Neurodevelopmental Outcomes in Infants Requiring Resuscitation in Developing Countries

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Objective To determine whether resuscitation of infants who failed to develop effective breathing at birth increases survivors with neurodevelopmental impairment.

Study design Infants unresponsive to stimulation who received bag and mask ventilation at birth in a resuscitation trial and infants who did not require any resuscitation were randomized to early neurodevelopmental intervention or control groups. Infants were examined by trained neurodevelopmental evaluators masked to both their resuscitation history and intervention group. The 12-month neurodevelopmental outcome data for both resuscitated and non-resuscitated infants randomized to the control groups are reported.

Results The study provided no evidence of a difference between the resuscitated infants (n = 86) and the non-resuscitated infants (n = 115) in the percentage of infants at 12 months with a Mental Developmental Index <85 on the Bayley Scales of Infant Development-II (primary outcome; 18% versus 12%; $P = .22$) and in other neurodevelopmental outcomes.

Conclusions Most infants who received resuscitation with bag and mask ventilation at birth have 12-month neurodevelopmental outcomes in the reference range. Longer follow-up is needed because of increased risk for neurodevelopmental impairments. *(J Pediatr 2012;160:781-85)*.

Infants who require resuscitation at birth are at increased risk of neonatal mortality,[1] cerebral palsy,[2] and intellectual disabilities.[3] Approximately 6% to 10% of all newborn infants need some assistance to establish normal breathing at birth.[4-6] Once spontaneous breathing is established, most of these infants survive without requiring further support during the postnatal period.[4]

A multi-national controlled study (First Breath Trial) in which community birth attendants were trained in the World Health Organization (WHO) Essential Newborn Care course (which included bag and mask ventilation with room air) reduced stillbirths and perinatal mortality in deliveries performed by birth attendants.[7] In a multicenter first-level facility controlled study, implementation of the same educational program reduced 7-day (early) neonatal mortality.[8]

Because infants who survive after bag and mask ventilation are at higher risk for neurodevelopmental impairment, a subgroup of infants resuscitated during the FIRST BREATH Trial is being followed as part of a randomized controlled trial to determine whether a home-based intervention program can improve neurodevelopmental outcome at 3 years. Before efforts to substantially scale up neonatal resuscitation are instituted, it is important to confirm that there will not be a marked increase in handicapped survivors. Thus, the investigators evaluated the 1-year data on the control groups (both resuscitated and not resuscitated) to assess the neurodevelopmental outcome without unblinding the trial. This study was to explore the hypothesis that infants who received bag and mask resuscitation but did not have severe encephalopathy during the neonatal period

ASQ	Ages and Stages Questionnaire, second edition
BRAIN-HIT	Brain Research to Ameliorate Impaired Neurodevelopment-Home-based Intervention Trial
BSID-II	Bayley Scales of Infant Development-II
MDI	Mental Development Index
PDI	Psychomotor Development Index
RTI	Research Triangle Institute
WHO	World Health Organization

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would have comparable risk of low Mental Developmental Index (MDI, <85) at 12 months to infants who did not require any resuscitation.

Methods

Infants in 3 countries (India, Pakistan, and Zambia) in the FIRST BREATH Trial who had received bag and mask resuscitation were screened for the Brain Research to Ameliorate Impaired Neurodevelopment-Home-based Intervention Trial (BRAIN-HIT, clinicaltrials.gov ID# NCT00639184). The BRAIN-HIT is a randomized controlled trial aimed at ameliorating impaired neurodevelopment in survivors after bag and mask resuscitation with a home-based, early developmental intervention delivered by parents who were instructed and supervised by trained home visitors (parent trainers). Details on the trial design have been published.[9] Birth asphyxia was defined as the inability to initiate or sustain normal breathing at birth by using the WHO definition.[10] This definition is very inclusive, because in developing countries many neonates die because of primary or secondary apnea, which is coded as birth asphyxia. Infants were ineligible when they weighed <1500 g at birth, their neurological examination at 7 days was severely abnormal (grade III with the Ellis classification),[11] or the mother was <15 years old or unable/unwilling to participate. Infants with birth asphyxia unresponsive to stimulation and who had bag and mask ventilation at birth were randomly selected during the first week after birth with a computer-generated list from infants enrolled in the FIRST BREATH Trial. These infants were matched for country and month of birth to infants without birth asphyxia or other perinatal complications. Consent was obtained after the 7-day neurological assessment. The study was approved by the institutional review boards at the University of Alabama at Birmingham, Research Triangle Institute (RTI) International, and each participating clinical site.

