Evidence Summary: Preventative Oral Iron Supplementation (OIS) of infants at risk of iron deficiency

Undertaken on behalf of the Anaemia Expert Advisory Group of the Remote Primary Health Care Manuals

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Flinders UNIVERSITY

NORTHERN TERRITORY GOVERNMENT

Contents

List of abbreviations

Acronyms	Full form
AAP	American Academy of Pediatrics
AI	Adequate Intake
AIHW	Australian Institute of Health and Welfare
BMDI	Bayley Mental Development Index
BPDI	Bayley Psychomotor Development Index
CARPA	Central Australian Rural Practitioners Association
EAR	Estimated Average Requirements
ESPGHAN	European Society of Paediatric Gastroenterology Hepatology & Nutrition
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
Hb	Haemoglobin
HU5K-PF	Healthy Under 5 Kids - Partnering with Families
ID	Iron deficiency
IDA	Iron deficiency anaemia
IO	Iron overload
MCV	Mean corpuscular volume
MD	Mean difference (continuous variables)
MeSH	Medical Subject Heading
NBAA	National Blood Authority Australian
NHMD	National Hospital Morbidity Database
NHMRC	National Health and Medical Research Council
OIS	Oral iron supplementation
PCIS	Primary Care Information System
PDMS-2	Peabody Developmental Motor Scale - Version 2
PF	Plasma ferritin
RACGP	Royal Australian College of General Practitioners
RDI	Recommended Daily Intake
RPHCM	Remote Primary Health Care Manuals
RR	Risk ratio (dichotomous data)
SF	Serum ferritin
SMD	Standard mean difference
sTfR	Serum transferrin receptors
STM	Standard Treatment Manual
TS	Serum transferrin
UL	Upper Limit
WHO	World Health Organization
YLD	Years Lived with Disability
ZPP	Zinc protoporphyrin

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Executive summary

This evidence review was undertaken to collate the latest evidence for providing preventative oral iron supplementation (OIS) to predominantly breastfed infants from four months of age or earlier. This review was undertaken to inform the updating of the anaemia in children protocol in the Remote Primary Health Care Manuals (RPHCM) Standard Treatment Manual (STM), which currently recommends this practice. A systematic literature review was undertaken to determine if OIS improves iron stores, prevents anaemia, preserves mental and/or motor development in this age group, and whether there are any unintended adverse effects. The review also clarified the optimal dose, schedule and duration of iron supplementation, as well as the recommended age range to initiate OIS and which infants should be supplemented.

The current literature highlights the importance of iron in early life. Iron is found in all structures of the brain and is required for the development of neural pathways. It also plays crucial roles in oxygenation of tissues, immune system function, energy production, cell proliferation and DNA synthesis. Iron status is a continuum with iron deficiency eventually resulting in iron deficiency anaemia (IDA). IDA has documented systemic impacts on child development, behaviour, and cognition, even after IDA is corrected with iron treatment. While there are many causes of anaemia, iron-deficiency accounts for up to 50% of cases worldwide, particularly during infancy. Prevention of IDA is a key strategy in promoting optimal childhood development with lasting impacts on social and economic determinants of health.

Anaemia is a significant public health problem affecting nearly one third of the global population with greater prevalence amongst vulnerable groups. Risk of anaemia is highest during periods of rapid growth, particularly during pregnancy and early childhood. The world bank estimates that approximately 14% of Australian children under 5 years of age are anaemic. However, Aboriginal and Torres Strait Islander children are frequently reported to have anaemia prevalence rates exceeding 25 percent in early childhood, with some studies detailing prevalence of over 60 percent. The highest prevalence rates are among children aged from 6 to 12 months of age, with some data indicating that anaemia under 6 months of age is also a concern. Infants risk factors for IDA include: mother having anaemia or diabetes during pregnancy; low birth weight and/or premature; from multiparous birth; early umbilical cord clamping; delayed introduction to iron-rich complementary foods; early introduction to cow's milk; and/or food insecurity, hygiene or housing concern.

Infants are often introduced to complementary foods before or around 6 months of age, however their iron intakes are inadequate with less than 50% of infants meeting Recommended Dietary Intake (RDI) of iron. Experts have indicated that it is practically impossible for infants aged six to twelve months of age to consume adequate amounts of iron from unmodified complimentary foods. Poorly bioavailable iron-fortified foods contribute the greatest proportion of infant iron intakes. Dietary modelling also supports the conclusion that it is that most infants are not consuming adequate amounts of iron-rich foods prior to nine months of age. This is of greater concern for infants who commence life with depleted iron stores.

A number of scientific associations globally now recommend OIS for breastfed infants from 4 months of age, however there are inconsistencies around whether universal or targeted OIS is recommended. There are also differences in guidelines between iron dose, age of commencement and frequency of OIS. However, a consistent recommendation is that OIS should continue until children are consuming adequate amounts of iron from their diet, especially for high-risk infants.

Key findings from this literature review indicate that:

- OIS is safe to provide to infants at risk of IDA from 4 months of age and helps to prevent ID and IDA at 6 months of age, impacts on motor and cognitive development are mixed and difficult to measure
- Commencing OIS earlier than 4 months of age may be beneficial in preventing earlier onset iron deficiency
- OIS should continue until adequate dietary sources of iron are consumed
- Studies demonstrating the best outcomes of OIS provided low preventative doses of between 1-2mg/kg, with the 2mg/kg dose more effective at preventing IDA
- Intermittent low dose OIS is generally associated with fewer side effects, better compliance and possibly a reduced risk of oxidative damage. Daily OIS provides more protection against the decline in iron stores and onset of IDA but is associated with additional side effects and increased potential risk of harm
- Supervised OIS improves outcomes more effectively than unsupervised administration. Safety considerations of unsupervised iron in the home environment also need to be considered
- The composition of the iron formulation does not influence outcomes
- While no single approach may be universally acceptable, a low dose intermittent OIS protocol will likely provide the best course of action that balances benefits and potential risk
- Universal OIS is recommended for high-risk groups and could be implemented in areas where prevalence exceeds 10%. Alternatively, a targeted approach towards infants with risk factors for anaemia could be more feasible in some settings.
- While studies have focused on infants who are predominantly breastfed, the iron intake of Australian children who are exclusively formula fed is well below the safe upper limits of iron intake. Therefore, the strategy could be extended to all infants in high-risk environments
- OIS prevention strategies need to be undertaken alongside other holistic IDA prevention strategies that address the wider determinants of iron-deficiency and should complement anaemia prevention strategies in pregnancy

Background

The current (7th) edition of the Central Australian Rural Practitioners Association (CARPA) Standard Treatment Manual (STM) recommends administration of low dose preventative oral iron supplementation (OIS) to all breastfed infants aged between four and six months of age (Table 1)[1]. Preterm and small babies are at additional risk of iron deficiency (ID) and iron deficiency anaemia (IDA) and are recommended to receive iron from one to 12 months. Oral iron is recommended to be provided daily if possible, or twice weekly under supervision of a health professional. This change in practice was underpinned by the American Academy of Paediatrics (AAP) guideline[2], which recommends "exclusively breastfed term infants receive an iron supplementation of 1 mg/kg per day, starting at 4 months of age and continued until appropriate iron-containing complementary foods have been introduced" (p.1044). However, the dose recommended in the STM (6mg elemental iron daily if possible or twice per week supervised) is lower than that recommended in the AAP and other similar guidelines[3,4]. The AAP guidelines generated international debate following their release[5-8], partly due on reliance of a single small Randomised Controlled Trial (RCT) that was used to justify the recommendation[9]. In response, the AAP emphasised the importance of preventing iron deficiency (ID) and iron deficiency anaemia (IDA) in infants without waiting for unequivocal evidence[10], due to likely benefits in psychomotor function[11]. Despite this criticism, the AAP recommendation remains in place within the United States in 2021.

Table 1. CARPA Standard Treatment Manual recommendations for prevention of iron deficiency anaemia in infancy using oral iron supplementation

From around 4 months	**Preterm and small babies**

• Give supplementary oral iron to all breastfed babies — 1mL (6mg elemental iron) per dose
  ○ Once a day if possible
  ▪ Provide 2 weeks supply at a time — review uptake after 2 weeks
  ○ *OR* give daily dose twice a week under supervision in clinic or community by same (dedicated) staff member
• Check Hb at 6 months
  ○ If normal — stop supplement and promote age appropriate food
  ○ If low — start treatment regime — see Table 2.2
	• Give supplementary oral **iron** from 1 month — 1mL (6mg elemental iron) per dose
	  ○ Once a day if possible
	  ▪ Provide 2 weeks supply at a time — review uptake after 2 weeks
	  ○ *OR* give daily dose twice a week under supervision in clinic or community by same (dedicated) staff member
	• Check Hb level at 6 months
	  ○ If normal — continue supplementary oral **iron** 1mL twice a week until 1 year
	  ○ If low — start treatment regimen. See Table 2.2

Source: Remote Primary Health Care Manuals (CARPA STM 7th Edition)[1]

Following the release of the CARPA guidelines, consultation workshops were undertaken in five regions across the Northern Territory in 2017 to determine how the OIS would be implemented and evaluated. Strong concerns were raised by diverse groups of health professionals in each region due to *i)* limited evidence presented underpinning the recommended practice, *ii)* a lack of consultation with health practitioners in developing recommendations, and *iii)* lack of clarity for implementation e.g. whether to supplement

infants with mixed feeding methods (Appendix A). Due to these concerns, this recommendation has not been endorsed or translated into remote primary healthcare practice by NT Health Services and many non-government organisations until a more rigorous review of the evidence is completed.

Purpose of this review

This review was undertaken to collate the latest evidence for providing preventative OIS to predominantly breastfed infants from four months of age or earlier. The evidence was evaluated on whether OIS improves iron stores, prevents anaemia, preserves mental and/or motor development in this age group, and whether there are any unintended adverse effects. The review will also clarify the optimal dose, schedule, and duration of iron supplementation, as well as the recommended age range for OIS and which infants should be supplemented.

Rationale for the prevention of anaemia in infancy

The first 1000 days of life refers to the period between conception and a child's second birthday. It is now well recognised that this critical period shapes a child's health, growth, neurodevelopment and wellbeing across the lifespan[12,13]. The early years represents a period of vulnerability as significant physiological changes occur that require increased energy and nutrient requirements[13]. Deficits in key nutrients such as iron can cause detrimental effects on growth and development[14-16],including lifelong alterations in brain function[17,18]. During the foetal period and early childhood, neurological development is extremely rapid[19] (Figure A). Undertaken as a scaffolding process, with each phase dependent on the completion of the earlier stage[19,20], this process lays the foundation for a high functioning brain in adulthood[21] (Figure B). Therefore, it is imperative that nutrition required for normal brain development is available, and any deficits identified and corrected early[19].

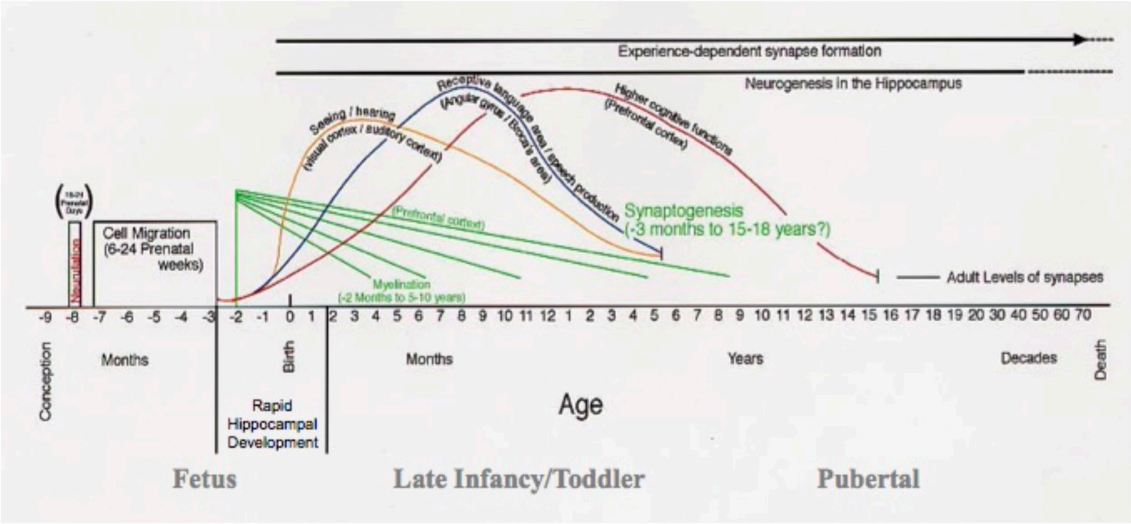


Figure A. Human brain development: rapid growth and neural changes early in life
Source: Nevins, 2016 (adapted from Thompson & Nelson, 2001)[22]

Role of iron early in life

Iron plays a critical role in numerous biological processes in humans, including tissue oxygenation, immune system functioning, energy production, cell proliferation and DNA synthesis[23]. Approximately 60 percent of iron is found in haemoglobin (Hb) molecules, which is used for the production of red blood cells (RBCs)[24]. RBCs perform a critical role in transporting oxygen to cells and tissues[24].

During pregnancy iron needs increase significantly due to the large increase in blood volume needed to support the growing foetus[25]. Throughout the perinatal period and the first years of life, iron is key for the rapid growth and development of the foetus central nervous system[26,27]. Brain growth triples in weight from birth to 3 years by which time it has reached 85% of the adult size[17]. Iron is found in all structures of the brain and is required for the development of neural pathways. The neonatal brain is highly metabolically active, consuming around 60% of total oxygen supplied, compared to 20% in adulthood[13]. Environmental insults to the developing brain during this sensitive period can cause irreversible developmental delays that can persist, even after anaemia is corrected with iron therapy[28].

