HHS Public Access

Author manuscript

Infants Young Child. Author manuscript; available in PMC 2021 June 01.

Published in final edited form as:

Infants Young Child. 2020 June ; 33(2): 95–107. doi:10.1097/iyc.0000000000000161.

Adapting the Ages and Stages Questionnaire to Identify and Quantify Development Among Children With Evidence of Zika Infection

Jacob E. Attell, MPH,
Eagle Global Scientific, LLC, Atlanta, Georgia

Charles Rose, PhD,
National Center for Birth Defects and Developmental Disability, U.S. Centers for Disease Control and Prevention, Fort Collins, Colorado

Jeanne Bertolli, PhD,
Division of Human Development and Disability, U.S. Centers for Disease Control and Prevention, Atlanta, Georgia

Kim Kotzky, MPH,
Division of Human Development and Disability, Oak Ridge Institute for Science and Education, Atlanta, Georgia

Jane Squires, PhD,
College of Education, Center on Human Development, University of Oregon, Eugene

Nevin K. Krishna, MS,
Division of State and Local Readiness, U.S. Centers for Disease Control and Prevention, Atlanta, Georgia

Ashley Satterfield-Nash, DrPH,
Division of Human Development and Disability, Oak Ridge Institute for Science and Education, Atlanta, Georgia

Georgina Peacock, MD,
Division of Human Development and Disability, U.S. Centers for Disease Control and Prevention, Atlanta, Georgia

Isabela Ornelas Pereira, MPH,
Transmissible Diseases Department, Ministry of Health of Brazil

Ana Carolina Faria E. Silva Santelli, MD,
Overseas Strategy and Management Branch Brazil, Division of Global HIV & Tuberculosis, U.S. Centers for Disease Control and Prevention, Brasilia, Brazil

Correspondence: Jacob E. Attell, MPH, Civil Services Group, Booz Allen Hamilton, 1349 W Peachtree St NW #1400, Atlanta, GA 30309 (jacobattell@outlook.com).
Mr Attell is now with Booz Allen Hamilton, LLC, McLean, Northern Virginia.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.iycjournal.com).

Camille Smith, EdS
Division of Congenital and Developmental Disorders, U.S. Centers for Disease Control and Prevention, Atlanta, Georgia

Abstract

This article describes novel methods of applying the Ages and Stages Questionnaire—3rd edition (ASQ-3) to assess and quantify developmental delay among children following the 2015–2016 Zika virus outbreak in Brazil. Many of the children with Zika virus infection were expected to have severe developmental delay. However, administering the ASQ-3 to caregivers of these children according to standard protocol would have screened for the overall presence of delay but not the severity of delay. We adopted an amended protocol for administration of the ASQ-3 to quantify the developmental functioning of children severely affected by Zika virus infection in this investigation. Protocols for administering the ASQ-3 among this population were drafted in consultation with developmental measurement experts and are presented here. Specific developmental estimates are discussed, including developmental age equivalents, developmental quotients, and developmental quotient *z* scores. The calculations of these estimates are presented with examples in the context of the 2015–2016 Zika virus outbreak and associated microcephaly among prenatally infected children from 2 states in northeastern Brazil. Potential applications of these methods for estimating developmental ability among similar pediatric populations are discussed.

Keywords

Ages and Stages Questionnaire; child development; developmental screening; microcephaly; neurotropic infection; quantitative methods; Zika virus

THE NEURODEVELOPMENTAL trajectories of children who are affected by congenital Zika virus infection are still being investigated (Wheeler, 2018). However, we know that the damage to the brain from in utero infection and its long-term impact will be severe for many children and their families (Satterfield-Nash et al., 2017; Wheeler et al., 2018). During the 2015–2016 Zika virus outbreak in Brazil, an appropriate assessment tool to quantify developmental functioning in children with severe neurologic damage was needed because full diagnostic evaluation of developmental delay can be costly, requires highly specialized training (Gordon-Lipkin, Foster, & Peacock, 2016; Thomas, Ellis, Konrad, Holzer, & Morrissey, 2009), and was often unavailable in the areas most affected by Zika. Quantifying the variation of developmental delay severity among children exposed to Zika virus infection was necessary to further understanding of long-term effects of this emerging infection and to investigate the association of delay severity with child characteristics observable in the neonatal period, such as head circumference and length, for the purpose of early monitoring and intervention.

In circumstances in which diagnostic evaluation is unavailable, developmental screening tools are often used to assess children's development and make recommendations for subsequent monitoring and referral for diagnostic evaluation. The Ages and Stages Questionnaire—3rd edition (ASQ-3) is an empirically validated developmental screening

tool often used among low-resource populations and low- and middle-income countries to assess child development (Filgueiras, Pires, Maissonette, & Landeira-Fernandez, 2013; Kvestad et al., 2013; Squires, Potter, Bricker, & Lamorey, 1998; Wei et al., 2015). However, the ASQ-3 was not designed to assess children with very severe developmental delay like many of those born with congenital Zika infection. Building on the work of Bricker, Squires, and Clifford (2010) to extend the capability of the ASQ-3, this article describes a novel protocol for administering the ASQ-3 among at-risk children with profound developmental delay to quantify their level of functioning. Potential applications of these methods to other populations are discussed and examples are given to illustrate the calculation of relevant estimates with the adapted protocol.

INTRODUCTION

Child development is at the core of children's social, emotional, educational, and functional ability and is associated with outcomes across the life course (Feinstein & Bynner, 2004; U.S. Centers for Disease Control and Prevention, 2018). These outcomes include critical educational factors such as school readiness (Oberer, Gashaj, & Roebers, 2018; Welsh, Nix, Blair, Bierman, & Nelson, 2010), achievement, and school performance (Blankson et al., 2017). Identifying children with developmental concerns as early as possible is optimal for providing timely services to support brain development and healthy functioning throughout life (U.S. Centers for Disease Control and Prevention, 2018). Developmental screening is a method of identifying children who are at risk for developmental delay and is generally used to determine the frequency of monitoring for an individual child and/or whether a child should be referred for diagnostic evaluation (U.S. Centers for Disease Control and Prevention, 2018). The American Academy of Pediatrics recommends that all children should be screened for developmental delays, generally performed at routine well-child visits at age of 9 months, 18 months, and 24 or 30 months (American Academy of Pediatrics, 2006).

