# Alterations in visual acuity and visual development in infants 1-24 months old either exposed to or infected by Zika virus during gestation, with and without microcephaly

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**PURPOSE** To evaluate visual acuity and visual acuity development in children from the state of São Paulo, Brazil, who were exposed to the Zika virus (ZIKV) gestationally.

**METHODS** Children who had been exposed to ZIKV during gestation and age-matched control subjects received visual acuity and funduscopic examination. ZIKV exposure was confirmed by maternal quantitative polymerase chain reaction testing or serology assay. The ZIKV group was divided into two subgroups: exposed (ZE), with only the mother having confirmed ZIKV infection, and infected (ZI), with confirmed infection. Visual acuity development was compared with prior norms and quantified by measuring visual acuity correlation with age.

**RESULTS** A total of 110 children were included: 47 who had been exposed to ZIKV (ZE, 23; ZI, 24) and 63 controls. Abnormal visual acuity was found in 5 of 24 ZI children. Of the 4 children with microcephaly, only 2 had visual acuity loss (only 1 also had abnormal funduscopic findings). There was significant correlation between age and visual acuity in both the control group ($R^2 = 0.8$; $P < 0.0000$) and the ZE subgroup ($R^2 = 0.6$; $P < 0.0000$). However, visual acuity did not correlate with age in the ZI subgroup ($R^2 = 0.04$; $P = 0.38$). Furthermore, the increment in octaves/month was much lower in the ZI subgroup.

**CONCLUSIONS** Our data indicate that visual acuity losses only occur in infants who suffered gestational-infection, not simply exposure. Lack of correlation between age and visual acuity in the ZI subgroup suggests a slowing of visual development even in the absence of microcephaly. This result may have broad implications for the deleterious effects of ZIKV on the central nervous system. (J AAPOS 2019;23:215.e1-7)

The Zika virus (ZIKV) is a single-stranded, positive sense RNA arbovirus, family flaviviridae,[1,2] first identified in the Zika Forest of Uganda.[1] ZIKV was first reported in Brazil in 2014-2015.[2,3] By 2016 the World Health Organization[4] had declared ZIKV a global health emergency. The main vector for ZIKV transmission is the mosquito *Aedes aegipty*.[2,3] Other modes include semen, breast milk, and vertical transmission from

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*Financial support: Sao Paulo State Research Foundation (FAPESP) Thematic Project #2014/26818-2 and Coordination for the Improvement of Higher Level Education Personnel (CAPES) Pró Amazonia 2013/3263 grant (DFV); visiting professorship (RDH) with DFV through a Science without Borders CAPES grant; FAPESP MSc student fellowships (LCPB, DSL, LAS, HST); FAPESP postdoctoral fellowships (KSV, VCRMF); CAPES doctoral fellowship (DD); National Council for Scientific and Technological Development (CNPq) Productivity Research Fellows (DFV, MZ, MFC). The sponsors or funding organizations had no role in the design or conduct of this research.*

*Submitted October 19, 2018.*

*Revision accepted March 31, 2019.*

*Published online June 20, 2019.*

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*1091-8531/$36.00*

*https://doi.org/10.1016/j.jaapos.2019.03.005*

mother to child via placenta.[3] Gestational ZIKV infection may lead to congenital Zika syndrome (CZS).[5-8] The most dramatic manifestation of CZS is microcephaly,[5,9-11] although CZS includes a multitude of manifestations, mainly due to neurological damage and severe intracranial volume loss.[5] CZS is associated with a partially collapsed cranium, and neurological effects such as thin cerebral cortices, seizures, polymicrogyria, subcortical calcifications, ventriculomegaly, hypoplasia or loss of the corpus callosum, decreased myelination, cerebellar hypoplasia, and brainstem and basal ganglia calcifications as well as host of somatic abnormalities such as hypertonia, limb contracture, arthrogryposis, altered craniofacial proportions, spasms, irritability, problems in swallowing and hearing losses.[5,7,8]

