Measurement Tools of Pediatric Nutrition and Health Suitable or Adaptable for Low- and Middle-Income Countries in Field Research Settings

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Abstract: *Background*: Micronutrient status, body composition, gastrointestinal (GI) functioning, and neurological functioning are important facets of pediatric nutrition and health. When studied in low- and middle-income countries (LMIC), information about these elements is usually obtained via standardized surveys and traditional anthropometry. While convenient, these evaluations offer limited information that may be prone to error and bias. However, a variety of underutilized objective measurement tools exist which can promote a more objective, comprehensive, and deeper understanding of these aspects of pediatric nutrition and health in LMIC.

Objective: Identify field-friendly, relatively low-cost, and portable tools that provide objective measurements of micronutrient status, body composition, GI functioning, and neurological functioning in young children.

Methods: A narrative review of the literature was conducted to assess the state-of-the-art field-friendly research tools targeting micronutrient status, body composition, GI functioning, and neurological functioning in children in LMIC.

Results: A number of field-friendly tools addressing the domains of micronutrient status, GI health, body composition, and neurological functioning were identified. While many tools remain to be fully validated, these tools have yet to be used to their full potential in field-based pediatric nutrition and health research in LMICs.

Conclusions: More robust, field-friendly assessment methods will help to refine knowledge on the state of pediatric health of vulnerable children in LMIC. Such awareness could contribute to the design of interventions, programs and policies, and further research.

Keywords: Pediatrics, field research, low- and middle-income countries, nutrition and body composition, gastrointestinal disease, neurodevelopment.

HIGHLIGHTS

This literature review describes pediatric nutrition and health measurement tools for field research in LMIC, focusing on measurements of micronutrient status, body composition, GI health, and neurological functioning. This review is directed toward field researchers to expand their awareness of available tools to measure important aspects of pediatric health.

INTRODUCTION

Outside of research that focuses on particular disease entities, much field research addressing general child health in low- and middle-income countries (LMIC) is limited to inquiries about common conditions, such as stunting and wasting, respiratory illness, diarrhea, and fever. These conditions provide an important yet incomplete picture of pediatric health as many health domains remain inadequately assessed in field research. Micronutrient status, body composition, gastrointestinal (GI), and neurological functioning are areas of particular relevance given the rapid changes in growth and development in young children, yet they are inadequately assessed in field research. One reason for this gap in research is the perception that these important conditions are difficult or expensive to measure under the field conditions encountered in LMICs. However, many tools have been developed in recent years that can be applied to assess a wide variety of important health measures. This literature seeks to bring awareness to various field-friendly tools for pediatric health across the domains of micronutrient status, body composition, GI health, and neurological functioning

There is a unique and multidirectional interplay between the domains of micronutrient status, body composition, and GI and neurological functioning. For example, suboptimal GI functioning can hinder micronutrient status, as well as desirable body composition measures. Poor micronutrient status can also impact neurological development and functioning during the crucial early years of a child's development. This paper describes currently available and emerging approaches to the measurement of these domains, with the goal of increasing awareness and expanding their use. Expanding the analysis of child health by using these novel tools would help address current

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gaps in pediatric nutrition and health field research and provide evidence-based guidelines for future health policies and public health interventions.

Current Field Surveys and their Limitations

Demographic and Health Surveys (DHS) are commonly used to assess a variety of health domains and are frequently adapted by field researchers who wish to study pediatric health [1]. These surveys often use retrospective reporting by caregivers regarding the health of their children and typically focus on a timeframe of the past two weeks. However, this varies depending on the survey. While two weeks is a reasonable time to expect caregivers to recall health-related information, this acts more like a snapshot of the child's health than a longer-term measure [1-3]. Potential issues with the use of common health surveys include underreporting of symptoms by parents due to inadequate symptom detection. For example, a parent may lack access to a thermometer for verifying a fever, be unaware of diarrhea if the child toilets independently, or not recognize an important symptom. Other potential shortcomings include parental misunderstanding of questions, over-reporting of more prominent symptoms, and underreporting less prominent and/or chronic symptoms [4]. Another possible source of error is reporting bias, as indicated by observed discordances between parent reports of their child's health and that assessed by a field health provider [5-7]. Some of these differences in assessment may arise due to social desirability bias and may vary with regional, cultural, socioeconomic, and educational differences, making cross-country comparisons difficult. Further, survey-based assessments cannot address health conditions unobservable by caregivers, such as certain nutrient deficiencies or undesirable shifts in body composition. These weaknesses of field surveys used for health assessment and research support the need for field-friendly research tools which can provide objective measures.

Defining Field-Friendly

For this review, a field-friendly tool is defined as one that is relatively portable and feasible to use in the field setting in LMICs and relatively low cost and feasible to use without the need for significant user training. The determination of a country as low-and-middle-income was determined by the original authors of the research cited within this review. While not all tools included in this review meet all of these criteria, for the domains of health included in this review, many of the presented tools are more feasible in the field setting compared to their gold standard counterparts that require access to sophisticated equipment and extensively trained professionals. This review focuses on tools for the assessment of infants (but not neonates), children, and adolescents.

