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| **Supplemental Table 3. Development of children exposed to ZIKV *in-utero* without congenital zika syndrome** |
| **Study Design / reference / Study location** | **Sample size****CZS or ZIKV Exposure vs No CZS or Controls** | **Zika lab confirmation** | **Age of evaluation\*** | **Assessment** | **Main Outcomes** |
| Case Series.No control groupLopes Moreira et al., (2018)Rio de Janeiro, Brazil | 131(This study does not identify or separate children with CZS from those without) | Yes | 12-18m | Brain Imaging in 115Eye and Hearing 112, BSID-III in 104 | Abnormal findings on neuroimaging 34%. Of these, 11% had structural abnormalities. Children with normal brain imaging were 20% less likely to have a Bayley-III score 2 SD below the mean (±SD) score than those with abnormal brain imaging. |
| Cohort study.Control group.Einspieler et al., (2019)Rio de Janeiro and Belo Horizonte, Brazil | 111 prenatally exposed to ZKV: 35 CZS, 76 without CZSand 333 control group matched for sex, GA | No (Clinical criteria) | 9-20 wks12 m | GMAMOSBSID-III | 333 control infants had normal general movements and neurotypical development.76 Infants prenatally exposed without microcephaly: 84% had normal general movements and as group scored significantly lower on the MOS than neurotypical controls. GMA was a good predictor of development at 12 months. BSID-III at 12 months was abnormal in 10 children (18%) in 5 of them BSID 70-85, and in 4 <70.  |
| Cohort study: ZIKV exposed in-uteroNo control groupNielsen-Saines  et al., (2019)Rio de Janeiro, Brazil | 216 children of ZIKV infected mothers (only 6 children could have CZS) | Yes | 7-32 m | BSID-IIIHINEComplete eye and hearing exams | Prematurity 13%. Microcephaly in 6 (3.5 %).31% below-average neurodevelopment and/or abnormal eye or hearing assessments. 146 children assessed with BSID-III: 71.3% normal development. A score between 84–70 in 28% and a score <70 in at least one domain in the 12%. Language function altered in 35%. Autism in 3 childrenAn earlier gestational age at the time of ZIKV infection was a significant predictor of below average neurodevelopment. |
| Cross-sectionalNo control groupCardoso et al., (2019)Rio de Janeiro, Brazil. | 19 children of ZIKV infected mothers | NR | 1-7 m | Neuro examAIMSDDST-II | Only one child had a normal neurological evaluation. All others (18) had some signs of developmental abnormality: Hypotonia (2), hypertonia (16), Ataxia (10), dyskinesia (8), irritability (8), postural asymmetry (6). AIMS: normal 12 (63%); suspect (4); delay (3); DDST-II: normal 12 (63%), suspect 7 (37%). |
| Cross-sectional: Valdes et al., (2019)Puerto Rico | 65 infants of ZIKV infected mothers36 (55.4%) ZIKV negative and 29 (44.6%) ZIKV positive | Yes | 8.98±3.19 m(9-12) | MSEL | General cognitive and motor scores did not differ between ZIKV positive and ZIKV negative, except for receptive language score. ZIKV+ and Hurricane Maria exposure were associated with lower receptive language. |
| Cohort study.No control groupBertolli et al., (2020)Pernambuco, Brazil | 43 infants with anthropometric and laboratory criteria vs 77 with only laboratory or anthropometric criteria | Yes | Median age 23(19-26) | HINEASQ3 | Infants with anthropometric and laboratory criteria: developmental delay (79%). Severe motor impairment (61%), cerebral palsy (58%). Impaired response to auditory and visual stimuli: 54% and 49, respectively. Ocular abnormalities: retinal (16%); abnormal fixation and following (37%). Seizure screening positive (43%)Infants with only laboratory criteria or anthropometric criteria: Developmental delay mild/moderate (46%); severe (5%). |
| Case-series No control groupFaiçal et al., (2019) Salvador, Brazil | 29 children of ZIKV infected mothers | Yes | 18.2 ±3.8 | BSID-IIIOphthalmological evaluation | Delay in at least one of the BSID-III scale domains (34%), language delay (31%). Language function was the most impaired domain among the children evaluated.Cognitive: mean 102.2 ±16.9. Range 70-145. < 70: 0; 70-84: 13.8%. Language: mean 93.8±18.5. Range 47-135. < 70: 2, 70-84: 24%. Motor: mean 103.5±12.0. Range 79-127. < 70: 0, 70-84: 3.4%. Ophthalmological evaluations: no abnormalities identified. |