CZS also includes ophthalmological alterations and visual deficits.[3,5,6,12] Some ZIKV-related ophthalmological findings are structural eye alterations (microphthalmia, coloboma), cataracts, intraocular calcifications and fundoscopic alterations, such as chorioretinal atrophy, optic nerve atrophy/anomalies, optic disk anomalies, unilateral microcornea, vascular changes, retinal focal spots, severe retinal vessel attenuation, and macular pigmentation alterations, including pallor.[5,6,13,14] The effects of ZIKV-exposure on visual development have not yet been adequately characterized, especially in infected children without microcephaly. Ventura[6] reported visual loss in children with CZS (all with microcephaly): all subjects had losses in visual acuity measured with Teller Acuity Cards and changes in visual development and oculomotor function (strabismus and nystagmus).[6] Two other recent studies reported visual losses in children with confirmed or presumed ZIKV infection. Most subjects had microcephaly or other cognitive impairments and also had ophthalmologic and visual function (mainly ocular motility) damage.[13,14] The purpose of the present study was to measure visual acuity in infants and children who had been exposed to ZIKV during gestation, regardless the occurrence of microcephaly. Functional sensory evaluation of these children lets us evaluate the effects of ZIKV in exposed babies who are otherwise apparently healthy.

The measure of functional vision used in this study was grating acuity, assessed behaviorally using Teller Acuity Cards,[15] a reliable visual acuity predictive instrument, albeit with increased variability in visual acuity scores across age groups in clinical populations.[16,17] By examining a population from a region in Brazil (São Paulo, southeast of Brazil) far from Brazil's northeast (the epicenter of the ZIKV outbreak), where many cases of microcephaly have been reported, the present study helps document regional differences in the effects of the infection that may be due to differences between strains of the virus or genetic host susceptibility.[18-20]

## Subjects and Methods

This study adhered to the tenets of the Declaration of Helsinki and was approved by the University of São Paulo Institute of Psychology Ethics Committee for Human Research as well as by the University of Jundiai Medical School Ethics Committee on Research. An informed consent was signed by the parents or accompanying adult of all study subjects after the nature and purpose of the study were explained fully.

The Zika Jundiai Cohort is a ZIKV research cohort that investigates gestational exposure to ZIKV in the city of Jundiaí (SP - Brazil). It was organized in 2016 by the research team of the University Hospital of University of Jundiai Medical School led by coauthor SDP. The cohort followed 782 pregnant mothers from the beginning of pregnancy through the children's first years of life.

The study cohort comprised a gestationally exposed group of children, largely drawn from the Zika Jundiai Cohort, whose mothers had confirmed ZIKV infection during gestation. This group was divided into two subgroups: exposed (ZE) children, who were uninfected themselves but whose mothers were infected during gestation; and infected (ZI) children, who were infected gestationally. Infection was generally confirmed by RT-qPCR testing, although in some cases serologic testing and clinical evaluation were used to establish infection.

Infants were considered ZIKV exposed if their mothers had at least one positive test during pregnancy. Infants were considered to be vertically ZIKV infected if they had a positive test result within 10 days of birth to minimize the chances of including postnatally infected infants. The testing as well as the RNA extraction were performed either at the University Hospital of University of Jundiai Medical School or by the Human Genome and Stem Cell Research Center, São Paulo, using standard methods and procedures.[21]

Each child underwent a full fundus examination performed by an ophthalmologist (FMD or KSV) and a clinical evaluation performed by the Jundiai Cohort's research team to document any clinical signs and symptoms associated with the CZS.[22]

Visual acuity was assessed using the Teller Acuity Cards II (TAC II; Stereo Optical Co, Chicago, IL, in collaboration with Vistech Consultants Inc, Dayton, OH).[23,24] In children born prematurely, age was corrected (from postnatal to post-term, ie, age relative to 37 weeks), and their visual acuity was classified in comparison to norms based on post-term age, assuming that there are no differences in visual acuity between terms and healthy preterms.[25-29]

The Teller Acuity Cards consist of 15 gray 25.5 × 55.5 cm cards (35% reflectance). Each card has a peephole of 4 mm of diameter in the center to allow the experimenter to observe the child's looking behavior. Each card contains a 12 × 12 cm square-wave grating (black and white stripes, approximately 95% contrast) on one side of the central peephole. The gratings on the set of cards were 0.32, 0.43, 0.64, 0.86, 1.3, 1.6, 2.4, 3.2, 4.8, 6.5, 9.8, 13.0, 19.0, 26.0 or 38.0 cycles/cm, spaced at approximately half an octave between them. The space-averaged luminance of each grating is equal to the card's gray background.