Early identification of children at risk for delay and referral for diagnostic evaluation is essential for confirming the presence of delay and coordinating appropriate follow-up care. However, diagnostic evaluation can be challenging to obtain (Antezana, Scarpa, Valdespino, Albright, & Richey, 2017; Gordon-Lipkin et al., 2016; Samms-Vaughan, 2014). Developmental screening measures are often more accessible than diagnostic evaluation and can provide an assessment of child functioning to determine the need for further testing and evaluation, which may require travel and additional resources for diagnostic certainty.

Ages and stages questionnaire

The ASQ-3 is an empirically validated tool used to screen young children for developmental delays. The ASQ-3 is a caregiver-report instrument that helps determine whether a child's development is on track, identifies children at risk for developmental delay, and encourages caregiver involvement. This tool has been validated, studied, and used for screening children in diverse international settings, including the United States, Turkey, Ecuador, Brazil, and others (Filgueiras et al., 2013; Handal, Lozoff, Breilh, & Harlow, 2007; Kapci, Küçüker, & Uslu, 2010; Singh, Yeh, & Blanchard, 2017). The ASQ-3 also has high concurrent validity,

having 90% agreement with the Battelle Developmental Inventory second edition (Pool, 2008). Furthermore, when compared with the Bayley Scales of Infant Development II, also known as the Bayley, the ASQ-3 had 100% sensitivity and 87% specificity among children with severe delays at age 24 months (Gollenberg et al., 2010). The ASQ-3 consists of 21 questionnaires for use among children from ages 1 month to 5½ years, referred to as "intervals." Each interval of the ASQ-3 consists of 30 questions about a child's abilities, organized into five domains: Communication, Gross Motor, Fine Motor, Problem Solving, and Personal–Social. For each of these questions, caregivers choose one of three possible responses for whether the child is demonstrating the skill described: "yes," "sometimes," and "not yet." The ASQ-3 was selected for a number of reasons—ease of administration, previous validation and adaptation to Brazil, commercial availability in Brazilian Portuguese, ease of training, type of staff who could be trained (i.e., those without advanced clinical training), and the capability for building capacity in a low-resource setting. Approximately 30–40 people were trained to administer the ASQ-3, which can continue to be administered in northern Brazil. In addition, as there was not a "certified" translated version of a psychological test like the Bayley, there was some urgency to use a test that had already been used and validated in Brazilian Portuguese. We consulted with the developers of the ASQ to ensure that we were not "overstepping" in the interpretation.

METHODS

Zika virus is a neurotropic infection that is associated with a host of health challenges among congenitally infected children, including microcephaly, seizures, impaired hearing and vision, and severe motor impairment (Satterfield-Nash et al., 2017). The 2015–2016 Zika virus outbreak in Brazil raised concern among clinicians and the public about the long-term health and development of children born with congenital Zika infection (Porter & Mimm, 2017). The Brazilian Ministry of Health and the U.S. Centers for Disease Control and Prevention collaborated on the Zika Outcomes and Development in Infants and Children (ZODIAC) investigation. The ZODIAC investigation was an effort to describe children conceived during the 2015–2016 outbreak with laboratory and/or clinical evidence of congenital Zika infection in the Paraíba (Macroregions 1 and 2) and Ceará states in Brazil.

The ZODIAC investigation followed a previous case-control study in Brazil and aimed to assess the long-term health and development of children with evidence of congenital Zika virus infection. The investigators recruited 150 families of children aged 15–26 months who had laboratory and/or clinical evidence of congenital Zika infection, or a blood specimen from birth available for Zika virus testing. Laboratory evidence was defined by serologic evidence that indicated either confirmed or probable infection, and clinical evidence was defined by head circumference and length measurements that indicated microcephaly, small size, or disproportionate size for gestational age and sex (Krow-Lucal et al., 2018). The children had either participated in (1) the 2016 case-control study, $n = 121$ (Krow-Lucal et al., 2018) or (2) had been reported to Registro de Eventos em Saúde Pública—Microcefalia, the national microcephaly registry for Brazil, and were participants in a previous clinical case series in Ceará, $n = 29$.

Families were recruited through up to three phone calls and one home visit. The child's primary caregiver was invited to accompany their child to an assessment visit at a participating health facility. In some cases, a second visit was necessary for follow-up evaluations. Transportation was provided to and from the health facility. Primary caregivers who were interested in participating provided written consent for themselves and their child. The ZODIAC data were collected through clinical and developmental assessments, caregiver interviews, and medical record review. Multidisciplinary data collection teams consisted of Brazilian–Portuguese-speaking pediatricians, neurologists, ophthalmologists, epidemiologists, data clerks, a data manager, administrative staff, and a field supervisor. The ZODIAC investigation methods have been described more fully elsewhere (Kotzky et al., 2019; Satterfield-Nash et al., 2017).

One of the developmental assessments used in the ZODIAC investigation was the Brazilian-adapted ASQ-3, also known as the ASQ-BR, which has been translated and validated in community settings in Brazil (for details of adaptation, see Filgueiras et al., 2013; Santana, Filgueiras, & Landeira-Fernandez, 2015). The ASQ-3 required minimal training for field staff to administer and allowed for timely identification of children with developmental concerns. The ASQ-3 has been used to assess other at-risk populations, including children born very preterm (Kerstjens et al., 2015), homeless children (Chiu & DiMarco, 2010), children with prenatal mercury exposure (Vejrup et al., 2018), and children hospitalized with human parechovirus infection (Britton et al., 2017). Trained staff and parents used the ASQ-3 materials kit to elicit and directly observe children's abilities in tandem with caregiver report following the amended protocol outlined later. The ASQ-3 materials kit was not adapted for the Brazilian population because almost all materials provided therein were not language- or context-specific (e.g., crayons, building blocks); one storybook (English language) with pictures for use with children older than 2 years was included in the kit. Future researchers may wish to translate specific materials in the kit for use in additional languages.