METHODS

To identify relevant methods for this manuscript, PubMed, Google Scholar, EBSCO, and the Cochrane Library were used to search the literature with years limited to 1990-2021. The subject areas of micronutrient status, body composition, GI functioning, and neurological functioning were selected as key determinants of pediatric health and areas in need of further research. Then papers relevant to the health and nutrition of children and adolescents in LMIC were identified. A Boolean search was conducted using the following terms "low- and middle-income countries," "childhood adversity," "field surveys," "health tracking," "pediatric health," "field research," "research priorities," and "child morbidity and mortality." The subject areas of micronutrient status, body composition, GI functioning, and neurological functioning were selected as they were described as key determinants of pediatric health and areas in need of further research. These domains have a unique interplay where GI functioning directly affects micronutrient status and body composition, thereby impacting a child's resultant neurological status. Once these subject areas were selected, themes within each of these domains were further researched using a Boolean search with the following search terms: "parent report," "point of care," "diarrhea," "mobile health," "rapid diagnostics," "parasitic infection," "event-related potentials," "eye-tracking measures," "functional near-infrared spectroscopy," "micronutrients," "body composition," "anthropometrics," "dipstick diagnosis," "stunting," "environmental enteric dysfunction," "neurological function," and "cognitive function." Papers relevant to the health of children and adolescents in LMIC were reviewed. Papers focusing on research tools with potential for use in the field setting were prioritized. Snowball searching was also applied by reviewing references of articles obtained through Boolean searching. There were 310 articles in total, of which 135 articles most relevant to the determined health domains were selected and reviewed.

RESULTS AND DISCUSSION

Micronutrient Status

Addressing micronutrient deficiencies is one of the most cost-effective interventions to advance global development progress and achieve the United Nation's sustainable development goals [8, 9]. While micronutrient supplementation programs have been implemented globally, identifying micronutrient deficiencies and their associated consequences, as well as the impact of supplementation efforts, is an ongoing challenge. Micronutrients play a vital role in a number of bodily functions, such as immunological support, neurodevelopment, growth, wound healing, and many other functions. Children in LMIC are at particular risk of deficiency of vitamins A, D, and B_{12}, iron, zinc, and folate, nutrients of special importance for pediatric health and development [10-12].

Hidden Hunger

The phenomenon of hidden hunger, where micronutrient deficiencies exist despite a normal body mass index (BMI), has become increasingly recognized in LMIC, highlighting the importance of micronutrient assessment [13]. While dietary assessment methods can document micronutrient intakes, these measures are imprecise due to reporting bias, unavailability of nutritional information for local foods, and lack of quantitative information, and additionally require significant training for administration and analysis. Without direct measurements, the child's micronutrient status is not known with certainty. Although measurement of biomarkers associated with specific dietary patterns is emerging as a promising area in nutrition research, this approach requires further research and validation in children and low-resource field research settings [14-16].

Impact of Inflammation on Micronutrient Biomarkers

An individual's inflammatory status not only affects their overall health and nutritional status but can also significantly affect the interpretation of micronutrient biomarkers, as an inflammatory burden can lead to significant under- or overestimation of micronutrient adequacy [17-20]. Considering the prevalence of inflammatory illnesses in LMIC, such as diarrheal diseases and environmental enteric dysfunction (EED), assessing inflammatory status at the time of micronutrient assessment is necessary to interpret results. This can be done by measuring biomarkers of inflammation, such as serum C-reactive protein (CRP) or plasma alpha-1-acid glycoprotein (AGP), in addition to other biomarkers of inflammation.

Measures of Micronutrient Status

Certain immunosensor-based tools are currently available to measure a number of micronutrients and inflammatory markers. A number of on-site tests exist to assess micronutrient status that use a variety of biological mechanisms with samples of whole blood, serum, and even nail clippings, to measure micronutrient biomarkers. Also described are x-ray fluorescence-based tools, in addition to other immunosensor, chemical, affinity pair, and enzymatic sensor-based tests that are under development and show promise in proof-of-concept testing. These tests offer several benefits, such as rapid results, user-friendliness, and low training needs for execution and interpretation. Additionally, some of the tests offer the ability to run multiple tests using one sample (multiplexing) while being portable and, for some tests, affordable. General limitations of the tools discussed include that many are in the early stages of development, some produce qualitative but not quantitative results, and some have not yet been validated in the pediatric setting. Table **1** compares various modalities of both available and emerging on-site micronutrient tests.

Available On-Site Tests for Assessment of Status of Vitamins A, B12, and D and Iron

An active and promising area of research is the application of field-friendly tests to measure certain micronutrients and inflammatory markers through the use of immuno-sensing technology. Vemulapati and colleagues described a lateral flow immunoassay (LFIA) with a smartphone-assisted portable imaging device to measure vitamin D from a finger-prick blood sample [21]. This tool has been validated, has demonstrated the accuracy of 90.5% in human trials, and reliably distinguishes between normal and insufficient vitamin D status [21]. The NutriPhone is another validated smartphone-assisted tool developed by Lee and colleagues that was tested in a small human trial of 12 participants [22]. The NutriPhone uses LFIA technology to quantify vitamin B_{12} status with a drop of blood [22]. Additionally, the ICHECK is another rapid test that utilizes high-performance liquid chromatography (HPLC) that has been shown to determine serum retinol levels and was tested in 89 school-aged children in Morocco [23]. Lastly, finger prick hemoglobin testing is a well-established method of testing for anemia that provides rapid results [24]. One of its main limitations is its variable accuracy depending on the selected measurement tool and the multifactorial contributors to anemia [24]. Overall, these aforementioned tests offer a number of benefits: they provide rapid results and are user-friendly, portable, and affordable. Additionally, they require minimal training for the collection of samples and for the execution and interpretation of tests.