Neurotransmitter metabolism	Energy metabolism	Myelination
• Most direct effect of iron is thought to be on the synthesis of the monoamine neurotransmitters, dopamine, serotonin and norepinephrine (Lynch *et al.* 2018). Monoamine synthesis begins in mid-gestation, until about 3 years of age.	• Iron deficiency affects neuronal energy metabolic balance, especially in the hippocampus, the region responsible for recognition memory processing and other cognitive functions (Rao *et al.* 2003; Lozoff & Georgieff 2006)	• Iron deficiency, particularly in the late fetal and early childhood period, results in hypomyelination, a decrease in the production and quality of myelin, the fatty acid sheath surrounding neurons (Beard *et al.* 2003; Ortiz *et al.* 2004)
• Altered monoamine metabolism results in disturbed sleep cycles, motor control, memory and social–emotional development (Herlenius & Lagercrantz 2004; Beard 2008)	• Disrupted energy metabolism results in abnormal arborisation (branching) of dendrites and synapse formation, leading to long-lasting morphological changes (Tran *et al.* 2008)	• Hypomyelination impacts all brain regions, but disturbances in the auditory and visual systems of infants have been most closely linked to impaired myelination (Algarin *et al.* 2003; Amin *et al.* 2013)

Figure B. Role of iron in the developing brain
Source: McCarthy & Kiely, 2019

Iron requirements in early life

Having adequate iron stores is critical for periods of rapid growth. Table 2 shows recommended iron requirements during infancy and pregnancy. Iron requirements during pregnancy (27 mg per day) exceed those at any other stage of life[29]. Pregnant women are particularly vulnerable to ID and anaemia, as approximately 1000 mg of iron is needed during pregnancy to support development of the foetus, while preserving maternal iron stores[30]. If iron stores are low, foetal iron requirements are prioritised over maternal needs[31]. Maternal ferritin concentrations less than 12µg/L is suggestive of thresholds below which foetal iron accretion is affected[30]. It is especially important that iron needs are met in the last trimester of pregnancy, since the foetus accumulates most (>66%) of their iron stores for early life in their liver during the last 10 weeks of gestation[13,32]. Therefore, infants born preterm are at greater risk of ID in early life. Infants born to anaemic mothers have an increased risk of ID and IDA later in infancy, even when neonatal iron stores are adequate at birth[30]. Obtaining sufficient iron during this period is challenging[33], reflected in the high rates of maternal anaemia worldwide[34,35].

During the first four to six months of age, infants predominantly rely on iron stores accumulated during gestation for their iron needs (approximately 75 mg/kg in foetuses and newborns)[15]. A healthy, term infant can double its birth weight before iron stores are depleted[15]. Breast milk contains only small quantities of iron (0.2-0.4mg/L)[15,29], however, it is highly bioavailable[36]. This is potentially due to the iron-binding protein lactoferrin which is available in breast milk, which facilitates a unique mechanism for absorption early in life[15].

The literature on specific iron needs of exclusively breastfed infants contains conflicting data and contrary views[37,38]. Some studies indicate that breast milk can only meet about 15 to 20 percent of the overall iron requirements for older breastfed infants[39]. Although breast milk is well utilised, healthy infants receiving breast milk for longer than 4 to 6 months are at risk of developing IDA, in the absence iron supplements or iron-fortified complementary foods[15]. Several guidelines recommend that healthy breastfed infants are introduced to iron rich foods from 4 months of age, along with iron supplements at 4 months to prevent early ID[2,10,37,40]. However, other guidelines suggest that healthy breastfed infants born at term will have adequate stores and exogenous iron is not needed until around 6 months of life, when complementary foods are introduced[6,24,41,42].

There is no recommended iron intake for formula fed children under 6 months of age. The iron in formula has shown to be much less bioavailable (10-20%) than in breastmilk in early studies and the NHMRC has concluded that formula-fed infants require much higher intakes[29]. More recent studies using stable isotopes suggest smaller or no differences in iron absorption between breast milk and infant formula[15]. The American Academy of Pediatrics (AAP) recommends that standard infant formulas containing 10 to 12mg/L of iron are adequate to meet the needs of infants for the first year of life[2], which is 50 to 60 times higher than the level of iron in breast milk. However, several studies have shown that infant formulas fortified with higher quantities of iron had no additional benefit on iron stores compared to formulas with lower quantities of iron in healthy infant populations[43-45].

Once iron endowment from birth is depleted, infants depend on iron-rich complementary foods for their iron due to the low iron content of human milk[46]. The period of introduction to complementary foods is a time of particularly vulnerability to ID due to high iron requirements, as a significant proportion of nutrition continues to be provided by human milk. There are no specific dietary guidelines for infants aged from six to twelve months of age. These are difficult to determine due to the rapid changes in growth, as well as individual variance in the transitionary process and child development[46]. Iron recommendations are also fraught due to varying absorption of different dietary sources of iron and reliance on poorly bioavailable commercial infant cereals to meet iron requirements[36].

According to the NHMRC, the average concentration of iron in human breast milk was used to estimate the adequate intake (AI) of iron for healthy full-term infants up to six months of age. It is noted that the iron needs of infants do not suddenly jump from 0.2 to 11 mg per day at 7 months of age[37]. The disjuncture between the requirements is the result of very different methods for determining these values.

Experts have noted that it is "practically impossible" to provide enough iron from unmodified complementary foods to meet the needs of infants at around six months of age[3]. Initially, infants are only able to consume small quantities of solid foods (2-3 teaspoons), increasing to two to three small meals (around 250g/d) by around eight months[46]. Depleted birth stores of iron must be replenished by this limited quantity of solid foods[47]. Dietary modelling studies lend support to these findings. When modelled to be consistent with the Foundation diet[48], the iron content of a hypothetical diet for breastfed infants from 6 to 12 months of age (5.8 mg) was approximately half the RDI (11 mg, 53%)[46]. This suggests iron requirements from six months of age cannot be met through current recommendations for healthy diets[46].

The Upper Level (UL) of intake for iron in infants 0 to 12 months of age is 20 mg per day[29], based on potential adverse effects on growth[49]. Although difficult to exceed iron requirements through dietary sources, infants receiving iron supplements are at risk of toxicity.

Table 2. Recommended daily intake of iron for Australian pregnant women and infants[29]

	Estimated Average Requirement (EAR)	Adequate Intake (AI)	Recommended Daily Intake (RDI)	Upper Limit (UL)
Pregnant women	22-23mg/d		27mg/d	45mg/d
Breastfed Infants 0-6mo		0.2mg/d		20mg/d
Infants 7-12mo	7mg/d		11mg/d	20mg/d
Children 1-3yo	4mg/d		9mg/d	20mg/d

Iron absorption

The absorption of iron is complex[15] and regulated primarily through the intestine (Figure C)[24]. Once absorbed, iron is stored in a non-reactive state either as ferritin, within serum (SF) or cells. Only a very small amount is maintained in the circulatory system in plasma, where it is bound to transferrin (TS)[23]. When iron is required for metabolic processes, it is released into the blood and transported by TS to body tissues and bone marrow. Iron surplus to physiological needs, is stored as ferritin in cells lining the intestine (enterocytes), as well in the liver, spleen and bone marrow[24]. Iron binding to TS prevents the formation of unbound iron, which is highly toxic because it catalyses formation of oxidative radicals[50].

The human body is very efficient at conserving iron. This is achieved through recycling the iron that is obtained from breakdown of old RBCs[51]. Thus, only five percent of iron requirements are acquired from dietary sources[52]. Iron is consumed through the diet in two forms:

1. Haem-iron from animal products, which have high bioavailability (30%)[52]
2. Non-haem iron from cereals (often fortified with iron) and vegetable products, which have low bioavailability (10%)[52]. Absorption of low haem iron sources can be altered

through interactions with other nutrients that enhance (e.g. Vitamin C) or inhibit (e.g. oxalates, phytates and calcium) absorption[51,53].

Risks of iron overload (IO)

While iron is indispensable for human life, unbound iron can catalyse the formation of harmful oxidative radicals which are toxic to cells and iron-dependent pathogens, such as enterobacteria in the gastrointestinal tract. Infants are particularly vulnerable to infection due to an undeveloped immune system[50] and both ID and IO early in life have been linked to long-term effects on the central nervous system[14,54-56], gut microbiota[57-61] and immune system[14,18,21,62], which may persist into adulthood.

Iron homeostasis is critical for children[50] and is tightly regulated at a systemic and cellular level to prevent both ID and IO, and the resultant detrimental effects[18]. There is evidence of adaptations to the homeostasis processes in infancy that assist in enhancing absorption of dietary iron and iron stores to prevent ID[63]. Iron homeostasis occurs through the regulation of iron absorption from the gastrointestinal tract via the hepatic peptide hormone, hepcidin. Excess iron and inflammation induce high serum levels of hepcidin which block iron release[24]. To cope with increased demands for iron during times of stress, such as iron deficiency, hepcidin production is downregulated to increase intestinal absorption of iron can be increased three- to fivefold[52], ensuring that there is sufficient iron supply to the bone marrow for production of RBCs[50]. Alternatively, when iron stores are high or during periods of inflammation, infection or disease, upregulation of hepcidin prevents release of iron by decreased expression of ferroportin. This is part of the host defence system, which limits supply of iron to iron-dependent pathogens[21,59].

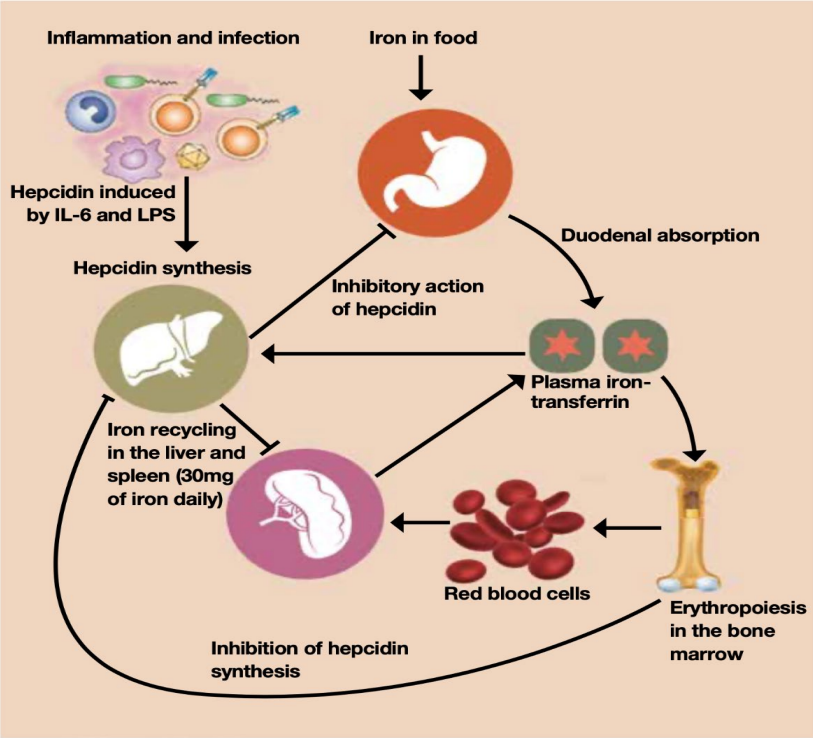


Figure C. Iron homeostasis
Source: Australian Doctor, 2017[51]

Iron deficiency (ID) and iron deficiency anaemia (IDA)

Iron status is a continuum and deficiency advances in stages (Figure D)[51,64]. Initially, if the demand for iron exceeds iron stores, iron is used faster than it can be replenished, leading to iron depletion[51,64]. Biochemically, this results in a reduction in SF, while other measures of circulating iron (serum iron, TS, sTfR, MCV, ZPP [Table 3]) remain within the normal range. Without intervention, progression to iron deficiency (ID) will occur[51,64]. This means that body iron stores are exhausted and body tissues have insufficient iron to meet physiological demands. This is characterised by a drop in serum iron, TS and MCV, while sTfR increases. If the iron deficit is still not corrected, iron deficiency anaemia (IDA) will develop[51,64]. At this point, RBC synthesis is compromised, resulting in reduced haemoglobin (Hb) concentration and further changes to the biomarkers of ID. During this period, TS falls, and once below 16%, there is inadequate iron for erythropoiesis. IDA severity increases as haemoglobin concentration or haematocrit values decrease below the reference range[51,64].

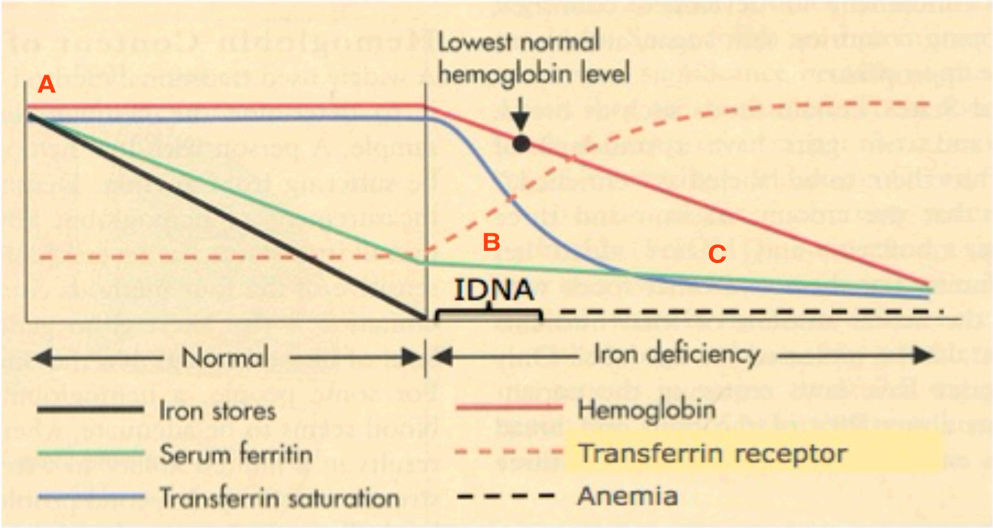


Figure D. Levels of markers of iron status levels across the continuum of deficiency: normal iron status (A); iron deficiency without anaemia (IDNA)(B); iron deficiency anaemia (C, black dashed line).
Source: Nevins, 2016 (adapted from Guthrie, Picciano & Scott, 1995)[22]

Iron deficiency (ID) is a key cause of anaemia and is the most common micronutrient deficiency in infants and young children worldwide[64]. ID is defined as a state in which insufficient iron is available to maintain normal physiologic functions and can be categorised into absolute or functional, depending on underlying cause (Figure E)[64].

