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Narrative review

Long-term impact of serious neonatal bacterial infections on neurodevelopment

Reenu Thomas [1, *], Merijn W. Bijlsma [2, 3], Bronner P. Gonçalves [4], Firdose L. Nakwa [1], Sithembiso Velaphi [1], Paul T. Heath [5]

[1] Department of Pediatrics and Child Health, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[2] Department of Neurology, Amsterdam Neuroscience, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands
[3] Department of Pediatrics, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands
[4] Independent Researcher, Oxford, UK
[5] Centre for Neonatal and Paediatric Infection, St George's, University of London, London, UK

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ABSTRACT

Background: Neonatal bacterial infections have long been recognized as an important cause of acute morbidity and mortality, but long-term neurodevelopmental consequences have not been comprehensively described and discussed.
Objectives: We aimed to summarize evidence on the pathogenesis, diagnosis, and epidemiology of long-term sequelae after neonatal bacterial sepsis and meningitis. We also discuss approaches for future studies to quantify the public health impact of neonatal infection-associated neurodevelopmental impairment.
Sources: We identified studies, both research articles and reviews, which provide mechanistic information on the long-term disease, as well as epidemiological studies that describe the frequency of neurodevelopmental impairment in children with and, for comparison, without a history of neonatal bacterial infection. Tools currently used in clinical practice and research settings to assess neurodevelopmental impairment were also reviewed.
Content: We first enumerate potential direct and indirect mechanisms that can lead to brain injury following neonatal infections. We then discuss summary data, either frequencies or measures of association, from epidemiological studies. Risk factors that predict long-term outcomes are also described. Finally, we describe clinical approaches for identifying children with neurodevelopmental impairment and provide an overview of common diagnostic tools.
Implications: The limited number of studies that describe the long-term consequences of neonatal infections, often undertaken in high-income settings and using variable designs and diagnostic tools, are not sufficient to inform clinical practice and policy prioritization. Multi-country studies with follow-up into adolescence, standardized diagnostic approaches, and local comparator groups are needed, especially in low and middle-income countries where the incidence of neonatal sepsis is high.
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Epidemiology of neonatal sepsis and meningitis

Neonatal invasive bacterial infections have a high acute fatality risk and can lead to long-term sequelae, despite adequate treatment (Fig. 1). The two most clinically consequential presentations of neonatal bacterial infections are sepsis, which broadly corresponds to bloodstream infection with systemic inflammation, for which attempts have been made to establish consensus definitions

* Corresponding author. Reenu Thomas, Department of Pediatrics, Metabolic Unit, Chris Hani Baragwanath Academic Hospital, 26 Chris Hani Road, Diepkloof, PO Bertsham 2013, Johannesburg, South Africa.
E-mail address: reenu.thomas@wits.ac.za (R. Thomas).

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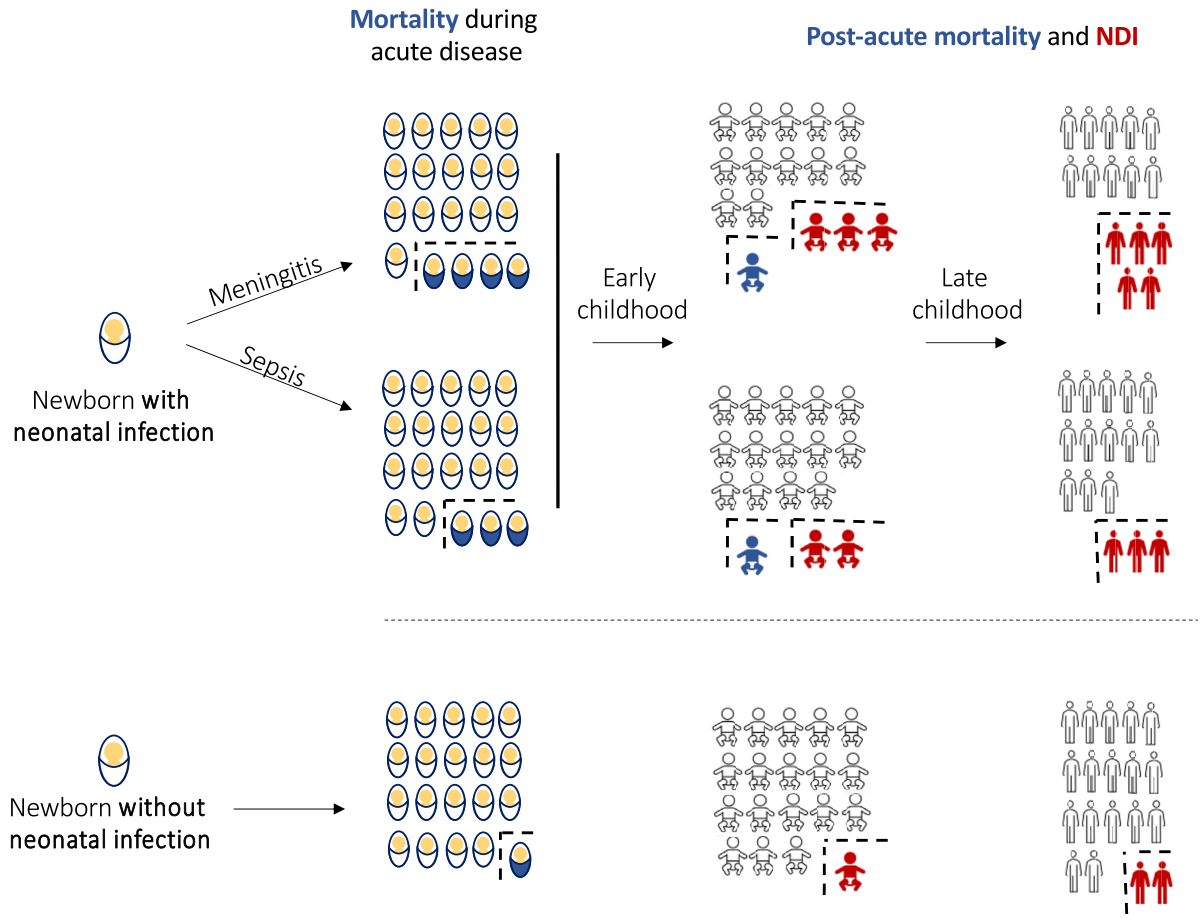

Fig. 1. Neurodevelopmental impairment and mortality linked to neonatal infections. This illustrates key epidemiological observations: (a) both acute mortality and risk of NDI seem to be higher in children who develop neonatal bacterial meningitis than those diagnosed with neonatal sepsis; (b) several studies, cited in the main text, provide evidence of post-acute mortality linked to neonatal infection; and (c) studies with long follow-up (e.g. 10 years or more) are more likely to capture the full burden linked to NDI, as mild and moderate manifestations become apparent over time. Of note, the proportions presented in this figure are only illustrative, as to our knowledge, no studies have generated comparative data that inform long-term outcomes after neonatal sepsis and meningitis using standardized NDI assessment tools, and available studies vary by period, geographical region, population characteristics and pathogen types. Although findings from nationwide cohort studies on GBS sepsis and meningitis and on infancy bacterial meningitis in the Netherlands and Denmark provide evidence for these patterns, prospective studies on all-pathogen neonatal sepsis and meningitis are urgently needed to quantify the relative public health impact of these syndromes. GBS, Group B *Streptococcus*; NDI, neurodevelopmental impairment.

