contribution of ZIKV congenital infection. Furthermore, the population attributable fractions of congenital ZIKV infection reported by Pomar et al. for any adverse and severe adverse outcomes were 47% and 61%, respectively, suggesting the importance of other contributing factors to the congenital ZIKV symptomatology[5]. No control group was included by Nielsen-Saines et al., further limiting the conclusions. In agreement, prematurity, which may be an important confounding factor, was significantly associated with an abnormal developmental score and may have contributed to a potential overestimation of the risk (see Supplemental Table 1 in ref. [1]). Maternal coinfection may have played the same role. This further emphasizes the need for controlled studies with information about other potential contributing factors and the necessity to systematically test exposed newborns at birth.

Overall, we believe that this first prospective analysis of long-term outcomes by Nielsen-Saines et al. provides reassuring information and highlights the fact that the overall risk of severe adverse outcomes in cases of maternal ZIKV infection remains low and similar to what is known for other congenital infections[4]. ❐

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Author contributions

All authors contributed equally to the discussion regarding the Nielsen-Saines et al. study. M.V. and D.B. wrote the draft. D.B. supervised the work.

Competing interests

The authors declare no competing interests.

Reply to 'A critical analysis of neurodevelopmental and neurosensory outcomes after 2 years for children with in utero Zika virus exposure'

Nielsen-Saines et al. reply — In reference to the observations made by Vouga et al.[1], 31.5% of children with PCR-confirmed antenatal Zika virus (ZIKV) exposure had below-average neurodevelopment and/or hearing or visual deficits in our cohort[2]. We should emphasize that all children in our study were born to women with symptomatic ZIKV infection and confirmed ZIKV viremia or viruria during gestation (i.e., a high-risk cohort of children). There were 28 preterm infants (13%); 18 (two-thirds of preterm children) were born between 35 and 37 weeks. Fourteen preterm children had below-average Bayley-III results[3]; the others were developmentally normal. Three preterm children had severe neurologic abnormalities with structural brain defects characteristic of congenital Zika syndrome, and one additional child also had macular hypoplasia. Hearing deficits were noted in six preterm children, including one child with structural brain defects. Five preterm children scored 2 s.d. below average (developmental delay) and nine scored 1 s.d. below average (at risk for developmental delay) in one or more Bayley-III domains[3,4]. An association between prematurity and Bayley-III scores ≤ -1 s.d. was noted ($P = 0.008$)[1], while a statistically significant association was not seen for scores ≤ -2 s.d. ($P = 0.09$). We concur prematurity may influence neurodevelopment. Nevertheless, eight preterm children had other findings suggestive of congenital infection (characteristic neuroimaging and/or hearing loss). Preterm infants in the cohort by definition had ZIKV in utero exposure, so we cannot rule out one condition versus the other. Because ZIKV antenatal exposure induces poor neurodevelopmental outcomes in a subset of children, it is possible delayed neurodevelopment was potentiated in infants already at risk. We acknowledge the absence of a control group as a study limitation. However, because Zika was epidemic in Rio de Janeiro, it was very challenging to rule out antenatal ZIKV exposure in a control pediatric population of the same age and from the same environment, as control group mothers could have had asymptomatic ZIKV infection during pregnancy. This is further complicated by the difficulty in diagnosing ZIKV infection retrospectively because of the narrow period of viremia and short-lived IgM responses, plus serologic cross-reactivity with dengue viruses[5]. It is important to stress, however, that we observed a very skewed distribution towards below-average neurodevelopment in our pediatric cohort. In a general population comprising healthy children, a normal bell-shaped curve distribution across Bayley-III domains ranging from very above average, above average, average, below average and very below average (>2 s.d. to < −2 s.d.) would be generally anticipated[2], with most children falling within 1 to −1 s.d. of the normal range (average development) and similar proportions of children falling in above average and below average categories. Our findings emphasize the need for long-term follow-up of ZIKV-exposed children. We have established a cohort of children born to women with no symptoms of ZIKV in pregnancy during the time of the Rio epidemic. We are in the process of performing extensive serologic testing to ensure only ZIKV-unexposed children are followed as controls. For future neurodevelopmental assessments, we will report results in both populations. In regard

to coinfections, all mother–infant pairs were tested for additional maternal or congenital infections including toxoplasmosis, syphilis, cytomegalovirus, herpes simplex virus, HIV, chikungunya, Epstein-Barr virus and parvovirus B-19, among others[6], so it seems unlikely that abnormalities were attributable to other infections. We recently completed an analysis of ZIKV vertical transmission in our cohort, and results will be forthcoming. ❐

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Competing interests

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