- **Absolute ID** occurs when iron stores are low or exhausted, meaning biological requirements can no longer be met. This is especially prevalent in pregnant women, infants and young children due to high iron requirements during periods of rapid growth, which deplete iron stores[51,64].
- **Functional ID** often occurs when inflammation is present, causing withholding of iron from plasma and reducing supply to bone marrow. Even though iron stores are adequate, ID erythropoiesis and anaemia are promoted.

Absolute and functional ID can occur individually or in combination to cause anaemia. Functional ID can also promote absolute ID through sustained impairment of iron absorption.

Iron deficiency anaemia (IDA) is defined by the presence of anaemia plus ID, and is usually determined by presence of low haemoglobin [Hb][64].

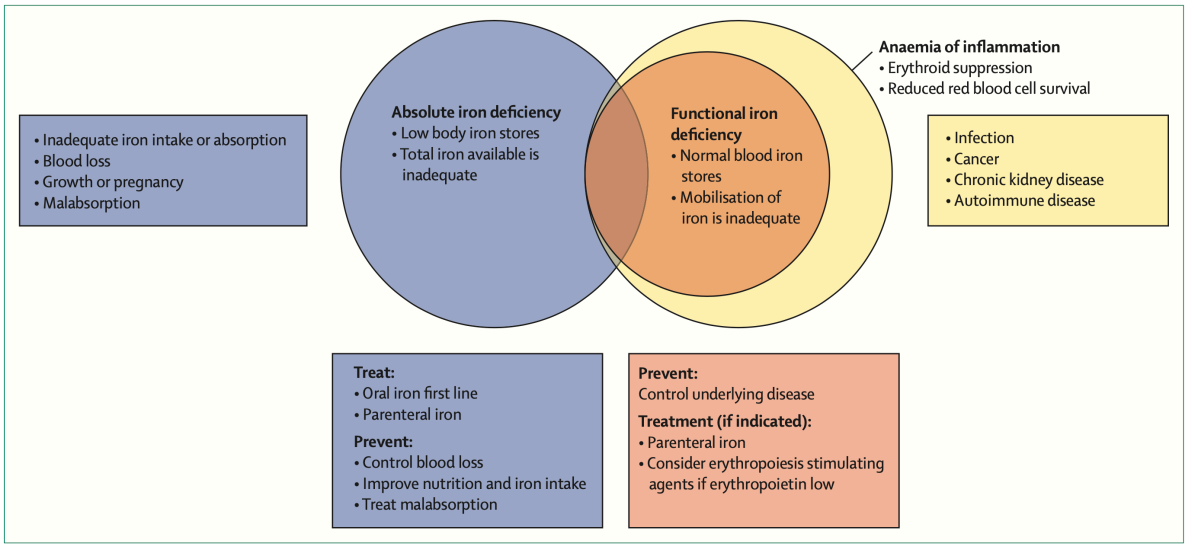


Figure E. Absolute and functional iron deficiency
Source: Pasricha et al., 2020[51]

Iron markers and measurement of ID and IDA

Several challenges exist assessing anaemia and iron status and a number of blood biomarkers are used to diagnose ID and IDA[51], each with advantages and disadvantages[23].There are is also complexity in using multiple indicators to measure different aspects of IDA, knowledge gaps relating to the choice and thresholds for different indicators, limited research available comparing the accuracy of different tests for assessment of iron status, and the lack of simple technologies to quickly measure iron status in the field[51,64].

Haemoglobin (Hb) concentration is most commonly used to assess and define anaemia, as it is determines the adequacy of the circulating red cell mass[64]. However, to identify ID or IDA, Hb must be combined with other measures of iron status[65]. Measuring Hb is inexpensive and easy to measure outside of laboratory settings using Point of Care tests[66,67]. However, Hb is not a specific or sensitive indicator of iron status[64]. In addition, Hb levels may not fall below cut-offs until iron stores have dropped to up to one-third[64]. Hb can also be affected by other conditions and deficiencies[64]. Commonly used cut-off values for identifying IDA from 6 to 12 months of age are Hb <110 g/L[42,65,68,69].

Remote Primary Health Care Manuals definition of anaemia in infants:
Blood haemoglobin (Hb) concentration of less than 105 g/L for children aged between 6 and 12 months[1]. Severe anaemia is characterised by Hb < 90g/L and can be fatal.

The most commonly used measure of iron status is serum ferritin (SF), which is a marker of iron storage; 1 µg/L of SF corresponds to 8 to 10 mg of available storage iron[51]. Ferritin can also be measured in plasma (PF)[70], and although highly correlated with SF, discrepancy between measures exists[71].The advantage of SF is that it is a sensitive indicator of iron

deficiency, however, it is also increased in the presence of inflammation[51,64]. Therefore, ferritin is not a specific indicator for ID. Cut-off values between 10-12 µg/L are widely used in research and clinical practice to denote depletion of iron stores in adults and children[51,70,72], however these values are extrapolated from adults and may not be appropriate for infants[51]. There are several other markers of iron function and metabolism outlined in table 3. However, cut-off values for TS, MCV, ZPP and sTfR are even less well defined in infants and young children and these measures of iron status are particularly difficult to interpret due to changes in physiology and metabolism during growth and development in infancy, as well as the impact of infection[64]. Serum iron is a poor indicator of the body's total iron stores and should not be used to diagnose ID[68]. The gold standard to determine absolute ID is absent stainable bone marrow iron, though this is rarely used in practice due to the expense and invasiveness of bone marrow aspiration[51].

Table 3. Markers of iron function and metabolism[64,73]

Haemoglobin (Hb)	Determines the adequacy of the circulating red cell mass
Serum Ferritin (SF)	Marker of iron storage
Serum transferrin (TS)	Reflects iron transport capacity
Erythrocyte mean corpuscular volume (MCV)	Measure of the average size and volume of RBCs
Zinc protoporphyrin (ZPP)	Indicates defective haemoglobin synthesis (the iron in protoporphyrin is substituted by zinc)
Serum transferrin receptors (sTfR)	Signifies cellular need for iron (unlike SF is not affected by inflammation, which helps differentiate between ID and anaemia of chronic disease)

Consequences of ID and IDA

Anaemia accounts for approximately 9% of the total global disability burden from all conditions and has numerous consequences on human health[74]. In pregnancy, severe anaemia is associated with maternal and perinatal mortality, claiming approximately 1 million lives globally per year[66]. Severe anaemia during infancy can cause organ damage and haemodynamic instability, and is a major driver of high death rates in poorer countries[75]. However, the impacts of mild to moderate IDA can have significant consequences on social and economic development. Many observational studies have shown associations between IDA in early childhood, and detrimental effects on the developing brain causing neurological dysfunction[18,25,76,77]. IDA has been linked to developmental delay of cognitive and psychomotor functions, including slower visual and auditory processing[27,78-85], and may have negative influences on psychosocial interactions and behaviour[81,86]. If undetected and untreated during critical periods, the World Bank has concluded that moderate-severe IDA in infancy likely leads to irreversible cognitive deficits[64,74]. As such, anaemia is one of the world's leading causes of disability in children and the adverse consequences are manifold[74]. Neurological deficits impact on related factors such as mental health and educational attainment, influencing social and economic potential in later life and associated determinants of health[87,88]. These impacts can persist across the lifespan and have intergenerational consequences[88,89].

Anaemia is also associated with significant economic costs[90]. Recent Global Burden of Disease studies have highlighted anaemia as the leading cause of impairment (Years Lived with Disability- YLD) in low and lower middle income countries and fourth highest cause in high and middle income countries[91]. The 2017 report identified anaemia as the leading cause of YLD for females, males, and both sexes combined and estimated that approximately 58.2 million YLD (95% CI 39.5, 83.0) were due to anaemia[92]. Addressing anaemia will therefore bring about significant fiscal benefits with the benefit-to-cost ratio of iron interventions estimated to be as high as 200:1, based on improvements in cognitive development, schooling, physical productivity and resource savings[93]. Despite the significant burden that anaemia places on health systems and economies[94], global progress has been slow. From 1990 to 2010, the global prevalence of anaemia improved by only 0.2 to 0.3 percent[75], resulting in the inclusion of anaemia within global nutrition targets by the World Health Assembly[95,96].

An emerging area of research has indicated that early life iron deficiency may adversely affect brain function. Several studies have highlighted that ID during critical periods in infancy may cause long-lasting and irreparable damage to neural tissue in the brain[18,27,54]. Sensitive periods for nutrient actions exist; if a key nutrient is not available during a critical time, the impacts may be profound and irreversible[19]. When iron supply does not meet demand, hierarchical prioritisation of iron occurs to various organs[18,77]. The liver, which accrues iron stores, is deficient before skeletal muscle, heart, and brain[19]. In negative iron balance, the brain is prioritized above all other non-haematologic organs, however the key exception is RBCs[19]. Because RBCs are prioritised when ferritin is low, the brain can be significantly iron deficient before anaemia can be detected[19,77]. Similar to prioritisation between organs, prioritisation within organs exists[19]. Iron-containing proteins that deliver oxygen (e.g. globins) take precedence over hemeproteins involved in energy production (e.g. cytochromes)[19,77,97]. Thus, parts of the brain may become iron deficient when iron markers are within the normal range[17,19].

The implications of deficiency include reduced synaptic plasticity and smaller synaptic heads, reduced complexity of dendritic branching, and decreased electrical potential in key areas of the brain[17-19,54,77]. When iron stores are insufficient during infancy, highly metabolic areas of the brain such as the hippocampus are at greatest risk[54,98-100], which is important for learning, memory, and cognition[101]. Given that iron transport across the blood-brain barrier is developmentally regulated[18,97],
residual iron deficiency in the brain may be responsible for the persistent neurological deficits observed in children with early life ID[97]. Studies have shown that early life ID is associated with lower IQ, reduced processing speed, impaired auditory recognition memory, and deficits in behavioural functions, attention, motor development and cognition[18,77,102]. Impairments link to areas of the developing brain that are vulnerable to ID[18]. These findings indicate that prevention of ID in early infancy is key. Delaying until anaemia is identified and subsequently treated may not prevent ID-induced neurological deficits once they have occurred.

However, one of the key challenges is distinguishing the specific consequences of anaemia from the correlates[73]. Much of the evidence relating to the health consequences of anaemia in children is also derived from cross-sectional, case-control, and prospective studies that have examined links between haemoglobin or anaemia on cognitive outcomes, with much of the evidence relating specifically to IDA[66]. Therefore, the ability to infer a causal role between iron deficiency and brain dysfunction is limited. However, plausible physiological mechanisms exist that have been substantiated in animal studies[18,25,77,103-105], while the inclusion of iron replete comparison groups from comparable environments in human populations adds validity to findings[106,107]. Overall, further research is needed to better understand the link between both ID and IDA in childhood and brain dysfunction, with longer term follow up to understand subsequent impacts on adult productivity.

Epidemiology

Anaemia is a significant global public health problem affecting nearly one third of the global population[66]. Approximately 42% of children under 5 years were estimated to be anaemic globally in 2016[51], with over 1.2 billion cases of IDA[91]. The prevalence of IDA is influenced by socioeconomic factors, especially household wealth and maternal education level[64,66] and continues to disproportionately effect disadvantaged children in urban, rural and remote areas[108]. In Australia, rates of anaemia highlight the inequitable distribution in health between Indigenous and non-Indigenous Australians as Aboriginal and Torres Strait Islander children have the highest reported burden, although data are limited in many settings[109].

The WHO classifies prevalence of anaemia greater than five percent as a mild public health problem, 20 to 40 percent as a moderate and greater than 40 percent as severe[110]. Fourteen percent of Australian children under 5 years of age were estimated to be anaemic by the World Bank in 2016, with the proportion increasing in more recent years[111]. Aboriginal and Torres Strait Islander children across Australia are however reported to experience much higher rates with studies consistently reporting prevalence greater than 25 percent, and several studies reporting rates greater than 60 percent[112-115].

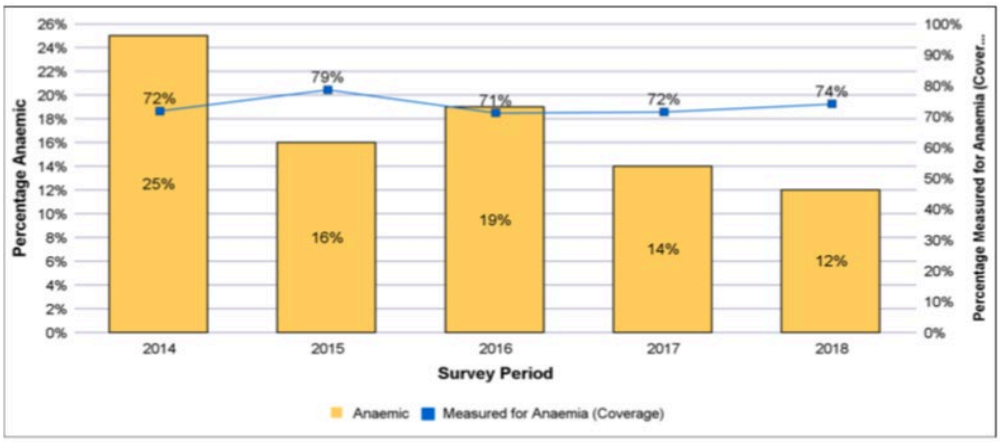
Table 4. Prevalence of anaemia in Australian Aboriginal and Torres Strait Islander children

Setting	Year	Data source	Age of children	Prevalence of anaemia
Remote Northern Territory *(internal publication)*	2020	Healthy Under 5 Kids – Partnering with Families database	6-59mo	16% at 6mo (coverage 72%) 27% at 12mo (coverage 75%)
25 remote communities Northern Territory (unpublished)	2018	Audit of medical database records	6-24mo (*n* = 495)	60% 6-24mo
Remote Northern Territory[116]	2014-2018	HU5K – annual growth and Nutrition report 2018	6-59mo	25% in 2014 12% in 2018: -17% 6-11mo -25% 12-17mo

Remote Northern Territory[117]	2008-2013	PCIS data (child and maternal records); Midwives data; AIHW National Hospital Morbidity Database (NHMD)	0-5 years (*n* = 10,575) <6mo (*n* = 315) Mothers of these children (*n* = 8,197)	39% had anaemia at least once in first 5 years of life 26% before 6mo 48% 6-12mo 26% mothers had anaemia in pregnancy
Remote Northern Territory[114]	2004-2006	Audit of medical records	6-12mo (*n* = 338) Mean age at diagnosis 7.6mo	68%
3 remote communities near Katherine, Northern Territory[118]	2004-2014	Retrospective cohort study	<24mo (*n* = 196) 86% children in communities tested for anaemia	47% 6mo (18% severe anaemia Hb <90g/L) 50% 12mo
Far North Queensland[119]	2006-2010	Retrospective cohort study	6-23mo (*n* = 708)	61%
109 Primary Health Care Centres in Australia (urban, rural, and remote)	2012-2014	Clinical audit data	6-59mo (*n* = 2287)	57% 6-11mo 43% 12-23mo 22% 24-59mo

In the Northern Territory, childhood anaemia is included within Aboriginal Health Key Performance Indicators, with measurement and prevalence of anaemia regularly monitored and reported on by government and non-government organisations. The NT Government Healthy Under Five Kids – Partnering with Families (HU5K-PF) program provides regular well-child health checks for Aboriginal children. This includes six monthly haemoglobin measurements for all children aged under 5 years living in remote areas, which will soon be expanded to include urban children. Routine screening for anaemia is undertaken using HemoCue point-of-care capillary testing[120]. If low Hb is identified, iron treatment is provided as per CARPA recommendations[1]. However, iron deficiency is not routinely screened for in the Northern Territory or other jurisdictions, so the extent of ID in early childhood is unknown.

