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Feeding modifications and additional primary caregiver support for infants exposed to Zika virus or diagnosed with congenital Zika syndrome: a rapid review of the evidence

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Abstract

OBJECTIVE Infants exposed to Zika virus (ZIKV) or diagnosed with congenital Zika syndrome (CZVS) may present dysphagia, regurgitation and other feeding difficulties. They may require special feeding practices to minimise the risk of mortality, morbidity and developmental problems. Improving knowledge, skills and behaviours of caregivers may preserve health, maximise development and promote quality of life among affected infants. We reviewed intervention studies of modified feeding practices and additional primary caregiver support to improve outcomes among infants 0 to 12 months of age exposed to ZIKV or diagnosed with CZVS.

METHODS Rapid review and meta-analysis. We searched PubMed/MEDLINE and contacted experts. The search is current to 18 July 2020. We planned a meta-analysis using fixed-effect models; if unfeasible, we intended to summarise studies narratively. We planned to assess risk of bias of included studies and quality of evidence using Cochrane guidance.

RESULTS We identified 42 records for title and abstract screening; 14 were eligible for full-text assessment. Among these, no intervention studies were found. Eight observational studies reported on the nutritional status, feeding practices and outcomes among infants affected by ZIKV or diagnosed with CZVS. They are presented and discussed to provide a basis for future research.

CONCLUSIONS While no intervention studies were found, evidence from eight observational studies highlights the need for early nutrition interventions and caregiver support among infants affected by ZIKV or diagnosed with CZSV. More research is needed to assess whether modifications of feeding practices and provision of additional primary caregiver support will impact outcomes of interest.

keywords Zika, congenital, syndrome, feeding, caregiver, support

Sustainable Development Goals (SDGs): SDG 3 (good health and well-being), SDG 17 (partnerships for the goals)

Introduction

Antenatal Zika virus (ZIKV) transmission after both symptomatic and asymptomatic infection in the mother may result in congenital malformations collectively referred to as congenital Zika syndrome (CZVS) [1, 2]. The true risk of congenital malformations after ZIKV infection in pregnancy remains unknown; however, it has been estimated at about 5–15% [2]. CZVS includes microcephaly, limb contractures, high muscle tone, hearing loss, ventriculomegaly, joint abnormalities and ocular abnormalities [3, 4]. Microcephaly may result in seizures, hearing and vision deficits, intellectual disability, developmental impairment and higher mortality [5]. Reported neurological complications include Guillain–Barré syndrome, myelitis, encephalitis and neuropathy [6, 7].

CZVS manifestations may result in feeding problems such as swallowing dysfunction or dysphagia (e.g. difficulty breathing coughing or choking while feeding, or extended feeding times), or regurgitation [8]. Feeding problems may reduce nutritional intake and increase the risk of mortality, morbidity, growth abnormalities and developmental problems.

Low nutritional intake and abnormal metabolic demands due to spasticity, gastroesophageal reflux and delayed gastric emptying also associated with CZVS may result in poor nutritional status among infants exposed to ZIKV or diagnosed with CZVS [9]. Modifications to feeding may be warranted depending on the spectrum of manifestations and their severity. Current WHO guidance recommends that infants born to mothers with suspected, probable or confirmed ZIKV infection during pregnancy,

even without microcephaly, should be assessed for signs of neurodevelopmental abnormality and feeding difficulties during follow-up visits at 3, 9 and 24 months of age at a minimum [7]. Infants with CZVS presenting irritability, seizures and swallowing dysfunction or dysphagia should receive comprehensive neurodevelopmental assessment and supportive therapy [7].

Current management recommendations of dysphagia include postural correction, thickened feeds, pacing and spoon placement technique [10, 11]. Placement of a nasogastric or orogastric tube may be warranted. Recommendations for avoiding gastroesophageal reflux include slow feeding, keeping the infant upright after meals and elevating the head of the bed with support under the mattress. Supplementation may be appropriate for children with poor weight gain through additional feeds and food fortified with micronutrients [11].

Improving knowledge, skills and behaviours of caregivers of infants exposed to ZIKV or diagnosed with CZVS may be imperative for preserving health, maximising development and promoting quality of life while reducing the need for additional healthcare services [12–15]. Caregivers of children with special healthcare needs report negative impacts to their health, economics and social-related domestic areas [16, 17], and report greater rates of depression [18–20]. Stigma and discrimination are common, negatively impacting their ability to seek educational services and access healthcare needs [11].

