnormalities: parenchymal and subcortical calcifications (particularly at the gray-white matter junction and in the basal ganglia), malformations of cortical development (lissencephaly, pachygyria, simplified gyral pattern), defective neuronal migration, corpus callosum hypoplasia or agenesis, ventriculomegaly, and brainstem and cerebellar hypoplasia. Positron emission tomography studies in animal models have demonstrated global neuroinflammation. The molecular basis involves direct ZIKV infection of neural progenitor cells (NPCs), leading to cell cycle disruption, apoptosis, and disrupted neurogenesis—processes mediated by ZIKV's tropism for the hippocampus and cortical NPCs.

A critically important clinical observation, emerging from longitudinal cohort studies in Brazil, is that CZS does not invariably manifest as microcephaly at birth. Between 65% and 83% of infants with confirmed ZIKV exposure are asymptomatic at birth. A significant proportion subsequently develop postnatal-onset microcephaly, neuromotor delay, epilepsy, or other neurological manifestations in the first months of life. This 'hidden' burden of CZS has profound implications for surveillance, as cases may be substantially undercounted in surveillance systems relying solely on microcephaly at birth.

Epilepsy affects a substantial proportion of children with CZS, with seizures reported in 48–83% of microcephalic infants in some series, often presenting as infantile spasms or multifocal epilepsy that is frequently refractory to standard anticonvulsant therapy. Hypertonia and extrapyramidal signs, including dystonia, are near-universal in severely affected children, and essentially all children with severe CZS exhibit severe cerebral palsy.

3.2. Ophthalmological Manifestations

Ocular involvement in CZS is well-established, with macular scarring and focal pigmentary retinal mottling recognized as cardinal features. Additional ophthalmic abnormalities include optic disc hypoplasia, chorioretinal atrophy, and, less commonly, microphthalmia and cataracts. Ocular manifestations may occur in the absence of microcephaly, and their identification requires systematic ophthalmic evaluation of all infants with confirmed or suspected ZIKV exposure. The estimated prevalence of ophthalmic findings ranges from 22% to 55% in different cohort studies.

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3.3. Auditory and Musculoskeletal Manifestations

Sensorineural hearing loss has been documented in a subset of CZS-affected infants, with reported prevalences of approximately 6% in some cohorts. Given the neurosensory nature of the hearing loss and the known neurotropism of ZIKV, auditory brainstem response testing is recommended as part of the comprehensive evaluation of CZS-affected children. Musculoskeletal manifestations, including arthrogryposis (congenital joint contractures), hypertonia-related limb deformities, and hip dysplasia, are observed particularly in severely affected infants and complicate rehabilitation.

3.4. Neurodevelopmental Outcomes Over Ten Years

Longitudinal follow-up studies conducted over the past decade have progressively delineated the developmental trajectory of CZS-affected children. Children with severe CZS—characterized by microcephaly, cortical abnormalities, and associated findings—demonstrate profoundly impaired outcomes across all developmental domains: gross and fine motor function, cognitive development, language acquisition, and social-emotional development. Standardized developmental assessments document performance at or near the floor of available instruments in most severely affected children.

By contrast, children exposed to ZIKV in utero without microcephaly or brain abnormalities at birth appear to follow neurodevelopmental trajectories largely within the normal range, though subtle deficits in specific cognitive and behavioral domains have been identified in some cohorts, warranting extended surveillance. The trimester of maternal infection is a critical determinant: first-trimester exposure confers substantially higher risk for severe fetal brain disruption than second- or third-trimester exposure.

Head circumference trajectories in longitudinally followed cohorts reveal that many infants without microcephaly at birth subsequently develop postnatal microcephaly within the first six months of life, even in the absence of initial brain abnormalities on neuroimaging. This dynamic pattern underscores the necessity of serial head circumference measurements and neurodevelopmental monitoring over extended periods.

