Microcephaly not a reliable indicator of congenital Zika virus syndrome in infants

França GVA, Schuler-Faccini L, Oliveira WK, Henriques CMP, Carmo EH, Pedi VD, Nunes ML, Castro MC, Serruya S, Silveira MF, Barros FC, Victora CG. (Secretariat of Health Surveillance, Ministry of Health, Brasilia; Programa de Pós-Graduação em Epidemiologia, Universidade Federal de Pelotas, Pelotas; Universidade Federal do Rio Grande do Sul, Rio Grande do Sul, Brazil; Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA; American Center for Perinatology, Women and Reproductive Health, Montevideo, Uruguay.) Congenital Zika virus syndrome in Brazil: A case series of the first 1501 livebirths with complete investigation. *Lancet* 2016;**388:**891–7.

SUMMARY

This study, the largest published case series on suspected Zika virus infection till date, presents a review of 1501 live-born infants in Brazil. The study uses data from the Brazilian Ministry of Health (MoH) surveillance system set up in November 2015, for microcephaly and central nervous system (CNS) malformations possibly associated with congenital infection. Researchers reviewed all 1501 live-born infants with suspected congenital Zika virus infection for whom investigation by medical teams at the state level had been completed by 27 February 2016. The analysis included clinical (gender, gestational age, imaging findings, maternal history of rash, mortality) and anthropometric (head circumference and birth weight) characteristics. Based on neuroimaging and laboratory findings, the suspected cases were further classified into five categories according to diagnostic certainty of Zika infection: definite (laboratory evidence of Zika virus infection), highly probable (specific neuroimaging findings, laboratory tests negative for other congenital infections), moderately probable (specific neuroimaging findings, but other congenital infections could not be ruled out), somewhat probable (imaging studies not reported in detail and laboratory tests for other congenital infections negative or unavailable), and discarded (not included in the above categories).

Of the 1501 suspected cases of congenital Zika virus syndrome reported to the Brazilian MoH, 899 (60%) cases were discarded and 602 (40%) cases were classified into definite or probable groups (76 definite, 54 highly probable, 181 moderately probable and 291 somewhat probable). Clinical, anthropometric and survival differences were minor among the four groups. However, the 899 discarded cases, when compared to the other four groups, had larger head circumferences (mean Z scores –1.54 *v.* –3.13), lower first-week mortality (14 per 1000 *v.* 51 per 1000), and their mothers were less likely to experience a rash during pregnancy (21% *v.* 61%). The earlier the rash occurred during pregnancy, the smaller was the mean head circumference at birth, suggesting a causal association. However, rashes in the third trimester of pregnancy were also linked with brain abnormalities despite normal head sizes. About 20% of definite or probable cases presented head circumferences in the normal range (above –2 SD below the median of the InterGrowth standard) and history of rash was not reported in the mothers of one-third of definite and probable cases. Predictably, the peak of the microcephaly epidemic occurred in November 2015, about 6 to 9 months after the peak of the Zika virus epidemic in northeast Brazil.

Zika virus congenital syndrome is a new teratogenic disease and findings of this study suggest that many definite and probable cases have normal head circumference values and their mothers do not

experience a rash during pregnancy. On the contrary, most suspected cases ended up being normal newborn babies with small heads. Newborns infected with the virus late in pregnancy may go unreported, even if they have brain defects, due to their head size being within the normal range. Hence, Zika virus infection cannot be accurately diagnosed in newborns solely on the basis of microcephaly screening and these criteria need to be revised in order to detect all affected newborn babies.

COMMENT

The emergence of Zika virus, a mosquito-borne virus of the Flaviviridae family in Brazil in 2014 and its subsequent causal association with microcephaly and other brain defects in newborn infants of infected mothers,[1,2] was acknowledged by the WHO and the Centers for Disease Control and Prevention (CDC), USA in April 2016.[3–5] It is now apparent that the virus, discovered in 1947 in Uganda and hitherto associated mostly with asymptomatic or mild illness, can cause substantial neurological complications as evidenced by the dramatic surge in the incidence of Guillain–Barré syndrome and microcephaly coinciding with the Zika epidemic in northeastern Brazil.

Zika represents an unprecedented emergency and consequences of brain damage due to microcephaly and other Zika-related birth defects can be devastating with long-lasting social and economic repercussions.[6] In the context of a public health emergency with several uncertainties and rapidly evolving scientific data, this evidence-based study is timely and highlights the drawbacks of current screening methods for congenital Zika virus infections.

Microcephaly has been considered the hallmark of congenital Zika virus syndrome in infants. However, this study confirms that Zika virus infection cannot be accurately diagnosed solely on the basis of screening for microcephaly. The sensitivity of microcephaly alone (head circumference ≤32 cm) to detect definite or probable cases was 83%, which increased slightly to about 87% when a history of rash in the mother was considered. The positive predictive value of a rash in suspected cases was only 71% suggesting that the screening criteria must be revised in order to detect all affected newborn babies. Signs and symptoms of the infection and other neurological abnormalities should be included in screening, regardless of the head circumference of newborns. In a linked comment to this study, Heukelbach and Werneck highlight the urgent need for an accurate serological test which can be included in routine prenatal care.[7]

The limitations of this study include incomplete documentation intrinsic to routine surveillance systems and restricted information about other infectious causes of microcephaly. Since the study subjects were selected on the basis of screening for microcephaly, this would have led to a potential bias and overestimation of specificity and sensitivity of diagnosis in the study.[7] Since knowledge about Zika virus congenital syndrome is rapidly evolving, the cut-off point for head circumference used for microcephaly screening in this study may need to be modified in future.

Zika virus infection has not been reported in India thus far; serological evidence of Zika was reported in a study published in 1954,[8] but it could be a result of cross-reactivity with other flaviviruses such as dengue. However, it is prudent not to be complacent about Zika, since a recent study projects India to be at high risk for Zika transmission due to several factors including large number of travellers from Zika-affected countries, presence of suitable climate and vectors to aid transmission, and limited health resources.[9] Therefore, rigorous surveillance and preparedness for Zika virus is warranted in India.[10] The current evidence on pathogenesis and the developmental defects caused by Zika infection indicate that it should be considered a TORCH pathogen[11] and future research and public health measures should be planned to mitigate the medical, social and economic consequences of Zika virus infection.

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