Emerging Methods of On-Site Assessment of Micronutrient and Inflammatory Status Invasive Tests (Requiring Blood Samples)

Similar blood and serum-based immunosensor tools using smartphones also exist, such as the VitaAID tool (vitamin D), which has shown promise in preliminary research and requires further investigation [9]. Other tests also exist to measure retinol-binding protein (RBP), CRP, AGP, vitamin E, folate, ferritin, and transferrin [9]. In a study by Brindle and colleagues, a multiplex test using dried blood spots as the sample for test analysis was used to determine levels of seven biomarkers (AGP, CRP, ferritin, histidine-rich protein 2, RBP, soluble transferrin receptor, and thyroglobulin) and its use was validated for measuring levels of AGP, RBP, and soluble transferrin receptor [25]. The advantage of dried blood spots over liquid blood is that samples can be collected and dried by inexperienced users. The drying process eliminates the need for subsequent cold chain management, where the samples can then be sent to an outside lab for further processing and analysis [25]. In addition to portable and providing rapid results at the point of administration, these tools are lower cost and have produced results similar to gold standard methods such as enzyme-linked immunosorbent assays (ELISA) [9]. A multiplex tool described by Kartalov *et al*. can also simultaneously measure ferritin and CRP within a single test [26].

A study by Watstein and colleagues demonstrated proof-of-concept for the use of a whole-cell zinc biosensor kit using serum samples [27]. The test is low-cost, field-friendly, and easy to interpret.

It demonstrates the degree of zinc deficiency by producing different-colored pigments that correspond to zinc status. For this test, blood must be centrifuged. Low-cost, field-friendly centrifuges may be used, such as hand-powered, ultra-low-cost paper-based centrifuges, as well as hand-powered eggbeaters – an emerging area of research and interest for low resource settings [27-29]. Other tests using different mechanisms such as electrochemical and affinity pair-sensing exist for on-site detection of zinc and vitamin B12; these also require further validation, as reviewed in Table **1** [9].

Non-Invasive Tests

Non-invasive hemoglobin testing is another emerging tool that has shown promise in testing. However, it requires further research and validation in low-resource settings. It can be performed in various manners, such as by pulse oximetry and analysis of nailbed coloring by evaluation of smartphone photos [30-32].

X-ray fluorescence is another non-invasive and portable tool that can detect levels of zinc using whole nail or nail clippings that reflect zinc status over the previous months [33-35]. Compared to other on-site tests, it avoids the need for blood collection. Although it is not sensitive to recent fluctuations, it produces rapid results (3 minutes) and can detect cumulative micronutrient levels. Disadvantages include the risk of external contamination of samples and subsequent inaccurate test readings, the sensitivity of device measurements to nail clipping placement within the device, exposure of the subject to ionizing radiation when using the whole nail, and variable sensitivity depending on the device used [33, 34]. Further testing is required to refine and validate this method of zinc assessment.

Limitations of Emerging On-Site Tests of Micronutrient and Inflammatory Status

Limitations of these emerging tests include that some of these methodologies have not yet been fully validated. Additionally, some tests only provide binary results (e.g., deficient or not; present or absent), which can be of limited use depending on the field research objective [9]. Future steps for research include looking at the capability to run multiple tests simultaneously using a single blood sample and the ability to provide quantitative results and validate their accuracy.

Measures of Body Composition

The prevalence of the double and triple burdens of malnutrition are rising in LMIC. Double burden refers to the concurrent presence of overweight, obese, or underweight status and diet-related non-communicable disease within an individual, household, life course, or population setting [36]. The triple burden refers to concurrent overweight, obese, or underweight status and micronutrient deficiencies in the settings mentioned above [37]. While the use of anthropometry is valuable, shifts in body composition are difficult to capture with anthropometrics alone. Body composition measurements may also help assess the future likelihood of overweight/obesity and non-communicable disease [38]. A feasible way to assess body composition would facilitate field research to improve the understanding of the relationship between body

Table 1: Comparison of Available and Emerging Methods of On-Site Assessment of Micronutrient and Inflammatory Status

Micronutrient or Inflammatory Marker Measured	Test	Sample Collection	Analysis and Results	Cost
Available Tools				
Vitamin B12 [9, 22] Vitamin D(25-(OH)D) [9, 21]	Lateral flow immunoassay (LFIA) testing using smartphone assistance	Whole blood using finger-prick samples Low to moderate training needed for sample collection with minimal sample processing required	Rapid results (within minutes) at point of administration Low to moderate training required for interpretation of results Certain tests use smartphones with accessories and software for analysis, such as the Nutriphone for vitamin B12 and VitaAID for vitamin D	Low to moderate
Retinol [23]	High performance liquid chromatography (ICHECK Fluoro®)	Serum Low to moderate training needed for sample collection with minimal sample processing required	Rapid results (within 15 minutes) at point of administration Low to moderate training required for interpretation of results	Low to moderate
Anemia/iron status [24]	Various available tests, such as those from Hemocue	Whole blood using finger-prick samples Low to moderate training needed for sample collection with minimal sample processing required	Rapid results (within minutes) at point of administration Low to moderate training required for interpretation of results	Low to moderate
Emerging Tools				
Alpha-1-acid glycoprotein (AGP, inflammation) [9] C-Reactive Protein (CRP, inflammation) [9] Retinol binding protein (RBP) [9, 21, 128] Vitamin E [9] Ferritin [9, 128, 129] (Inflammation and iron status) Folate [9] Transferrin [9, 130]	Mobile kit-based immuno-sensing technology such as LFIA, labelled immuno-sensing, and label-free immuno-sensing	Whole blood using finger-prick samples Low to moderate training needed for sample collection with minimal sample processing required	Rapid results Low to moderate training required for interpretation of results Certain tests use smartphone and smartphone software for analysis	Low to moderate
AGP [25] (Inflammation) CRP [25] (Inflammation) Ferritin [25] Histidine-rich protein 2 [25] RBP [25] Soluble transferrin receptor [25] Thyroglobulin [25]	Multiplexed immunoarray	Dried blood spots Low to moderate training needed for sample collection with minimal sample processing required	Dried blood spots shipped to lab for analysis (no cold chain required) Low to moderate training required for interpretation of results	Low to moderate
Zinc [27]	Whole-cell zinc biosensor portable kit	Serum Whole blood from a finger prick will need to be collected and centrifuged using low cost methods (eggbeater or paper centrifuges) to obtain serum [28, 29] Moderate training needed for sample collection	Rapid results Low to moderate training required for interpretation of results	Low

(Table 1). Continued.