4. Diagnostic Advances

4.1. Laboratory Diagnosis

Laboratory confirmation of ZIKV infection relies primarily on molecular and serological methods. Reverse transcription polymerase chain reaction (RT-PCR) of serum, urine, amniotic fluid, or cerebrospinal fluid constitutes the gold standard for confirming acute or recent ZIKV infection. However, viremia is transient, typically detectable for five to seven days following symptom onset, limiting the clinical utility of RT-PCR in subacute or retrospective settings. Urine RT-PCR may extend the diagnostic window by several days beyond that of serum.

Serological assays detect anti-ZIKV IgM and IgG antibodies; however, cross-reactivity between ZIKV and other flaviviruses—particularly dengue virus—represents a significant diagnostic challenge, particularly in regions co-endemic for multiple flaviviruses. Plaque reduction neutralization testing (PRNT) offers improved specificity but is technically demanding and not universally available. In the neonatal context, the persistence of maternal IgG complicates serodiagnosis, necessitating reliance on IgM detection in cord or neonatal blood, and RT-PCR of neonatal specimens.

Over the past decade, significant diagnostic advances have been achieved, including the development of multiplex molecular assays capable of simultaneously detecting ZIKV, dengue, and chikungunya viruses; point-of-care rapid diagnostic tests utilizing recombinant antigens; and NS1-based serological assays with improved flavivirus specificity. Whole genome sequencing has enabled phylogenetic characterization of circulating strains and molecular epidemiological tracking of ZIKV spread.

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4.2. Prenatal and Neonatal Evaluation

Prenatal diagnosis of fetal ZIKV infection and CZS has been refined through ultrasound surveillance protocols in exposed pregnancies. Fetal ultrasound findings associated with CZS include microcephaly, intracranial calcifications, ventriculomegaly, decreased brain volume, and cortical abnormalities. Fetal MRI has been used in specialized centers to more precisely characterize cortical development abnormalities. Amniocentesis with ZIKV RT-PCR of amniotic fluid has been employed in confirmed maternal infection to assess fetal infection, though the sensitivity of this approach varies by gestational timing.

For neonates, comprehensive evaluation protocols—recommended by the Brazilian Ministry of Health, the CDC, and the WHO—include head circumference measurement, neurological examination, cranial CT or MRI, ophthalmological examination, auditory brainstem response testing, and laboratory confirmation. Standardized protocols have enabled more systematic identification and documentation of CZS cases.

5. Clinical Management and Multidisciplinary Care

In the absence of a specific antiviral therapy for CZS, clinical management is fundamentally supportive and multidisciplinary. The complexity of CZS necessitates coordinated care involving neonatology, pediatric neurology, pediatric rehabilitation medicine, ophthalmology, audiology, physiotherapy, speech-language pathology, occupational therapy, nutritional support, and social work. Early intervention programs, initiated in the first months of life, aim to optimize developmental outcomes through intensive rehabilitation and habilitation.

Anticonvulsant therapy forms a cornerstone of management for the substantial proportion of children with refractory epilepsy. Ketogenic diet, vagal nerve stimulation, and other adjunctive anti-epileptic strategies have been explored given the frequent pharmacoresistance observed. Management of spasticity and dystonia—through physiotherapy, botulinum toxin injections, oral baclofen, and, in selected cases, intrathecal baclofen pump implantation—constitutes a major component of rehabilitation.

Nutritional management is critical, as dysphagia and gastroesophageal reflux are common, particularly in severely affected children. Gastrostomy tube placement is frequently necessary to ensure adequate caloric intake and prevent aspiration. Orthopedic interventions—including serial casting, orthoses, and surgical procedures for contractures—are required in a significant number of patients.

The family-centered nature of CZS management has been increasingly recognized. Caregivers—predominantly mothers—experience substantial psychological burden, including depression, anxiety, post-traumatic stress, social isolation, and financial stress resulting from the intensive caregiving demands of a severely affected child. Integrative family support programs, including psychosocial counseling, caregiver support groups, and social protection measures, are recognized as essential components of comprehensive CZS care.