[1,2], and meningitis, an infectious process involving the meninges and subarachnoid space. Globally, these conditions represent an important burden to children, with approximately 1.3 million cases of neonatal sepsis and other neonatal infections estimated to have occurred in 2017 and a large fraction of the 2.8 million all-age meningitis cases in 2016 occurring in neonates [3]. A recent meta-analysis estimated the risk of neonatal sepsis as 28 per 1000 births, with a 3.5-fold higher risk in low-income than in high-income countries [4]. Incidences and relative frequencies of causative pathogens also depend on the timing of infection, i.e. on whether the onset of symptoms occurs during the first days or week of life (early onset) or later during the neonatal period (late onset). Table 1 summarizes different aspects of the epidemiology of neonatal sepsis and meningitis.

There are robust data on the acute severity of neonatal infections, with case fatality risks of sepsis and meningitis in low-middle-income countries (LMIC) of 18% and 40–58%, respectively, and in high-income countries of 4% and 8%, respectively [4–7]. However, data on the long-term outcomes of neonates who survive acute infection are limited in quantity and geographical representation. In this narrative review, we describe evidence for the risk of neurodevelopmental impairment (NDI) after neonatal bacterial sepsis or meningitis. In particular, we discuss clinical studies providing mechanistic information on NDI associated with neonatal sepsis, as well as epidemiological studies that describe the frequency of NDI in children with and, for comparison, without a history of neonatal bacterial infection. Tools currently used in clinical practice and research settings to assess NDI were also reviewed. Finally, we discuss the consequences of increased NDI risk for the clinical management of children and possible research directions.

Pathogenesis of brain injury

Brain injury in neonatal infections is best understood for meningitis, where there is direct infiltration of the central nervous system (CNS) by bacteria and subsequent inflammation. However, brain injury might result from neonatal sepsis without direct bacterial invasion of the CNS, evidenced by the associated increased risk of NDI [8,9].

Direct bacterial invasion of the CNS and cytotoxicity through the activation of local inflammatory responses are important mechanisms of brain injury in meningitis. Toll-like receptors play an important role in the recognition of infectious pathogens and activation of pro-inflammatory responses, as well as increasing the risk of hypoxia-ischaemia, resulting in neuronal cell injury [10,11]. In

Table 1
Epidemiology of neonatal bacterial sepsis and neonatal bacterial meningitis

Pathogens	
Early Onset disease	Late Onset disease
Group B *Streptococcus* *Escherichia coli* *Listeria monocytogenes* Other Gram-negative organisms	Coagulase-negative *Staphylococcus* Group B *Streptococcus* *Staphylococcus aureus* Enterococci *E. coli* *Klebsiella pneumoniae* *Enterobacter cloacae* *Acinetobacter baumannii* *Candida* species
Use of microbiological culture	
The sensitivity of blood culture for the identification of the pathogen causing sepsis is dependent on several factors including the volume of blood sampled and whether antibiotics were administered before sample collection. Because a large fraction of presumed cases of neonatal sepsis has negative culture results with current culture practices, epidemiological studies that estimate infection incidence, including only culture-confirmed cases, are likely to underestimate neonatal sepsis incidence. Furthermore, epidemiological studies that assess long-term outcomes of survivors in culture-confirmed sepsis or meningitis cases only might overestimate the long-term impact of all neonatal sepsis.	
Factors influencing incidence estimates	
Lack of a standardized case definition for neonatal sepsis Variations in the availability of laboratory/diagnostic facilities Hospital-based vs. community-based studies Antibiotic treatment before sample collection Variable performance of the lumbar puncture Difficult access to healthcare, with fatal outcomes before admission	
Risk factors for neonatal bacterial sepsis or meningitis	
Early-onset disease	Late-onset disease
Prematurity Sex Maternal bacterial colonization (GBS) Intrapartum antibiotic prophylaxis Caesarean section Premature or prolonged rupture of membranes Chorioamnionitis	Prematurity Birth weight Sex Invasive procedure in hospital Infant colonization Human immunodeficiency virus

GBS, Group B *Streptococcus*.

Table 2
Pathogenesis of brain injury in neonatal sepsis and meningitis

Pathogenesis	Neonatal sepsis	Neonatal meningitis
Direct mechanisms	The disruption of BBB by direct exposure to bacterial cell wall components, such as LPS, and inflammatory cytokines [12]. The entry of cytokines into the CNS results in inflammatory responses and cytotoxicity [13,15]	Direct invasion of the BBB by pathogenic organisms [12]. Multiplication of bacteria in the subarachnoid space and intraventricular space. Recognition by TLR of pathogenic organisms and bacterial cell wall components, such as LPS [17] Activation and up-regulation of local inflammatory responses, the production of cytokines, chemokines, and oxygen free radicals [10,11]. Dysregulated immune response resulting in direct cytotoxicity [13,15].
Indirect mechanisms	Circulatory instability resulting from septic shock and hypotension [18]. Pressure passive circulation leading to cerebral hypoperfusion Resultant hypoxia-ischaemia to the brain.	Vasculitis Cerebral venous thrombosis Circulatory instability resulting from septic shock and hypotension [18]. Resultant hypoxic-ischaemic injury to the brain.

BBB, blood-brain barrier; CNS, central nervous system; LPS, lipopolysaccharide; TLR, toll-like receptor.

neonatal sepsis without meningitis, disruption of the blood-brain barrier by exposure to systemic bacterial cell wall components and inflammatory cytokines and entry of cytokines into the CNS resulting in inflammation and cytotoxicity have been described as a potential pathogenic mechanism [12,13]. Cytokines have been locally identified in brain tissue and cerebrospinal fluid (CSF) of neonates with brain injury [14,15]. Data from a study assessing levels of oxidative products in CSF of preterm infants with magnetic resonance imaging evidence of brain injury support the role of cytokine-induced oxidative damage in the pathogenesis [16]. These and other direct and indirect mechanisms of brain injury in neonatal sepsis and meningitis are summarized in Table 2 [17,18].

The resulting injury is to the cerebral white matter and pre-myelinating oligodendrocytes, caused by inhibition of the proliferation of neuronal precursor cells, activation of astrogliosis, stimulation of oligodendrocyte cell death, and ultimately cystic periventricular leukomalacia and non-cystic diffuse white matter injury [19–21]. Consistent with this, infants with bacterial sepsis and meningitis are more likely to develop periventricular leukomalacia compared to controls without sepsis [22,23]. In addition,

neonates with recurrent culture -proven infections are at a higher risk of progressive white matter injury [24]. Preterm infants are particularly at risk, owing to the maturation-dependent vulnerability of their developing brain. Other neurologic manifestations associated with foetal and neonatal infectious-inflammatory processes that can be detected on neuroimaging include intraventricular haemorrhage, cerebellar haemorrhage, and reduction in cerebral growth and volume, which can all translate into poor neurodevelopmental outcomes [8,25].

Bacterial sepsis and NDI

Bacterial sepsis is often grouped as early or late onset, culture-positive, or culture-negative, by the causative pathogen and whether it is a single or recurrent episode.

