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Infants less than 6 months of age at risk of poor growth and development: evidence gaps identified during WHO guideline development

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INTRODUCTION

Over 10 million infants under 6 months of age worldwide are at risk of poor growth and development (henceforth 'infants u6m').[1] Risks include short-term mortality and non-communicable disease in later life for survivors.[2] Affected infants are especially vulnerable to all of these risks across the lifespan.[3]

The 2023 WHO guideline on the prevention and management of wasting and nutritional oedema represents major advances for this group.[4] The 2013 guideline[5] focused on infants u6m with severe wasting (low weight-for-length) and/or nutritional oedema, but the 2023 version addresses a broader population of concern including infants with: underweight (low weight-for-age); low mid-upper arm circumference (MUAC); poor growth; or underlying vulnerabilities (box 1).[4] The interdependent maternal-infant dyad is now emphasised, as are interventions combining treatment and prevention roles. There are four new good practice statements and four updated recommendations (table 1).

SUMMARY BOX

⇒ The 2023 WHO guideline on wasting and nutritional oedema includes four recommendations and four good practice statements on the management of infants less than 6 months of age at risk of poor growth and development, prioritising this vulnerable yet often neglected group.

⇒ Evidence across the five prioritised guideline questions for this population was limited, notably by a lack of directly relevant evidence from randomised controlled trials in infants who meet criteria and are beyond the neonatal period.

⇒ Evidence gaps identified during the guideline development process included questions on: identifying and managing infants at risk of poor growth and development; addressing and managing breastfeeding challenges; and indications for use of supplemental milks; effective maternal-directed interventions; using antibiotics in this broader population of infants.

⇒ To complement randomised controlled trial evidence on intervention efficacy, implementation research should explore feasibility, acceptability, equity and values as perceived by carers, communities and front-line healthcare workers. Greater co-creation of future interventions is also needed.

WHY EVIDENCE GAPS ARE A PARTICULAR PROBLEM FOR INFANTS U6M

Evidence for infants u6m was especially sparse, with three of the four recommendations based on low or very low certainty evidence and the fourth based on moderate certainty evidence. Numerous questions for future research emerged from Guideline Development Group (GDG) discussions during the 2023 WHO guideline development process. We urge researchers and funders to refer to those listed in the guideline to ensure that their efforts and investments are prioritised with potential for impact on policy and programming.

Here, we follow the original guideline framework to highlight topics where research is urgently needed to strengthen future management of infants u6m at risk of poor growth and development. Addressing these will also help prevent wasting and nutritional oedema in older infants and children aged 6–59 months.

Box 1 Summary of criteria used to identify infants less than 6 months of age at risk of poor growth and development

Infants less than 6 months of age at risk of poor growth and development are those with one or more of the below:

⇒ Poor growth based on sequential measures.

⇒ Poor anthropometry based on a single measure (low weight-for-age; low weight-for-length; nutritional oedema; low mid-upper arm circumference).

⇒ Known risk factors for poor growth and development (neurodevelopmental concerns; feeding concerns; maternal physical or mental health risk; history of hospitalisation).

⇒ Infants at risk due to poor birth outcomes (preterm birth; low birth weight; small for gestational age).

Source: abridged from 2023 WHO guideline on the prevention and management of wasting and nutritional oedema (acute malnutrition) in infants and children under 5 years

Identifying and managing infants at risk of poor growth and development

Clear criteria for identifying infants u6m at risk of poor growth and development are critical for research, policy and programming. These were agreed by the GDG based on a systematic review of prognostic factors, expert experience and indirect evidence. Introducing underweight and low MUAC are transformative aspects of this guideline. Underweight is widely used in growth monitoring and other child health and development programmes and facilitates close links between nutrition and other services. Rapid adoption is thus possible, but data are needed to determine:

- Caseload and cost implications of the expanded weight-for-age and MUAC criteria—which will also depend on the exact intervention being applied;
- Which criteria (anthropometric and other) best identify infants at highest mortality/morbidity risk, and implications for subsequent management;
- The added value and logistical/time implications of keeping weight-for-length as an essential programme enrolment criterion; and
- The most effective methods and/or tools to assess breastfeeding, underlying disability and clinical admission criteria.