Micronutrient or Inflammatory Marker Measured	Test	Sample Collection	Analysis and Results	Cost
Zinc [33, 35]	X-ray fluorescence of nail clippings	Nail clippings Moderate training needed for sample collection Cleaning and pretreatment of nail clippings required (acetone, water, and heating treatments). May be possible in the field depending on facilities available	Rapid results Requires a portable X-ray fluorescence unit [33] Moderate training to interpret results	Moderate Depends on device used

composition and child health – current and long term – in LMIC [39-41].

Beyond Anthropometry: Body Composition Measurement Devices

Assessment of the nutritional status of children covers a number of domains: anthropometry (weight, height, weight for length, triceps skinfold, head circumference, mid-upper arm circumference [MUAC]), body composition (such as fat mass [FM], fat-free mass [FFM], and bone), and micronutrient status as previously discussed. While the use of anthropometry is valuable and accessible in the field research setting; shifts in body composition are difficult to capture with anthropometrics alone. Detailed body composition measurements may also help assess the future likelihood of overweight/obesity and non-communicable disease [38].

Currently, no gold standard exists for measuring pediatric body composition. However, cost-prohibitive measures such as dual-energy x-ray absorptiometry (DEXA) and total body potassium are often used as references in body composition research [38, 42]. Measures such as dilution methods, air displacement plethysmography, DEXA, computed tomography (CT), and magnetic resonance imaging (MRI) are established tools for body composition assessment but are suited for laboratory and clinical settings due to cost and equipment limitations [43]. This section briefly reviews devices that are more appropriate for use in the field, such as bioelectrical impedance analysis (BIA), handgrip strength (HGS), ultrasonography (US), near-infrared spectroscopy (NIRS) measurements, and 3-dimensional optical scanning (3DO).

Bioelectrical Impedance Analysis (BIA)

BIA is a tool that can be used in children that estimate total body water (TBW) by passing an electrical current through the body to provide an indirect measure of FFM and FM. This takes place while the participant is either standing or in a supine position, depending on the BIA device used [44, 45]. FFM and FM are regarded as important indicators of body composition and nutritional status. FFM captures muscle, bone, organs, and fluid, whereas FM is a measure of body fat [46]. Testing conditions for BIA should be standardized and should preclude the recent exercise or excessive sweating and account for hydration status [47, 48]. Many of the tools used to conduct BIA are inexpensive, portable, and battery-operated and have been tested in children under 18 years of age [45, 49]. Additionally, the use of smartphone-based, handheld BIA and application of BIA in infants are areas of current investigation [50, 51].

Handgrip Strength (HGS)

Handgrip strength (HGS) is an economical and field-friendly tool that provides an indirect measure of FFM, muscular strength, and malnutrition status of an individual [52, 53]. HGS measures are obtained by using a dynamometer, where the individual fully exerts their strength by squeezing the dynamometer with their dominant hand to measure grip pressure [53]. The higher the HGS measure, the greater the strength of the individual [54]. This measure is typically repeated three times and then averaged. Interpretation of results may vary significantly given the research population at hand, as Otero and colleagues found that children of higher socioeconomic status had lower HGS in their research on Colombian children [55]. Álvarez and colleagues had similar findings in their 3 country study (Spain, Chile, and Colombia), including 1273 children. Consideration of the socioeconomic diversity of the research population, particularly in countries undergoing economic and nutritional transitions, will be important to note and measure in research to contextualize HGS measures better. HGS is extremely field-friendly with these considerations given its safety, portability, affordability, user-friendliness, and non-invasive nature.

Ultrasonography (US)

Through the application of sound waves, US measures adiposity and muscle thickness at various body sites. Additionally, it distinguishes between visceral and subcutaneous adipose tissue and measures bone thickness [56]. In comparison to triceps skinfold thickness – an anthropometric measurement prone to inaccuracy with inexperienced users – use of US may require less training to achieve reliable, accurate, and reproducible results [56]. It is safe, non-invasive, portable, relatively inexpensive (depending on the model chosen), and field-friendly. While typically powered by electricity or battery, solar-powered US has been described and may be more efficient than battery-powered options in certain field circumstances [57, 58]. Handheld US devices are also available, its results are comparable with high-end US systems for various uses such as detection of ascites and other medical conditions. Information on the use of handheld US devices for body composition assessment is limited; however, it is an area of development [59].

Near-Infrared Spectroscopy Measurements (NIRS)

Through the use of a portable handheld device, NIRS measures the skin’s absorption or reflectance of light, allowing estimates of subcutaneous fat at different sites of the body, where lean tissue mass can then be predicted through the application of equations [60]. It has been studied in neonatal, pediatric, adult, and, more recently, low-resource settings [47, 61, 62]. In the neonate, NIRS has also been found to be more sensitive when less fat is present, making it appropriate for the detection of undernutrition [61, 63]. The applicability of this to undernourished children outside of the neonatal period is unknown. When studied in adults, NIRS provided estimates of body fat similar to DEXA [47]. Accuracy may be limited by hydration status and skin color; however, these factors are areas of the ongoing investigation. NIRS is a field-friendly tool; it is safe, rapid, non-invasive, inexpensive, and portable and can be connected to portable computing devices such as laptops [61, 63, 64].