Both early and late-onset sepsis are associated with NDI. Early-onset sepsis has been associated with severe intraventricular haemorrhage and an increased relative risk of death or NDI at 2-years of age and cerebral palsy (CP) [26–28]. Extreme preterm infants with bacteraemia at 2 to 4 weeks postnatal age were found to have increased risk of intellectual impairment at 10 years of age [29]. A recent study in Denmark and the Netherlands compared NDI after confirmed Group B streptococcal (GBS) sepsis in the first 3 months of life to matched controls with no GBS disease. NDI was 1.5 to 2 times more common in survivors of GBS sepsis [30].

Many studies have reported on the association between sepsis and NDI based on whether it was culture-positive or culture-negative sepsis. In a multicentre cohort study of preterm infants <28 weeks, multivariate analysis showed that the odds of having CP in neonates with proven sepsis were increased by three folds when compared with culture-negative sepsis and those without sepsis [31]. Although the odds of having NDI appear to be higher with culture-proven sepsis than with culture-negative sepsis, the latter is much more common. In a study of late-onset culture–negative sepsis-affected infants had a higher risk for NDI unaffected infants [9]. In another prospective study of very low-birthweight infants, 43% of infants with culture-negative sepsis had NDI at 18 to 22 months of age, compared with 29% in uninfected infants [8].

Studies have reported variable findings on the association between the type of bacteria causing sepsis and the degree of NDI. One study reported that Gram-positive sepsis was associated with a four-fold risk of CP, and a two-fold risk for NDI compared with no sepsis, whereas gram-negative sepsis was not associated with NDI [31]. Some studies have reported the opposite, with a higher risk of NDI in sepsis due to gram-negative pathogens [28,32,33]. These differences are likely related to the design of studies, and confounders adjusted for. For example, high mortality related to gram-negative sepsis may result in an underestimation of its effect on NDI and potential differences in statistical power. Neurodevelopmental outcomes of neonates with multi-drug resistant (MDR) infections compared with those with susceptible infections are not well studied. A study performed in Taiwan that analysed 376 gram-negative bacteraemia episodes reported higher rates of neurological sequelae in MDR infections compared to non-MDR infections [34]. Neonates with MDR infections have higher illness severity scores, higher rates of complications, prolonged duration of mechanical ventilation, and prolonged hospital stay compared with neonates with non-MDR infections [35]; these may relate to intrinsic features of the bacteria themselves, the types of babies affected, or the duration before receiving ‘appropriate’ antibiotics. Some of these factors may themselves be associated with the risk of NDI, and hence, studies assessing if MDR infections are an independent risk factor for NDI are warranted.

Recurrent infections during the hospital stay in very preterm infants have been associated with poor motor outcomes [24,36]. Most studies reporting on the association between NDI and neonatal sepsis are from high-income countries, with only few studies from LMIC [37], despite these countries having a high burden of neonatal sepsis. Two studies from Brazil reported that the prevalence of adverse neurodevelopmental outcomes was greater in very low-birthweight infants with sepsis than non-affected infants [38,39]. One of these studies reported a 47% prevalence of cognitive impairment and 33.7% of neuromotor impairment at 12 months of assessment [38].

Bacterial meningitis and neurodevelopmental impairment

The risk of NDI after neonatal bacterial meningitis is higher than the corresponding risk after neonatal sepsis. Multiple studies have found that NDI is common in survivors of neonatal bacterial meningitis, with overall estimates ranging from one in three survivors for moderate to severe NDI to more than half for any NDI [40]. High rates of developmental delay, cognitive, auditory, visual, speech and motor impairments, behavioural problems and neurological complications such as CP, hydrocephalus, and seizure disorders have been reported. A meta-analysis of eight published studies between 1989 and 2008 from the UK, Nigeria, and America found point estimates of moderate or severe impairment in individual studies ranging from 16% to 38% [41]. Two studies from the United Kingdom reported outcomes after 5 years from 172 of 280 patients who survived neonatal bacterial meningitis between 1985 and 1987 [42], and 166 of 256 neonates who survived meningitis during 1996–1997 [43]. The authors found that despite a significant decline in acute phase mortality, serious long-term disability remained high: 26% in the 1986–1987 cohort and 24% in the 1996–1997 cohort. In both studies combined, at 5 years, 9% of survivors were diagnosed with CP, 5% with epilepsy, and 3% with sensorineural hearing loss. Eight percent in the first study were diagnosed with learning problems, and in the second study, 5% of survivors attended special schools and 20% attended a mainstream school with some form of additional support. A competing risk for studies assessing NDI is post-hospitalisation premature death. Although most children who do not survive neonatal bacterial meningitis die during the acute phase, death rates in survivors remain higher than among controls [44]. This may be explained by the increased risk of mortality secondary to associated long-term neurological impairments, although other risk factors such as underlying co-morbidities may also play a role [45]. In one study from the United Kingdom, 13 disabled patients of the 200 who survived the acute phase died before the age of 5 years [42].

Multiple studies have studied predictors of poor outcomes in neonatal bacterial meningitis [46–48]. CSF culture positivity has been observed as a predictor of long-term disability [43]. Other predictors of death or NDI were seizures, abnormal neurological examination, need for inotropic support, low blood leukocyte count, low CSF glucose and high CSF protein, and abnormal brain imaging [46,48].

Clinical spectra of neurodevelopmental impairment and diagnostic tools

Assessing NDI in survivors of neonatal sepsis or meningitis is important because early interventions can improve outcomes [49]. Assessments may take the form of surveillance, screening, and specific/formative testing.

Surveillance

Surveillance is the process of assessing for developmental delay at well baby visits, or at consultation with primary physicians or paediatricians [50–53]. Assessments include obtaining a history noting concerns from the caregiver, milestone checks, and a neurological examination including assessment of hearing and vision. Surveillance is necessary for all neonates and children and more so for those with a history of sepsis or meningitis. Surveillance is not very sensitive and is often subjective [49].

Screening

The American Academy of Pediatrics, United Kingdom National Institute for Health and Care Excellence (NICE), and European guidelines recommend screening with validated tools at 9 months, 18–24 months, and 30–36 months [54–56]. There are tests that can be administered in the neonatal unit before or at discharge. Some of the available screening tests that fall under the category of clinical assessments are shown in Table 3 [57–60]. The listed screening tests are not exhaustive, but include ones that are more widely used.

Specific/formative testing

If abnormalities are detected on surveillance or screening tests, a specific testing should be conducted. These tests may be physician or parent administered. The most widely used physician-administered tests are the Bayley Scale of Infant and Toddler Development III and the Griffiths Mental Development Scale (GMDS) [61]. Trained personnel are essential to conduct these tests. The most commonly used parent-administered test is the Ages and Stages III (ASQ-3) [62].

Ages and stage III

The ASQ-3 is a parent-administered test, which looks at five domains: fine motor, gross motor, communication, problem-solving and personal-social [62]. In a study in the Netherlands, the sensitivity of ASQ-3 to detect NDI was excellent (100%), its specificity was acceptable (76%), its negative predictive value was 100% and there was a good correlation between ASQ-3 failures and NDI on the Bayley Scale of Infant and Toddler Development III in the preterm cohort [63]. The ASQ-3 has been used in 23 LMICs and translated into 16 languages [64].