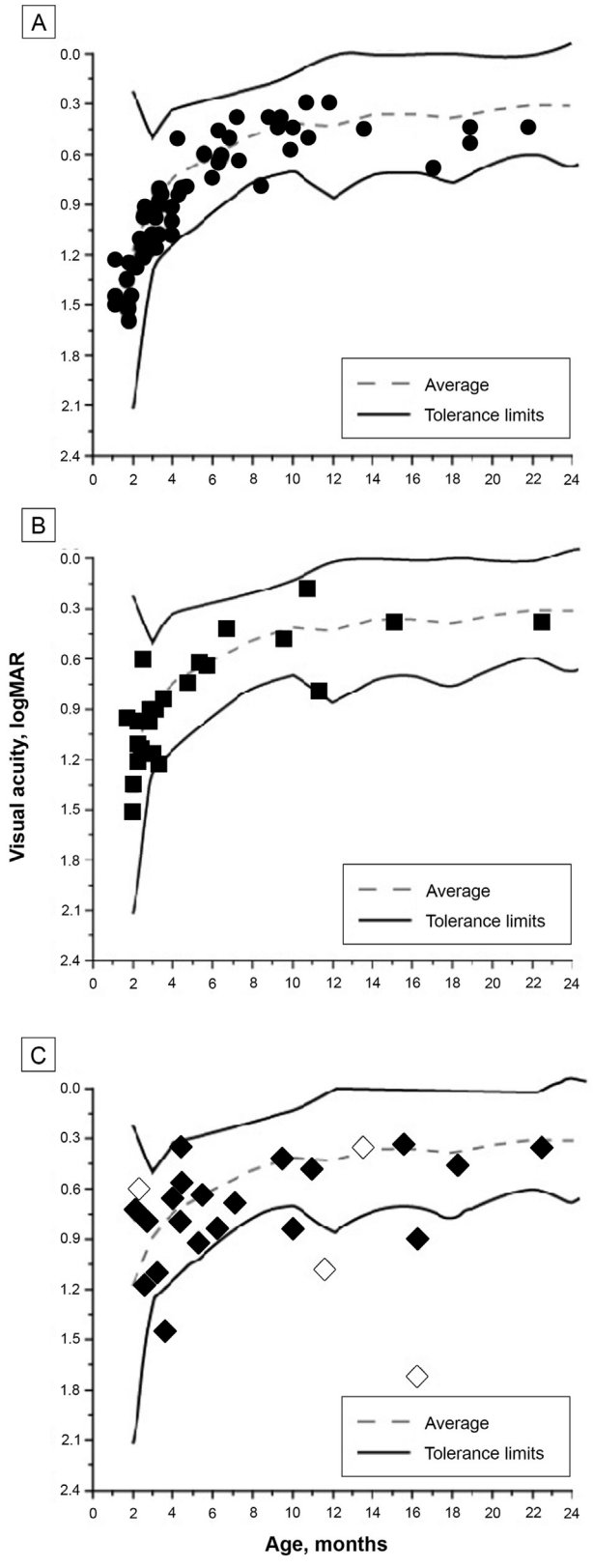


**FIG 1.** Visual acuity versus age. Dashed lines show average visual acuity versus age from Salomao and Ventura[23]; solid lines, the upper and lower tolerance limits. A, Individual data for the control group (n = 63). B, Individual data for the ZIKA-exposed (ZE) subgroup (n = 23). C, Individual data for the ZIKA-infected (ZI) subgroup (n = 24). Children with microcephaly in the ZI subgroup are marked as traced diamonds.