The most recent published report shows the percentage of anaemic children in remote NT communities from 2014 to 2018 (Figure F)[116] with more recent unpublished data described in Table 4 above, indicating that rates continue to remain stable While improvements in identification and treatment have occurred over this timeframe, a high incidence of anaemia remains in the first 6-12 months of life (Figure G).



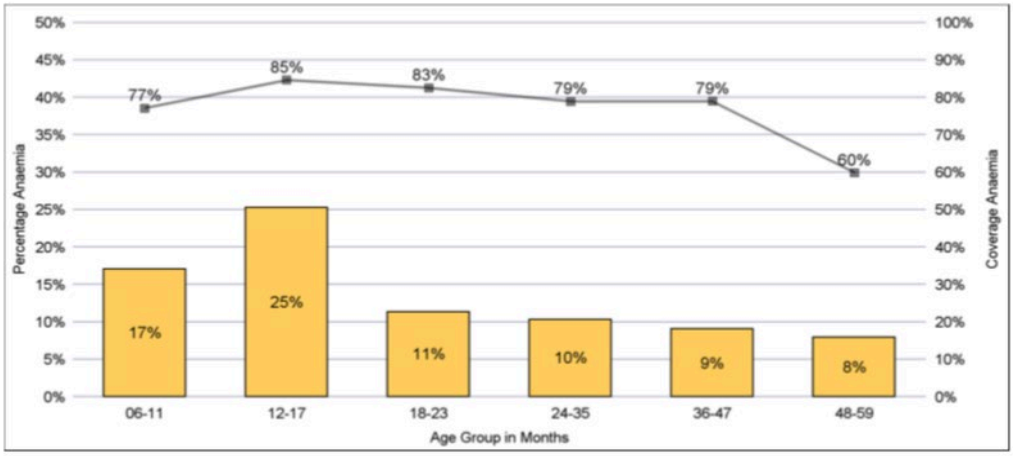
Anaemia *	2014	2015	2016	2017	2018
Number of resident children measured for anaemia	2,119	2,190	2,052	1,777	1,783
Number of resident children identified as anaemic	528	355	383	251	213
% of measured resident children identified as anaemic	25%	16%	19%	14%	12%
Number of resident children	2,948	2,780	2,881	2,483	2,405
Coverage (Resident children measured / number of resident children) **	72%	79%	71%	72%	74%

* The above trend chart and table only include the communities participating during this reporting period.
** Numbers in red indicate that coverage is less than 80%

Anaemia status criterion as per CARPA Standard Treatment Manual, 7th Edition 2017. Diagnosis of anaemia if haemoglobin (Hb) cut-off is <105 g/L (for children 6-12 months old); <110 g/L (12-60 months)

Figure F. Percentage of measured children in remote NT communities aged 6 months to 5 years of age who are anaemic by survey period (2014-2018)

Source: NT Health Under 5 Kids Annual Growth and Nutrition Report, 2018[116]



Age (Months)	06-11	12-17	18-23	24-35	36-47	48-59	Total
Number of resident children measured for anaemia	182	198	203	397	386	417	**1,783**
Number of resident children identified as anaemia	31	50	23	41	35	33	**213**
% of measured resident children identified as anaemic	17%	25%	11%	10%	9%	8%	**12%**
Number of resident children	236	234	246	503	489	697	**2,405**
Coverage (Resident children measured / number of resident children) *	77%	85%	83%	79%	79%	60%	**74%**

* Numbers in red indicate that coverage is less than 80%

Figure G. Percentage of measured children aged 6 months to 5 years of age who are anaemic by age group for the 2018 survey period

Source: NT Health Under 5 Kids Annual Growth and Nutrition Report, 2018[116]

Prevalence data from the NT Health and AIHW data linkage project[117] (Table 4) also showed high rates of anaemia in the first 5 years of life. This data indicated high rates of anaemia amongst mothers with 26 percent of mothers having anaemia in pregnancy (*n* = 2,107/8,197), with these mothers being much more likely to have a child with a diagnosis of anaemia (69%; *n* = 1,451). While anaemia is not routinely screened for in children aged under 6 months of age this study also included a cohort sample of 315 children where data was available for each six-month period from birth to 59 months (from 2008 to 2013). Data showed that 26 percent of infants under the age 6 months had anaemia, indicating a high burden in the first six months of life. These findings suggest a need for effective policies and programs that aim to prevent onset of anaemia early in life during critical growth periods.

Risk factors and determinants of anaemia in infancy

The causes of anaemia are diverse and complex[64,121], but major contributors in early life include inadequate dietary iron intake, malabsorption (often caused by inflammation) and health conditions that increase iron requirements[73,74,122]. Anaemia's diverse aetiology also includes infectious disease, such as soil-transmitted helminthiasis, autoimmune diseases, genetic impairments and acute or chronic blood loss[78]. Anaemia caused by ID accounts for approximately 42-50% of cases of anaemia worldwide[123], although geographical variability exists[35,51]. Risk factors for IDA in early infancy are illustrated in Figure H. These are multifactorial and include *i)* maternal iron status and presence of diabetes in pregnancy *ii)* gestational and birthing factors such as twin pregnancy and early cord clamping, *iii)* child feeding practices, and *iv)* socio-economic status. Maternal lifestyle factors such as poor nutrition and smoking also increase the likelihood of infants being born growth restricted or premature, with low iron stores[64].

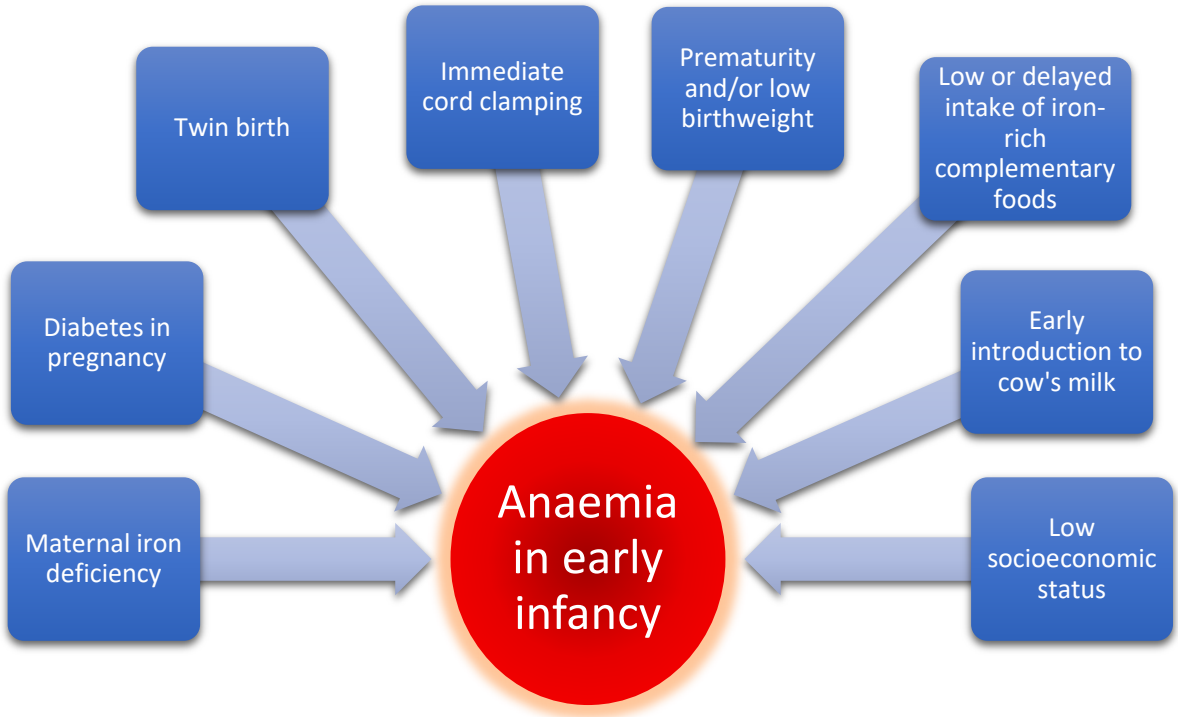


Figure H. Risk factors for anaemia in early infancy[26,64,124-126]

Anaemia is also determined by multiple, interrelated and intergenerational factors that are largely rooted in poverty and social exclusion[64,127], as displayed in Figure I. Socio-economically disadvantaged groups are disproportionately impacted by anaemia. This include recent migrants, refugee populations and Indigenous people[34,123,128], with health literacy gaps amplifying disadvantage[129]. Iron and other micronutrient deficiencies in remote Northern Australia are also linked to food insecurity and restricted access to fresh food sources[130-133]. Poor environmental conditions characterised by household overcrowding, poor sanitation and hygiene, inadequate food storage and preparation facilities also effect nutritional intake of Aboriginal and Torres Strait Islander people residing in remote areas[134-136]. A high burden of infections caused by enteric pathogens is also common, with one recent study from a NT remote community showing 60% of children had evidence of at least one enteric pathogen in their stool (n = 62)[129]. Other studies have similarly shown high rates of infectious disease early in life, causing early gut mucosal dysfunction leading to malabsorption and anorexia, and contributes to high rates of anaemia[128,137-139]. Thus, anaemia prevention strategies require multifaceted and long-term changes to address diverse social, economic, and environmental determinants of anaemia.

In the NT, the specific causes of anaemia are not well known, however the positive response to treatment with OIS for anaemic pre-school-aged and school-aged children indicates that iron deficiency is likely a predominant cause of childhood anaemia[115,140]. Given high iron needs in infancy and insufficient birth stores, it is likely that inadequate dietary iron when complementary foods are introduced is a significant cause.

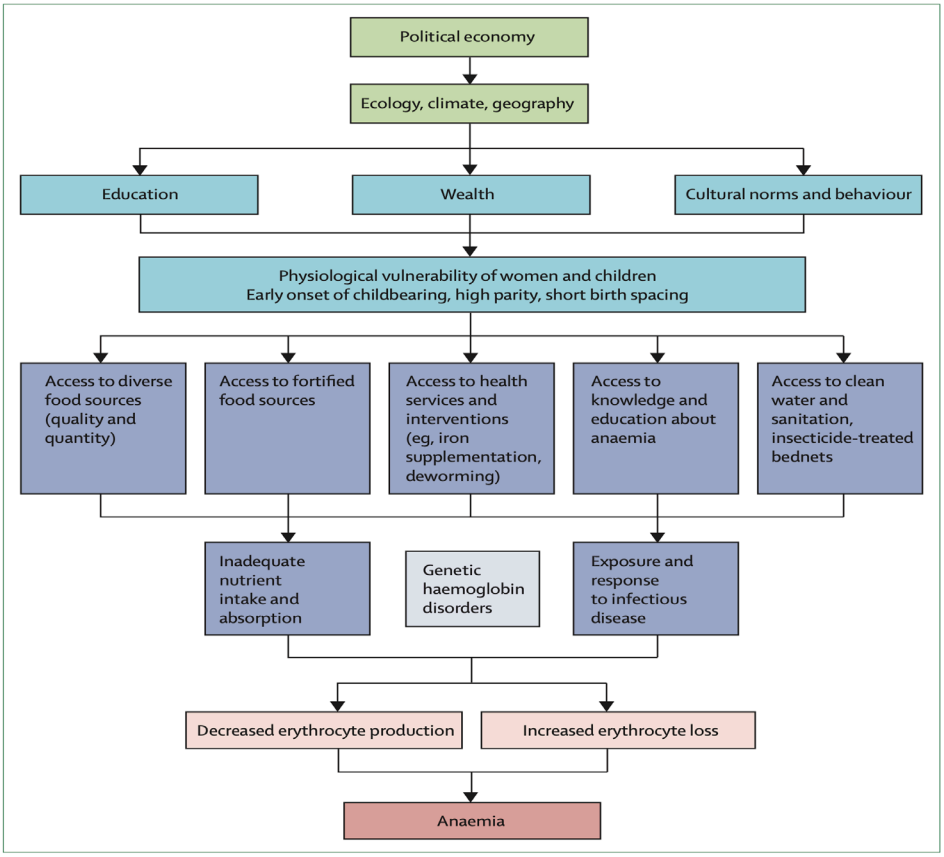


Figure I. Determinants of anaemia conceptual model
Source: Balarajan et al 2011[66]

A data linkage project undertaken by NT Health and AIHW used administrative data between 2008 and 2013 to explore determinants of anaemia[117]. Records of mothers and their children (aged under 5 years of age) living in remote areas of the Northern Territory were matched and analysed. Available child and maternal Primary Care Information System (PCIS) data were linked with NT Midwives' data and AIHW National Hospital Morbidity Database (NHMD). PCIS data included 10,641 children aged under 5 living in remote areas of the Northern Territory and who attended a health clinic, with 6790 having a Hb test during this timeframe. Data showed that children whose mother had anaemia in pregnancy were more likely to have an episode of anaemia (69%, *n* = 1451/2107), compared with children of mothers who did not have anaemia (38%, *n* = 2329/6090). In addition, Aboriginal children under one year of age were 19 times more likely than non-Indigenous children to be hospitalised with a primary or secondary diagnosis of anaemia. In a logistic regression model, the odds of a child having anaemia were:

- 31% higher if the mother was aged under 20 when they gave birth, compared to children whose mother was aged 30 to 34 (95% CI = 1.21, 1.41);
- 26% higher if the mother had pre-existing diabetes (95% CI = 1.12, 1.41);
- 21% higher if the mother had anaemia in pregnancy (95% CI = 1.16, 1.26); and
- 8% higher if born with low birthweight (< 2500g) (95% CI = 1.01, 1.14).