3-Dimensional Optical Surface Scanning (3DO)

3DO uses visible and infrared light to capture body measurements through various device systems, such as scanning booths, portable scanners, and, more recently, mobile phone applications and camera scanning [65]. In less than a minute, 3DO obtains hundreds of different anthropometrics (such as weight, height, arm circumference, and more) from which various body composition measures can be predicted through statistical algorithms [66, 67]. This method reduces variability, error, and bias in anthropometric measurements and increases accuracy, efficiency, and the number and variety of measures obtained when compared to manual measurements. Estimates of 3DO body composition and measurements were similar to those obtained by DEXA (without exposure to ionizing radiation) and manual anthropometry, with a strong agreement for estimations of FFM and FM that were calculated based on anthropometric measures using statistical algorithms [67, 68]. A 2021 study suggests that 3DO scanners would benefit from being optimized for children to account for small body size, restlessness, and unwanted movement during scanning [69]. Pricing for 3DO scanners ranges from <$10,000-$100,000 depending on the model. Limitations of 3DO include sensitivity to movement during testing, startup costs, access to testing facilities (depending on the device chosen), and staff training [67, 70]. However, the availability and convenience of mobile-phone-based 3DO scanners may increase its feasibility in the field research setting in LMIC.

Gastrointestinal (GI) Health

GI infections and diarrheal diseases are leading causes of preventable mortality in children [71]. Overall, GI function plays an important role in determining a child's global health status [72]. The GI system has specialized enteric immune and neurologic functions. It regulates nutrient absorption, thus making it a key player in determining micronutrient status, growth and development, and resultant neurologic development and function [73-75]. Chronic inflammation, particularly in the GI tract, can reduce the absorption of macro-and micronutrients, leading to suboptimal nutritional status, and as a result, altered body composition [76]. Chronic inflammation has also been associated with increased and decreased adiposity; however, more research is needed [76]. The true burden of GI diseases may be missed if diarrhea is the only indicator assessed, as is common in field surveys. Acute diarrheal illnesses, environmental enteric dysfunction, and parasitic infections are among the common gastrointestinal disturbances that are common in LMIC.

Table 2: Strengths and Weaknesses of Available Field-Friendly Body Composition Measures

	Measures	Materials Required	Cost	Subject Compliance with Testing	Training Needs for Testing and Analysis	Safety	Requires Fasting
Bioelectrical impedance (BIA) [47, 70]	Fat mass (FM) and fat-free mass (FFM)	BIA device	Low/ Moderate	Varies	Low	High	Yes
Handgrip Strength (HGS) [52, 53]	FFM (indirect measure)	Dynamometer	Low	Good	Low/Moderate	High	No
3-Dimensional optical scanning (3DO) [67, 69, 70]	Hundreds of anthropometrics (such as weight, height, waist-hip ratio, and others) from which body composition is predicted using statistical algorithms	3DO scanner May require a smartphone and/or dedicated testing facility depending on portability of device chosen Computer for data analysis	Moderate	Good/ Moderate	High	High	Yes
Near-infrared spectroscopy (NIRS) [47, 61, 63]	Subcutaneous fat, from which lean tissue mass is predicted using statistical algorithms	NIRS system and computer for data analysis	Low	Good	High	High	No
Ultrasound (US) [56, 70]	Fat, muscle, and bone mass	US machine	Low/ Moderate	Good	High	High	No

Footnote: The costs of these systems are highly variable and dependent on the model, other functionalities, intended uses, and settings of the application. Costs of these systems will likely fluctuate with time, advancements in technology, and market shifts. This table was adapted and modified from Shepherd *et al.* [70].

Emerging Rapid Diagnostic Tools for Infectious Diarrhea

Novel tools such as rapid stool dipstick diagnosis methods exist for on-site diagnoses of *Shigella sonnei, Shigella flexneri, Shigella dysenteriae 1,* and *Vibrio cholerae* [77-84]. Rapid dipstick diagnostic methods also exist for *Yersinia pseudotuberculosis, Yersinia enterocolitica, and Entamoeba histolytica.* These tools can assist in the early detection and treatment of diarrheal illness before escalation to widespread outbreaks, which may be particularly useful to public health professionals [78-83, 85]. Rapid dipstick diagnostic tools work by a number of mechanisms, depending on the test and organism of concern. Dipstick diagnostics are particularly promising for field research, as they often require minimal training and low technical skill to administer [79]. The dipstick tests typically produce rapid results, thus eliminating the need for transport of stool samples, maintenance of cold chain, lab processing, and use of highly skilled personnel.

In a proof-of-concept study, Reis and colleagues tested a "lab-on-a-stick," which detects certain bacteria such as *Salmonella* and *E. coli* and the potential antibiotic resistance of these organisms [86]. Rapid dipstick tests for *Vibrio cholerae*, a highly virulent cause of diarrhea, have also been researched, such as the SMART™, Medicos™, and Institut Pasteur tests [87, 88]. Depending on the test, rectal swabs or stool samples can be used. Results can be obtained in 10-15 minutes and interpreted immediately [88]. Further investigation is needed to refine and validate these promising rapid diagnostic tools for use in the field setting.

Environmental Enteric Dysfunction (EED)

A small intestinal biopsy is currently the gold standard for diagnosis of EED, but obtaining a biopsy is costly, invasive, and labor-intensive, rendering it unfeasible to perform in the field [91, 92]. However, there were many stool, urine, and blood-based measures available to study EED that can be performed in the field and are significantly more feasible than a small intestinal biopsy. While these measures still require the collection of a stool, urine, or blood sample, as well as for cold-chain and access to laboratory services. They are more feasible than small intestinal biopsies, and their further analysis can help shed light on EED's domains of intestinal permeability, inflammation, and potential absorptive capacity in children in LMIC.