Support for caregivers of children exposed to ZIKV or diagnosed with CZVS may be a protective factor for long-term optimal nutritional status, attainment of developmental milestones and enhanced quality of life. To our knowledge, there are no reviews assessing feeding modifications and additional primary caregiver support for infants exposed to ZIKV or diagnosed with CZVS. We therefore conducted a rapid review in order to (1) assess existing specific infant (0–12 months) feeding recommendations among those exposed to ZIKV or diagnosed with CZVS; and (2) whether primary caregivers of infants (0–12 months) exposed to ZIKV or diagnosed with CZVS should receive additional support to improve infant feeding.

Methods

WHO commissioned this review as part of an effort to update current guidance on infant feeding in areas of ZIKV transmission [21]. The protocol for this review was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/) under numbers CRD42020151827 and CRD42020151822. The protocol and review results were reported in accordance with the PRISMA statement [22] (Figure 1).

Types of studies

Studies that included an intervention and a comparison group or comparison to standard care were eligible. We searched for intervention studies that compared modified infant feeding practices to no modified infant feeding practices (typical, standard or recommended feeding by age) to improve outcomes in infants exposed to ZIKV or diagnosed with CZVS. We also searched for intervention studies that compared additional primary caregiver support, including but not limited to social support, respite care, medical support, caregiving competence support and financial support to no additional caregiver support or standard of care to improve infant outcomes in infants with complications associated to ZIKV. Tables S1 and S2 show the inclusion and exclusion criteria for this rapid review in further detail and in PICO format.

Type of participants

Infants, 0–12 months, exposed to ZIKV or diagnosed with CZVS, who presented microcephaly with or without seizures, hearing and vision deficits, intellectual disability, developmental impairment, swallowing dysfunction or dysphagia (e.g. difficulty breathing with feeding, coughing or choking during feeding or extended feeding times), irritability or regurgitation, among other symptoms associated with CZSV. For the caregiver support question, we included primary caregivers (e.g. mothers or guardians) of infants (0–12 months) exposed to ZIKV or diagnosed with CZVS.

Type of exposure

Modification of infant feeding practices for infants, 0–12 months, exposed to ZIKV or diagnosed with CZVS and additional caregiver support to infants exposed to ZIKV or diagnosed with CZVS.

Types of outcomes

The outcomes included addressed both infant feeding practices and additional support to primary caregivers. These were:

- Prevalence of infant feeding complications such as swallowing dysfunction or dysphagia (i.e. difficulty breathing with feeding, coughing or choking during feeding or extended feeding times), irritability or regurgitation;
- All-cause infant mortality;