Clinical assessments performed on all children included a physical examination, ophthalmologic examination, and neurologic assessment. Referrals for diagnostic hearing evaluation were made if the score on the ASQ-3 communication domain was below the cut point available in the ASQ-3 User's Guide (Squires, Twombly, Bricker, & Potter, 2009). Families received referrals for computed tomographic scans and diagnostic hearing evaluations based on other clinical assessments administered as part of the ZODIAC investigation. All results were discussed with caregivers and maintained in their personal medical records.

ASQ-3 amended protocol

Many of the children with Zika virus infection were expected to have severe developmental delay. Administering the ASQ-3 to caregivers of these children according to standard protocol would have screened for the overall presence of delay but not the severity of delay. We adopted an amended protocol for administration of the ASQ-3 to quantify the developmental functioning of children severely affected by Zika virus infection in this investigation. The amended protocol allowed the use of ASQ-3 questionnaire intervals

appropriate to an individual child's *functional* skills, as opposed to the typical practice of assigning the questionnaire interval appropriate for a child's biological age, adjusted for prematurity. This amended protocol was designed by the ZODIAC team in consultation with two of the authors, an ASQ-3 subject matter expert (C.S.) and a developer of the ASQ-3 (J.S.). When selecting the appropriate questionnaire interval for an individual child on one of the five developmental domains, trained field staff were instructed to:

1. Start with the 6-month interval, regardless of chronological age.
2. If the child does not have the abilities assessed by the first two questions in the domain, go back by one age interval and administer the items in that domain.
3. If the child has the abilities assessed by all questions in the domain, move up by one age interval and administer the items in that domain.
4. Continue increasing intervals until an age interval questionnaire is administered for which the child has the abilities assessed by some but not all questions in a domain.
5. Complete and score the domain for this age interval.

See Figure 1 for visualization of this protocol. The first two questions on each ASQ questionnaire were selected for this protocol because these items represent developmental skills 2 standard deviations (*SD*s) below the average for an interval. Earlier items on each questionnaire are tasks/abilities that most children in the given age group (covered by the questionnaire) should be able to meet, given their biological age and typical development. The first two items reflect approximately 2 *SD*s below the average ASQ score for the age group covered by the questionnaire, the third and fourth items reflect approximately 1 *SD* below the mean, and the fifth and sixth items reflect approximately average or above average developmental function in the domain area. Above average functioning is not typically assessed with the ASQ-3 but may be captured by the adapted protocol described here (i.e., children in this study could be 22 months of age but advance to the 24-month questionnaire). Children for whom this is true will have a slightly upward-adjusted developmental quotient (DQ), given our adjustment by $(\frac{\text{Age}^{\text{test}}}{\text{Age}^{a}})$ as shown in Equation 2 (see Table 1). This administration protocol was performed for each domain of the ASQ-3 (i.e., communication, gross motor, fine motor, problem-solving, and personal–social) and could result in the use of multiple different age intervals for a single child. In some cases, that is, when clinicians judged children to have more typical overall development, the caregivers started with the 12-month interval questionnaire for each domain. The ASQ-3 questions were read aloud to caregivers in Brazilian Portuguese and the ASQ-3 materials kit was available to help elicit children's abilities.

The ASQ-3 screener is most often used for making decisions regarding monitoring or referral based on cutoff scores, representing 1–2 *SD*s below the mean and greater than 2 *SD*s below the mean, respectively, for each domain and questionnaire interval. Children with a score that is 1–2 *SD*s below the mean on any domain for the appropriate interval for their biological age, adjusted for prematurity, are typically considered to be at risk of developmental delay and are closely monitored and reassessed to determine whether referral

for diagnostic evaluation is indicated (Squires et al., 2009). In contrast, a score that is 2 *SD*s or more below the mean on any domain is taken as an indication for immediate referral to a specialist for diagnostic evaluation of developmental delay (Squires et al., 2009).

An ASQ-3 cutoff value can also be represented as a DQ. A DQ is a number expressing the development of a child by dividing the developmental age by the child's biological age and multiplying by 100. When the standard protocol for administering the ASQ-3 is followed, a child's caregiver will be given the ASQ questionnaire that is appropriate for his or her child's biological age (i.e., if a child is 6 months old, the caregiver would receive the 6-month questionnaire). A clinician can compare the child's score on this questionnaire with the average score of other children on the questionnaire to assess whether the child appears to be developing similarly to other children of the same age. If the child's score is below average, a clinician can examine the extent to which the child is deviating from the expected scores for his or her age and the age at which the child is functioning. In the ZODIAC investigation, ASQ-3 mean scores and *SD*s among Brazilian children were used for comparison between individual children and their peers (Filgueiras et al., 2013).

Calculation of estimates and classification

In Table 1, four equations are presented that estimate the (1) ASQ *z* score, (2) adjusted DQ, (3) DQ *z* score, and (4) developmental age equivalent. To estimate the extent of delay and to incorporate the amended protocol, we used Equation 1 to calculate an ASQ *z* score on each domain using a child's score on the instrument compared with the mean and *SD*, on that domain, of Brazilian children who received that same questionnaire (Filgueiras et al., 2013). We then used these ASQ *z* scores to obtain a DQ, a DQ *z* score, and a developmental age equivalent for each child on each domain (Equations 2–4). The DQ *z* score quantified how each child's DQ compared with the mean DQ in terms of *SD*s, and the developmental age equivalent represented the estimated functional age of the child, expressed in months.

A DQ *z* score for each child on each domain was calculated using Equation 2. Applying Equation 1, we created a *z* score for each child's numeric ASQ score, based on the distribution of ASQ scores for Brazilian children (i.e., means and *SD*). Using Equation 2, we then converted that *z* score to the distribution of DQs to which the ASQ was normed. To convert between distributions required a conversion factor to adjust the ASQ *z* score to the DQ scale. The conversion factor, 10/9, was determined with algebraic equations using *SD*s and percent delay values (e.g., −1.5 *SD* = 25% delay, 75 DQ) given in Figure 2 (see Supplemental Digital Content, available at: http://links.lww.com/IYC/A15, for additional details and derivation). The DQ estimate was adjusted by the ratio of the age interval of the questionnaire the caregiver was administered to the child's age to account for the fact that the child's age could be different from the questionnaire the caregiver received (consistent with our amended protocol). This adjustment allowed the DQ to be estimated and scaled according to the ratio of the child's functional age to actual age (Equation 2). Finally, the estimated DQ was used to calculate both an adjusted DQ *z* score (Equation 3) and a developmental age equivalent, expressed in months (Equation 3) for each child on each domain.