A WHO-led risk stratification project examining some of these issues is already in progress.[6] However, this and most other current research focus on mortality and growth outcomes. Morbidity and developmental outcome data are sparse. Though related to growth, these might be better predicted by other variables or by different anthropometric thresholds. Despite its widespread use, anthropometry is an imperfect proxy measure for health and development.[7] Future research should therefore assess health and developmental outcomes so that

Table 1 Overview of recommendations and GPSs for infants less than 6 months of age at risk of poor growth and development

Recommendation or GPS number	Subject	Strength	Certainty
A1	Regular care and monitoring of mothers/caregivers and their infants	N/A (GPS)	
A2	Criteria for admission for inpatient care, in-depth assessment or enrolment to outpatient care	Conditional	Low
A3	Criteria for transfer from inpatient to outpatient care	Strong	Moderate
A4	Frequency of outpatient visits and final review at 6 months of age	Conditional	Very low
A5	Comprehensive assessment of the mother/infant pair and resolution of breastfeeding/lactation challenges	N/A (GPS)	
A6	Decisions about supplementary milk in addition to breastfeeding	N/A (GPS)	
A7	Breastfeeding and supplementary milks, specifically for infants less than 6 months with severe wasting and/or nutritional oedema who are admitted for inpatient care	Strong	Very low
A8	Comprehensive assessment and support of mothers/caregivers	N/A (GPS)	

Source: 2023 WHO guideline on the prevention and management of wasting and nutritional oedema (acute malnutrition) in infants and children under 5 years
GPS, good practice statement; N/A, not applicable.

enrolment, referral, transfer and exit criteria for nutrition programmes can be optimised. Longer-term follow-up is particularly important to better understand these.

Intervention studies should explore whether using adjusted case definitions of infants u6m at increased risk of mortality/morbidity/poor development can improve treatment outcomes. This would guide investments towards infants who could benefit the most.[8] Randomised controlled trials exploring risk-differentiated care would determine whether care pathways based on certain criteria improve outcomes, and for which infants. Data on risk/benefit balances and costs are needed. Adverse outcome data (eg, nosocomial infection following hospital admission and economic shock) is particularly lacking in the current literature.

Consistently used case definitions are essential to testing interventions in comparable populations. Otherwise, intervention performance might depend on confounders differing by setting (eg, rates of prematurity or low birth weight). Some of these are not yet feasible to measure everywhere (eg, ultrasound gestational age estimation).

Addressing and resolving breastfeeding challenges and indications for use of supplemental milks

Assessing and resolving breastfeeding difficulties is critical for managing infants u6m since their target diet is exclusive breastfeeding. There are, however, notable evidence gaps on how exactly to do this, with most current evidence focusing instead on non-human supplementary milks (which to use, amount, etc). We thus join calls for a 'paradigm shift' away from research on non-human supplemental milks and towards studies on supporting and restoring breastfeeding as the key intervention for undernutrition in this age group.[9–11]

Pressing areas for research include how to better identify and tackle drivers of poor growth. Risk factors (eg, breastfeeding difficulties, inadequate breastfeeding support, physical and mental illness, disability and social disadvantage) are well described in epidemiological studies, but can be difficult to identify in individual patients in busy clinics or hospital wards where malnutrition is most common. Better screening and identification tools are needed, as are better interventions.

Second, researchers should examine how staff and systems factors affect the success of breastfeeding assessment and support. Programme planners and managers need more guidance on which staff cadres should be responsible. Specialist nurses and breastfeeding counsellors may seem ideal but are expensive and often unavailable in typical settings. Defining competencies for essential breastfeeding support for other staff across the healthcare system is important (eg, hospital and tertiary care settings; nurses and clinical officers based in secondary care; community staff in primary care services). Evidence on the effectiveness of training approaches is also needed: which pedagogical methods best promote competency development and what training packages can be delivered at scale in resource-constrained systems.

Alongside evidence on maintaining and restoring exclusive breastfeeding in both outpatient and inpatient settings, the GDG also recognised situations where some infants do not respond to high quality breastfeeding support alone. Guideline questions thus asked if and when infants should be given supplemental milks and, if given, which milks should be used. A commissioned systematic review highlighted major evidence gaps.[9] Only two relevant studies included infants with severe wasting and/or nutritional oedema. The GDG used this evidence to update the 2013 recommendation on types of supplemental milks recommended for infants u6m with severe wasting and/or nutritional oedema admitted for inpatient care. Options include: the mother's own expressed breast milk, donor human milk, human milk from a wet nurse, commercial infant formula, F-75, F-100 and diluted F-100 milk. Aside from a strong preference for human over non-human milks, a hierarchy of supplemental milks could not be established based on the available efficacy/effectiveness evidence. Furthermore, no evidence was found to inform the appropriate duration or indicators to stop supplemental milk for infants who require them.