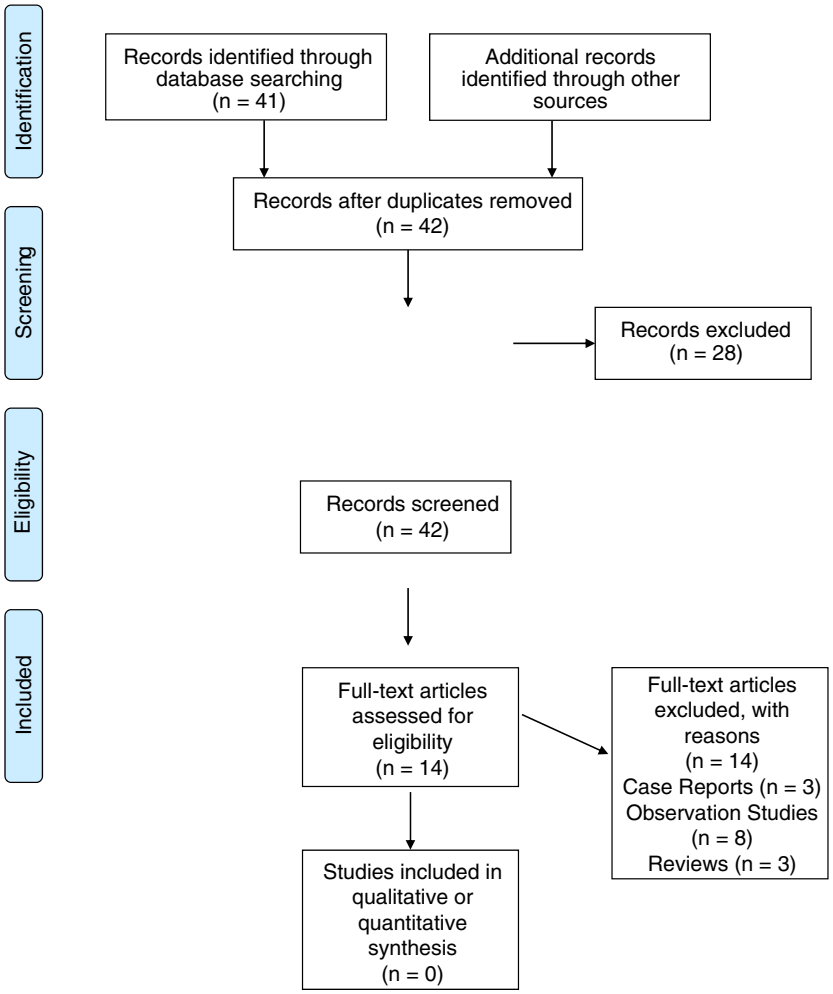

Figure 1 Prisma diagram [Colour figure can be viewed at wileyonlinelibrary.com]

- Active infant infection: respiratory infections from birth until 12 months of age within any setting such as hospital, home, health facility, etc.;
- Infant hospital admission: admissions from birth until 12 months of age;
- Growth outcomes: as assessed with WHO growth curves [23] (BMI-for-age, head circumference-for-age and weight-for-length);
- Developmental outcomes: age when the infant achieved the following WHO gross motor development milestones [24]: sitting without support, hands-and-knees crawling, standing with assistance, walking with assistance, standing alone and walking alone.

Search strategy

We searched PubMed/MEDLINE for articles in English, Spanish and Portuguese from inception until 18 July 2020. US National Library of Medicine Medical Subject Headings (MeSH) terms and text words associated to feeding, breastfeeding, breast milk, bottle feeding, weaning, complimentary feeding, babies, neonate, newborn, child and Zika virus were used. Complications related to ZIKV or part exposure or CZVS such as swallowing, choking, dysphagia and microcephaly were removed from the original search strategy in order to broaden the search. Table S3 shows the full search strategy. Additional search strategies for the identification of ongoing

and unpublished studies included contacting the WHO, Centers for Disease Control and Prevention (CDC), and researchers working on Zika-related studies in Brazil, Colombia, Puerto Rico and the United States.

Study selection

Two authors independently screened titles and abstracts and the full text of eligible studies. Discrepancies were solved by discussion or by consulting a third author. The selection process was recorded and documented following PRISMA guidance [22].

Data extraction and management

A data extraction form was developed for this review. We had planned to extract data in duplicate and independently. Discrepancies would have been solved by discussion or by consulting a third author.

Assessment of risk of bias in included studies

We had planned to assess risk of bias using the Cochrane risk-of-bias tool available in the Cochrane Handbook for Systematic reviews of Interventions [25]. The GRADE approach was going to be used for assessing the quality of the evidence [26].

Ethical considerations

We registered the protocol of this review prospectively in PROSPERO. No ethical committee approval was needed since this study did not involve human subjects or biological samples.

Results

We identified 42 records for title and abstract screening, 28 of which were excluded, mostly for study design. The fourteen remaining references were assessed in full text, but all were excluded due to study design: case reports (n = 3), observational studies (n = 8) and reviews (n = 3).

The full-text review articles encountered during the search for this rapid review covered topics on the evolving situation in 2016 of the exposure to ZIKV and CZVS in Latin American [27–29]. As previously stated, these articles were not eligible, but they also did not describe any nutrition or feeding-related findings and their effect on infant outcomes and nor the effect of support for primary caregivers on infant outcomes. The case reports we identified were clinical and laboratory studies related to testing breast milk of infected mothers for ZIKV in French Polynesia [30], New Caledonia [31] and Brazil [32].

The eight observational studies, however, reported on the nutritional status, infant feeding practices and outcomes in infants with microcephaly and without microcephaly (Table 1). These studies come from cohorts and caregivers attending clinics in Brazil. Some of these studies also contained information on support needs of the caregivers of infants exposed to ZIKV or diagnosed with CZVS.

As shown in Table 1, several of the observational studies described growth outcome differences among children exposed to ZIKV or diagnosed with CZVS compared to children unexposed to ZIKV. Weight, length, head circumference, arm circumferences and fat-free mass were lower among children exposed to ZIKV or diagnosed with CZVS at different ages [33–35], including infants hospitalised during the first days of life [36]. Weight status was also affected by type of feeding, with lower weight among those fed orally as compared to those with nasogastric or orogastric tube feeding [36] or those fed infant formula compared to breast milk (breastfeeding, expressed milk or milk bank) [36].