Developmental delay was categorized using *z* scores as commonly defined in the United States (Early Childhood Technical Assistance Center, 2015), and each domain was categorized for each child as follows:

1. At risk = 2 or more *SD*s below the mean.
2. Monitor = 1 or more *SD*s below the mean but above 2 *SD*s below the mean.
3. On track = Above 1 *SD* below the mean.

When recommended ASQ procedures cannot be followed because developmental delay is severe, these classifications of results from implementation of the amended protocol can be considered along with clinical judgement about a child's development. According to these classifications, children in Group 1 ("at risk") may be referred to a specialist for diagnostic evaluation/service provision and children in Group 2 may be monitored over time. Children in Group 3 ("on track") may be screened for delay at regular intervals as recommended by clinical practice guidelines (American Academy of Pediatrics, 2006).

Example of calculations

The caregiver of a 24-month-old child born full-term with microcephaly completed the ASQ-3 interval questionnaire for communication appropriate for an infant at 6 months of age ($\text{Mean}_{\text{Br}} = 37.1$, $SD_{\text{Br}} = 13.6$). Based on the parent's responses, the child received a score of 10. Using Equation 1, we first calculated the communication ASQ *z* score, given the child's score on the questionnaire by comparing it with the mean and *SD* for Brazilian children on the 6-month interval questionnaire for communication. Then using Equation 2, we calculated the developmental quotient for communication using the child's ASQ *z* score, the questionnaire interval the child's caregiver completed, and the child's biological age. Using Equation 3, we converted the DQ to a *z* score scaled to the distribution of DQs to which the ASQ was normed. Finally, using the DQ and Equation 4, we estimated the child's developmental age equivalent.

$$\text{ASQ}_z = \frac{10 - 37.1}{13.6} = -1.99$$

$$\widehat{\text{DQ}}_{\text{adj}} = \left[100 + 15\left(\frac{10}{9}\right)(-1.99)\right]\left(\frac{6}{24}\right) = 16.71$$

$$\widehat{\text{DQ}}^{z}_{\text{adj}} = \frac{16.71 - 100}{15} = -5.55$$

$$\widehat{\text{AE}} = \frac{16.71}{100}(24) = 4.01 \text{ months}$$

For this child, the DQ was 16.71 and the adjusted *z* score was −5.55, indicating that the child's communication ability was estimated to be far below that of his or her peers. Functionally, the child's communication ability was estimated to be the equivalent of that of an infant at 4 months of age, a difference of 20 months from the child's biological age. Using the classifications for delay, this child was classified as being at risk for delay, and referral for diagnostic evaluation and follow-up services was indicated.

RESULTS

Of the children included in the ZODIAC investigation, 74 were female (49.3%) and 76 were male (50.7%). The average age at developmental screening was 21.9 months (*SD* = 2.2). Specifically, five children were 15–17 months (3.3%), 30 were 18–20 months (20.0%), 54 were 21–22 months (36.0%), 46 were 23–24 months (30.7%), and 15 were 25–26 months (10.0%). To visualize developmental *z* scores among children with possible congenital Zika virus infection, children's development was analyzed by whether the children had microcephaly, defined as head circumference (in centimeters) less than the third percentile for age and sex at ZODIAC assessment. Of the 150 children included in the ZODIAC investigation, 50 children had microcephaly (33.3%) and 100 did not have microcephaly (66.6%). For children without microcephaly, DQ *z* scores were roughly normally distributed around zero (see Figure 3). The majority of children with microcephaly had DQ *z* scores around −6 on all domains, indicating that their development was substantially delayed relative to that of their peers (Figure 3). Children with microcephaly (average biological age = 20.3 months) had a median developmental age equivalent, averaged across all ASQ domains, of 2.2 months, compared with a median developmental age equivalent of 23.1 months among children without microcephaly (average biological age = 22.7 months). These estimates of age equivalents among children with microcephaly are similar to published estimates derived from the Denver Developmental Screening Test (Alves, Paredes, Silva, Mello, & Alves, 2018). In total, 96.0% of children with microcephaly had evidence of delay on at least one domain (*n* = 48), compared with 13.0% of children without microcephaly (*n* = 13). The ASQ-3 domain-specific delay classifications by microcephaly status are shown in Table 2.

DISCUSSION

For children with profound developmental delay, the standard ASQ administration and scoring procedures do not provide estimates of the extent of developmental delay. Given the substantial developmental delay anticipated among children in the context of the 2015–2016 Zika virus outbreak in Brazil, we developed an amended protocol that allowed us to administer ASQ-3 questionnaires appropriate to children's development. We also describe estimation of the DQ, DQ *z* score, developmental age equivalents, and classification of estimates using recommended clinical referral cutoffs. Wheeler et al. (2018) also used the ASQ-3 to assess the developmental level of children in Brazil with profound developmental delay attributable to congenital Zika virus infection. However, our method differed from that of Wheeler et al., in that we followed a systematic protocol for administration of the ASQ-3 questionnaires. Furthermore, our estimates of the functional ages of the children reflected comparison with the children's peers in Brazil and accounted for the difference between a child's age and the age interval of the questionnaire used to assess the child's skills. The amended protocol presented here may be relevant for similar assessment efforts in which children's anticipated developmental age is substantially below their biological age and quantification of delay is necessary. For example, such efforts might include assessment of children with other congenital neurotropic infections (e.g., parechovirus, rubella, and others), children born following hypoxic events during delivery (Okereafor et al., 2008), and

children with exposures to environmental toxins such as lead or mercury (Polanska et al., 2013).

The ASQ-3 is not a diagnostic tool and confirmatory evaluation is necessary for a formal diagnosis of developmental delay. Implementation of a standardized test for diagnostic evaluation, such as the Bayley Scales of Infant and Toddler Development, may be considered if appropriate resources are in place to support diagnostic assessment. However, diagnostic evaluation services for child development may be too costly or otherwise inaccessible to families. Use of a developmental screener may sometimes be the only option to quantify developmental delay in low-resource settings and could aid decisions regarding referral of children to specialty care appropriate to a child's developmental needs. In addition, a wider variety of professionals can be trained to administer the ASQ when compared with diagnostic assessment, such as the Bayley, and can help build capacity in low-resource settings.