These data suggest that maternal anaemia was a far more significant risk factor for early onset anaemia than LBW or gestational age[118], a finding observed in other NT research[118]. For reasons that are not yet clear, maternal diabetes in pregnancy was also associated with early onset anaemia, which is supported in international literature[64,99,141].

Iron intakes of infants and young children

There is limited data to describe the dietary intakes of children aged under two years in Australia and minimal studies have explored the diets of young Aboriginal children. Studies across Australia (Table 5) indicate that few infants and children consume adequate iron with mean iron intakes of infants (mean age 9.1 months) reported at 9.1mg/day[142] (RDI 11mg/day) and toddlers reported at approximately 7mg/day[142,143] (RDI 9mg/day). Main sources of iron were iron-fortified formula for infants and cereals for toddlers[142,144] and total dietary iron intake was positively associated with regular intakes of non-haem iron foods such as cheese, breads, fats/oils and water, which are generally seen as less bioavailable, and negatively associated with red meats and fortified fruit and vegetable products[143,144].

Table 5. Iron intakes of Australian children

Location	Age Group	Dietary method	Iron intakes
Melbourne	Infants (mean age 9.1m) n=485 Toddlers (mean age 19.6m) n=423	24-hour food recall	9.1mg/day infants 6.6mg/day toddlers
National	2-6yo		Total diet 6.3mg/day Haem iron 1.9mg/day

Adelaide	Toddlers (n=828)	3 non -consecutive days of 24-hour recall and 2-day food records	7mg/day 18% of children's intakes <4mg/day
		24-hour recall over 3 days	13% met RDI (11mg/day)

Most dietary studies of Aboriginal children are based in urban areas. There are many similarities between the reported dietary intakes of Aboriginal and Torres Strait Islander young children who live in remote and urban areas, which aligns with the intakes of Australian children in general. However, many more Aboriginal and Torres Strait Islander children living in remote areas of Australia are reported to be breastfed, with higher rates of both initiation and duration of breastfeeding[145,146]. Anecdotally, rates of formula feeding are increasing in remote Aboriginal and Torres Strait Islander communities however there may also be significant rates of mixed feeding. Aquino *et al* 2013 reporting that across 6 remote communities in Northern Australia 67 percent of children were breastfed with 80 percent of children aged 6 to 12months receiving some breastmilk and 20 percent receiving infant formula[113]. Similarly, Tonkin *et al* 2020 described that 85 percent of children were breastfed, however few children under 12 months of age were formula fed[131].

The Gomeroi gaaynggal study[147,148], a prospective longitudinal cohort study of Aboriginal and Torres Strait Islander mother-child dyads from rural New South Wales, describes similar feeding patterns to those described for the Australian population. Iron intake was low for both infants and for their mothers during pregnancy was also low, with iron being the micronutrient least likely to be adequately consumed when compared to other key nutrients needed for optimal reproductive health (folate, iron, calcium, zinc and fibre)[149].

Two key studies describe the diets of young Aboriginal children living in remote communities across Northern Australia (Sprinkles study)[113,122,131] using 24-hour food recalls and food variety checklists. Both studies described diets with low dietary diversity, which was reduced further during non-pay week. The most recent study[131] described that only 13% of 6-24 month old children met the RDI for iron with low intakes of non-haem sources of iron- vegetables and wholegrain cereals and only 48 percent of children met dietary recommendations for meat consumption. 55 percent had frequent consumption of traditional foods, however higher consumption of traditional foods (mostly meats) did not impact on iron intakes.

A doctoral dissertation by Brand 2020 also described low intake of iron rich foods in a qualitative study of children aged between 3 months and 3 years living in a remote Central Australian community[150]. Caregivers in this study described the determinants influencing their feeding practices and reported that children were unlikely to consume iron rich foods until they reached certain developmental indicators, for example eruption of 4 teeth, walking, or reaching their first birthday (reflected in the below statements). These milestones are generally met between 9 and 12 months of age, indicating that despite the introduction of complementary foods to these children between 5-6 months of age, they

were unlikely to consume adequate amounts of iron prior to 9 months of age. Table 6 shows the iron content of foods introduced over the first year of life[150].

> *"caregivers shared the widely held belief that children could not safely consume firm foods such as meats prior to the eruption of four teeth, they told me that cost of meat was too prohibitive for regular purchasing, especially if money was obtained from others to purchase food, and they described that they did not have safe places to store meats or the equipment needed to prepare and cook meals." p. 217*

> *"caregivers could identify and had existing knowledge of iron rich foods and many applied strategies to either obtain these foods from others through acts of reciprocity or they would substitute other foods such as eggs, bacon and ham, if the child was deemed developmentally capable of consuming these foods safely and they had the money available to purchase these foods." p. 217*

Table 1. Iron content of foods introduced over the first year of life described by Brand 2020

Food	Amount of Iron (mg/100g)	Age of introduction
Rice#	0	4-6 months
Pumpkin/potato#	0.3	4-6 months
Tinned spaghetti#	0.3	8-10 months
Jar of vegetable-based baby food	0.5	4-6 months
Pasta#	0.6	4-6 months
Jar of meat-based baby food	0.8	4-6 months
Baked beans#	1.0	9-12 months
Tuna	1.2	9-12 months
Peanut butter#	1.8	9-12 months
Bread#	1.48- 7.08*	9-12 months
Egg	1.98	8-10 months
Minced/roast/stewing beef	2.3	9-14 months
Weetbix#	14	4-6 months

Source: Brand 2020[150] (p.216)
*Iron fortified breads are available in some remote communities
#Non-haem iron sources (low absorption)

Preventative oral iron supplementation (OIS) guidelines

Iron supplementation is a widely recommended strategy to prevent IDA in settings where anaemia is highly prevalent and where dietary ID exists[74]. OIS is used for two reasons:

1. to prevent IDA in at-risk populations or vulnerable groups
2. to treat individuals with a diagnosis of anaemia[64]

Several international and local guidelines exist that recommend preventative OIS to infants and young children, however key differences exist. Since 2010, the AAP have recommended that all breastfed full-term infants receive 1 mg/kg per day of oral iron from 4 months of age until adequate iron-containing complementary foods are introduced[2]. Other guidelines, including the World Health Organization, only support this recommendation in populations with risk factors when a high prevalence of IDA exists[26,151 74,152]. The WHO recommendation is supported by evidence from four systematic reviews of efficacy trials that adhered to

Cochrane conventions and GRADE methodology[153-156] (*strong recommendation, moderate quality of evidence*). In addition, ESPGHAN[26] report that:

- *"there is strong evidence that iron supplementation of infants from 4 to 6 months of age reduces the prevalence of an[a]emia and may improve neurodevelopment in populations with a high prevalence (>10%) of IDA in infants". However:*
- *"there is insufficient evidence that general iron supplementation of exclusively or mainly breast-fed infants from 4 to 6 months reduces IDA or has any other health benefits in populations with a low prevalence of IDA"* p.126.

Table 7. Oral Iron Supplementation guidelines for breastfed infants

Organisation	**Oral Iron Supplementation Recommendation**		
	Age	**Dose**	**Notes**
American Academy of Pediatrics (AAP) 2010[2]	4 months until consuming adequate iron containing foods	1mg/kg/d	Also recommended for partially breastfed infants (>50% breastmilk)
The ESPGHAN Committee on Nutrition[26]	4-12mo*		High prevalence of IDA in infants 6-12mo (>10%)
World Health Organisation[152]	6-24mo	10-12.5mg daily	For 3 months of the year where prevalence >40% In areas where prevalence of anaemia is between 20-40%, intermittent iron supplementation can be considered
National Blood Authority Australia[151]	Infants for whom there is a delay in starting iron-rich solids, until appropriate dietary sources are introduced	1mg/kg/d	
The Royal Australian College of General Practitioners (RACGP)[157]	Normal birth weight term babies under 6 months if IDA risk factors are present (in consultation with a paediatrician)	1-2mg/kg/d (RCH guidelines)	Risk factors include history of low birth weight (LBW) or preterm birth; maternal anaemia, twins, chronic infections, failure to thrive, and cow's milk intake <1 year of age
UpToDate[158]		1mg/kg/d (Max. 15 mg/day)	Supplement breastfed infants ≥ 4 months until consuming adequate iron-rich complementary foods

**ESPAHGN: 4-12mo: ongoing supplementation after onset of complementary feeding is only recommended for infants from "high risk groups" = low socioeconomic status, living in areas with high prevalence of IDA, or low intake of iron-rich complementary foods.*

Efficacy trials have established that providing OIS to children aged under two years of age increases iron stores and reduces the risk of ID and IDA[155]. However, there is considerable variation in the literature regarding when to initiate OIS, appropriate dosage, frequency (e.g. daily versus intermittent), duration, composition of the supplement, and how to enhance adherence[74,153,155,156,159].

Literature review

The aims of this literature review are to summarise the evidence for providing preventative OIS to predominantly breastfed infants from four months of age or earlier to inform the updating of the RPHCM guidelines. This review will assess whether OIS *i)* improves iron stores; *ii)* prevents anaemia, ID, or IDA; *iii)* preserves mental and motor development; and *iv)* has any unintended adverse effects. The review will also clarify optimal regimen considerations regarding age of initiation, duration, frequency, dosing amount, formulation comparisons, adherence and whether universal or targeted supplementation should occur. Finally, a summary of the safety of preventative OIS will be provided.

Methods

Search strategy

On 6 March 2021, the following databases were searched for relevant literature: PubMed, MEDLINE (OVID), CINAHL, Scopus, Cochrane Libraries (including CENTRAL, HTA and DARE), PsycINFO and PsycLIT (psychology databases). Databases from international organisations including WHO, UNICEF and World Bank were also searched along with reference lists from relevant book chapters.

The following Medical Subject Heading (MeSH) terms, keywords and boolean operators were used to systematically search for relevant publications:

1. “anaemi$” OR “anemi$” OR “iron” OR “iron def$” OR “iron supplement$” OR “ferr$” OR “micronutrient” AND
2. “child$” OR “infant”

The search strategy was adapted for specific databases. Studies identified were screened by title and relevant abstracts reviewed. Reference lists and recent citations of key articles were scanned to identify additional relevant studies. Google Scholar was also used to check for citations of key articles. Relevant grey literature was also reviewed, including internal Department of Health and other local reports and guidelines.

Eligibility criteria for meta-analyses, systematic reviews and RCTs

All systematic reviews and meta-analyses were included that assessed whether preventative oral iron supplementation improved iron status in children. Individual experimental trials were included if an OIS intervention was used in exclusively or predominantly breastfed healthy, term infants aged 4 months or earlier. No restrictions were applied on publication date or country. All articles with an abstract in English were reviewed. Trials were excluded if they contained low birth weight or preterm infants, the intervention commenced after four and a half months of age, infants in the sample were different ages and no breakdown of ages was provided, or infants were predominantly formula fed.

Results and discussion

Meta-analyses & systematic reviews

Several systematic reviews and meta-analyses have investigated outcomes of oral iron supplementation in children[155,159-163]. However, most of these reviews have focused on older children or infants with mixed ages, limiting the generalisability of results. Only one meta-analysis by Cai *et al* 2017[160] investigated whether OIS provided by four months of age improved outcomes (Table 8). Providing OIS to children after six months may miss critical periods when infants are anaemic or iron deficient, as indicated by NT data.

In the meta-analysis by Cai *et al* 2017[160], the effects of daily OIS in healthy predominantly breastfed infants aged 4-6 months were assessed (four RCTs; 511 infants from five different study sites; Canada, Sweden, Honduras, Turkey and China). Compared to placebo, infants supplemented with iron had significantly increased Bayley psychomotor developmental indices (BPDI) at 13 months and MCV. There were no significant differences in IDA or ID between iron supplemented infants and controls, despite a 42 percent overall reduction in the prevalence of ID/IDA in the OIS group. This may have been due to the high prevalence of anaemia in control groups. OIS did not significantly affect Hb or PF. Iron supplementation was associated with reduced weight gain and head circumference. The authors' concluded that OIS did improve iron status of breastfed infants, however small sample sizes and a limited number of RCTs means further trials are needed to build on the limited evidence base in this age group.

Table 8. Daily OIS in healthy breastfed infants 4 to 6 months

Results of OIS	
Significantly increased Bayley psychomotor development index (BPDI) at 13mo	MD 7.00; 95% CI 0.99,13.01; 1 RCT; *n* = 46
Significantly increased MCV (fL)	MD 2.17; 95% CI .99, 3.35; 2RCTs; *n* = 87
42% reduction in the prevalence of ID/IDA (not significant)	RR 0.59; 95% CI 0.27-1.30; 3 RCTs; *n* = 251
No significant difference on Hb or PF	RR 1.78; 95% CI -1.00-4.57; 2 RCTs; *n* = 96 RR 17.26; 95% CI -40.96, 75.47; 2 RCTs; *n* = 87
Reduced weight gain and head circumference	MD -0.04; 95% CI -0.07, -0.01; 3 RCTs; *n* = 272 MD -0.14; 95% CI -0.18, -0.09; 2 RCTs; *n* = 212

A Lancet meta-analysis by Pasricha *et al* 2013[155] reviewed the evidence for efficacy and safety of daily OIS in children aged 4 to 23 months (Table 9). The authors' found that iron supplementation reduced anaemia in children in most trials and prevented ID and IDA. RCTs that failed to show a difference in anaemia prevalence between OIS and placebo generally reported adherence issues when mothers administered iron to their infants. There were no significant differences in Bayley's Mental Development Index (BMDI) or BPDI scores, however a subgroup analysis of iron deficient children showed significant improvements in BMDI. Children receiving OIS had slightly lower gains in length and weight and more vomiting and fever than children randomly allocated to placebo. There were no absolute

differences in growth (cm, kg, or Z-scores). Longer duration of OIS (> 3 months vs 1 month to 3 months) had a greater effect on ferritin and TS (both *P* = 0.005), but not haematological markers. Meta-analysis of supervision or adherence was not possible because of heterogeneity in reporting between RCTs.