Bayley scales of infant and toddler development III

The Bayley Mental Developmental Scale is regarded as the reference standard and may be administered up to 42 months of age. It has five scales which include the Cognitive Scale, Language Scale, Motor Scale, Social-Emotional Scale, and Adaptive Behaviour Scale, all individually validated with sensitivity between 93% and 98% and specificity between 95% and 98% [65,66].

Griffith's mental developmental scale

The GMDS has been used extensively in developmental paediatric research, with a well-documented cognitive validity [61]. In a study on extremely low-birthweight neonates, a GMDS general quotient (GQ) score at 1 year had a low sensitivity of predicting low IQ at 5 years but a 3-year-GQ score had a higher sensitivity [61]. Other studies have shown a GQ score at 2 years to correlate better with NDI [67]. In comparison with the Weschler Preschool and Primary Scale of Intelligence Revised, the GMDS may be a better measure of overall development but may not be indicative of language development [68].

There are many other tests available for screening infants for NDI, as summarized in Table 4 [69–74]. It is recommended to choose a test that is age-specific, valid, reliable, and has both cognitive and neuromotor subsets that will aid with longitudinal follow-up (Figs. 2 and 3). The tests used also depend on the resources available such as expertise, cost, time constraints, and availability of tools to conduct the tests.

Clinical consequences for follow-up

Quantifying the risks of NDI is important to allow appropriate counselling and follow-up of those at risk and to prioritize

Table 3
Screening tests for at-risk neonates (neurological and motor assessments)

NDI screening tests for at-risk infants	Number of items	Administration time	Predicted outcomes	Sensitivity	Specificity	Test population	Availability of training
Hammersmith neonatal neurological examination (HNNE) [57]	34	10–15 min	Neurosensory impairment, cognitive delay, and NDI	50–64%	73–77%	Preterm and term	Online. Permission to download and use forms.
Infant neuromotor assessment (INA) [58]	18	15 min	Motor delay CP	98%	76–98%	Preterm and term	Online video training. No cost.
Amiel Tison neurological assessment (ATNA) [59]	41	10–15 min	Neurological impairment Lower IQ	38%	98%	Up to 6 y	Online pictures and videos and scoring sheet. No cost.
Hammersmith infant neurological examination (HINE) [60]	26	10 min	CP Intellectual disability	90–100% 51–82%	85–100% 71–90%	3 mo–2 y	Online. Permission to download and use forms.
Standardized Infant NeuroDevelopmental Assessment (SINDA) [59]	28	10 min	CP and/or intellectual disability CP	83–89% 91–100%	94–96% 81–85%	6 wk–12 mo	Purchase manual at a cost, with accompanying online videos. No formal training.
General movement assessment (GMA) [59]	1	3–5-min video	CP Autism spectrum disorders Hyperactivity disorders	98%	91%	Up to 4–5 mo corrected age	Expertise and extensive training required. Training at a cost.
Test of infant motor profile (TIMP) [59]	27 spontaneous movements 25 motor movements	20–40 min	CP Motor delay	41–72%	87–91%	34 wk PMA –16 wk CA	Workshop training at a cost.
Infant motor profile (IMP) [59]	80	25–30 min	CP	93%	81%	3–18 mo	Workshop training at a cost with the manual.

CP, cerebral palsy; IQ, intelligence quotient; NDI, neurodevelopmental impairment; PMA, post-menstrual age; CA, chronological age.

Table 4
Available neurodevelopmental assessment tools

Neurodevelopmental assessment tool	Test population	Sensitivity	Specificity	Outcome measured	Validated	Availability of tests
Ages and Stage Questionnaire-3 (ASQ-3) [62]	0–66 mo	78%	76%	fine motor, gross motor, communication, problem-solving, and personal-social	Yes	Online Training available for clinicians Parents require no training Cost of forms as a once-off and then copies may be made
Parents Evaluation Developmental Status (PEDS) [69]	0–8 y	75–79%	70–80%	Developmental impairment	Yes	Online, face-to-face training for clinicians Parents require no training Purchase the forms and the once -off fee for researchers
DENVER Developmental Screening test (DDST)[a] [70]	0–8 y	83%	26–43%	Developmental impairment	Yes No longer used due to concerns of validity	Administered by trained personnel Purchase kit at a cost
Bayley Mental Developmental Scale III BMDS-III [65]	1–42 mo	86% (MDI) 88.3% (PDI)	95–100% (MDI) 88.5% (PDI)	Cognitive Scale, Language Scale, Motor Scale, Social-Emotional Scale, and Adaptive Behaviour Scale	Yes	Toolkits to be purchased Require training
Griffiths Mental Developmental Scales (GMDS) [61,71] Griffiths Mental Developmental Scales Extended Revised (GMDS-ER)	0–2 y 2–8 y	64–90%	97–100%	Locomotor, personal and social, hearing and language/speech, eye and hand coordination and performance	Yes	Require Training Purchase of the toolkit At a cost for the kit
Movement Assessment Battery for Children (MABC-2) [72]	3–16 y	64–67%	100%	Manual dexterity, aiming and catching, and balance	Yes	No specific training. Toolkit and checklist at a cost
Alberta Infant Motor Scale (AIMS) [73]	0–18 mo	77–86%	66–85%	Motor development	Yes	No specific training required Checklists purchased at a cost
Weschler Preschool and Primary Scale of Intelligence Revised WPPSI-R [74]	5 y and beyond	60%	94%	Intellectual development	Yes	Administered by a trained psychologist Toolkit at a cost

MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index
[a] No longer used—concerns with validity.