The description of methods for calculating developmental delay estimates to classify children for follow-up monitoring or referral for evaluation is a contribution of this article. These calculations allowed us to quantify developmental delay by domain as a *z* score for individual children, even when the extent of delay was substantially outside the range of an ASQ-3 interval appropriate to the child's biological age. Furthermore, the calculation of developmental estimates for children both with and without microcephaly is of note, as previous research has focused predominantly on the former (Alves et al., 2018). Future researchers might examine the validity of the ASQ estimates presented here among this or similar populations concurrently with a developmental evaluation instrument, such as the Bayley or Battelle Scales.

For the ZODIAC investigation, we used published ASQ-3 mean and *SD* data specific to Brazil; such context- or country-specific data may be available for calculation of ASQ *z* scores in other geographic areas. In the absence of context-specific data, one may consider use of data from the ASQ-3 User's Guide (Squires et al., 2009), where appropriate. We were unable to compare calculated developmental estimates with an established diagnostic evaluation instrument for developmental delay, such as the Bayley Scales, in the present investigation. Future research might validate the present methodology with a developmental tool for diagnostic evaluation, including estimating sensitivity and specificity. In addition, future research could examine the feasibility and validity of computer-adapted protocols of this methodology. Adaptation of these methods for computer assessment may facilitate simpler administration and accessibility.

CONCLUSION

Particularly for children presumed to be "at risk," methods to quickly screen for and assess the severity of developmental delay are important for public health response to outbreaks and environmental exposures, monitoring of population health for resource allocation, and focusing prevention activities. The methods presented in this article describe how clinicians and researchers can screen children for developmental delay and estimate the degree of delay, even in situations in which children are expected to have profound developmental

delay. Thus, the methods presented in this article potentially make quantifying developmental delay accessible in a variety of settings and for children representing a broader spectrum of severity. Comprehensive testing and evaluation of these procedures are advisable to confirm their validity and reliability across populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors give special thanks to Dr. Lara Robinson, all ZODIAC participants, and investigation staff.

This research was made possible through support provided by the Office of Infectious Diseases, Bureau of Global Health, U.S. Agency for International Development (USAID), under the terms of an Interagency Agreement with the Centers for Disease Control and Prevention (CDC) and Cooperative Agreement number NU2G GH001152.

The findings and conclusions in this report and those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

REFERENCES

Alves LV, Paredes CE, Silva GC, Mello JG, & Alves JG (2018). Neurodevelopment of 24 children born in Brazil with congenital Zika syndrome in 2015: A case series study. BMJ Open, 8(7):e021304.

American Academy of Pediatrics, Council on Children with Disabilities, Section on Developmental Behavioral Pediatrics, Bright Futures Steering Committee, Medical Home Initiatives for Children with Special Needs Project, Advisory Committee. (2006). Identifying infants and young children with developmental disorders in the medical home: An algorithm for developmental surveillance and screening. Pediatrics, 118(1), 405–420. doi:10.1542/peds.2006-1231 [PubMed: 16818591]

Antezana L, Scarpa A, Valdespino A, Albright J, & Richey JA (2017). Rural trends in diagnosis and services for autism spectrum disorder. Frontiers in Psychology, 8, 590. doi:10.3389/fpsyg.2017.00590 [PubMed: 28473784]

Blankson AN, Weaver JM, Leerkes EM, O'Brien M, Calkins SD, & Marcovitch S (2017). Cognitive and emotional processes as predictors of a successful transition into school. Early Education and Development, 28(1), 1–20. doi:10.1080/10409289.2016.1183434 [PubMed: 28785157]

Bricker D, Squires J, & Clifford J (2010). Developmental screening measures: Stretching the use of the ASQ for other assessment purposes. Infants & Young Children, 23(1), 14–22. doi:10.1097/IYC.0b013e3181c816cc

Britton PN, Khandaker G, Khatami A, Teutsch S, Francis S, McMullan BJ, & Jones CA (2017). High prevalence of developmental concern amongst infants at 12 months following hospitalised parechovirus infection. Journal of Paediatrics and Child Health, 54(3), 289–295. doi:10.1111/jpc.13728 [PubMed: 28960646]

Chiu S-H, & DiMarco MA (2010). A pilot study comparing two developmental screening tools for use with homeless children. Journal of Pediatric Health Care, 24(2), 73–80. doi:10.1016/j.pedhc.2009.01.003 [PubMed: 20189059]

Early Childhood Technical Assistance Center. (2015). States' and territories' definitions of/criteria for IDEA Part C eligibility. Retrieved from https://ectacenter.org/~pdfs/topics/earlyid/partc_elig_table.pdf

Feinstein L, & Bynner J (2004). The importance of cognitive development in middle childhood for adulthood socioeconomic status, mental health, and problem behavior. Child Development, 75(5), 1329–1339. doi:10.1111/j.1467-8624.2004.00743.x [PubMed: 15369517]

Filgueiras A, Pires P, Maissonette S, & Landeira-Fernandez J (2013). Psychometric properties of the Brazilian-adapted version of the Ages and Stages Questionnaire in public child daycare centers.