In Brazil, where the CZS burden has been greatest, multidisciplinary reference centers for CZS were established in major pediatric tertiary centers, including those in Recife, Fortaleza, and Rio de Janeiro. These centers have generated the majority of longitudinal clinical data available on CZS outcomes. However, coverage has been uneven, with many affected families in underserved rural and peri-urban areas facing significant barriers to accessing specialized care.

6. Therapeutic and Preventive Advances

6.1. Antiviral Drug Development

No specific antiviral agent for ZIKV infection has received regulatory approval as of early 2026. Drug repurposing screens conducted in the years following the 2016 outbreak identified several candidate compounds with in vitro anti-ZIKV activity, including sofosbuvir (an NS5B inhibitor approved for hepatitis C), ribavirin, favipiravir, and antiparasitic agents such as ivermectin and

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chloroquine. However, translation to clinical efficacy has not been established, and concerns regarding teratogenicity preclude the use of several candidates in pregnant women—the primary target population.

Host-directed therapeutic approaches have been explored, targeting cellular pathways exploited by ZIKV for replication, including the AXL receptor tyrosine kinase (a major ZIKV entry receptor on neural progenitor cells), autophagy pathways, and the interferon signaling cascade. Humanized monoclonal antibodies (mAbs) targeting the ZIKV envelope protein have demonstrated potent neutralization in vitro and protection in animal models; in vivo, passive transfer of anti-envelope and anti-domain III sera has protected mice against lethal ZIKV challenge. Human mAb development represents a promising avenue for both therapeutic and pre-exposure prophylactic application in high-risk populations.

6.2. Vaccine Development

Vaccine development against ZIKV has been one of the most rapidly advanced research efforts in modern vaccinology. Following the 2016 emergency, over 45 vaccine candidates were identified within a two-year period, spanning DNA, mRNA, inactivated whole-virus, live-attenuated, viral vector-based (including adenovirus and modified vaccinia Ankara platforms), virus-like particle (VLP), and recombinant subunit vaccine platforms.

The immunodominant antigen across platforms is the envelope (E) protein, with the prM-E combination used in most leading candidates to promote subviral particle formation and robust neutralizing antibody responses. DNA vaccine candidates, including those developed by NIAID (VRC5283 and VRC5288), demonstrated immunogenicity in Phase 1 trials in both flavivirus-naïve and seropositive participants, with neutralizing antibody responses persisting for at least 12 months following a two-dose schedule.

mRNA-based vaccines have advanced rapidly following the validation of this platform by COVID-19 vaccines. Moderna's mRNA-1893 completed Phase 2 evaluation in approximately 800 adults in the United States and Puerto Rico. These mRNA vaccines employ nucleoside-modified mRNA encapsulated in lipid nanoparticles (LNPs) expressing prM-E sequences, and have demonstrated robust and long-lasting neutralizing antibody titers in both mice and non-human primates, with protection demonstrated against ZIKV-induced congenital disease in murine pregnancy models.

Inactivated vaccine candidates include ZPIV (purified formalin-inactivated ZIKV), developed by WRAIR and subsequently advanced by Sanofi Pasteur, and VLA1601, developed by Valneva (an adjuvanted, aluminum hydroxide-adsorbed, purified inactivated candidate). VLA1601 is currently the most clinically advanced Zika vaccine candidate, with an additional Phase 1 trial initiated in March 2024. As of late 2025, 16 Zika vaccine candidates were identified in Phase 1 or 2 clinical trials, and three mAb candidates were in Phase 1 trials. Approximately USD 350 million in cumulative research funding has been mobilized for ZIKV vaccine development since 2016.

Despite this progress, no vaccine has advanced to Phase 3 efficacy trials. The primary challenge is epidemiological: the dramatic decline in ZIKV incidence since 2017 renders it practically impossible to power Phase 3 trials for the endpoint of prevention of infection or CZS under conditions of low natural transmission. Regulatory pathways including the FDA Animal Rule (extrapolating efficacy from animal models), controlled human infection studies, and correlate-of-protection approaches are under active discussion as potential avenues to licensure without traditional Phase 3 efficacy data.