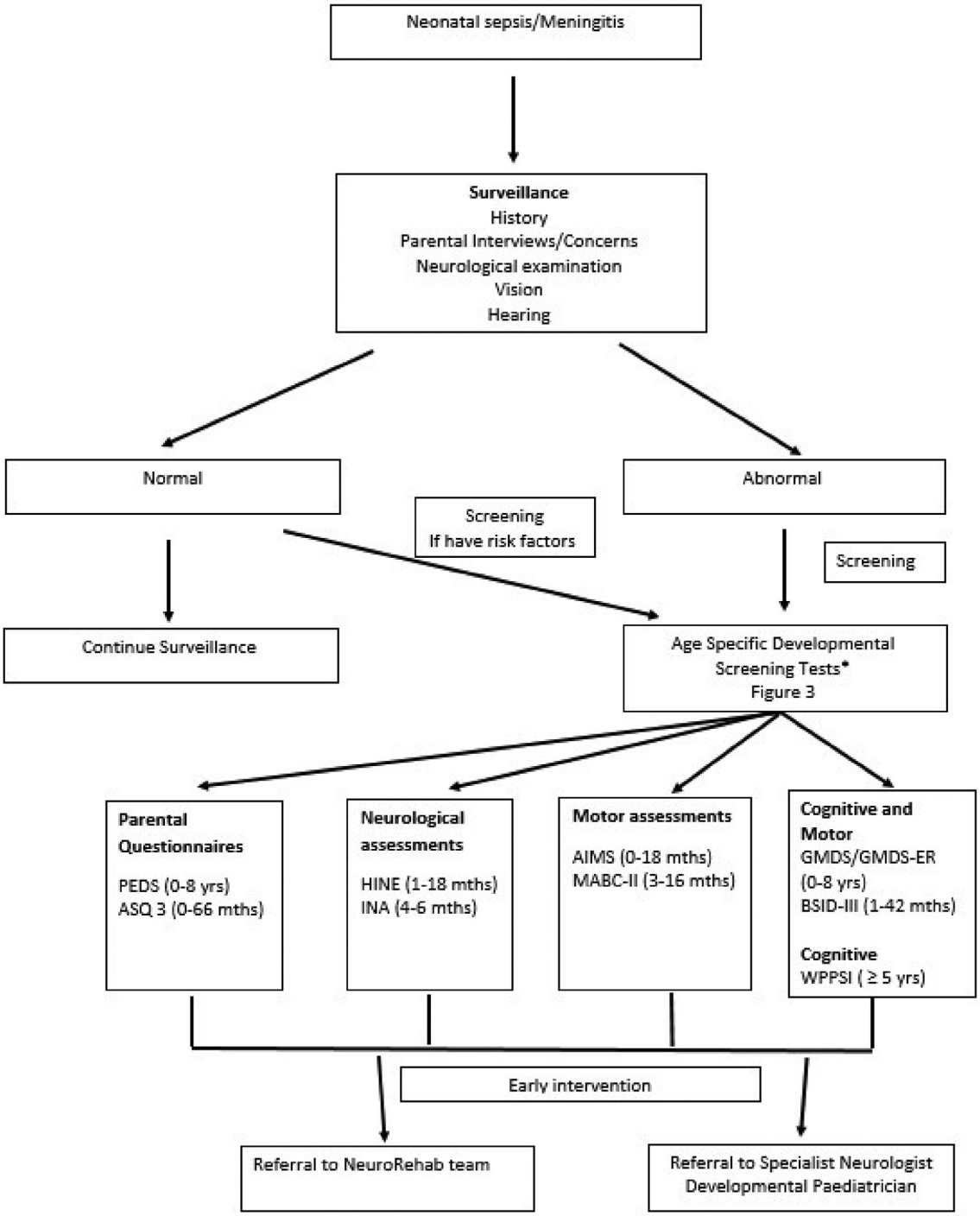

Fig. 2. Suggested flow diagram for assessment of NDI in at-risk infants/children. AIMS, Alberta Infant Motor Scale; ASQ 3, Ages and Stages Questionnaire 3; BSID-III, Bayley Mental Developmental Scale III; GMDS, Griffiths Mental Developmental Scales; GMDS-ER, Griffiths Mental Developmental Scales Extended Revised; HINE, Hammersmith Infant Neurological Examination; INA, Infant Neuromotor Assessment; MABC-II, Movement Assessment Battery for Children 2; mths, months; PEDS, Parents Evaluation Developmental status; WPPSI-R, Weschler Preschool and Primary Scale of Intelligence Revised; yrs, years.

treatment and prevention strategies. Early identification of impairment and institution of appropriate interventions has been shown to improve outcomes of affected babies, including motor and cognitive outcomes, as well as hearing outcomes [75,76].

Knowledge of the NDI burden associated with sepsis and meningitis may justify the consideration of new management strategies, including new antibiotics or adjunctive therapies, while the identification of the burden associated with specific pathogens (such as *GBS, Klebsiella and Escherichia coli*) may justify the investment needed for the development and implementation of novel maternal vaccines.

Suggestions for future studies

Box 1 summarizes the major methodological difficulties in interpreting the results of studies conducted in this field. We

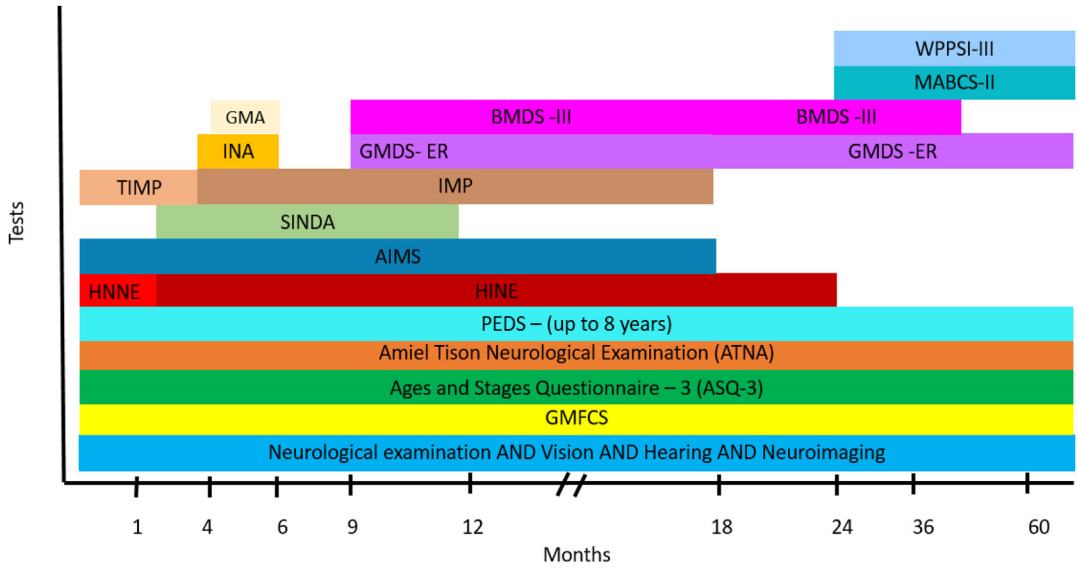

Fig. 3. Age timelines for neurodevelopmental assessments. AIMS, Alberta Infant Motor Scale; BMDS-III, Bayley Scales of Infant and Toddler Development 3rd Edition; GMA, General Movement Assessment; GMFCS, Gross Motor Function Classification System; GMDS-ER, Griffiths Mental Developmental Scales Extended Revised; HINE, Hammersmith Infant Neurological Examination; HNNE, Hammersmith Neonatal Neurological Examination; IMP, Infant Motor Profile; INA, Infant Neuromotor Assessment; MABC-II, Movement Assessment Battery for Children 2; PEDS, Parents Evaluation Developmental status; TIMP, Test of Infant Motor Profile; SINDA, Standardized Infant NeuroDevelopmental Assessment; WPPSI-R, Weschler Preschool and Primary Scale of Intelligence Revised.

Box 1
Methodological difficulties associated with studies of sepsis and neurodevelopmental impairment (NDI)

Methodological issues associated with studies of sepsis and NDI:

- Definition of sepsis used (culture positive, culture negative, presence of clinical signs)
- Inadequate exclusion of meningitis through appropriate cerebrospinal fluid examination
- Consideration of the impact of other factors on NDI (especially prematurity; but also, sex, year of birth, type of facility, specific pathogen), either as confounders or effect modifiers
- Use of an appropriate control group
- Loss to follow-up
- Age at follow-up assessment
- The assessment tool employed (for assessments of intellectual, motor, vision, and hearing impairments)
- Assessment of associated healthcare costs
- Competing risk of post-acute mortality (i.e. children with more severe NDI might have increased mortality, and thus might not be included in estimates of NDI risk)

strongly advocate for further studies and for the use of a standardized approach to their conduct. One possible study design is a prospective cohort study of survivors of neonatal infections, together with a comparator group and with multi-domain assessments (Box 2). The linkage of large databases is another approach that can be used for this purpose, as recently demonstrated [44]. However, this approach also has methodological problems, including the lack of standardized assessments as well as the likely inclusion of only those with severe NDI in these databases.