Early Human Development, 89(8), 561–576. doi:10.1016/j.earlhumdev.2013.02.005 [PubMed: 23507472]

Gollenberg AL, Lynch CD, Jackson LW, McGuinness BM, & Msall ME (2010). Concurrent validity of the parent-completed Ages and Stages Questionnaires, 2nd Ed. with the Bayley Scales of Infant Development II in a low-risk sample. Child: Care Health and Development, 36(4), 485–490. doi:10.1111/j.1365-2214.2009.01041.x

Gordon-Lipkin E, Foster J, & Peacock G (2016). Whittling down the wait time: Exploring models to minimize the delay from initial concern to diagnosis and treatment of autism spectrum disorder. Pediatric Clinics of North America, 63(5), 851–859. doi:10.1016/j.pcl.2016.06.007 [PubMed: 27565363]

Handal AJ, Lozoff B, Breilh J, & Harlow SD (2007). Effect of community of residence on neurobehavioral development in infants and young children in a flower-growing region of Ecuador. Environmental Health Perspectives, 115(1), 128–133. doi:10.1289/ehp.9261 [PubMed: 17366832]

Kapci E, Küçüker S, & Uslu R (2010). How applicable are Ages and Stages Questionnaires for use with Turkish children?. Topics in Early Childhood Education, 30(3), 148–161. doi:10.1177/0271121410373149

Kerstjens JM, Nijhuis A, Hulzebos CV, van Imhoff DE, van Wassenaer-Leemhuis AG, van Haastert IC, … Dijk PH (2015). The Ages and Stages Questionnaire and neurodevelopmental impairment in two-year-old preterm-born children. PLoS One, 10(7), e0133087. doi:10.1371/journal.pone.0133087 [PubMed: 26193474]

Kotzky K, Allen JE, Robinson LR, Satterfield-Nash A, Bertolli J, Smith C, … Peacock G (2019). Depressive symptoms and care demands among primary caregivers of young children with evidence of congenital Zika virus infection in Brazil. Journal of Developmental and Behavioral Pediatrics, 40(5), 344–353. [PubMed: 30921104]

Krow-Lucal ER, de Andrade MR, Cananéa JNA, Moore CA, Leite PL, Biggerstaff BJ, … Arena JF (2018). Association and birth prevalence of microcephaly attributable to Zika virus infection among infants in Paraíba, Brazil, in 2015–2016: a case-control study. The Lancet Child & Adolescent Health, 2(3), 205–213. doi:10.1016/S2352-4642(18)30020-8 [PubMed: 30169255]

Kvestad I, Taneja S, Kumar T, Bhandari N, Strand TA, & Hysing M (2013). The assessment of developmental status using the Ages and Stages Questionnaire-3 in nutritional research in north Indian young children. Nutrition Journal, 12, 50–50. doi:10.1186/1475-2891-12-50 [PubMed: 23617745]

Oberer N, Gashaj V, & Roebers CM (2018). Executive functions, visual-motor coordination, physical fitness and academic achievement: Longitudinal relations in typically developing children. Human Movement Science, 58, 69–79. doi:10.1016/j.humov.2018.01.003 [PubMed: 29353093]

Okereafor A, Allsop J, Counsell SJ, Fitzpatrick J, Azzopardi D, Rutherford MA, & Cowan FM (2008). Patterns of brain injury in neonates exposed to perinatal sentinel events. Pediatrics, 121(5), 906. [PubMed: 18450893]

Polanska K, Hanke W, Sobala W, Trzcinka-Ochocka M, Ligocka D, Brzeznicki S, … Magnus P (2013). Developmental effects of exposures to environmental factors: The Polish mother and child cohort study. BioMed Research International, 2013, 11. doi:10.1155/2013/629716

Pool JL (2008). Parent-completed developmental screening for preschool children: A study of concurrent validity and reliability (Doctoral dissertation). Retrieved from https://scholarsbank.uoregon.edu/xmlui/handle/1794/7498

Porter S, & Mimm N (2017). Infants with congenital Zika virus infection: A new challenge for early intervention professionals. Infants & Young Children, 30(1), 17–27.

Samms-Vaughan M (2014). The status of early identification and early intervention in autism spectrum disorders in lower- and middle-income countries. International Journal of Speech–Language Pathology, 16(1), 30–35. [PubMed: 24397842]

Santana CMT, Filgueiras A, & Landeira-Fernandez J (2015). Ages & Stages Questionnaire—Brazil-2011: Adjustments on an early childhood development screening measure. Global Pediatric Health, 2, 1–12. doi:10.1177/2333794X15610038

Satterfield-Nash A, Kotzky K, Allen J, Bertolli J, Moore CA, Pereira IO, … Peacock G (2017). Health and development at age 19–24 months of 19 children who were born with microcephaly and

laboratory evidence of congenital Zika virus infection during the 2015 Zika virus outbreak—Brazil, 2017. MMWR Morbidity and Mortality Weekly Report, 66(49), 1347–1351. doi:10.15585/mmwr.mm6649a2 [PubMed: 29240727]

Singh A, Yeh CJ, & Blanchard SB (2017). Ages and Stages Questionnaire: A global screening scale. Boletín Médico del Hospital Infantil de México, 74(1), 5–12. doi:10.1016/j.bmhimx.2016.07.008 [PubMed: 29364814]

Squires J, Potter L, Bricker D, & Lamorey S (1998). Parent-completed developmental questionnaires: Effectiveness with low and middle income parents. Early Childhood Research Quarterly, 13(2), 345–354. doi::10.1016/S0885-2006(99)80043-X

Squires J, Twombly E, Bricker D, & Potter L (2009). ASQ-3 user's guide. Baltimore, MD: Paul H. Brooks Publishing Co.

Thomas KC, Ellis AR, Konrad TR, Holzer CE, & Morrissey JP (2009). County-level estimates of mental health professional shortage in the United States. Psychiatric Services, 60(10), 1323–1328. doi:10.1176/ps.2009.60.10.1323 [PubMed: 19797371]

U.S. Centers for Disease Control and Prevention. (2018). Developmental monitoring and screening. Atlanta, GA: Centers for Disease Control and Prevention.