Table 9. Daily OIS in children 4 to 23 months (*n* = 31 RCTs)

Results	
Reduced prevalence of anaemia	RR 0.61; 95% CI 0.50, 0.74; 17 RCTs; *n* = 4825; *P* < 0.0001
Prevention of ID	RR 0.31; 95% CI 0.15, 0.60; 9 RCTs; *n* = 2464; *P* < 0.0006
Prevention of IDA	RR 0.14; 95% CI 0.10, 0.22; 6 RCTs; *n* = 2145; *P* < 0.0001
No difference in Bayley's psychomotor development index scores	MD 1.65; 95% CI -0.63, 3.94; 6 RCTs; *n* = 1093; *P* = 0.16
No difference in Bayley's mental development index scores Significant difference in subgroup analysis of children with ID	MD 1.05; 95% CI -1.36, 3.46; 6 RCTs; *n* = 1086; *P* = 0.39 MD 5.90; 95% CI 1.81, 10.00; 3 RCTs; *n* = 281; *P* = 0.005
Slightly lower growth rate in length and weight	SMD –0.83; 95% CI –1.53, 0.12; 8 RCTs; *n* = 868; *P* < 0.02 MD –1.12; 95% CI –1.19, 0.33; 8 RCTs; *n* = 868; *P* < 0.0005
Increased incidence of vomiting and fever	RR 1.38; 95% CI 1.10, 1.73; 3 RCTs; *n* = 1020; *P* < 0.006 RR 1.16; 95% CI 1.02, 1.31; 4 RCTs, *n* = 1318; *P* < 0.02

A more recent meta-analysis by Petry *et al* 2016[161] reviewed the evidence for low dose OIS and low dose dietary fortification in early childhood (6 to 23 months). Studies were excluded that involved severely unwell children, however studies containing anaemic or malnourished children (underweight, stunted, wasted) were included. Administering up to 15 mg of additional daily iron increased mean Hb by 4.1 g/L, mean SF concentration by 17.6 µg/L, reduced anaemia risk by 41%, and reduced ID risk by 78% and risk IDA by 80%. There were no significant effects on growth (either weight or length) length for age, BPDI or BMDI.

Table 10. Low dose OIS and dietary fortification in children 6 to 23 months up to 15mg/d iron

Results	
Increased mean Hb by 4.1g/L	95% CI 2.8, 5.3; 30 RCTs; *n* = 6569; *P* < 0.001
Increased mean SF by 17.6 µg/L	95% CI 13.5, 21.2; 21 RCTs; *n* = 4291; *P* < 0.001
Reduced anaemia risk by 41%	95% CI 0.49, 0.70; 22 RCTs; *n* = 5647; *P* < 0.0001
Reduced risk of ID by 78%	95% CI 0.14, 0.35; 13 RCTs; *n* = 3698; P < 0.0001
Reduced risk of IDA by 80%	5% CI 0.11, 0.37; 8 RCTs, *n* = 3464; P < 0.0001
No significant impact on Bayley's psychomotor development index or mental development index scores	MDI: MD 0.6; 95% CI −1.2, 2.4; 4 RCTs; *n* = 1062, *P* = 0.50 PDI: MD 0.6; 95% CI −1.2, 2.4; 4 RCTs; *n* = 1062; *P* = 0.50
No significant impact on growth weight for age Z-score or length for age Z-score	WFA: MD −0.01; 95% CI −0.08, 0.05; 10 RCTs; *n* = 3511; *P* = 0.69 LFA: MD −0.02; 95% CI −0.08, 0.04; 10 RCTs; *n* = 3511; *P* = 0.57

Sub-group analysis stratified by iron dose showed no significant difference in effect sizes on haemoglobin at endpoint when comparing doses of 6-8 mg/day (MD 4.4g/L, 95% CI 2.1, 6.8, 7 RCTs), 8-10 mg/day (MD 5.48g/L, 95% CI 3.4, 7.6, 14 RCTs), and 11-15mg/day (MD 2.7g/L, 95% CI -2.33, 7.8, 4 RCTs) (*P* = 0.12). The largest effect sizes for the 41% reduction in anaemia risk were observed in trials that provided between 6 to 8 mg per day (RR 0.54, 95% CI 0.44, 0.66, 7 RCTs *n* = 2089) or 8 to 10 mg per day (RR 0.59, 95% CI 0.45, 0.77, 9 RCTs, *n* = 2575), but not a higher dose of 11-15 mg per day (RR 0.82, 95% CI 0.51, 1.33, 4 RCTs, *n* = 489). In sub-group analyses stratified by type of intervention (OIS versus fortification using equivalent quantities of iron), an increase in Hb and SF were significantly higher for OIS trials (Hb MD 5.6 g/L, 95% CI 3.4, 7.7, 15 RCTs, *n* = 3516; SF MD 27.2 µg/L, 95% CI 18.2, 36.3, 8 RCTs, *n* = 1747) compared to fortification trials (MD = 2.6 g/L, 95% CI 1.3, 3.9, 16 RCTs, *n* = 3053, *P* < 0.01); SF MD 11.3 µg/L, 95% CI 13.7, 21.4, 13 RCTs, *n* = 2544, *P* < 0.001).

A Cochrane review by Wang *et al* 2013[163] investigated the effects of OIS on developmental status and cognitive function in children under three years of age with IDA. The authors' found that OIS did not improve Bayley PDI scores (MD -1.25; 95% CI -4.56, 2.06; *P* = 0.65; *n* = 225, 5RCTs, low quality evidence) or Bayley MDI scores 1.04 (MD 1.04; 95% CI -1.30, 3.39; *P* = 0.79; *n* = 225; 5 RCTs, low quality evidence) within 30 days of commencement. Only two RCTs (*n* = 160) examined the effects of OIS more than 30 days after commencement of treatment. One study demonstrated improvements in mean number of skills gained on the Denver Developmental Screening Test after two months of OIS compared to controls (MD 0.8; 95% CI -0.18, 1.78; *P* = 0.11; moderate quality evidence). The second RCT reported that four months of OIS improved scores on the Bayley PDI (MD = 18.40; 95% CI 10.16, 26.64; *P* value <0.0001; moderate quality evidence) and MDI (MD 18.80; 95% CI = 10.17, 27.43; *P* value <0.0001; moderate quality evidence) compared to placebo. The authors concluded there was no evidence that OIS improves psychomotor development or cognitive function within 30 days of treatment in young children with IDA, while the outcomes from longer-term treatment were unclear. One other systematic review of OIS in young children assessed the effects on mental performance and psychomotor development[11,164]. This review concluded that there may be a moderate positive effect of OIS on PDI score, which is most evident at 12 months of age[11].

The meta-analysis by De-Regil *et al* 2011[159] using GRADE methodology concluded that intermittent OIS was effective at improving haemoglobin concentrations (MD 5.20g/L; 95% CI 2.51, 7.88; 19 RCTs; *n* = 3032, low quality evidence) and ferritin levels (MD 14.17 µg/L; 95% CI 3.53, 24.81; 5 RCTs; *n* = 550, low quality evidence) and reducing rates of anaemia (RR 0.51; 95% CI 0.37, 0.72; 10 RCTs; *n* = 1824, moderate level evidence) and iron deficiency (RR 0.24; 95% CI 0.06, 0.91; 3 RCTs, *n* = 431, very low level evidence) compared to placebo in children younger than 12 years of age. In 15 RCTs for children under 60 months,
Trials included were from settings with moderate to high anaemia prevalence. When comparing intermittent and daily supplementation in children under 12 years, the authors' concluded that intermittent OIS achieved similar outcomes for haemoglobin (MD −0.60 g/L, 95% CI −1.54, 0.35; 19 RCTs; *n* = 2851, low level evidence) and ferritin (MD −4.19 µg/L, 95% CI −9.42, 1.05; 10 RCTs; *n* = 902, low level evidence) compared to children receiving daily supplementation. However, children receiving intermittent OIS were at higher risk of developing anaemia (RR 1.23, 95% CI 1.04, 1.47; 6 RCTs; *n* = 980, low level evidence). A comparison of intermittent and daily OIS in children aged 0 to 59 months showed similar

outcomes on haemoglobin (MD −0.75 g/L, 95% CI −1.80, 0.29; 14 RCTs; *n* = 2270) and ferritin (MD −3.10 µg/L, 95% CI −6.59, 0.39; 8 RCTs; *n* = 582), but a significantly higher risk of developing anaemia (RR 1.26, 95% CI 1.05, 1.51; 3 RCTs; *n* = 770).

Review of Randomised Controlled Trials (RCTs)

A total of 10 trials published between 2001 and 2019 were identified that met the inclusion criteria, with findings that were described across 12 separate articles[3,9,49,165-173]. Nine of the ten trials were RCTs with a double blinded placebo arm. Samples sizes varied considerably between trials, from 77 to 1482 infants. Trials with multiple arms that included a non-iron intervention are included in the review, however non-iron arms are not described. Appendix B outlines the characteristics and main results of the ten included trials. The results are outlined below in terms of the following: *i)* biochemical outcomes, including presence of ID or IDA; *ii)* mental/motor development*, iii)* growth, and *iv)* adverse effects.

Biochemical outcomes

Table 11 presents summary data for biochemical outcomes. All trials reported on haematologic and iron outcomes for infants. One trial did not include a control group[166], however Hb, hematocrit, PF and TS all significantly increased in both OIS groups from 4 to 9 months. Six out of nine studies saw an increase in Hb in the OIS group relative to controls after outcomes were assessed following supplementation[3,9,167,168,170,173]. In the three studies where Hb was not significantly higher, the general prevalence of IDA was low (<3%)[171,172] or the adherence to OIS was poor[169]. Serum or plasma ferritin, which reflects adequate stores of iron, also significantly increased at the end-point for the OIS group compared to placebo in six studies[3,167,168,171-173], and approached significance in another study that was underpowered (P = .06)[9]. A number of trials assessed changes in MCV and in these studies the OIS groups had significantly higher MCV at six months (three out of six trials)[3,9,172], with two trials demonstrating a sustained elevation in MCV at 9 months[3,172].

There was considerable variation in definitions for ID and IDA between trials. However, most trials defined ID when SF concentrations were <12 µg/L, whereas IDA was typically categorised as Hb <110 g/L, in addition to SF <12 µg/L. There were seven studies that were sufficiently powered to detect differences in ID and IDA between the intervention group and placebo when outcomes were assessed. In the five studies where the prevalence of ID and IDA was high in the general infant population (> 10%), all trials demonstrated significantly lower rates in the OIS groups compared to placebo (Indonesia x 2, Honduras, Canada, China)[3,9,168,169,173]. There was no significant difference between OIS and placebo groups in settings where the prevalence of ID and IDA was low (< 10%) (Sweden, India)[3,167].

Two trials randomised mothers to iron or placebo in pregnancy, and their infants to iron or placebo. In one double RCT, OIS in infancy, but not pregnancy, reduced ID risk at 9 months, independent of ID status at birth[169]. There was no additional benefit of maternal supplementation over OIS in infancy and no benefit of OIS in pregnancy when iron in infancy was not provided. In the second trial, OIS from the second day after birth improved iron status (Hb, SF) at 6 months among infants at high risk for early iron deficiency (mothers were iron deficient and early cord clamping was standard practice)[167]. There was no significant difference in outcomes among iron supplemented infants with different quartiles

of maternal Hb or cord blood Hb. However, there was a significant difference in the effect of OIS on SF and Hb among infants with different quartiles of cord SF (P <0.001).

Table 11. Biochemical outcomes

Key Findings	Number of Studies	Comments
Significant increase in Hb with OIS relative to controls	6 out of 9	Studies with no significant increase had low prevalence (<3%) of IDA or low adherence to OIS
Significant increase in serum or plasma ferritin at endpoint of OIS compared to controls	6 out of 9	Additional underpowered study demonstrated increase but not significant (P=.06)
Significant increase in MCV at 6 months with OIS relative to controls	3 out of 6	2 studies demonstrated sustained elevation in MCV at 9 months
Significantly lower rates of ID and IDA with OIS compared to controls in populations with prevalence >10%	5 out of 7	No significant difference (2) in setting where prevalence was <10%
OIS in infancy but not pregnancy reduced ID risk at 9 months of age independent of iron status at birth	1	

Mental/motor development outcomes

Only 3 trials reported on mental or motor development. One trial provided OIS or placebo to mother-infant pairs, in pregnancy and/or in infancy at 1.5 months and assessed developmental scores at 9 months (Peabody Developmental Motor Scale – Version 2; PDMS-2)[165]. Iron supplementation in infancy (but not pregnancy) improved gross motor scores, reflexes, stationary and locomotion. Iron supplementation in infancy improved motor scores by 0.3 SD compared with no supplementation or supplementation during pregnancy alone. Another trial determined that supplemented infants performed significantly better on BPDI than placebo at 13 months of age after receiving OIS from 1 to 6 months. Infants receiving OIS also demonstrated improved visual acuity[9]. No differences were observed between groups on Mental Development Indexes. The third trial assessing neurodevelopmental outcomes found that motor development was closer to age-appropriate norms in the OIS group compared to placebo[167]. The treatment effect on motor outcome was consistent after controlling for maternal age, maternal Hb quartiles, mode of delivery, parity, infant birth weight, cord blood Hb and cord SF.