Box 2
Suggested study design for future studies on neonatal sepsis and NDI

A prospective cohort study of survivors of neonatal sepsis, matched with suitable controls and using appropriate and standardized neurodevelopmental assessment tools

Potential cases to be included:

- culture-proven sepsis (with no evidence of meningitis)
  - by pathogen
  - by MDRO versus non-MDRO
- sepsis of different severities (e.g. severe versus mild, according to a neonatal sepsis severity score).
- culture-negative sepsis cases (using a standardized clinical definition).

Controls

sex and gestation-matched, with no history of sepsis at hospital discharge.

Standardized follow-up at 2 years and 5 years of age:

- use of neurodevelopmental assessment tools validated for country, language, and age and suitable for the setting and study.
- standardized audiological and visual assessment.

could also incorporate:

- a direct comparison of different neurodevelopmental assessment tools

Sample size sufficient to assess differences in overall NDI frequency as well as in domain -specific impairments. Will depend on population, case-mix, and background rates of NDI

MDRO, multidrug-resistant organisms; NDI, neurodevelop-mental impairment.

Author contributions

All authors equally contributed to the conceptualization, literature review, writing, review, and editing of the manuscript. R.T. is the lead and corresponding author, who in addition, lead the writing, integration and editing of the manuscript.

Transparency declaration

The authors declare that this narrative review was conducted in the absence of any commercial or financial relationships, activities, or interests that could be construed as a potential conflict of interest. No external funding was received to conduct this review.

References

[1] McGovern M, Giannoni E, Kuester H, Turner MA, van den Hoogen A, Bliss JM, et al. Challenges in developing a consensus definition of neonatal sepsis. Pediatr Res 2020;88:14–26. https://doi.org/10.1038/s41390-020-0785-x.
[2] Vergnano S, Buttery J, Cailes B, Chandrasekaran R, Chiappini E, Clark E, et al. Neonatal infections: case definition and guidelines for data collection, analysis, and presentation of immunisation safety data. Vaccine 2016;34:6038–46. https://doi.org/10.1016/j.vaccine.2016.03.046.
[3] Global, regional, and national burden of meningitis. 1990-2016: a systematic analysis for the global burden of disease study; 2016 - the lancet neurology. https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(18)30387-9/fulltext. [Accessed 20 September 2022].
[4] Fleischmann C, Reichert F, Cassini A, Horner R, Harder T, Markwart R, et al. Global incidence and mortality of neonatal sepsis: a systematic review and meta-analysis. Arch Dis Child 2021;106:745–52. https://doi.org/10.1136/archdischild-2020-320217.
[5] Systematic review: neonatal meningitis in the developing world –PubMed. https://pubmed.ncbi.nlm.nih.gov/21395927/. [Accessed 20 September 2022].
[6] Born S, Dame C, Matthäus-Krämer C, Schlapbach LJ, Reichert F, Schettler A, et al. Epidemiology of sepsis among children and neonates in Germany: results from an observational study based on nationwide diagnosis-related groups data between 2010 and 2016. Crit Care Med 2021;49:1049–57. https://doi.org/10.1097/CCM.0000000000004919.
[7] Okike IO, Johnson AP, Henderson KL, Blackburn RM, Muller-Pebody B, Ladhani SN, et al. Incidence, etiology, and outcome of bacterial meningitis in infants aged <90 days in the United Kingdom and Republic of Ireland: prospective, enhanced, national population-based surveillance. Clin Infect Dis 2014;59:e150–7. https://doi.org/10.1093/cid/ciu514.
[8] Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al. Neurodevelopmental and growth impairment among extremely low-birthweight infants with neonatal infection. JAMA 2004;292:2357–65. https://doi.org/10.1001/jama.292.19.2357.
[9] Mukhopadhyay S, Puopolo KM, Hansen NI, Lorch SA, DeMauro SB, Greenberg RG, et al. Neurodevelopmental outcomes following neonatal late-onset sepsis and blood culture-negative conditions. Arch Dis Child Fetal Neonatal Ed 2021;106:467–73. https://doi.org/10.1136/archdischild-2020-320664.
[10] Mallard C, Wang X. Infection-induced vulnerability of perinatal brain injury. Neurol Res Int 2012;2012:102153. https://doi.org/10.1155/2012/102153.
[11] Weighardt H, Holzmann B. Role of toll-like receptor responses for sepsis pathogenesis. Immunobiology 2007;212:715–22. https://doi.org/10.1016/j.imbio.2007.09.010.
[12] Barichello T, Generoso JS, Collodel A, Petronilho F, Dal-Pizzol F. The blood-brain barrier dysfunction in sepsis. Tissue Barriers 2021;9:1840912. https://doi.org/10.1080/21688370.2020.1840912.
[13] Kadhim H, Tabarki B, Verellen G, De Prez CD, Rona AM, Sébire G. Inflammatory cytokines in the pathogenesis of periventricular leukomalacia. Neurology 2001;56:1278–84. https://doi.org/10.1212/wnl.56.10.1278.
[14] Kadhim H, Tabarki B, De Prez C, Sébire G. Cytokine immunoreactivity in cortical and subcortical neurons in periventricular leukomalacia: are cytokines implicated in neuronal dysfunction in cerebral palsy? Acta Neuropathol 2003;105:209–16. https://doi.org/10.1007/s00401-002-0633-6.
[15] Basu S, Agarwal P, Anupurba S, Shukla R, Kumar A. Elevated plasma and cerebrospinal fluid interleukin-1 beta and tumor necrosis factor-alpha concentration and combined outcome of death or abnormal neuroimaging in preterm neonates with early-onset clinical sepsis. J Perinatol 2015;35:855–61. https://doi.org/10.1038/jp.2015.86.
[16] Inder T, Mocatta T, Darlow B, Spencer C, Volpe JJ, Winterbourn C. Elevated free radical products in the cerebrospinal fluid of VLBW infants with cerebral white matter injury. Pediatr Res 2002;52:213–8. https://doi.org/10.1203/00006450-200208000-00013.