| Cohort studyNo control groupMulkey et al., (2020)Atlántico Department, Colombia, and WashingtonDC, USA | 77 children of ZIKV infected mothers70 No CZS7 CZS | Yes | 4-18 m | WIDEAAIMS | Of 70 without CZS, 40 (57%) infants were evaluated between 4 and 8 months of age and 60 (86%) assessed between 9 and 18 months of age. Head circumference z scores no decline over time. The median WIDEA total score was 60.5 (58-62 IQR) at time point 1 and 102.5 (83.3-123.8) at time point 2 in the 70 infants. Multidomain neurodevelopmental assessment scores deviated from normal scores as the children became older. |
| Cross-sectional: Control group Gerzson et al., (2020)Tangará da Serra, Brazil | 17 children of ZIKV infected mothersControl group 20 | Yes | 18-29 | BSID-III | Cognitive, motor and language scores: similar to 20 non-exposed infants of the same setting and same age. Only one child in the ZIKVG presented low cognitive score, the same in the control group. |
| Case-series No control groupPeçanha et al., (2020)Rio de Janeiro, Brazil | 84 children of ZIKV infected mothers | Yes | 9.7±3.1 (6-18)15.3±3.1 (12-24) | BSID-III | Assessment at 9.7m: language (12%) or motor (3.5%) delay. None children had two or more domains affected simultaneously.Assessment at 15.3 m: delay in one of the three domains (50%): cognition (5%), language (37%), motor performance (24%). 7 children at least two domains affected. Abnormalities were mainly in the language domain during the first two years of life. |
| Cross-Sectional Control groupSobral da Silva et al. 2020.,Recife, Pernambuco, Brazil | 274 children who were born in epidemic outbreak134 CZS94 no CZS46 Control group | Yes | 10-45 | SWYCBPSCPPSC | The 94 prenatally exposed babies without CZS showed a risk frequency of developmental delay similar to the control group but 2.2% showed epilepsy. |
| Case-seriesNo control groupAbtibol-Bernardino et al., (2020)Manaus, Amazonas, Brazil | 26 children of ZIKV infected mothers | Yes | 37.8 ± 3. 95m (25–42) | BSID-III | 34.6% presented abnormal results: mild delays 26.9%, moderate motor delays 3.8% and severe language delays 3.8%.4 (15%) had one abnormal domain, four (15%) two abnormal domains and one (3.8%) three abnormal domains. The most impaired domain was language, with an alteration in 30.7% (8/26) of children. Alterations of motor skills were present in 19.2% (5/26). |
| Cross-sectional study Power et al., 2020Rio de Janeiro, Brazil | 163 children of ZIKV infected mothers51 microcephaly (CZS)112 normocephalic at birth. | Yes | 19.6m(4.9 - 40.1) | BSID-IIIperformed only in all normocephalic children.In microcephaly not routinely undertaken | 112 normocephalic infants: mean composite language score of 90.3±13.1 (range 47 - 115). Mean composite motor score of 95.3±12.4, (range 50 - 124) and mean composite cognitive score of 102.8±13.5 (range 65 – 145). 26% presented severe delay for the language domain, 20% severe delay for the motor domain and 11% severe delay for the cognitive domain.Odds of microcephaly were higher in families with lower household income and higher household crowding. Maternal secondary and higher education appeared to have a protective effect for microcephaly compared to primary education. |
| Cohort studyBlackmon et al., 2020Grenada | 71children of ZIKV-uninfected mothers71 children of ZIKV infected mothers | Yes | 24 m | Pediatric epilepsy screening questionnaireVideoelectroencepha-lography | Epilepsy in 2/71 children of ZIKV infected mothers (IR: 2.8%; 95% CI: 0.34–9.81%) and 0/71 in children of ZIKV-uninfected mothers (IR: 0.00; 95% CI: 0.00–5.36%). Global epilepsy incidence rates range from 0.10% to 0.15% in the first year of life. |