Table 12. Mental/motor development outcomes

Key Findings	Number of Studies	Comments
OIS in infancy improved gross motor scores by 0.3 SD at 9 months (overall: $P < 0.001$, reflexes: $P = .03$, stationary: $P < 0.001$, locomotion: $P < 0.001$)	1	Compared with no supplementation or supplementation in pregnancy alone
Motor development of OIS infants (MD 5.83 ± 0.69) was closer to age-appropriate norms compared to placebo (MD 5.18 ± 1.35; $P < 0.01$)	1	Treatment effect was consistent when controlling for maternal age, maternal Hb, mode of delivery, parity, infant birth weight, cord blood Hb and SF
OIS provided to infants from 1 to 6 months of age significantly increased Bayley Psychomotor Development Indexes (PDI) at 13mo (100 ± 12) compared to placebo (98 ± 9)	1	No differences between groups for Mental Development Indexes
Infants receiving OIS from 1-6mo demonstrated significantly increased visual acuity compare to placebo	1	

Growth

Seven trials reported on the effects of OIS on growth (Table 13). In six of the seven trials, there were no significant differences between groups on any growth measures, or among infants who were iron sufficient at birth[9,168-170,172]. In one trial, infants who received OIS from 4–9 months of age had significantly reduced weight and head circumference compared to placebo, in a setting where infants were predominantly iron replete (Sweden), whereas a negative effect on growth was observed in Honduran infants only among infants receiving OIS with an initially low Hb from 4 to 6 months[49].

Table 13. Growth outcomes

Key Findings	Number of Studies	Comments
No significant differences in growth (weight, length, head circumference) between infants receiving OIS and controls or infants who were iron sufficient at birth	6 out of 7	Negative effect on growth between 4 to 6 months was observed in Honduran infants receiving OIS who had an initially low Hb

Adverse effects

Eight of the trials reported on whether OIS had adverse effects. Most common side effects reported included vomiting, decreased appetite, blackened stools, diarrhoea, constipation and stained teeth. One study reported a decreased tendency for diarrhoea when supplementation was provided to infants with low Hb (<110g/L) at 4 months, and an

increased likelihood of diarrhoea when Hb was normal (>110g/L)[3]. In another study, more infants with ID at birth saw a doctor for upper respiratory infections or fever in OIS group 145/307 (47.2%) vs placebo 119/304 (39.1%)[169]. However, most trials were insufficiently powered to determine significant differences in morbidity data between supplemented infants and placebo, due to insufficient sample sizes. Adverse effects are described in further detail in the subsequent section using pooled data in meta-analyses.

Limitations of these trials include heterogeneity in choice of haematological markers of anaemia, as well as definitions and cut-offs for ID and IDA. Risk factors and prevalence rates for anaemia also varied considerably across trials (3% to 66% reported). In addition, few RCTS assessed motor and mental development. Those that did used different validated instruments and no long-term outcomes were assessed beyond 13 months of age. One study relied on a very small sample (*n* = 44) when assessing outcomes[9]

Summary of regimen considerations

Age of initiation

There is evidence that supplementation earlier than 4 months (*n* = 4 trials) improves iron status, reduces ID/IDA, and improves indicis of psychomotor and neurodevelopment. Four studies in this review commenced OIS before 4 months: one at 1.5 months[165,169], two at 1 month[9,172], and another 36 hours after birth[167] (Table 14). In the study by Friel *et al*, OIS from one month of age prevented IDA at six months, whereas 14% of those in the placebo group developed IDA[9]. In the study by Bora *et al* 2019, supplementation from the second day after birth improved iron status and motor development at 6 months of age in a population of infants with a high prevalence of anaemia at baseline. The authors justified commencement of OIS at this age because waiting to begin iron supplementation at 4 months may have been too late to prevent early iron deficiency anaemia and the associated risk of neurodevelopmental deficits[167]. Unlike RCTs that commenced at 4 months, all three trials assessing psychomotor development reported significant improvements compared to controls when outcomes were assessed[9,165,167,169].

Table 14. Age of initiation less than 4 months

Age at which OIS commenced	Effect	Comments
36 hours post birth	Improved iron status and motor development at 6mo	High prevalence of anaemia in population, 85% mothers' anaemic at time of delivery, 40% infants with anaemic mothers had ID at birth (cord SF < 75µg/L)
OIS provided from one month of age (Friel)	No infants in OIS group (*n* = 28) had IDA at 6 months compared to 14% in placebo group (*n* = 21)	
<4mo (36 hours post birth, 1 month, 1.5 months) *n* = 3 RCTs	Significant improvement in psychomotor development compared to controls	

Six RCTs commenced OIS at 4 months of age[3,49,166,170,171,173]. In the two Indonesian studies (Dijkhuizen *et al* 2001 and Wieringa *et al* 2003), preventative OIS from 4 months of age to 10 months reduced the prevalence of IDA by more than 75 percent compared to placebo groups[168,173]. However, outcomes at six months of age were not assessed and no baseline data were collected, so the extent to which OIS prevented early ID was unknown. In the RCT by Yurdakok *et al* 2004, OIS from 4 months of age was effective at reserving iron status (SF) in exclusively breastfed infants at 6 months of age compared to controls, where SF decreased. This trial included a healthy population whereby infants appeared to have adequate dietary iron intake at around 6 months. Domellof *et al* 2001 showed that providing OIS from 4 months of age, the was a significant increase in Hb at six months, independent of study location, initial Hb or baseline iron status[3]. The authors' hypothesized that regulation of infant iron metabolism at four months of age was immature, with iron being absorbed and used for Hb synthesis independent of iron status. The authors' noted that by 6 months of age, this effect on Hb was no longer constant. Hb at six months increased significantly more in Honduran infants receiving OIS, due to higher IDA prevalence (25% vs 3% in Swedish infants). Domellöf *et al* suggested that iron supplementation at 4 months of age was not superior to OIS started at 6 months of age[3]. However, given that 25% of Honduran infants receiving placebo had IDA by 6 months of age, it could be argued these infants benefited from earlier intervention, particularly when potential consequences of early brain ID are considered[18].

Table 15. Age of initiation for OIS

Age at which OIS commenced	Effect	Comments
4 to 10 months	Prevalence of IDA reduced by >75% compared to placebo	Indonesia Population had high baseline prevalence of anaemia
4 months	Infants not receiving OIS had decreased SF at 6mo	Healthy population. Infants and mothers with ID/IDA at baseline excluded. Infants consumed high iron diet at around 6mo (SF significantly increased in all groups at 7 months)
4 months	Significant increase in Hb at 6mo	Results were independent of study location, initial Hb or baseline iron status Greater increase in Honduran infants with higher IDA prevalence, compared to Swedish infants

Frequency and duration of OIS

To help increase iron absorption, intermittent regimens are often preferred[174]. The absorptive benefit may be due to improved absorption when OIS is administered during intestinal mucosal renewal, with each dose received by new cells[105,175,176]. Intermittent OIS can also reduce both GI side-effects and transient overload of iron, when compared to daily OIS[177]. A daily dose of iron can also reduce absorption of subsequent doses due to enterocytes being saturable[64]. One meta-analysis showed that intermittent OIS was

comparable to daily OIS at improving Hb and SF in children, but was less effective in reducing IDA[159] (Table 16). In addition. there were no differential effects on outcomes determined for type of intermittent OIS regimen (e.g. one, two or three times a week) or length of the intervention (>3 months or less than 3 months). The author's concluded that intermittent supplementation may be a more viable public health approach in settings where daily supplementation was not feasible.

Table 16. Frequency of supplementation

Frequency of OIS	Effect	Comments
Daily vs weekly OIS from 4-6mo	Reduced SF at 6mo in daily but not weekly group	Weekly was more effective at reserving iron status
Weekly vs twice weekly OIS for 6-18mo	Both groups had increased mean Hb and reduced prevalence of anaemia	Results were more significant in the twice weekly group

Oral iron dose

Lower doses have appeared effective in a number of trials and are associated with fewer side-effects[64]. Upregulation of hepcidin by OIS also limits the absorption efficiency of higher doses of OIS[51]. In a study comparing dosing and frequency of OIS from five to nine months of age, infants receiving 2mg/kg second daily showed less side effects than a daily dose of 2mg/kg, while demonstrating increased absorption compared to 1mg/kg/d[175]. The authors concluded that 2mg/kg every second day was more effective than the AAP recommendation of 1mg/kg/day, with fewer adverse effects. In another RCT of preschool children with low iron status (n = 65), children for eight weeks received either a daily OIS of 30 mg/day, or 30 mg twice per week[178]. Hb, SF, and ZPP increased significantly in both groups ($P < 0.001$), and there were no significant differences between groups after correction for initial hemoglobin concentration. The authors concluded that twice weekly OIS has a similar on iron status to daily OIS. However, another study reported that daily OIS was more efficacious than twice weekly for the treatment of childhood anaemia[179], while another found that twice weekly OIS was not effective in settings where other micronutrient deficiencies may have been present[180]. The meta-analysis by De-Regil *et al* 2011 showed there were no significant differences between different total weekly doses of elemental iron (25mg or less, 25 to 75mg, greater than 75mg).

In the study by Yurdakok *et al*[171], infants four months of age were randomly assigned to three groups, the first group receiving daily OIS, the second weekly OIS and the third group placebo for eight weeks. At 6 months of age, SF levels decreased in daily (27.5 µg/L ± 23.1) and control groups (31.9 µg/L ± 23.8) but did not decrease in the weekly group (40.4 µg/L ± 26.6). The authors concluded that weekly OIS was more effective than daily at reserving iron status (SF) in exclusively breastfed infants at 6 months of age. In another trial with infants aged 6-18 months (n = 78), 25 mg elemental iron was provided either weekly or twice weekly[181]. Both weekly and twice weekly OIS increased mean Hb concentration and reduced anaemia, although twice weekly OIS provided more significant findings.

Composition of OIS

For preventative OIS, there are a number of iron preparations available, however the most common is ferrous sulfate[64], due to low cost and high bioavailability[174]. In a trial comparing different iron formulations, infants received either 2 mg/kg/day ferrous sulfate (Fe^{2+}) or 2 mg/kg/day ferric polymaltose (Fe^{3+}) from 4 to 9 months[166]. At 9 months, the ferrous sulfate group had significantly higher Hb ($P < 0.001$), haematocrit ($P < 0.001$), MCV ($P < 0.0025$) and TS ($P < 0.001$) than the ferric polymaltose group. There was no significant difference in ID or IDA prevalence between the ferrous sulfate group (30.3%; 5.8%) vs ferric polymaltose group (41%; 19.2%) after supplementation. Side effects were comparable between groups with 35% of infants having adverse effects such as diarrhoea, constipation, vomiting or tooth staining. To optimise absorption and reduce adverse gastrointestinal effects, novel iron formulations such as Sucrosomial iron are emerging[182]. However, they are fiscally prohibitive and not yet evaluated for use in infants[51].

Similarly, the meta-analysis by De-Regil *et al* 2011 showed no significant differences in outcomes when comparisons between composition of the iron supplement were made (e.g. ferrous sulfate vs other formulations.

Adherence and supervision

Limited data is available focusing specifically on factors that enhanced provision of OIS to young infants. Of the studies included in the review, the key strategy to improve adherence was supervised delivery by trained health workers. The two studies using this approach demonstrated the best overall compliance rates[168,173]. Another study described high compliance rates for unsupervised OIS that was provided to infants 4 to 6 months of age (92%), but gave no indication how this was achieved[49].

In one RCT, iron administration to infants was significantly improved when mothers were concurrently taking OIS to treat anaemia, compared to mothers who were not[169]. Other strategies reported to improve compliance of iron supplementation include involving families in the therapeutic strategy, providing reminders about taking OIS, warning about possible side effects early on, and ensuring supplements are available at all times[183]. The least favorable compliance rates were reported in a study that required mothers to request additional OIS when supplies ran out, which rarely occurred[165,169]. In other OIS trials, supervision did not always result in improved adherence. There was no additional benefit of supervised iron administration when compared with unsupervised OIS when accompanied with concurrent education and counselling programs in two RCTs[184,185].

A Cochrane systematic review by Nieuwlaat *et al* 2014[186] evaluated the evidence for interventions that enhance medication adherence. Despite a large number of RCTs included in the review ($n = 182$), the authors concluded there was very limited evidence of strategies that demonstrated both improved adherence and clinical outcomes (5 RCTs). Successful strategies included ongoing support and education from allied health professionals (e.g. pharmacists), daily treatment support, fostering additional support from family, and counseling e.g. motivational interviewing. However, no common characteristics for the successful RCTs could be identified. Even the most effective interventions only showed small improvements, despite considerable investment of effort and resources. Limited data on adherence were available in the meta-analysis by De-Regil[159], with very few trials reporting

on factors that improved compliance. There was a trend for better adherence among those children receiving intermittent compared to daily OIS, though this was not significant (RR 1.23, 95% CI 0.98, 1.54; 5 RCTs, *n* = 1130).

Northern Territory data on adherence and supervision

An iron treatment trial set in a remote NT Aboriginal community compared outcomes for two OIS treatment strategies in anaemic infants: *i)* twice weekly oral iron treatment administered by a health professional (supervised), with *ii)* OIS to be taken daily at home, provided by family[115]. In the supervised OIS group, Hb increased by 10.9 g/L (95% CI 7.6, 14.2) after 6 weeks of treatment, whereas unsupervised daily OIS produced no change in Hb (MD 0.96, 95% CI 0.63, 1.3). Relative risk of treatment failure in supervised versus unsupervised OIS was 7.7 (95% CI 2.6, 25.0, $P < 0.001$). Mean levels of compliance reported were < 5% in the unsupervised group compared to > 90% in the supervised group, with potential confounders such socioeconomic status and education having no reported effect. Poor compliance in this study was related to families needing to return for additional supply of iron (the initial supply only lasted 2-3 weeks), with only two families doing so, similar to the issue reported by Lozoff *et al*.[169]. The authors' concluded that twice weekly OIS supervised by a health worker was a feasible and effect strategy for treating IDA in a community where the prevalence was 40%.