Nutrition and feeding practices have also been described (Table 1). Mothers reported difficulties breastfeeding infants with CZVS, possibly due to the dysphagia [35] or mouth breathing, difficulty in swallowing and excessive salivation [34], among others [37]. Infants with CZVS also had limited variety of foods in their diet and lipid intakes below recommended allowances [35]. Starch-rich meals were used to avoid choking [35, 38], displacing foods that are more nutrient-dense [35]. Iron and other micronutrient supplementation and intake of ultra-processed foods were more common among children with CZVS compared to healthy children [34].

Infant feeding complications were more prevalent among infants with CZVS (Table 1). The prevalence of swallowing disturbances varied by study, including 18% for swallowing issues and reflux [33], 48% for choking and 23% reflux [35], and 29% for reflux, 48% for general swallowing disturbances and 28% for sucking difficulties [39] and 92% for dysphagia [40]. According to one study, infants with enteral nutrition through gastrostomy or jejunostomy (16%) were more likely to present upper labial frenulum, ogival palate, dental enamel defects and delay in dental eruption, which may also affect feeding [34].

Not all infants exposed to ZIKV during pregnancy had microcephaly. Microcephaly was a major determinant of other complications such as failure to thrive, cardiac malformations, excess nuchal skin and auditory and eye

Table 1 Findings from Observational Studies

Author/Study design	Participants	Main findings
de Oliveira Vianna *et al.* (2019) [40] Longitudinal observational study	Infants/Children: Children of mothers who developed a rash coinciding with the period of ZIKV Public Health Emergency of National Concern in Brazil during or up to 3 months before gestation. 70% enrolled before 6 months of age. CZVS diagnosed in 24% of the children. Caregivers: Mothers who had a rash during pregnancy. Most < 30 years old and received at least 9 years of schooling.	Of the children with CZVS (24/108), 92% had dysphagia, three required gastrostomy tube and seven had low weight for age. All CZVS children had motor abnormalities and developmental delays that persisted after 18 months of follow-up. About 37% of families earned one or less Brazilian monthly minimum wage and 54% were residents of informal human settlements. Rash was more prevalent in the second trimester of pregnancy (45%) compared to the first and third trimesters.
dos Santos *et al.* (2019) [35] Cross-sectional descriptive study	Infants/Children: Infants living with microcephaly who were exposed to the ZIKV at birth and 12–23 months of age. Caregivers: Mothers/guardians-no additional information	Significant decrease in z-scores for weight, height and head circumference from birth to time of study visit. 80% of infants had not been exclusively breastfed during the first 6 months of life. Difficulties breastfeeding were reported by 53.6% of the mothers. Few of the children met the minimum dietary diversity criteria. Consumption of ultra-processed foods was common.
dos Santos et al. (2019) [36] Longitudinal descriptive study	Infants/Children: Newborns diagnosed with microcephaly due to exposure to ZIKV Caregivers: Most of the mothers were 18–34 years of age, 61.9% had symptoms of ZIKV during pregnancy and 80% had no partner.	There was a decrease in mean values of weight-for-age z-scores at day 8 and 14 of admission to neonatology unit. Weight-for-age z-scores were lower for infants who were fed orally compared to nasogastric or orogastric tube feeding; more aggressive feeding practices may have positively affected growth outcomes. Infant formula was also associated with a longer stay in the neonatology unit compared to infants who received breast milk (breastfeeding, expressed milk or milk bank). Most of the mothers did not have a partner and about 48% did not have a work-related income at the time of birth. Most did not receive prenatal care before 6 months of pregnancy. Mothers with 12 or more years of education had infants with higher mean weight-for-age z-score than mothers will less education.
Soares et al., 2019 [33] Prospective cohort study	Infants/Children: Full-term neonates exposed and unexposed to ZIKV during gestation. Infants were excluded if diagnosed with microcephaly. Caregivers: New mothers with symptomatic and qRT-PCR confirmed ZIKV infection during pregnancy and new mothers with no evidence of ZIKV infection during pregnancy and good mosquito bite prevention strategies.	No differences in anthropometrics between exposed and unexposed infants at birth. Differences in mid-arm circumference, arm muscle circumference and fat-free mass were present between groups at 1 and 3 months of age. Weight and length were significantly lower in the ZIKV-exposed group. Infants exposed to ZIKV had greater rates of formula-feeding during the first month of life and by the third month of life. About 17.9% of ZIKV-exposed infants presented symptoms of dysphagia compared to none among unexposed infants. Mothers in the exposed group were more likely to be overweight and obese.
Cabral Cavalcanti et al. (2020) [37] Longitudinal descriptive study	Infants/Children: Children with confirmed diagnosis of CZVS 2-17 months of age. Caregivers: Mothers-no additional information	Most children had reduced head circumference at birth and over 50% had severe microcephaly. Although 89.9% of children were breastfed at birth, breastfeeding was interrupted before 6 months. Suckling, swallowing difficulties and gastroesophageal reflux were present in 27.8%, 48.0% and 29.2% of children, respectively.