The child sat in an adult's lap facing an observer holding the card. The cards were presented by the observer to the child from either 38 cm (infants ≤6 months of age) or 55 cm (children >6 months). At the start of each measurement, the observer was always masked to the left-right location of the grating on the card. The observer attracted the child's attention to the card and watched the direction of her gaze through the peephole. The observer's task on each trial was to make a forced-choice guess about the location of the grating based on the child's looking behavior. An assistant positioned behind the child could see the grating location, recorded the observer's guess on each trial and gave feedback to the observer.

The cards were presented in a sequence from lowest to highest spatial frequency (SF) up to the point at which the observer made an incorrect guess about the stimulus position. After the first error, a 1-down, 1-up staircase procedure was followed. A card with lower SF (half an octave lower) and randomized grating location was presented to the child. The observer proceeded in the staircase with forced-choice guesses at progressively lower-SF cards until a correct response was given. The staircase was then reversed again, with SF increasing until observer made an error. The staircase was completed after a minimum of three reversals. Visual acuity threshold was calculated as the geometric mean of the spatial frequencies of the gratings in the final reversals then converted to logMAR values.

## Results

A total of 110 children 2-18 months of age were studied: 63 healthy controls (mean age, 5.8 ± 4.7 months; 26 males) with no ocular alterations (58 were part of the Zika Jundiai Cohort; 5 were recruited by our research team) and a gestationally exposed group of 47 children (mean age, 6.5 ± 4.1 months old; 25 males). Of these, 45 were referred from the Zika Jundiai Cohort, and 2 were referred by one of the coauthors (MZ) from the Human Genome and Stem Cell Research Center of the Biosciences Institute of University of São Paulo. The ZE group comprised 23 subjects (mean age, 5.57 ± 3.5 months; 14 males); the ZI group, 24 (mean age, 8.44 ± 5 months; 11 males).

DNA for the RT-qPCR-confirmation of infection either came from urine (25 mothers, 11 children) or saliva samples (2 children). Infection was confirmed via serology in 5 cases (2 mothers, 1 child, 2 for both mother and child). In 3 cases the infection was confirmed in mothers by both RT-qPCR and serology. In 8 cases, positive ZIKV infection in both the mother and child were confirmed by different methods (RT-qPCR, serology or clinical evaluation). Eighteen children in the sample had been born prematurely (11 controls and 7 exposed) but were otherwise healthy.