Assessing Intestinal Inflammation, Permeability, Microbial Translocation, and Immune Responses in EED

Urine-Based Tests

The lactulose:mannitol test is commonly used to assess the malabsorptive component of EED. While more convenient than an intestinal biopsy, the lactulose:mannitol test is time- and labor-intensive as it requires careful dosing of sugars, subsequent four-hour urine collection, maintenance of cold chain, and shipping of urine samples to a sophisticated lab [91-93]. The test assesses both the malabsorption and permeability components of EED.

Stool-Based Tests

Intestinal inflammation and permeability can be assessed in stool samples tested for alpha-1-anti-trypsin, calprotectin, myeloperoxidase, neopterin, and lactoferrin [91, 92, 94, 95]. Collection of stool samples is feasible in a field setting, but these tests require maintenance of a cold chain and access to a sophisticated laboratory for analysis, which may involve national or international shipping [91-93]. EED scoring tools exist that combine values of the stool-derived biomarkers alpha-1-antitrypsin, neopterin, and myeloperoxidase to achieve a value ranging from 0-10. A score of 10 indicates a higher burden of EED [94, 96]. However, this scoring tool only captures the intestinal permeability and inflammatory aspects of EED but does not measure EED's malabsorptive component. Another tool, developed by Singh and colleagues, captures EED's intestinal permeability, inflammation, and gut defense domains by analyzing fecal mRNA transcripts compared to the lactulose:mannitol testing and stool biomarkers alpha-1-antitrypsin, neopterin, and myeloperoxidase [97]. This tool has shown agreement between particular fecal biomarkers of inflammation (myeloperoxidase) and intestinal permeability (alpha-1-antitrypsin), while the domain of gut defense was negatively associated with lactulose levels, implying that higher scores of gut defense suggest better overall gut health [97].

Blood Tests

Intestinal permeability, microbial translocation, and immune responses in EED can be assessed by blood tests for zonulin, plasma immunoglobulin G endotoxin core antibody (IgG EndoCAb), soluble CD14, anti-lipopolysaccharide (LPS), and anti-flagellin [93]. Serum anti-LPS IgA and IgG, as well as anti-flagellin IgA and IgG may also predict linear growth trajectories [98]. Several blood tests measure inflammatory burden, including CRP, erythrocyte sedimentation rate (ESR), and AGP. Rapid diagnostic tools for measuring AGP are currently under development [99].

Logistics of Testing for EED-Related Biomarkers

As with most tests requiring blood or fecal samples, maintenance of the cold chain, access to sophisticated processing labs, and skilled technicians are vital for the successful measurement of EED-related biomarkers. Depending on access to these services, local infrastructure, skill levels of staff, and the research questions at hand, these tests may be feasible in some field research studies. Further research on more feasible methods is justified to further elucidate and understand the burden of EED in LMIC.

Emerging Tests for Assessment of Inflammation and Enteric Function in EED

Gannon and colleagues have developed a mobile phone-based, a rapid diagnostic test to measure the inflammatory marker AGP using serum, urine, and saliva samples through LFIA with promising results [99]. Further study is needed to test larger sample sizes and examine diagnostic accuracy. Serum citrulline is an emerging biomarker for an enteric function that reflects enterocyte mass (the number of functioning intestinal epithelial cells) and intestinal absorptive capacity; and is currently used in the clinical setting for patients with short bowel syndrome, Crohn's disease, celiac disease, and are indicative of enterocyte activity [94, 100]. While more research is needed on the connection of citrulline and EED, it offers a modality of assessing intestinal activity and absorptive capacity, as well as potential future risk for compromised child development [94, 100].

Parasitic Infection

Parasitic infections can be identified using stool microscopy; however, microscopy tests require a high level of technical training and interpretation skills [101]. Development of smartphone, mobile, and handheld microscopy for parasite detection is an area of active investigation but has not yet been fully validated to the point of implementation in the field [102]. Smartphone diagnostics – such as smartphone-assisted imaging, biosensors, and analytics – are another emerging area in this domain [103, 104]. LFIA kits using stool samples, however, are a more field-friendly alternative.

Lateral Flow Immunoassay Tests (LFIA) for Parasitic Infections

LFIA tests such as the Rida® Quick Cryptosporidium/Giardia/Entamoeba Combi Kit is a convenient, quick, and field-friendly tools that can be used in the field to help identify specific parasites from a stool sample [101]. LFIA typically includes a small testing kit to which the prepared stool sample is added. The test then recognizes the biomarker of interest in the stool preparation as it passes through a porous membrane [101]. Advantages of LFIA testing are its ability to “be used and interpreted by relatively inexperienced personnel [101].” It can also differentiate among species and, in some cases, distinguish between active and past infections and identify treatment success [101]. While also useful in the clinical setting, this tool may be of particular use to public health researchers seeking to investigate the efficacy of deworming programs further and assess future needs for health programs and interventions.

Emerging Mobile Health Tools for Parasitic Infections and Other GI Illnesses

A promising area for parasite identification is the use of low-cost mobile phone microscopy through the application of smartphone-based analytical sensors [104]. These sensors are capable of detecting *Schistosoma haematobium* eggs in urine samples. The smartphone is modified with additional hardware to illuminate and magnify a microscope slide tray containing the sample [103]. While this technology is in its infancy, it has the potential to revolutionize field research, diagnosis, and treatment of parasitic infections; however, at its present stage of development, it still requires a high level of training for the execution and interpretation of the test.