The two groups compared in this study were derived from a total of 540 infants screened from November 2006 to November 2008 (**Figure**). A total of 188 of the 201 enrolled control infants who completed the 12-month evaluations are the subjects of this 1-year follow-up study. The infants randomized to developmental intervention are not reported because the investigators are masked to their outcome until the 3-year follow-up is completed.

All neurodevelopmental assessment instruments were administered by certified study neurodevelopmental evaluators (pediatricians and psychologists who were familiar with the

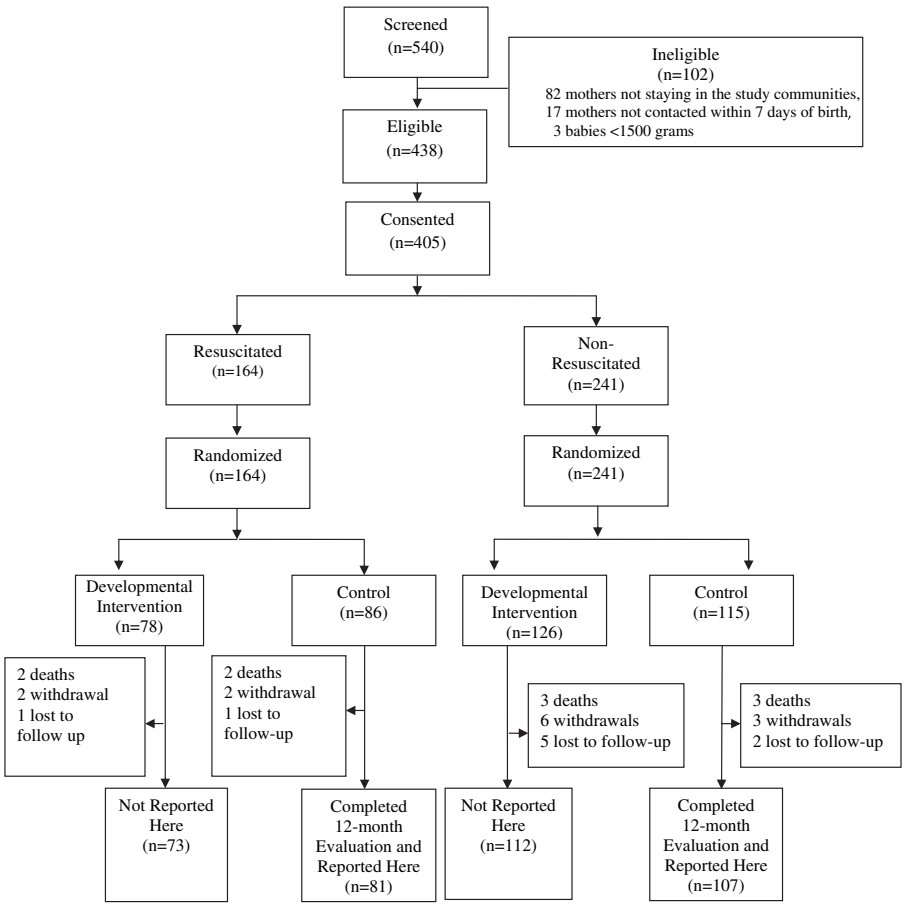

Figure. Screening and randomization flow chart. Only control infants are reported in this study.