Finally, the ethical challenges of research in this area were recognised.[12] One issue concerns the need for new research versus focusing on better implementing what is already known. There is also, under this specific topic area, a need to balance:

- The risks of non-human supplemental milks becoming normalised and used inappropriately, without healthcare workers first investing in proper breastfeeding support.
- The imperative to ensure that infants who do need supplements get them; towards this, robust yet practical definitions of 'need' are required.

Safety is of critical importance, and the frequency of common risks associated with supplementation, such as gastrointestinal infections and rarer but more serious risks, like sepsis, requires robust quantification.

Effective maternal-directed interventions

Although interventions to improve maternal/caregiver physical and mental health and nutrition can have positive impacts on infants,[13] maternal/caregiver health is itself important. Unfortunately, there was little evidence to inform recommendations in this area. Most studies focused on mothers/caregivers of preterm and/or low birth weight infants during the neonatal period. Interventions need to be tested through to age 6 months. Studies could identify high-risk pregnancies, facilitating improved future continuity of care to address antenatal determinants.

Using antibiotics in this broader population of infants

The GDG sought to determine whether routine antibiotics should be provided for infants u6m. This is

currently recommended for older infants and children with severe wasting and/or nutritional oedema.[4 5] No eligible studies were found among infants u6m, so recommendations could not be made. Since antibiotics are an affordable and easily deliverable intervention, (although with caveats around antimicrobial resistance and future metabolic and immune consequences) future research should address this question. Trials should target infants based on different risk factors, be conducted in different geographical areas to optimise generalisability, and be powered for mortality.

Overarching issues and ways forward

A need for direct evidence on infants u6m at risk of poor growth and development

Common to all the above areas was a lack of directly relevant evidence. Evidence for two groups, neonates and infants u6m without anthropometric deficit, was plentiful but extrapolation from this broader population is risky. Interventions that work well for these two groups may or may not be as effective for the target population of infants u6m at risk of poor growth and development. We call on researchers with data on:

- Neonates: to follow-up their cohorts for longer, up to 6 months of age and beyond. This would also support other closely related global initiatives, notably on small vulnerable newborns/small sick newborns.[14]
- All infants less than 6 months of age: to conduct subgroup analyses. Where such groups are too small and samples underpowered, consortia may pool datasets. Pooling data from different contexts may enhance generalisability.

A need for co-creation and greater carer, community and healthcare worker involvement

Researchers must do more to co-create future interventions in true partnership with mothers/caregivers, communities, front-line healthcare workers and local governments. Intervention sustainability and scalability depend on addressing stakeholders' perspectives and needs. The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) Evidence-to-Decision framework explicitly considers values, preferences, equity, acceptability and feasibility, but evidence in these domains is currently lacking and weak. Research on these issues within and across contexts is vital.

A need for packages, robustly tested in randomised trials and implementation research

Given multiple evidence gaps, we call on researchers and funders to note the issues highlighted in this commentary to help focus efforts. Best practice research prioritisation methods should be used, and still-relevant past exercises recognised.[15] Investigators must also be strategic. Magic-bullet, single solutions are rare, so promising interventions could be bundled and tested in integrated care pathways.[16] The Integrated Management of Childhood Illness (IMCI) is a major global child health strategy which already uses care pathways for numerous conditions.[17] There is great potential to further strengthen the care of infants u6m in IMCI.[18] Components of such pathways could be added or subtracted later to evaluate individual elements. Efficacy and effectiveness evidence from randomised controlled trials should be prioritised. However, implementation research is also required since many issues are context-specific and there is much to learn from real-world conditions which include staff, logistics and other resource constraints in already stretched health systems.

CONCLUSION

The 2023 WHO guideline has great potential to positively transform the care of infants u6m at risk of poor growth and development. However, the underlying evidence remains limited. By highlighting key evidence gaps across multiple areas and calling on researchers to focus on key matters including appropriate subgroup analyses and greater stakeholder involvement, we hope to enrich the evidence base for future updates to the 2023 WHO guideline and ultimately improve outcomes for disadvantaged infants and their mothers/caregivers.

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