Additional challenges include the potential for antibody-dependent enhancement (ADE) given cross-reactive immune responses with dengue virus (which is endemic in most ZIKV-affected populations), the ethical complexities of including pregnant women and children in vaccine trials, questions regarding the durability of vaccine-induced immunity, and the diminished commercial incentive for industry investment in the absence of sustained large-scale outbreaks.

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6.3. Vector Control and Preventive Strategies

In the absence of a licensed vaccine, prevention of ZIKV infection during pregnancy has rested predominantly on vector control measures and behavioral risk reduction strategies. Conventional vector control—including community-based source reduction (elimination of breeding sites), larviciding, and adult mosquito control with insecticides—remains the first-line approach. However, its effectiveness is limited in highly urbanized, resource-constrained settings, and insecticide resistance in Aedes aegypti populations has been increasingly documented.

Biological control strategies have gained prominence, most notably the deployment of Wolbachia-infected Aedes aegypti mosquitoes. The wMel strain of Wolbachia, an intracellular bacterium, reduces ZIKV replication within mosquitoes and decreases their vector competence. Wolbachia-based programs, operationalized by the World Mosquito Program, have been deployed in several cities in Brazil, Australia, and other countries, with a randomized trial in Yogyakarta, Indonesia demonstrating significant reduction in dengue incidence. Their impact on ZIKV transmission, while biologically plausible, has not been directly measured in efficacy trials.

The use of genetically modified (sterile or gene-drive) mosquitoes represents another emerging vector control strategy. Release of Oxitec's OX513A male Aedes aegypti—which carry a self-limiting gene suppressing offspring survival—has been trialed in Brazil and the Cayman Islands, with significant local suppression of Aedes populations. Transgenic and gene-drive approaches remain under evaluation for safety, ecological impact, and regulatory considerations.

Behavioral risk reduction measures—including the use of insect repellents containing DEET or picaridin, protective clothing, air conditioning or screened windows, and sexual transmission prevention through condom use or abstinence for travelers returning from ZIKV-endemic areas—are recommended by public health authorities. Preconception and antenatal counseling on ZIKV risk during pregnancy has been integrated into reproductive health services in endemic countries.

7. Congenital Zika Syndrome in the Context of Tropical Medicine

CZS shares fundamental characteristics with other neglected tropical diseases (NTDs): it predominantly affects populations in tropical and subtropical regions, is linked to poverty, poor sanitation, and inadequate vector control, disproportionately burdens women and children, generates catastrophic out-of-pocket healthcare expenditure for affected families, and has historically received insufficient research investment relative to its global burden.

The intersection of CZS with existing tropical disease vulnerabilities is particularly significant. Aedes aegypti, ZIKV's primary vector, is also the vector for dengue, chikungunya, and yellow fever. The co-circulation of these arboviruses in endemic regions creates diagnostic challenges, epidemiological complexity, and potential immunological interactions—including the controversial possibility that prior dengue infection may enhance ZIKV pathogenesis, or alternatively confer cross-protective immunity, depending on antibody specificities and titers.

Climate change is anticipated to expand the geographic range of Aedes mosquito vectors into previously non-endemic temperate regions, including parts of Southern Europe, North America, and highland areas of Africa and South America, thereby increasing the proportion of the global population at risk for ZIKV infection. This geographic expansion of vector habitat is one of the most significant long-term risk factors for future ZIKV outbreaks.

The burden of CZS falls most heavily on women—particularly young, low-income women in endemic regions—who not only face the risk of ZIKV infection during pregnancy but also disproportionately assume the caregiving burden for CZS-affected children. Studies documenting the psychosocial impact on caregivers—predominantly mothers—reveal high rates of depression, anxiety, social isolation, and financial impoverishment resulting from lifelong caregiving responsibilities and reduced labor market participation. This gender-differentiated burden has prompted calls for integrating CZS response into reproductive rights, women's health, and disability rights frameworks.