Vejrup K, Brandlistuen RE, Brantsæter AL, Knutsen HK, Caspersen IH, Alexander J, … Haugen M (2018). Prenatal mercury exposure, maternal seafood consumption and associations with child language at five years. Environment International, 110, 71–79. doi::10.1016/j.envint.2017.10.008 [PubMed: 29089166]

Wei QW, Zhang JX, Scherpbier RW, Zhao CX, Luo SS, Wang XL, & Guo SF (2015). High prevalence of developmental delay among children under three years of age in poverty-stricken areas of China. Public Health, 129(12), 1610–1617. doi:10.1016/j.puhe.2015.07.036 [PubMed: 26318615]

Welsh JA, Nix RL, Blair C, Bierman KL, & Nelson KE (2010). The development of cognitive skills and gains in academic school readiness for children from low-income families. Journal of Educational Psychology, 102(1), 43–53. doi:10.1037/a0016738 [PubMed: 20411025]

Wheeler AC (2018). Development of infants with congenital Zika syndrome: What do we know and what can we expect? Pediatrics, 141(Suppl. 2), S154–S160. doi:10.1542/peds.2017-2038D [PubMed: 29437048]

Wheeler AC, Ventura CV, Ridenour T, Toth D, Nobrega LL, Silva de Souza Dantas LC, … Ventura LO (2018). Skills attained by infants with congenital Zika syndrome: Pilot data from Brazil. PLoS One, 13(7), e0201495. doi:10.1371/journal.pone.0201495 [PubMed: 30048541]

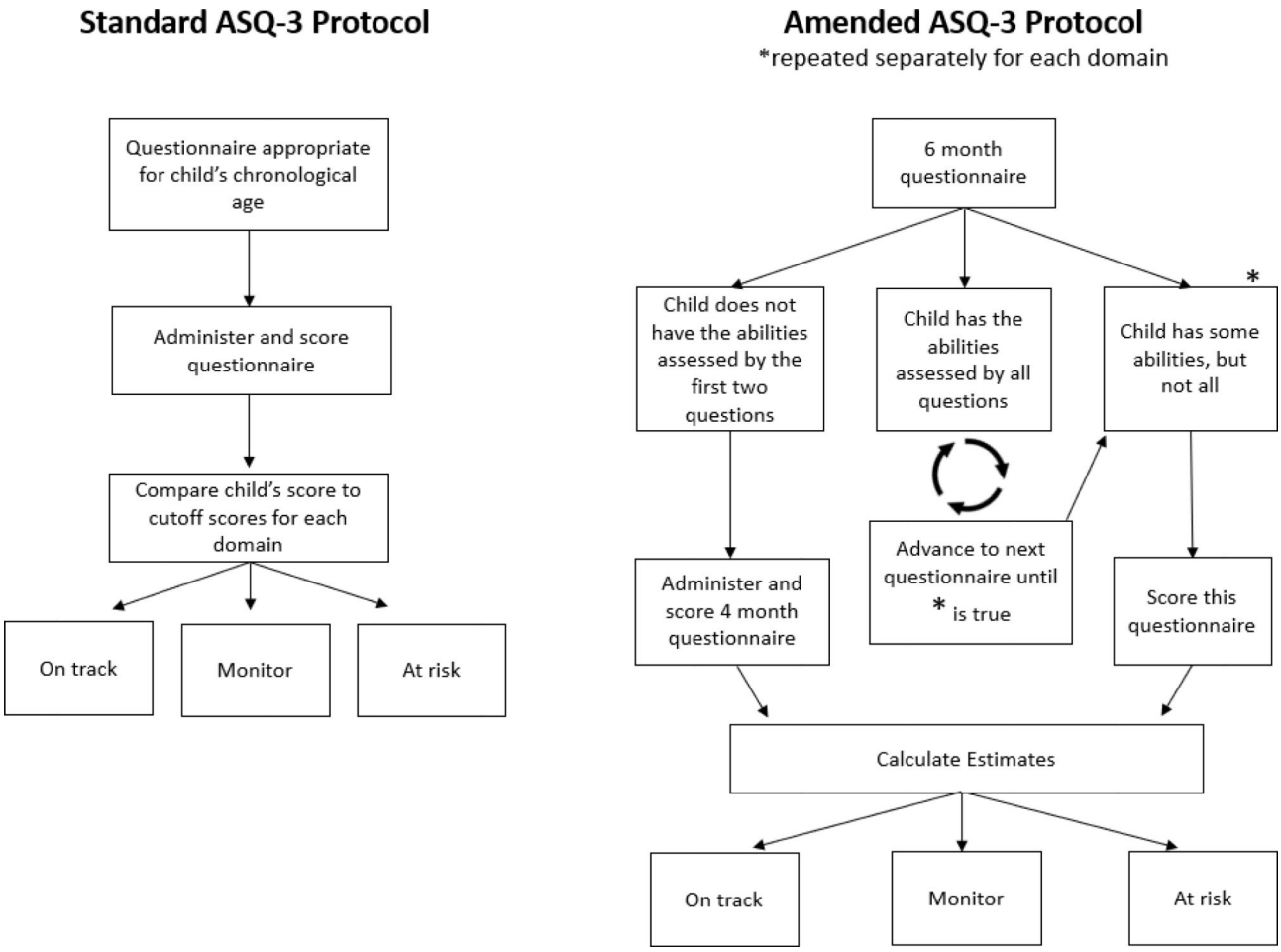

Figure 1.

Standard and amended ASQ-3 administration protocol flowchart. Standard protocol available from Squires et al. (2009), *ASQ-3 User's Guide*. The "first two items" referenced in the amended protocol represent developmental abilities 2 *SD*s below average for children of the same age as the given questionnaire. Thus, if a child cannot perform these abilities, his or her functioning is below average and the 4-month questionnaire is appropriate. ASQ-3 = Ages and Stages Questionnaire—3rd edition.

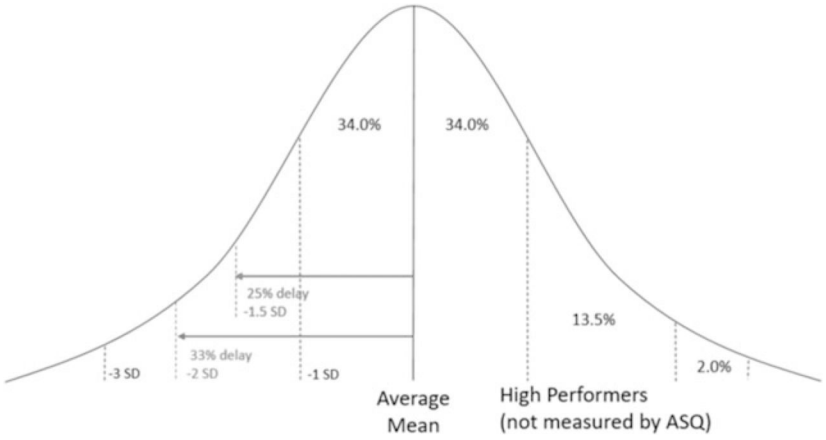

Figure 2.