Physiologic Measures of Neurodevelopment

Neurodevelopmental difficulties may be considerably more common in LMIC than in high-income countries [105, 106]. This can be potentially attributed to lower awareness and delayed identification of these conditions leading to overall underdiagnosis of neurodevelopmental difficulties. Additionally, children in LMIC face a greater number of neurodevelopmental barriers such as poverty, malnutrition, micronutrient deficiencies, and inflammatory burden from infections and other conditions such as EED, which are associated with negative impacts on neurodevelopment [107-110]. In a recent study, up to 43% of children under the age of 5

Table 3: Available Tools for Assessment of EED

Measures	Test	Sample Collection, Preparation, and Processing	Analysis and Results	Cost
Stool Tests				
Intestinal inflammation and permeability [91, 93, 96]	Alpha-1-anti-trypsin, neopterin, calprotectin, myeloperoxidase, and lactoferrin	Stool collection Low/moderate level of training for sample collection and preparation Samples require maintenance of cold chain at -80 degrees Celsius and may need to be sent to a lab abroad (typically United States or Europe), depending on lab and equipment access	Timing of results dependent on lab access and processing Need access to sophisticated lab and analytical devices Requires highly trained lab personnel and clinicians for interpretation	High
Blood Tests				
Intestinal permeability [91-94, 98]	Zonulin, plasma immunoglobulin G endotoxin core antibody (IgG EndoCAb), soluble CD14, antilipo-polysaccharide, and anti-flagellin	Blood tests using venous blood or finger prick (CRP, ESR, and AGP) depending on test and lab Low to moderate level of training for sample collection and preparation Samples require maintenance of cold chain of varying degrees depending on the manufacturer. Samples may need to be sent to a lab abroad (typically United States or Europe), depending on lab and equipment access	Timing of results dependent on lab access and processing Need access to sophisticated lab and analytical devices Requires highly trained lab personnel and clinicians for interpretation	Moderate to high
Systemic Inflammation [9, 94, 99, 131]	CRP, ESR, and AGP			
Enteric function and activity and intestinal absorptive capacity [93, 94]	Citrulline			

Table 4: Available and Emerging Tools for Assessment of Intestinal Parasitic and Bacterial Infections

Measures	Test	Sample Collection	Analysis and Results	Cost
Available Tools				
Cryptosporidium, Giardia, and Entamoeba [101]	Lateral flow immunoassay (LFIA) cassette (Rida® Quick Combi Kit)	Stool sample or rectal swab Low to moderate level of training needed for sample collection and pre-treatment with diluent	Results available 10 minutes after sample collection Low training needed for interpretation of results	Low to moderate
Emerging Tools				
Shigella sonnei, Shigella flexneri, Shigella dysenteriae 1, Vibrio cholerae, Salmonella, and *E. coli* [77-83, 88]	Dipstick testing using immunoassay techniques	Stool sample or rectal swab Low/moderate level of training for sample collection	Results available immediately Low training required for interpretation of results Requires further larger-scale validation	Low to moderate

in LMIC were estimated not to have reached their overall developmental potential (cognitive, motor, social skills); this global burden has not significantly improved since 1990 [111, 112]. Interestingly, citrulline levels, a marker of intestinal activity, have been found to be positively correlated with receptive language and gross motor scores in six-month-old infants [94, 100].

Standardized developmental tests or parental child development reports are widely used to assess neurodevelopment; however, results are not always validated in each cultural context. Standardized tests are training-intensive, prone to bias, difficult to standardize, and potentially expensive due to training and translation requirements, while parental child development reports may be inaccurate [6, 113]. Thus, more objective, physiologic measures of neurodevelopment are needed [113]. Further research on the neurodevelopmental status of children in LMIC would promote a better understanding of these complex relationships, improve the precision of prevalence estimates, and provide a basis for preventive interventions in at-risk populations [114].

"Culture-Free" Physiologic Measures of Neurodevelopment

Several physiologic measures of neurological function have been successfully used in low resource settings, including eye-tracking measures (ETMs), functional near-infrared spectroscopy (fNIRS), electroencephalography (EEG), and event-related potentials (ERP) [115]. Some field-friendly tools are nonetheless affected by the child's cooperation during testing, need for training of personnel, startup costs, access to electricity or solar power, and the subject's familiarity with screens and technology.

Eye-Tracking Measures (ETMs)

ETMs are used to assess socio-emotional processes (for example, motivation and response to rewards) and information processing. During testing, digital pictures determine the location of a child's gaze by capturing reflections in the cornea and retina of infrared illuminators [116]. ETMs include several sub-measurements, such as saccades, smooth-pursuit eye movements, structured observation, pupillary dilation, and fixations during scene and face perception [117]. ETMs are non-invasive and replicable, with favorable test completion rates and good acceptance among parents [118]. ETMs can run on electricity, solar power, and battery. Testing requires a quiet setting with no outside stimuli and is best performed in a portable tent or an enclosed room. The test involves the use of computer screens and technology; thus, screen familiarity may improve performance, while unfamiliarity with screens may hinder test performance [117, 118]. Factors such as eye color and eye moistness can also affect results [116]. The use of low-cost eye-tracking glasses is an area of current investigation in ETM research [119].

Functional Near-Infrared Spectroscopy (fNIRS)

fNIRS measures shifts in oxygenation in brain tissue, which reflect metabolic demand, neuronal activity, and tissue perfusion [64]. It assesses a range of cognitive functions, including various forms of sensory processing, language, perception, and potentially, learning ability [116, 120, 121]. fNIRS is low-cost, easily administered, and transportable. It has primarily been used in high-income countries, although its use in LMIC is emerging [116, 122]. To use fNIRS, a cap that contains electrodes is closely fitted to the child's head. The test can tolerate movement, making it suitable for the pediatric population. fNIRS runs on electricity but can also be battery operated [123]. Like ETMs, it performs better in quiet testing environments. It has low training requirements for the examiner. A limitation of fNIRS is that it only reaches the first 2-3 centimeters of the scalp, rendering deeper brain structures unmeasurable [121]. It can be difficult to identify fast responses to individual stimuli but may be able to detect responses to concurrent auditory and visual stimuli, which can be utile depending on the research question at hand [124]. Lastly, there is an overall lack of standardization of fNIRS given its relative novelty [125].