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The governance response to ZIKV has been instructive for tropical infectious disease preparedness more broadly. Brazil's rapid deployment of a national microcephaly surveillance system, the establishment of CZS reference centers, and the engagement of civil society organizations representing affected families demonstrated the value of coordinated, multi-level response. Conversely, gaps in the social protection system—inadequate disability benefits, limited access to specialized rehabilitation services in remote areas, and insufficient long-term support for affected families—have been extensively documented and remain incompletely addressed.

8. Discussion

Ten years after the first recognized cases of CZS, the syndrome has been comprehensively characterized as a severe, lifelong disability syndrome with origins in ZIKV teratogenesis. The past decade has witnessed transformative scientific progress: the rapid establishment of CZS as a novel teratogenic syndrome, the elucidation of ZIKV's neurodevelopmental mechanisms, the characterization of the full clinical spectrum from severe microcephaly to asymptomatic exposure, the development of standardized diagnostic and management protocols, and the unprecedented acceleration of vaccine candidate development across multiple platforms.

Yet the past decade has also revealed persistent and critical gaps. The absence of a licensed vaccine or specific antiviral therapy for ZIKV infection means that the primary defense against future CZS outbreaks remains vector control and behavioral prevention—strategies of demonstrably limited efficacy in resource-constrained endemic settings. The waning of the epidemic has simultaneously reduced both the urgency of vaccine development and the feasibility of traditional efficacy trials, creating a frustrating paradox in which scientific momentum has stalled precisely as the public health threat has receded.

The longitudinal follow-up of CZS-affected children has elucidated their highly complex and burdensome long-term needs, reinforcing the imperative for sustained, comprehensive, multidisciplinary care systems that extend across childhood and into adolescence and adulthood. The systemic challenges of delivering such care in low-resource health systems—where the burden is greatest—remain largely unresolved. The documented psychosocial and economic devastation experienced by families of CZS-affected children demands integration of social protection and psychosocial support into clinical management frameworks.

CZS also provides critical lessons for the management of emerging arboviral threats in the tropical medicine context. The intersection of climate change, urbanization, vector adaptability, and global connectivity creates conditions for the emergence or re-emergence of novel arboviruses with teratogenic potential. The scientific infrastructure, surveillance systems, and research networks built in response to ZIKV—while requiring ongoing investment—represent crucial preparedness assets for future threats. Investment in broad-spectrum antiviral strategies, platform vaccine technologies, and integrated vector management constitutes a rational and cost-effective approach to tropical infectious disease preparedness.

9. Conclusions

The decade since the recognition of Congenital Zika Syndrome has been marked by extraordinary scientific progress alongside sobering acknowledgment of the persistent gaps in prevention, treatment, and equitable care delivery. CZS has been established as a paradigmatic tropical infectious disease whose burden falls disproportionately on the most vulnerable populations in low- and middle-income tropical countries. The profound neurological, ophthalmological, auditory, and musculoskeletal consequences for affected children, and the lifelong burden imposed on their families and caregiving systems, demand sustained commitment from the global health community.

Key achievements of the past ten years include: (1) comprehensive clinical and neuroimaging characterization of CZS; (2) elucidation of ZIKV neurodevelopmental mechanisms, identifying neural

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progenitor cell tropism as central to teratogenesis; (3) longitudinal documentation of neurodevelopmental outcomes, revealing both the severity of CZS in exposed-with-abnormalities children and the relative preservation of development in those without brain abnormalities; (4) unprecedented vaccine development activity, with 16 candidates in clinical trials by 2025; and (5) improved diagnostic capacity and standardized management protocols.

Critical priorities for the next decade include: licensure of a safe and effective ZIKV vaccine through innovative regulatory pathways adapted to the challenge of low-incidence settings; development of specific antiviral therapeutics, particularly for use in pregnancy; strengthening of integrated vector control programs incorporating biological and genetic approaches; expansion of equitable access to multidisciplinary CZS care in resource-limited settings; sustained psychosocial and social protection support for affected families; and investment in surveillance systems capable of detecting future ZIKV outbreaks rapidly. The experience of CZS underscores the imperative of sustained research investment, global solidarity, and health equity in the global response to tropical infectious diseases.

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