

Assessment of infants with microcephaly in the context of Zika virus

Interim guidance

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1. Introduction

1.1 Background

Microcephaly is a condition where a baby has a head that is smaller when compared with other babies of the same sex and age. Microcephaly is a clinical sign and not a disease. Babies born with microcephaly are at risk of developmental delay and intellectual disability and may also develop convulsions and physical disabilities including hearing and vision impairment. However, a proportion of these infants will have normal neurological development [1].

Increased rates of congenital microcephaly have been reported in the context of the Zika virus outbreak in Brazil, beginning in late 2015. However, different anthropometric cut-offs of microcephaly i.e. the measurement used to determine if a newborn has a small head or not, have been used in both surveillance and clinical care settings. These have included: <-2 standard deviations (SD) i.e. more than 2 SD below the mean, $< 3^{\text{rd}}$ centile i.e. less than the 3rd centile; and <-3 SD i.e. more than 3 SD below the mean. A head circumference cut-off <-2 SD or $<3^{\text{rd}}$ percentile is more sensitive for identifying neonates with possible microcephaly, while <-3 SD is more specific. Using different cut-off levels and approaches i.e. SD or centiles, may affect the number of neonates identified with possible microcephaly and highlights the need for case definitions in order to standardise data for surveillance and clinical care.

This document aims to provide interim guidance on standard measurement of head circumference, growth reference standards, clinical assessment and investigations required to establish a diagnosis of microcephaly and if any neurological abnormalities are associated. Separate WHO guidance on *Pregnancy management in the context of Zika virus* is available at <http://www.who.int/csr/resources/publications/zika/pregnancy-management/en/>.

An expert meeting will be held in March 2016 to develop additional guidance on identifying, reporting and managing neonates with microcephaly and other possible neurological abnormalities in the context of Zika virus infection.

1.2 Target audience

The primary audience for this guidance are health professionals directly providing care to neonates and their families including paediatricians, general practitioners, midwives, and nurses. This guidance will also be useful to those responsible for developing national and local health protocols and policies, as well as managers of maternal,

newborn and child health programmes and policy-makers in regions affected by Zika virus.

2. Interim recommendations

- a. Head circumference should be measured using standardized technique and equipment at least 24 hours after birth and within the first week of life.
- b. Head circumference should be interpreted using SD scores specific for sex and gestational age.
- c. WHO Growth Standards for term neonates [2], and Intergrowth standards for preterm neonates [3] should be used. Health care providers should be trained to measure and interpret head circumference measurements according to these standards.
- d. Neonates with a head circumference of less than -2 SD i.e. more than 2 standard deviations below the mean should be considered to have **microcephaly**. Neonates with a head circumference less than -3 SD i.e. more than 3 standard deviations below the mean should be considered to have **severe microcephaly**.
- e. Neonates with a head circumference between -2 SD and -3 SD should have a clinical assessment and subsequent regular follow up during infancy including: rate of head growth; pregnancy history and maternal and family history to assess for genetic or other causes; developmental assessment; and physical and neurological examinations for associated disabilities. A proportion of these infants will have normal neurological development.
- f. Neonates with a head circumference less than -3 SD should have neuroimaging (CT scan or MRI. Ultrasound may perhaps be performed if the fontanelle is of a sufficient size) to detect structural brain malformations. In addition, they should also have a clinical assessment and subsequent regular follow-up during infancy including: rate of head growth; pregnancy history and maternal and family history; developmental assessment; and physical and neurological examinations including hearing and ocular assessments for associated problems.
- g. Neonates with microcephaly and structural brain abnormalities diagnosed by neuroimaging, or neurological or developmental abnormalities should be considered to have **microcephaly with a brain abnormality**.

3. Guidance development

3.1 Acknowledgements

The following individuals contributed to the development of this interim guidance: Professor Satinder Aneja (Director, Division of Pediatric Neurology, Lady Hardinge Medical College, New Delhi, India); Professor Helen Cross (Clinical Neurosciences, Institute of Child Health, London, United Kingdom); Dr Angelina Kakooza (Paediatric Neurologist, Department of Paediatrics & Child Health, Makerere University College of Health Sciences, Kampala, Uganda); Professor Steven Miller (Head, Division of Neurology and the Centre for Brain & Mental Health, The Hospital for Sick Children, Toronto, Canada); Dr Ganeshwaran H Mochida (Assistant Professor, Boston Children's Hospital and Harvard Medical School, Boston, United States of America); Dr Cynthia Moore (Director, Division of Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, United States of America); Professor Scott Pomeroy (Neurologist-in-Chief, Boston Children's Hospital and Harvard Medical School, Boston, United States of America); Dr Kiran Thakur (Assistant Professor, Department of Neurology, Columbia University College of Physicians and Surgeons, New York, United States of America); Dr Vanessa van der Linden (Paediatric Neurologist, Recife, Brazil).

WHO staff from the Departments of Maternal, Newborn, Child and Adolescent Health (Rajiv Bahl, Cynthia Boschi Pinto, Anthony Costello, Anayda Portela, Nigel Rollins), Mental Health and Substance Abuse (Tarun Dua, Shekar Saxena) and Reproductive Health Research (Ian Askew; Metin Gulmezoglu, Clara Menendez), WHO Geneva and the Centro Latinoamericano de Perinatología, Department of Women's and Reproductive Health, WHO Regional Office for the Americas (Pablo Duran, Rodolfo Gomez) also supported and contributed to the guidance.

3.2 Guidance development methods

Global experts in microcephaly were identified through existing networks of paediatric neurologists. These included experts from Africa, the Americas, south-east Asia and Europe. The paediatric neurologist in Brazil who first drew attention to the clustering of microcephaly and a representative from the United States Centers for Disease

Control and Prevention (Cynthia Moore) who had been involved with early surveillance of the Zika virus outbreak in Brazil were also included. Experts from the WHO Western Pacific and Eastern Mediterranean regions were not included due to time constraints.

A conference call was convened by the WHO Geneva Department of Maternal, Newborn, Child and Adolescent Health and the Department of Mental Health and Substance Abuse on 3 February 2016. Notes for the record were documented. Based on these, an interim guidance statement was prepared. The notes for the record and draft interim guidance were circulated to the experts and WHO regional office staff. Comments and references proposed by the experts were included in the revised guidance.

3.3 Declaration of interests

S Pomeroy declared that he is the recipient of a research grant from the US National Institutes of Health. This interest was deemed non-conflicting, and the individual participated fully in the guidance development process. No other competing interests were identified. No specific funds were used to develop this interim guidance.

3.4 Review date

These recommendations have been produced under emergency procedures and will remain valid until May 2016. The Departments of Maternal, Newborn, Child and Adolescent Health and Mental Health and Substance Abuse at WHO Geneva will be responsible for reviewing this guidance at that time or before, and updating it as appropriate.

4. References

1. Dolk H. The predictive value of microcephaly during the first year of life for mental retardation at seven years. *Dev Med Child Neurol* (1991) 33: 974-983
2. World Health Organisation. The WHO Child Growth Standards. Available from <http://www.who.int/childgrowth/standards/en/>
3. Villar, José et al. (2014). International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet*; (384). 9946: 857–868

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