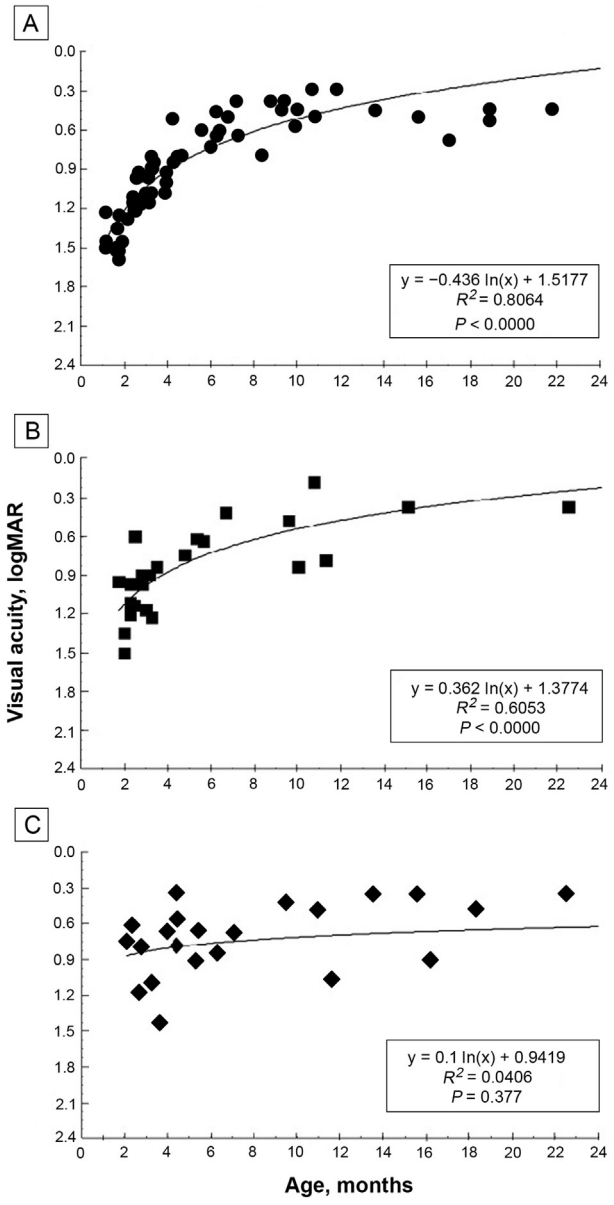


**FIG 2.** Nonlinear regression (exponential) fits to visual acuity data shown in Figure 1. A, Data from the control group showed a significant correlation (data fit between 2 and 24 months; $P < 0.0000$). B, The ZE subgroup ($P < 0.0000$) also had a significant correlation between visual acuity and age. C, The ZI subgroup ($P = 0.377$) did not have a significant correlation between visual acuity and age.

Figure 1 shows the data from the present study compared to norms from Salomão and Ventura,[30] using the same tolerance intervals they used.[30] The visual acuities of all children in the control group fell within the normal range (Figure 1A). Most children (42/47 [89%]) in both exposed subgroups had normal visual acuities (Figure 1B-C). The 5 children with below-normal visual acuity were from the ZI subgroup (5/24 [21%]; Figure 1C). Two of these had microcephaly; however, 2 other children in the ZI subgroup with microcephaly had normal visual acuity.

To quantify the time course of visual development, we calculated a nonlinear regression between logMAR visual acuity and age for each subgroup. The data and correlation lines are shown in Figure 2. There was a significant correlation between age and logMAR in both the controls ($R^2 = 0.8$; $P < 0.0000$; Figure 2A) and the ZE subgroup ($R^2 = 0.6$; $P < 0.0000$; Figure 2B) but not in the ZI subgroup ($R^2 = 0.04$; $P = 0.38$).

Even though the nonlinear regression provides us with information about the overall nonlinear trajectory of development of visual acuity, the change in visual acuity is quasi-linear over restricted age ranges, and clearly fastest during the early stages of development. We calculated a set of linear regressions over two or three restricted age ranges for each subgroup (Figure 3). For the control group (Figure 3A), the rates of increase of visual acuity with age were as follows: 0.9 octaves/month (1.2-3 months [n = 24]), 0.36 octaves/month (3.1-7.3 months [n = 23]), and 0.01 octaves/month (8.4-21.8 months [n = 16]); for the ZE subgroup (Figure 3B), 0.7 octaves/month (1.7-3 months [n = 11]), 0.6 octaves/month (3.2-6.7 months [n = 7]), and 0.07 octaves/month (9.6-22.5 months [n = 5]); for the ZI subgroup, divided into two age ranges due to small number (Figure 3C), 0.13 octaves/month (2.1-7.1 months [n = 14]) and 0.01 octaves/month (9.5-22.5 months [n = 10]). For comparison, Salomão and Ventura[30] normative data had rates of development close to our controls: approximately 1 octave/month (0.5-3 months), 0.21 octaves/month (4-8 months), and 0.01 octaves/month (10-36 months).

Only 2 of 4 children in the ZI subgroup with microcephaly had reduced visual acuity and only one had visual acuity loss and abnormal fundus examinations.

## Discussion

To our knowledge, the present study is the first to obtain functional sensory measures in infants and young children in all three categories of patients: (1) exposed to Zika virus during gestation but not infected, (2) gestationally infected without microcephaly, and (3) infected with microcephaly. The objective of our study was to characterize the ZIKV visual effects on these children, whether infected or exposed. Why some fetuses get infected but others do not is not well understood. Previous studies suggest that differences in immunologic resistance, nutrition, host susceptibility, gestational age of maternal infection, extent of placental disruption, and placental barrier resistance may help to explain this question.[18-20] Variability in infection rate of the fetuses poses a problem to the entire field of study of ZIKV. But because so little is known about the sensory-cortical developmental effects of ZIKV, the best that can be done is to quantitatively characterize all categories of exposure/infection.