Table 1 (*Continued*)

Author/Study design	Participants	Main findings
Cranston *et al.* (2020) [41] Retrospective cohort study	Infants/Children: Infants with confirmed ZIKV antenatal exposure (mother and/or infant) with or without microcephaly Caregivers: Mothers with abnormal prenatal ultrasonographic findings related to foetal ZIKV infection, maternal virus symptoms or laboratory-confirmed tests for ZIKV during pregnancy	Most of the children with microcephaly had mothers that had been infected with ZIKV during the first trimester of pregnancy. ZIKV-exposed infants with microcephaly compared to normocephaly had higher rates of failure to thrive, cardiac malformations, excess nuchal skin, auditory abnormalities and eye abnormalities. Children exposed to ZIKV with normocephaly still experienced neurological abnormalities such as hyperreflexia, abnormal tone, congenital neuro motor signs, feeding difficulties and abnormal brain imaging results. In those with normocephaly, a smaller head circumference at birth was significantly associated with below-average cognitive scores and language scores.
Falcão do Vale *et al.* (2020) [38] Cross-sectional qualitative study	Infants/Children: Children ages 1 to 2 years old with CZVS Caregivers: Family member of child with CZVS, 18 to 42 years of age (10 mothers and 1 aunt)	One mother had separated from the father of the infant, who did not recognise the infant as his child. Four mothers were in stable relationships, and 6 were single. Six women had finished high school and ten were unemployed. Disabled care facilities and rehabilitation services provided a care network that enabled mothers to meet the needs of their children, including stimulation to develop motor and cognitive skills to reduce disability. The consistency of the foods provided to the children was described as liquid, pasty and semi-solid.
Menezes de Oliveira *et al.* (2020) [34] Cross-sectional study	Infants/Children: Children with CZVS and microcephaly and a control group of healthy children matched in mother and infant characteristics (all < 24 months of age) Caregivers: Most mothers were married or in a stable relationship, <30 years of age, only primary school education and low family income.	Children with CZVS were more likely to present mouth breathing, difficulty swallowing and excessive salivation. Among children with CZVS, nonexclusive breastfeeding until 6 months of age, use of iron supplementation, vitamin and mineral supplementation, and intake of ultra-processed foods were more common than among healthy children. About 15.6% of the children with CZVS had a gastrostomy or jejunostomy tube for enteral feeding. Children with CZVS were more likely to have low weight z-score (≤2 SD) than healthy children. Abnormal insertion of the upper labial frenulum, ogival palate, dental enamel defects and delay in dental eruption were also more common in children with CZVS.

abnormalities [41]. However, infants without microcephaly exposed to ZIKV during pregnancy still experienced neurological conditions such as hyperflexia, abnormal tone, congenital neuromotor signs, feeding complications and irregular brain imaging results [41].

Many of the studies also described the primary caregivers of infants exposed to ZIKV or diagnosed with CZVS. Most primary caregivers were mothers less than 30 years of age who did not have a partner and who lived in low-income households [34, 36, 38, 40]. In one of the studies, over 60% of mothers had not received prenatal care before 6 months of pregnancy [36]. Higher education was related to better weight status in one of the studies [36]. Caretakers of children with CZVS had very demanding daily routines of household chores, care and oversight of siblings without CZVS, care of the child with CZVS and attending child rehabilitation/stimulation centres [38]. These activities left little time for leisure, self-care and employment. Availability of space to conduct stimulation exercises and having the necessary training to conduct stimulation exercises were important for motor and cognitive development [42].