[17] Mallard C, Welin AK, Peebles D, Hagberg H, Kjellmer I. White matter injury following systemic endotoxemia or asphyxia in the fetal sheep. Neurochem Res 2003;28:215–23. https://doi.org/10.1023/a:1022368915400.
[18] Kooi EMW, Richter AE. Cerebral autoregulation in sick infants: current insights. Clin Perinatol 2020;47:449–67. https://doi.org/10.1016/j.clp.2020.05.003.
[19] Shah DK, Doyle LW, Anderson PJ, Bear M, Daley AJ, Hunt RW, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. J Pediatr 2008;153:170–175.e1. https://doi.org/10.1016/j.jpeds.2008.02.033.
[20] Rezaie P, Dean A. Periventricular leukomalacia, inflammation and white matter lesions within the developing nervous system. Neuropathology 2002;22:106–32. https://doi.org/10.1046/j.1440-1789.2002.00438.x.
[21] Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol 2009;8:110–24. https://doi.org/10.1016/S1474-4422(08)70294-1.
[22] Ghotra S, Vincer M, Allen VM, Khan N. A population-based study of cystic white matter injury on ultrasound in very preterm infants born over two decades in Nova Scotia, Canada. J Perinatol 2019;39:269–77. https://doi.org/10.1038/s41372-018-0294-5.
[23] Shah DK, Daley AJ, Hunt RW, Volpe JJ, Inder TE. Cerebral white matter injury in the newborn following *Escherichia coli* meningitis. Eur J Paediatr Neurol 2005;9:13–7. https://doi.org/10.1016/j.ejpn.2004.09.002.
[24] Glass HC, Bonifacio SL, Chau V, Glidden D, Poskitt K, Barkovich AJ, et al. Recurrent postnatal infections are associated with progressive white matter injury in premature infants. Pediatrics 2008;122:299–305. https://doi.org/10.1542/peds.2007-2184.
[25] Goncalves LF, Cornejo P, Towbin R. Neuroimaging findings associated with the fetal inflammatory response syndrome. Semin Fetal Neonatal Med 2020;25:101143. https://doi.org/10.1016/j.siny.2020.101143.
[26] Mukhopadhyay S, Puopolo KM, Hansen NI, Lorch SA, DeMauro SB, Greenberg RG, et al. Impact of early-onset sepsis and antibiotic use on death or survival with neurodevelopmental impairment at 2 years of age among extremely preterm infants. J Pediatr 2020;221:39–46.e5. https://doi.org/10.1016/j.jpeds.2020.02.038.
[27] Sarkar S, Bhagat I, Dechert R, Schumacher RE, Donn SM. Severe intraventricular hemorrhage in preterm infants: comparison of risk factors and short-term neonatal morbidities between grade 3 and grade 4 intraventricular hemorrhage. Am J Perinatol 2009;26:419–24. https://doi.org/10.1055/s-0029-1214237.
[28] Mitha A, Foix-L'Hélias L, Arnaud C, Marret S, Vieux R, Aujard Y, et al. Neonatal infection and 5-year neurodevelopmental outcome of very preterm infants. Pediatrics 2013;132:e372–80. https://doi.org/10.1542/peds.2012-3979.
[29] Bright HR, Babata K, Allred EN, Erdei C, Kuban KCK, Joseph RM, et al. Neurocognitive outcomes at 10 years of age in extremely preterm newborns with late-onset bacteremia. J Pediatr 2017;187:43–49.e1. https://doi.org/10.1016/j.jpeds.2017.04.045.
[30] Horváth-Puhó E, van Kassel MN, Gonçalves BP, de Gier B, Procter SR, Paul P, et al. Mortality, neurodevelopmental impairments, and economic outcomes after invasive group B streptococcal disease in early infancy in Denmark and The Netherlands: a national matched cohort study. Lancet Child Adolesc Health 2021;5:398–407. https://doi.org/10.1016/S2352-4642(21)00022-5.
[31] Schlapbach LJ, Aebischer M, Adams M, Natalucci G, Bonhoeffer J, Latzin P, et al. Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extremely premature infants. Pediatrics 2011;128:e348–57. https://doi.org/10.1542/peds.2010-3338.
[32] Van der Ree M, Tanis JC, Van Braeckel KNJA, Bos AF, Roze E. Functional impairments at school age of preterm born children with late-onset sepsis. Early Hum Dev 2011;87:821–6. https://doi.org/10.1016/j.earlhumdev.2011.06.008.
[33] De Haan TR, Beckers L, de Jonge RCJ, Spanjaard L, van Toledo L, Pajkrt D, et al. Neonatal Gram negative and candida sepsis survival and neurodevelopmental outcome at the corrected age of 24 months. PLOS ONE 2013;8:e59214. https://doi.org/10.1371/journal.pone.0059214.
[34] Tsai MH, Chu SM, Hsu JF, Lien R, Huang HR, Chiang MC, et al. Risk factors and outcomes for multidrug-resistant Gram-negative bacteremia in the NICU. Pediatrics 2014;133:e322–9. https://doi.org/10.1542/peds.2013-1248.
[35] Nour I, Eldegla HE, Nasef N, Shouman B, Abdel-Hady H, Shabaan AE. Risk factors and clinical outcomes for carbapenem-resistant Gram-negative late-onset sepsis in a neonatal intensive care unit. J Hosp Infect 2017;97:52–8. https://doi.org/10.1016/j.jhin.2017.05.025.
[36] Glass TJA, Chau V, Grunau RE, Synnes A, Guo T, Duerden EG, et al. Multiple postnatal infections in newborns born preterm predict delayed maturation of motor pathways at term-equivalent age with poorer motor outcomes at 3 years. J Pediatr 2018;196:91–97.e1. https://doi.org/10.1016/j.jpeds.2017.12.041.
[37] Milner KM, Neal EFG, Roberts G, Steer AC, Duke T. Long-term neurodevelopmental outcome in high-risk newborns in resource-limited settings: a systematic review of the literature. Paediatr Int Child Health 2015;35:227–42. https://doi.org/10.1179/2046905515Y.0000000043.
[38] Ferreira RC, Mello RR, Silva KS. Neonatal sepsis as a risk factor for neurodevelopmental changes in preterm infants with very low birth weight. J Pediatr (Rio J 2014;90:293–9. https://doi.org/10.1016/j.jped.2013.09.006.
[39] Hentges CR, Silveira RC, Procianoy RS, Carvalho CG, Filipouski GR, Fuentefria RN, et al. Association of late-onset neonatal sepsis with late neurodevelopment in the first two years of life of preterm infants with very low birth weight. J Pediatr (Rio J 2014;90:50–7. https://doi.org/10.1016/j.jped.2013.10.002.