ASQ distribution and percent delay estimates. *Y*-axis represents the percentage of children in the ASQ-3 normative population with a score between each *SD* range (unpublished figure courtesy of Jane Squires). ASQ = Ages and Stages Questionnaire.

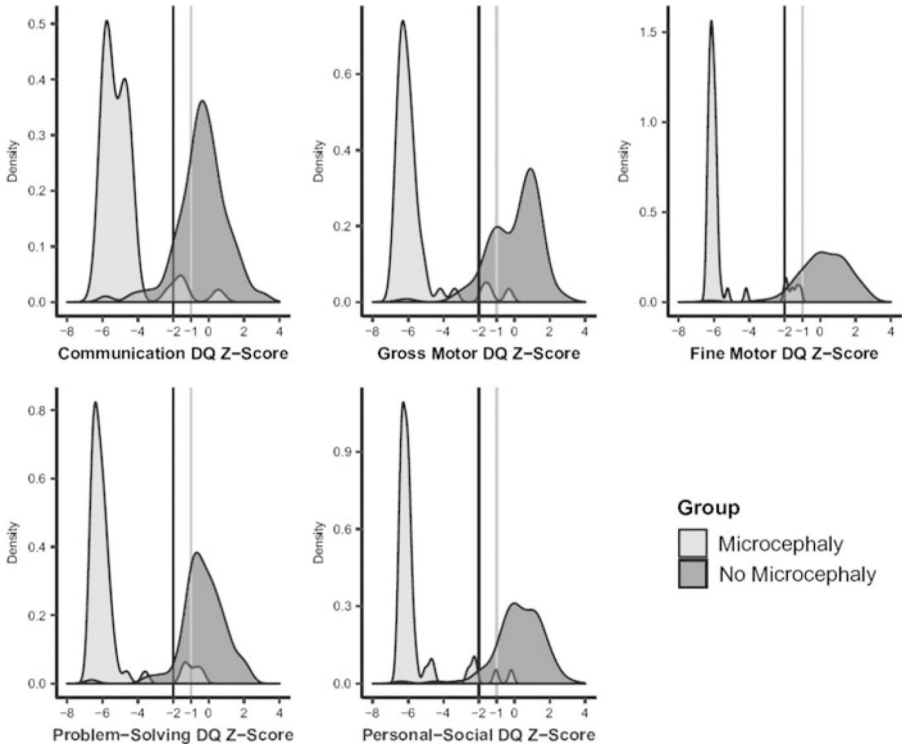

Figure 3.

Density plots of developmental quotient *z* scores by ASQ-3 domain among children with microcephaly ($n = 50$) and without microcephaly ($n = 100$). Black line at $x = -2$ represents the threshold value for at risk for delay and gray line at $x = -1$ represents the threshold for monitoring for delay. DQ = developmental quotient.

Table 1.

Developmental Estimates and Equations for Calculation

Number	Estimate	Equation
1.	ASQ *z* score	$\frac{(\text{ASQ score} - \mu_{\text{Br}})}{\sigma_{\text{Br}}}$
2.	Estimated developmental quotient (DQ)	$\widehat{\text{DQ}}_{\text{adj}} = \left[\mu^{\text{DQ}} + \sigma_{\text{DQ}}\left(\frac{10}{9}\right)\text{ASQ}^{z}\right]\left(\frac{\text{Age}^{\text{test}}}{\text{Age}^{a}}\right)$
3.	DQ *z* score	$\widehat{\text{DQ}}^{z}_{\text{adj}} = \frac{\widehat{\text{DQ}}_{\text{adj}} - \mu^{\text{DQ}}}{\sigma_{\text{DQ}}}$
4.	Developmental age equivalent (AE)	$\widehat{\text{AE}} = \frac{\widehat{\text{DQ}}_{\text{adj}}}{100}\left(\text{Age}^{a}\right)$

Note. ASQ = Ages and Stages Questionnaire; DQ = developmental quotient. μ^{DQ} is the population mean of a child with an average score on the questionnaire ($\mu^{\text{DQ}} = 100$). σ_{DQ} is the *SD* of the population ($\sigma_{\text{DQ}} = 15$). 10/9 is a conversion factor from ASQ *z* score to Developmental Quotient *z* score (see Kotzky et al., 2019, for additional details). The parameters μ_{Br} and σ_{Br} characterize the distribution of ASQ scores among Brazilian children and are specific to the questionnaire the child received and the domain (Filgueiras et al., 2013)—"Br" indicates Brazil. For the 4-month questionnaire, Brazilian data were unavailable. Thus, data for the 4-month questionnaire were drawn from the ASQ-3 User's Guide (p. 171, Table 18). Age^{test} on a given domain is the age in months of children for which the questionnaire was intended. Age^{a} is the child's biological age in months, adjusted if the child was premature. Adjustment was performed according to the ASQ-3 User's Guide (see later). (1) For preterm babies who were 24 months of age or younger, adjusted age = child's age in weeks: 38—gestational age. (2) For full-term babies and all children older than 25 months, adjusted age is equal to chronological age.

Table 2.

Percentage of Children With Evidence of Delay by ASQ-3 Domain and Microcephaly Status

	ASQ-3 Domain				
Development Classification	**Communication**	**Gross Motor**	**Fine Motor**	**Problem-Solving**	**Personal-Social**
Microcephaly (*n* = 50)					
No delay	1 (2%)	1 (2%)	0 (0%)	2 (4%)	1 (2%)
Potential risk	2 (4%)	2 (4%)	5 (10%)	2 (4%)	2 (2%)
Evidence of delay	47 (94)%	47 (94%)	45 (90%)	46 (92%)	48 (96%)
No microcephaly (*n* = 100)					
No delay	74 (74%)	77 (77%)	84 (84%)	79 (79%)	88 (88%)
Potential risk	17 (17%)	16 (16%)	11 (11%)	16 (16%)	8 (8%)
Evidence of delay	9 (9%)	7 (7%)	5 (5%)	5 (5%)	4 (4%)

Note. ASQ = Ages and Stages Questionnaire—3rd edition.