Based on our data, gestational exposure did not affect ocular status, visual acuity, or visual acuity developmental time course. All children with gestational exposure to ZIKV who were negative for infection (n = 23) had normal visual acuity and no signs of retinal lesions.

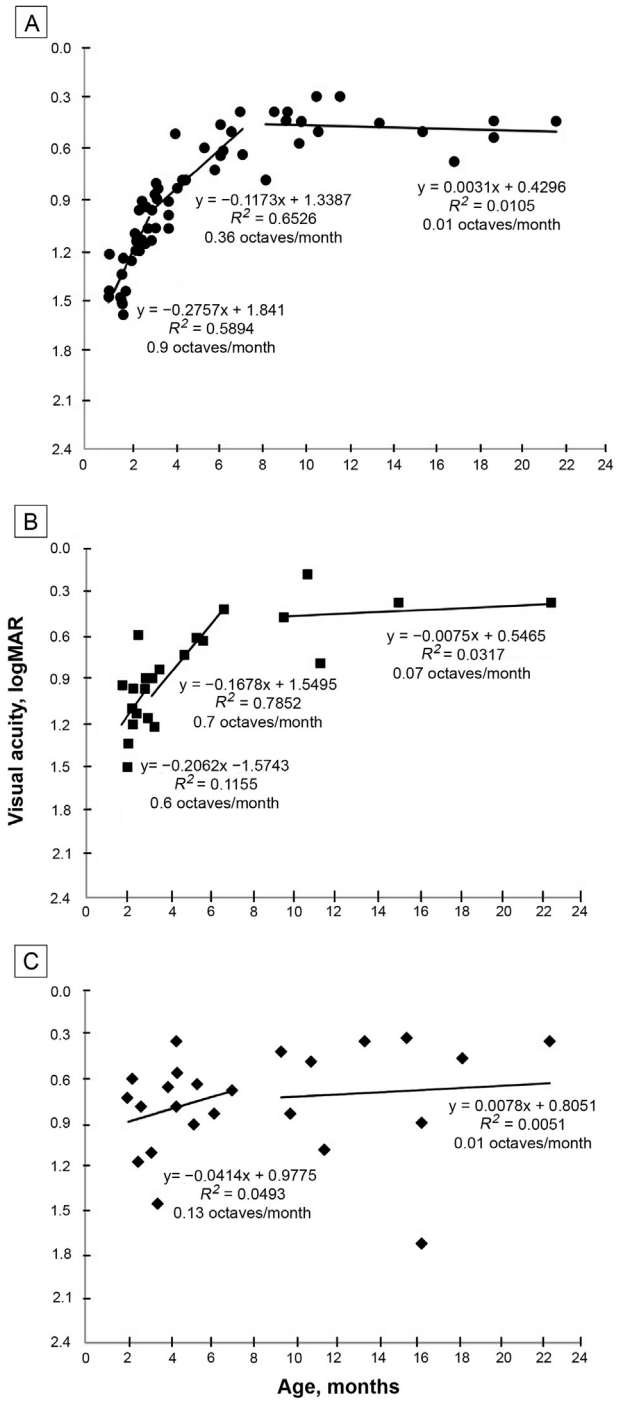


**FIG 3.** Linear regressions fits to data in different age ranges show the local rate of visual acuity development in octaves per month. Visual acuity data versus age for controls (top) and the two Zika subgroups. Solid lines show the linear regression fits for each age range with the corresponding equation and slope converted to octaves/month. A, Control group (0.9 octaves/month between 1.16 and 3 months; 0.36 octaves/month between 3.1 and 7.3 months; −0.01 octaves/month between 8.37 and 21.77 months). B, ZE subgroup (0.7 octaves/month between 1.73 and 3 months; 0.6 octaves/month between 3.17 and 6.7 months; 0.07 octaves/month between 9.57 and 22.5 months). C, ZI subgroup (0.13 octaves/month between 2.1 and 7.13 months; 0.01 between 9.53 and 22.5 months). In this subgroup we only divided the data into two age groups, because there were very few children 1-3 months. The rate of development (octaves/month) in the ZI subgroup is much slower compared with the control group and the ZE subgroup.