Discussion

We did not find any studies comparing either modified infant feeding practices or primary caregiver support against to no intervention among infants exposed to ZIKV or diagnosed with CZVS. We found, however, indirect evidence from observational studies highlighting the importance of early nutrition interventions to reduce the risk of diminished nutritional status over time in infants exposed to ZIKV or diagnosed with CZVS. Caregivers of infants exposed to ZIKV or diagnosed with

CZVS will most likely need continuing support in various areas of care and wellbeing [42, 43].

According to the identified observational studies, children exposed to ZIKV or diagnosed with CZVS were more likely to present dysphagia, mouth breathing, excessive salivation, reflux and other difficulties while feeding. These in turn resulted in limited nutritional intake, dietary diversity criteria and low weight and size for age. In addition, they presented motor abnormalities and developmental delays that persisted through time. These infants were more likely to receive formula and ultra-processed foods and less likely to be exclusively breastfed. It is safe to assume that strategies to improve infant feeding and provide the care and support needed in order to mediate growth and development outcomes are fundamental to the long-term quality of life for these children. Feeding practices may need to be adjusted depending on the severity of CZVS [44].

Continued research on how to maintain breastfeeding in these infant populations is of upmost importance as symptoms such as dysphagia and choking may impede the ability of the infant to properly breastfeed and reduce the risk for worse short-term and long-term outcomes related to growth and development [8]. WHO recommends exclusive breastfeeding for the first 6 months of life to promote optical growth and development of infants [45]. ZIKV has been detected in breast milk [30, 31, 46–52], and in at least two case reports, mother-to-child ZIKV transmission has been tracked to breast milk [51, 52]. Of these two case reports, one infant remained asymptomatic while the other developed microcephaly. A systematic review from 2019 included nine studies with 10 cases of ZIKV infection among infants [53]. Five of the cases were infected with ZIKV during pregnancy (transplacental route of infection or at delivery), one was infected 0-4 days after birth, two were infected 8 weeks to 6 months after birth, and two were infected beyond six months after birth. ZIKV was detected in the breast milk of the mothers of five confirmed cases. It is still unclear whether there is sufficient viral load in breast milk to cause infection, cold storage of expressed breast milk seems to inactivate the virus [54], and there may be mechanisms of adaptation of breastfeeding against a response to ZIKV [52].

Proper nutritional status is a great concern in infants with CZVS. As additional cases are being diagnosed in areas previously unaffected by ZIKV, such as in France [55] and other countries in Europe, and risk for CZVS continues in the other continents, information on feeding practices is warranted. There is a need for evidence on nutritional assessments, effects of nutrition and modified infant feeding practices in infants affected by ZIKV and CZVS and their effect on morbidity and mortality outcomes. As infants and children who are affected by ZIKV or diagnosed with CZVS mature, it is imperative to understand how nutrition modulates long-term growth and development outcomes and which feeding practices may be recommended to improve these outcomes and quality of life.

Providing the support needed to improve knowledge, skills and behaviours of caregivers of infants with CZVS may help to improve health, development and quality of life, which eventually will also affect the need for additional healthcare services or resources in the future. The observational studies identified in this review report that many mothers of children with CZSV are affected by poverty. Many live in low-income households and are raising their children without the help of a partner. Other researchers have shown that social isolation of caregivers and families impacted by an infant with CZVS may occur and these circumstances may bring about adverse mental health outcomes [42]. This was actually observed in Brazil among primary caregivers of children 15–26 months of age with CZVS, in which compared to caregivers of children without developmental delays, those attending children with developmental delays had significantly higher depression scores, greater economic and child care challenges, and spent more time providing health care at home [20]. These findings provide evidence that social, education and financial support for caregivers such as mothers may impact growth and development outcomes in infants with CZVS.

In conclusion, due to insufficient evidence, it cannot be determined whether modification of infant feeding practices or additional primary caregiver support will affect mortality, morbidity, growth and development in infants exposed to ZIKV or diagnosed with CZVS. Evidence is lacking on the efficacy of providing primary caregivers of infants exposed to ZIKV or diagnosed with CZVS additional support such as social support, respite care, medical support, caregiving competence support and financial support and their relationships to infant feeding complications, morbidity, mortality, growth and development outcomes.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Inclusion and exclusion criteria for modified infant feeding practices question.

Table S2 Inclusion and exclusion criteria for primary caregiver support question.

Table S3 Pubmed search strategy.

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