[40] Kohli-Lynch M, Russell NJ, Seale AC, Dangor Z, Tann CJ, Baker CJ, et al. Neurodevelopmental impairment in children after Group B streptococcal disease worldwide: systematic review and meta-analyses. Clin Infect Dis 2017;65:S190–9. https://doi.org/10.1093/cid/cix663.
[41] Seale AC, Blencowe H, Zaidi A, Ganatra H, Syed S, Engmann C, et al. Neonatal severe bacterial infection impairment estimates in South Asia, sub-Saharan Africa, and Latin America for 2010. Pediatr Res 2013;74:73–85. https://doi.org/10.1038/pr.2013.207.
[42] Harvey D, Holt DE, Bedford H. Bacterial meningitis in the newborn: a prospective study of mortality and morbidity. Semin Perinatol 1999;23:218–25. https://doi.org/10.1016/s0146-0005(99)80066-4.
[43] de Louvois J, Halket S, Harvey D. Neonatal meningitis in England and Wales: sequelae at 5 years of age. Eur J Pediatr 2005;164:730–4. https://doi.org/10.1007/s00431-005-1747-3.
[44] Snoek L, Gonçalves BP, Horváth-Puhó E, van Kassel MN, Procter SR, Søgaard KK, et al. Short-term and long-term risk of mortality and neurodevelopmental impairments after bacterial meningitis during infancy in children in Denmark and The Netherlands: a nationwide matched cohort study. Lancet Child Adolesc Health 2022;6:633–42. https://doi.org/10.1016/S2352-4642(22)00155-9.
[45] Abuga JA, Kariuki SM, Kinyanjui SM, Boele van Hensbroek M, Newton CR. Premature mortality, risk factors, and causes of death following childhood-onset neurological impairments: a systematic review. Front Neurol 2021;12:627824. https://doi.org/10.3389/fneur.2021.627824.
[46] Haffner DN, Machie M, Hone E, Said RR, Maitre NL. Predictors of neurodevelopmental impairment after neonatal bacterial meningitis. J Child Neurol 2021;36:968–73. https://doi.org/10.1177/08830738211026053.
[47] Klinger G, Chin CN, Beyene J, Perlman M. Predicting the outcome of neonatal bacterial meningitis. Pediatrics 2000;106:477–82. https://doi.org/10.1542/peds.106.3.477.
[48] Lin MC, Chi H, Chiu NC, Huang FY, Ho CS. Factors for poor prognosis of neonatal bacterial meningitis in a medical center in Northern Taiwan. J Microbiol Immunol Infect 2012;45:442–7. https://doi.org/10.1016/j.jmii.2011.12.034.
[49] Mackrides PS, Ryherd SJ. Screening for developmental delay. Am Fam Physician 2011;84:544–9.
[50] 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. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. Pediatrics 2006;118:405.e420.
[51] Noritz GH, Murphy NA, Neuromotor Screening Expert Panel. Motor delays: early identification and evaluation. Pediatrics 2013;131:e2016–27. https://doi.org/10.1542/peds.2013-1056.
[52] Hirai AH, Kogan MD, Kandasamy V, Reuland C, Bethell C. Prevalence and variation of developmental screening and surveillance in early childhood. JAMA Pediatr 2018;172:857–66. https://doi.org/10.1001/jamapediatrics.2018.1524.
[53] Barger B, Rice C, Wolf R, Roach A. Better together: developmental screening and monitoring best identify children who need early intervention. Disabil Health J 2018;11:420–6. https://doi.org/10.1016/j.dhjo.2018.01.002.
[54] Developmental follow-up of children and young people born preterm. 2017. Clinicalkey!/content/nice_guidelines/65-s2.0-NG72;NG72.
[55] Weitzman C, Wegner L. Section on developmental and behavioral pediatrics, committee on psychosocial aspects of child and family health, council on early childhood, society for developmental and behavioral pediatrics, American Academy of pediatrics. Promoting optimal development: screening for behavioral and emotional problems. Pediatrics 2015;135:384–95. https://doi.org/10.1542/peds.2014-3716.
[56] Follow-up and continuing care. EFCNI –European standards of care for newborn health. https://newborn-health-standards.org/standards/standards-english/follow-up-continuing-care/. [Accessed 15 March 2023].
[57] Lawford HLS, Nuamah MA, Liley HG, Lee AC, Botchway F, Kumar S, et al. Gestational age-specific distribution of the Hammersmith neonatal neurological examination scores among low-risk neonates in Ghana. Early Hum Dev 2021;152:105133. https://doi.org/10.1016/j.earlhumdev.2020.105133.
[58] Molteno CD, Thompson MC, Buccimazza SS, Magasiner V, Hann FM. Evaluation of the infant at risk for neurodevelopmental disability. S Afr Med J 1999;89:1084–7.
[59] Hadders-Algra M. Early diagnostics and early intervention in neurodevelopmental disorders-age-dependent challenges and opportunities. J Clin Med 2021;10:861. https://doi.org/10.3390/jcm10040861.
[60] Romeo DM, Ricci D, Brogna C, Mercuri E. Use of the Hammersmith infant neurological examination in infants with cerebral palsy: a critical review of the literature. Dev Med Child Neurol 2016;58:240–5. https://doi.org/10.1111/dmcn.12876.
[61] Barnett AL, Guzzetta A, Mercuri E, Henderson SE, Haataja L, Cowan F, et al. Can the Griffiths scales predict neuromotor and perceptual-motor impairment in term infants with neonatal encephalopathy? Arch Dis Child 2004;89:637–43. https://doi.org/10.1136/adc.2002.019349.
[62] Squires J, Twombly E, Bricker D, Potter L. The ASQ-3TM user's guide. Baltimore, MD: Paul H Brookes Publishing; 2009.
[63] Kerstjens JM, Nijhuis A, Hulzebos CV, van Imhoff DE, van Wassenaer-Leemhuis AG, van Haastert IC, et al. The Ages and stages questionnaire and neurodevelopmental impairment in two-year-old preterm-born children. PLOS ONE 2015;10:e0133087. https://doi.org/10.1371/journal.pone.0133087.
[64] Small JW, Hix-Small H, Vargas-Baron E, Marks KP. Comparative use of the Ages and Stages Questionnaires in low- and middle-income countries. Dev Med Child Neurol 2019;61:431–43. https://doi.org/10.1111/dmcn.13938.
[65] Bayley N. Bayley scales of infant and toddler development: administration manual. 3rd ed. United States and America: Psychorp; 2006.
[66] Del Rosario C, Slevin M, Molloy EJ, Quigley J, Nixon E. How to use the Bayley scales of infant and toddler development. Arch Dis Child Educ Pract Ed 2021;106:108–12. https://doi.org/10.1136/archdischild-2020-319063.
[67] Mbatha S, Nakwa FL, Thandrayen K, Velaphi S. Neurodevelopmental outcome in neonates with hypoxic-ischaemic encephalopathy managed with therapeutic hypothermia in a tertiary-level public hospital outside an intensive care unit setting. Paediatr Int Child Health 2021;41:171–6. https://doi.org/10.1080/20469047.2021.1967625.
[68] Sutcliffe AG, Soo A, Barnes J. Predictive value of developmental testing in the second year for cognitive development at five years of age. Pediatr Rep 2010;2:e15. https://doi.org/10.4081/pr.2010.e15.
[69] Glascoe FP. Parents' concerns about children's development: prescreening technique or screening test? Pediatrics 1997;99:522–8. https://doi.org/10.1542/peds.99.4.522.
[70] Frankenburg WK, Dodds J, Archer P, Shapiro H, Bresnick B. The Denver II: a major revision and restandardization of the Denver developmental screening test. Pediatrics 1992;89:91–7. https://doi.org/10.1542/peds.89.1.91.
[71] Ivens J, Martin N. A common metric for the Griffiths Scales. Arch Dis Child 2002;87:109–10. https://doi.org/10.1136/adc.87.2.109.
[72] Watter P. Movement assessment battery for children (movement ABC). Aust J Physiother 2006;52:68. https://doi.org/10.1016/s0004-9514(06)70071-x.
[73] Fuentefria RDN, Silveira RC, Procianoy RS. Motor development of preterm infants assessed by the Alberta Infant Motor Scale: systematic review article. J Pediatr (Rio J) 2017;93:328–42. https://doi.org/10.1016/j.jped.2017.03.003.
[74] Garred M, Gilmore L. To WPPSI or to binet, that is the question: a comparison of the WPPSI-III and SB5 with typically developing preschoolers. Aust J Guid Couns 2009;19:104–15. https://doi.org/10.1375/ajgc.19.2.104.
[75] Spittle A, Orton J, Anderson PJ, Boyd R, Doyle LW. Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. Cochrane Database Syst Rev 2015;2015:CD005495. https://doi.org/10.1002/14651858.CD005495.pub4.
[76] Ching TYC, Dillon H, Button L, Seeto M, Van Buynder P, Marnane V, et al. Age at intervention for permanent hearing loss and 5-year language outcomes. Pediatrics 2017;140:e20164274. https://doi.org/10.1542/peds.2016-4274.