When ZIKV-infection was confirmed, but *without* concomitant retinal abnormalities or microcephaly, visual acuity was normal in 79% of children (19/24). By contrast, of the small number of children in our sample with microcephaly (4/24), 2 (50%) had visual loss. This is consistent with data that Ventura and colleagues[6] found in the northeast of Brazil, where 73% of ZIKV-infected children with microcephaly (22/31) had visual acuity losses, and that Tsui and colleagues[13] and Zin and colleagues[14] found in Rio de Janeiro (southeast of Brazil), where 55.4% of cognitively impaired children (49/90) had ophthalmological damage, and 95% of cognitively damaged children (50/52), most with microcephaly, had abnormal visual function.

Microcephaly does not always correlate with fundus abnormalities or visual acuity loss.[6,31] Of the 4 children with microcephaly in our study cohort, only 1 had abnormal fundus findings; 2 had normal visual acuity and fundus examinations.

The ophthalmological examination of the children studied here did not reveal any fundus damage, with the exception of 1 child with microcephaly. Ventura and colleagues[6] found that, although all of their 32 patients with microcephaly had visual acuity loss, only 14 had retinal and/or optic nerve findings. This highlights the fact that the neurological damage in the central nervous system dominates ZIKV-caused visual impairment.

The visual acuities of most children in the ZI subgroup *without* microcephaly were within the normative tolerance limits, but a correlation analysis of the data suggests that the time course of visual acuity development has been slowed (see Figures 1C, 2C). The age versus logMAR visual acuity correlation was not significant for this subgroup. This was in contrast to the control and ZE data, where there was a significant developmental increase in visual acuity. The absence of correlation between logMAR and age suggests that when there is a ZIKV-infection, visual acuity development may be slowed even in the absence of microcephaly or immediate acuity loss.

The rate of visual acuity development (in octaves/month) in both age ranges of the ZI subgroup was substantially slower than the rate for both the control and ZE subgroups, supporting the hypothesis of a slowed rate of visual acuity development in ZIKV infection without microcephaly. Therefore, visual acuity development in this subgroup should be followed longitudinally to see whether it asymptotes to normal adult levels, and parents and educators should observe these children as they reach school age, because they may manifest learning problems associated with visual or other central nervous system deficits.

Our data further supports the idea that complete visual screening, including visual acuity testing, should be performed in all children with suspected ZIKV infection,[13,14] contrary to Brazil's current guidelines.[22,32] Our research indicates that even when ZIKV-infected children are otherwise healthy, they may have visual acuity impairment. Given that the prevalence of neurological effects of ZIKV infection in the absence of microcephaly is likely greater than the prevalence of ZIKV-induced microcephaly,[33] the potential public health implications become all the more serious.

ZIKV-exposure without infection during gestation does not seem to affect visual acuity or visual acuity development. However, when the virus is vertically transmitted to the fetus, the child may have visual impairment even without the presence of microcephaly. Our study agrees with prior research indicating that the probability of visual acuity loss is higher when the infected child also has microcephaly.

The analysis of the data from the ZI subgroup are consistent with the notion that ZIKV infection during gestation led to abnormal visual acuity development. If true, this finding has more general implications as well as profound public health relevance, because any effects on functional vision may be potential indicators of central nervous system damage, and ZIKV-infection without microcephaly is likely to be far more prevalent than the microcephaly cases.

Finally, it is worth noting that the lower incidence of microcephaly in the Jundiaí population compared with the incidence in the northeast of Brazil, and in another city in Brazil's southeast, Rio de Janeiro, is consistent with the hypothesis that there may exist important regional differences between the ZIKV viral strains or genetic host susceptibility meriting further research.

## Literature Search

PubMed, Web of Science, SciELO, and ScienceDirect at multiple points from 2016 to 2018, without date or language restriction, using the following terms: *Zika virus*, *ZIKV*, *congenital Zika syndrome*, *CZS*, *retina*, *vision*, *ophthalmology*, *visual acuity*, *VA*, and *microcephaly*.

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