| Case seriesNo control groupAndrade et al., 2021Rio de Janeiro. Brazil | 96 children of ZIKV infected mothers | Yes | 12-18 m | BSID-III | 35.4% scored below the normal range in at least one Bayley-III domain. The majority (91.2%) of the infants with delayed scores presented language delay, which was not associated with the gestational age at exposure. Receptive language was more affected than expressive language (27.0% vs 19.8%). Significant, association between the head circumference Z-score at birth and language delay. |
| Case seriesNo control groupAizawa et al., 2020Sao Paulo, Brazil | 31 children of ZIKV infected mothers | Yes | 33–38 m 36±1,24 m | BSID-III | Most children (74%) had average neurodevelopmental scores and 8 children (26%) presented delay in some domain. Language was the most affected: 7 (22.6%) had a delay in this domain (2 severe delay). Moderate delay was detected in the cognitive (3.2%) and motor (10%) domains. Maternal illness in the third trimester of pregnancy and later gestational age at birth were associated with higher Bayley-III scores |
| Case-seriesNo control groupCardona-Ospina et al., 2021Risaralda, Colombia | 16 normocephalic | Yes | 28 m(23-31) | Abbreviated neurodevelopment scale 2 validated for Colombia | Five patients presented post-natal microcephaly and six patients developed macrocephaly. Patients with a normal head circumference had normal neurodevelopment. 15/16 had normal neurodevelopment, only one patient with microcephaly persisted with impairment of the neurodevelopment at the end of follow-up. |
| Cohort studyGrant et al., 2021Guadeloupe, Martinique, and French Guiana | 156 of ZIKV infected mothers vs79 without ZIKV exposure | Yes | 24 m (±1 m) | ASQ3M-CHATFrench MacArthur Inventory Scales (IFDC) for French language acquisition. | 15.4% ZIKV-exposed toddlers and 25.3% ZIKV-unexposed toddlers had an ASQ result below the reference − 2SD cut-off (P = 0.10) for at least one of the five ASQ dimensions.*In utero* ZIKV exposure and sex were identified as independent predictors of an ASQ score for communication below the − 2SD cut-off. No differences in M-CHAT and in mean language acquisition. |
| Cohort studyFamiliar et al., 2021Yucatan, Mexico | 60 of ZIKV infected mothers vs60 without ZIKV exposure | Yes | Approximately 6 m | MSELFTII using automated eye-tracking instrumentation | All MSEL subscale scores, except expressive language, significantly lower among ZIKV exposed children compared to controls, including the overall standard composite (80 ± 10 vs. 87 ± 7.4, respectively).No statistical differences in FTII eye-tracking measures of fixation and gaze. |
| Age of evaluation: mean ± standard deviation or median (range). m=months, wks= weeks, y= years. AIMS - *Alberta Infant Motor Scale;* ICF: *The International Classification of Functioning Disability and Health*; ASQ-3 *Ages and Stages Questionnaire, 3rd edition*; BSID-III: *Bayley Scales of Infants and Toddler Development – 3rd edition*; BISQ: *Brief Infant Sleep Questionnaire;* BPSC: *Baby Pediatric Symptom Checklist*; *CFCS = communication function classification scale*; DDST: Denver Developmental *Screening Test II;* EABR:Electrical Auditory Brainstem Response; EADCS *= eating and drinking ability classification scale;* FTII = Fagan test of infant intelligence; GMA: *General Movements Assessment;* GMFM-66: *Gross Motor Function Measure;* GMFCS: *Gross Motor Function Classification System;* HINE: *Hammersmith Infant Neurological Examination*; IQR: interquartile range, MACS*: manual ability classification scale*, M-CHAT=Modified Checklist for Autism on Toddlers; MOS*: Motor Optimality Score;* MSEL: *Mullen Scales of Early Learning;* NR: *Non reported*; PEDI: *Pediatric Evaluation of Disability Inventory*;PPSC: *Preschool Pediatric Symptom Checklist;* SD: *standard deviation; SWYC:* Survey of Wellbeing of Young Children. WIDEA: *Warner Initial Developmental Evaluation of Adaptive and Functional Skills.* |

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