Electroencephalography (EEG)

EEG is a well-established tool used for monitoring electrophysiological brain activity in a number of settings [116]. EEG can be field-friendly, as it is relatively inexpensive (depending on the model chosen), non-invasive, and portable. One of its many advantages is that it "can follow cognitive processing from the early stages of stimulus encoding through the series of cognitive processing and response execution [126]." While training needs are low for test administration, it requires highly trained personnel to interpret the output. EEG data can be negatively affected by hotter climates and requires cooler temperatures and a distraction-free environment for

Table 5: Available Physiologic Tests to Measure Neurological Functioning

Measures	Test	Testing Considerations	Analysis and Results	Cost of Device
Neurocognitive processes [116-118, 132]	Eye-tracking measures (ETMs) such as saccades, smooth-pursuit eye movements, structured observation, pupillary dilation, and fixations	Requires screen monitor, eye-tracking hardware, computer, software, and tent set up or quiet enclosed space Requires quiet testing environment with no outside stimuli. Artificial lighting preferred, although ambient lighting can be tolerated Requires minimal training for test administration Can be simultaneously tested with fNIRS	Data quality can be immediately summarized at end of testing session High level of training needed for data analysis With increased sampling rate, data quality may be compromised depending on the instrument and manufacturer	Low to High [133] <$500-$25,000
Brain activity, various cognitive functions such as sensory processing, language, perception, and potentially, learning ability [116, 121, 123, 125, 132]	Functional near-infrared spectroscopy (fNIRS)	Requires adjustable headgear, computer, software, and tent set up or lab setting Requires a quiet testing environment with no outside stimuli. Performs best with cool temperatures or air conditioning Requires minimal training for test administration Can be simultaneously tested with ETMs	High level of training needed for data analysis	Moderate to High [133] Headgear ($5,000-$45,000) fNIRS system ($100,000-$400,000) Renting fNIRS system ($3,000/month)
Electrophysiological brain activity [115, 123, 134, 135]	Electro-encephalography (EEG)	Requires portable EEG system, adjustable headgear, computer, software, and tent set up Requires a quiet, disruption-free testing environment Requires minimal training for test administration	High level of training needed for data analysis	Low to high [134] $799-$175,000*
Neurocognitive processes [115, 132, 135]	Event-related potentials (ERP)	Requires EEG system, adjustable headgear, computer, software, and tent set Requires a quiet, disruption-free testing environment Requires minimal training for test administration	High level of training needed for data analysis	Low to high [133] $799-$175,000*

*Footnote: The costs of these systems are highly variable and dependent on the model, other functionalities, intended uses, and setting of application. Costs of these systems will likely fluctuate with time, advancements in technology, and market shifts.

successful data collection [116] EEG is available in mobile, battery-operated forms, making it a relatively accessible research tool for LMIC [116].

Event-Related Potentials (ERPs)

ERPs are one of the most widely used tools for developmental research. ERPs have been studied in disadvantaged populations and can help study specific sensory and cognitive processes, such as attention, memory, face perception, and reading [126]. The method works by capturing neural processes resulting from sensory and cognitive activity through the use of time-locked EEG recordings. ERP testing can also help identify abnormal cognitive development; literature has demonstrated its use in the setting of dyslexia, attention deficit disorders, and an autism spectrum disorder [126]. It is non-invasive and can assess information processing across a wide span of cognitive tasks, and can be used across a broad range of ages. However, it requires significant training and technical expertise for interpretation and is highly sensitive to ambient noise, thus requiring a disruption-free environment [115, 126, 127]. Given that it also uses an EEG system, ERP testing in the field can be performed using mobile, battery-operated EEG systems.

CONCLUSION

There is a need to improve measurements of pediatric nutrition and health through the application of less commonly used, field-friendly research tools. Expanding research efforts in the various domains of pediatric nutrition and health will help to reduce the significant gaps in pediatric literature in LMIC. Research in this arena should consider innovative, comprehensive, and convenient field-friendly tools across the many dimensions of pediatric nutrition and health, as identified in this review. By increasing and expanding pediatric field research, programs and policies would be better able to address nutrition and health needs in a more targeted and timely manner to help decrease downstream health burdens and costs to the individual, family, society, and economy. The next steps include further investigation and validation of field-friendly tools for pediatric nutrition and health assessment using novel methods such as smartphones, tablets, and rapid diagnostic tests. Cost analyses of the use and impacts of these tools and scaling up public health initiatives to address identified morbidities are also needed. With better methods, public health researchers and program developers can target their efforts more effectively to make strides in achieving the United Nation's sustainable development goals of reducing overall child morbidity, ending preventable child mortality, and improving child well-being.

LIST OF ABBREVIATIONS

3DO = 3-dimensional optical scanning
AGP = alpha-1-acid glycoprotein
BIA = bioelectrical impedance analysis
BMI = body mass index
CRP = C-reactive protein
CT = computed tomography
DEXA = dual-energy x-ray absorptiometry
DHS = Demographic and Health Surveys
EED = environmental enteric dysfunction
EEG = electroencephalography
ELISA = enzyme-linked immunosorbent assays
ERP = event-related potentials
ETMs = eye-tracking measures
FFM = fat-free mass
FM = fat mass
fNIRS = functional near-infrared spectroscopy
GI = gastrointestinal
HGS = handgrip strength
HPLC = high-performance liquid chromatography
LFIA = lateral flow immunoassay
LMIC = low- and middle-income countries
MRI = magnetic resonance imaging
MUAC = mid-upper arm circumference
NIRS = near-infrared spectroscopy
RBP = retinol binding protein
TBW = total body water
US = ultrasonography

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