A micronutrient fortification program conducted across the Top End of Australia provided "Sprinkles" (low dose iron) to infants aged 6 to 9 months who were consuming diets that were low in iron-rich foods[112,113]. It was calculated that infants could maintain a Hb in the normal range and prevent anaemia if at least 60 sachets (recommended dose) were ingested over a four-month timeframe. However, despite reporting that Sprinkles were generally well accepted by the community, micronutrient fortification was not supervised and only 31/204 (15%) infants with Hb measurements received the recommended dose. Food insecurity was the main problem reported relating to the small proportion of infants ingesting the recommended dose. Sprinkles were required to be ingested with food, which was often unavailable, resulting in sachets that were distributed but not used.

Balancing risks and benefits of additional iron

Any public health program for universal supplementation needs to consider whether subsections of the population could be harmed by the addition of the nutrient[8,59,187]. For example, the United Kingdom has not adopted mandatory folic acid fortification (to reduce risk of birth defects) due to concerns of masking pernicious anaemia in older populations and promoting tumour growth in cancer patients[59]. Conversely, Australia, Canada and the United States have opted for folate fortification. Thus, careful consideration must be given to the balance between benefits and potential risks. An important consideration is whether there are conditions whereby those receiving OIS could become iron overloaded, impairing health, or having life-threatening results. The literature does not support the conclusion that provision of preventative low dose OIS to infants is without risk, even in populations where IDA is common[14,21,56,59,188]. However, given the potential impacts on neurodevelopment caused by IDA[17,18,77,189], the view of many scientific societies is that the theoretical risks are far lower than the benefits associated with preventing the consequences of anaemia in populations with high prevalence, such as in remote Northern Australia[2,10,26].

Iron toxicity

The safe upper level of iron intake for Australian infants is set by the NHMRC at 20mg/day[29]. Young infants only receive small amounts of iron from breastmilk prior to the introduction of iron-rich foods when developmentally ready[131]. Modelling based on current dietary recommendations for infants would provide a 6-12 month old infant with approximately 5.8mg of iron per day, approximately half of the Recommended Daily Intake (RDI)[46]. OIS at the recommended dose of 1mg/kg/d would provide an average six-month infant (weight on 50th percentile) with up to 5.5mg iron per day, therefore it is unlikely that they would exceed the safe upper limit. Infant formula available for sale in Australia contains approximately 1-1.2mg iron per 100ml, however only 10-20% of this is absorbed by the body[41]. As illustrated in Table 17, the iron intake of exclusively formula fed intakes is less than half the safe upper limits of iron intake. Therefore, providing OIS to these infants until adequate intake of iron rich foods occurs will not exceed upper limits for iron.

Table 17. Iron provided from formula for exclusively formula fed infant

Age	Average formula needs for infant on 50th percentile	Iron provided	Maximum recommended formula intake for infant on 97th percentile	Iron provided
0-3mo	150-200ml/kg (3.3-4kg)	1mg/100ml = 7-8mg/d	150-200ml/kg (4.4-5.2kg)	1mg/100ml = 9-10.4mg/d
3-6mo	120ml/kg (4.1-4.9kg)	1.2mg/100mL= 6.4-7mg/d	120ml/kg (5.3-6.3kg)	1.2mg/100mL= 8-9mg/d
6-9mo	100ml/kg (5.2-5.6kg)	1.2mg/100mL= 6.7mg/d + iron from diet	100ml/kg (6.6-7.1kg)	1.2mg/100mL= 8mg/d + iron from diet
9-12mo	600ml/day	1.2mg/100mL= 7.2 mg/d + iron from diet	600ml/day	1.2mg/100mL= 7.2 mg/d + iron from diet

There is a significant risk that if oral iron is provided in the home environment that young children could accidentally consume the medication leading to toxicity. Paediatricians (personal correspondence) have advised that iron poisoning would be more likely from tablets as opposed to liquid preparations. An overdose of elemental iron at <20mg/kg would be asymptomatic, with GI symptoms only presenting at <60mg/kg and doses of >120mg/kg being potentially lethal (*RCH Clinical practice guidelines: iron poisoning*). As ferro-liquid contains 6mg/mL of elemental iron more than 10mL/kg would be required to cause GI upset and 20ml/kg would be a potentially lethal dose. For toddlers over 12.5kg (and under 25kg) an accidental consumption of an entire bottle (250ml) is unlikely but would cause GI upset but not death.

Adverse effects

Like many essential nutrients, iron exhibits a "U-shaped risk, in which risk of adverse outcomes increases with both low and high availability[190]. Research has primarily focused on the risks of iron deficiency in infants because of the high prevalence of ID and IDA. However, evidence is emerging on the potential for adverse outcomes due to excessive iron, particularly on iron-sufficient populations[18]. Oral iron supplementation is associated with a

number of acute and longer term health impacts, even in populations with IDA[56]. As highlighted earlier, the most common acute side-effects of OIS include nausea, vomiting, constipation, and dysgeusia[191]. A meta-analysis showed higher risk ratios for vomiting and fever in early childhood associated with daily OIS, which may be an antecedent to infection[155]. Concern about increased susceptibility to infection has also generated considerable attention in the literature, given that iron is important for growth and replication in both the host and invading pathogens[14]. Research has linked excess iron to an increased risk of gastrointestinal infections, although further research is needed to confirm specific effect profiles[192,193]. In the longer term, oral iron supplementation in infancy has also been associated with adverse effects on growth, especially in iron replete children[49,194]. The effects on growth may have been due to iron supplements inhibiting absorption of other key nutrients that positively influence growth, such as zinc[14]. However, a systematic review of RCTs found no conclusive evidence of this[195]. Additionally, adverse findings on growth demonstrated in individual RCTs have not been confirmed in meta-analyses[155,196].

Iron and the microbiota

Recent research is beginning to shed light on the effects of iron on the gut microbiota. Most bacteria require iron and have developed biological strategies to obtain it[59]. Bacterial species considered most beneficial (e.g. Lactobacillaceae and Bifidobacteriaceae families) have low to no requirements for iron, whereas potentially pathogenic enterobacteria have an obligate need[59]. A number of studies have investigated the effects of OIS on bacterial profile in the gut and described a decrease in beneficial bacteria and a shift toward a more toxic profile within the microbiota following supplementation, including increased markers of gut inflammation[57,61]. The long-term clinical relevance is still unknown and further research is needed investigating the influence of iron on the gut microbiota[62]. One perspective offered is that depletion of iron stores in early infancy may be an evolutionary mechanism to restrict the access of iron to potentially pathogenic bacteria in the microbiota[187]. Some authors' argue that fortification of dietary sources with iron and oral supplements could undermine this adaptive mechanism and result in an higher risk of gastrointestinal disease and infection in infants, particularly in areas with poor environmental conditions and hygiene[56,62].

Oxidative potential

Iron is also recognised as a reactive element, and as such, it has potent pro-oxidant properties[192]. Typically iron is protein-bound in the serum and tissues. However, under anoxic or anaerobic conditions and when iron-binding capacity is overwhelmed, non-protein bound iron can form reactive oxygen species[14]. Free iron can be toxic and generate superoxides and other free radicals through the Fenton reaction[18]. The potential toxicity includes CNS injury, damage to lipid membranes, and tissue injury, particularly in the liver[14]. However, given the "double-edged sword" features of iron, limited free iron is available in the circulation in usual circumstances[14]. Studies in infants given OIS up to 18 mg/kg daily have failed to show increased oxidative stress[18], with only one trial demonstrating adverse outcomes[197]. Thus, the theoretical health risks due to oxidative potential have yet to be confirmed in clinical trials.

Iron and the brain

Another concern about excessive iron exposure early in life relates to the potential effects of cumulative high brain iron. It has been hypothesized that iron supplementation during early infancy may linked to dysregulation of iron homeostasis, resulting in neurodegeneration in older adults[55,56]. Iron is not easily eliminated from the body and it is proposed that early-life iron overexposure could be a risk factor for neurodegenerative disease, such as Parkinson's and Alzheimer's disease[18]. Iron concentrations in the brain increase with age and conditions such as Parkinson's are associated with excess brain iron accumulation[56]. Animal studies have indicated potential biochemical mechanisms, however additional research is needed to draw conclusions[62,190].

Key points

Importance of iron	Iron is particularly important early in life. It is found in all structures of the brain and is required for the development of neural pathways Iron is also critical for oxygenation of tissues, immune system functioning, energy production, cell proliferation and DNA synthesis Iron deficiency when the brain is developing may cause irreversible developmental delays that can persist later in life, even after anaemia is corrected with iron treatment
Iron deficiency anaemia	Iron status is a continuum. Iron deficiency anaemia (low haemoglobin) is the end point of iron insufficiency. Iron deficiency anaemia occurs when body iron stores are exhausted and body tissues have insufficient iron to maintain normal physiologic functions Iron is prioritised for Red Blood Cell synthesis, and brain iron deficiency may occur without before anaemia is present
Prevalence of anaemia	The prevalence of anaemia in children in remote Aboriginal populations has been consistently high in all reported studies. Anaemia rates are highest in children between 6 and 12 months of age. The burden of iron deficiency in early infancy which may impact brain development is unknown.
Risk factors	Several conditions during the perinatal period increase the risk of iron deficiency anaemia in early infancy. These include: • Maternal iron deficiency/anaemia in pregnancy • Diabetes in pregnancy • Low birth weight and prematurity • Early cord clamping

	Dietary issues are the main cause of iron deficiency anaemia in infancy. These include: • Insufficient dietary intake of iron during early infancy • Poor absorption due to dietary sources with low bioavailability • Early introduction to cow's milk (before 12 months) • Extended exclusive breastfeeding beyond 6 months
Iron intakes	The average iron intake of Aboriginal infants at around six months is estimated to be low. Limited dietary data suggests that less than 50% of infants meet the RDI for iron, with most iron coming from poor quality (low haem) dietary sources.
Consensus of scientific societies	Low-dose oral iron supplementation is recommended to prevent anaemia in infancy by several expert global authorities when key risk factors are present: • High prevalence of anaemia in the population • Low intake of iron rich foods • Socioeconomically disadvantaged populations
Efficacy of oral iron supplementation	Low-dose oral iron supplements improves iron status in infant populations at risk of iron deficiency and prevents iron deficiency and iron deficiency anaemia In the few trials that assessed markers of neurodevelopment, iron supplementation from four months was associated with improvements in mental and motor development compared to infants not receiving iron, although a causal link is unclear Interventions that maintain adequate iron during the foetal period and early infancy (rather than correcting ID or IDA afterwards) are more likely to be effective in supporting early brain development.
Age of initiation	The available literature suggests that OIS is safe to use from four months of age and helps prevent anaemia at six months of age. It may be beneficial to commence OIS earlier to prevent iron deficiency earlier in life.
Dose	Studies demonstrating the best outcomes used doses between 1-2mg/kg. The higher dose is more effective at preventing iron deficiency anaemia
Duration	Iron supplementation should continue until adequate dietary iron sources are being consumed, especially if risk factors for IDA are present. Based on limited dietary data, iron intakes of most infants are inadequate to meet requirements at six months of age. Extension of iron supplementation until 9 months of age should be considered.
Frequency	Intermittent low dose OIS is generally associated with fewer side effects, better compliance, and possibly a reduction in risk of oxidative damage. Daily

	OIS provides more protection against the decline in iron stores and onset of IDA, but is associated with additional side effects and increased risk of potential harm
Supervision	Supervised administration improves iron outcomes more effectively than unsupervised administration
Benefits vs risks	While no single approach may be universally acceptable, a low dosage, intermittent OIS protocol will likely provide the best course of action that balances benefits and potential risks
Consumer acceptability	This review did not assess whether oral iron supplementation was socially or ethically acceptable to health professionals or the public. Further exploration is needed to answer this question prior to policy decisions on anaemia prevention
Future research recommendations	Determine the primary causes of anaemia in remote NT settings and their relative importance There are a limited number of RCTs focusing on preventative oral iron supplementation in young infants under 4 months of age. Further trials are needed that focus on optimal iron formulation, dose, schedule, and duration of OIS. Neurodevelopmental outcomes should be assessed in addition to iron status. The effect of different doses and durations on different prevalence, severity and causes of anaemia requires further exploration. Additional research is needed on factors that enhance adherence (for families to provide iron to infants) The literature on potential adverse effects is evolving and should be re-appraised frequently

Recommendations

1. Oral iron supplementation is provided to all children aged from 4 months of age until adequate intake of iron-rich complementary foods. In remote Aboriginal communities evidence indicates this may not occur until 9-12 months of age. Monitor emerging evidence for OIS in younger infants.
   - Recommendation does not need to be limited to breastfed children. The risk of exceeding safe limits of iron for formula fed children are low in this age group and provision to only breastfed infants contributes to mixed messages and potential contradiction of health promotion messages

2. The evidence indicates that an ideal dose is 1-2mg/kg/d provided daily under supervision however in practice this may not be feasible so a practice recommendation would be 2mg/kg/d, supervised twice weekly. The composition of the iron formulation does not influence outcomes. Safety considerations of unsupervised doses in the home environment need to be considered.

3. Universal OIS is recommended as best practice however health services could implement based on prevalence (ESPGHAN recommend OIS when prevalence is >10%) or to children who have two or more risk factors for anaemia (maternal iron deficiency, diabetes in pregnancy, twin/multiple birth, immediate cord clamping, prematurity or low birth weight, low or delayed intake of iron-rich complementary foods, introduction to cow's milk as a drink before 12 months of age or food insecurity, hygiene or housing concerns)

4. OIS as an anaemia prevention strategy needs to be undertaken alongside other holistic anaemia prevention strategies that address the wider determinants of iron deficiency and anaemia and should be paired with anaemia prevention strategies in pregnancy.

Concurrent practices to prevent iron deficiency anaemia in infants
• Increase coverage of pregnant women receiving antenatal care
• Monitor haemoglobin in pregnant women and women of reproductive age
• Implement universal delayed umbilical cord clamping
• Provide counselling to pregnant women on optimal dietary practices and the importance of taking oral iron supplements
• Dietary improvement strategies for mothers and infants

Conclusion

Anaemia remains a critical health issue that disproportionately affects Aboriginal infants living in remote communities in Northern Australia. The available evidence suggests a substantial burden of anaemia exists in remote Aboriginal settings, particularly between six to twelve months, but occurring as early as four months. This review suggests that administration of intermittent low-dose oral iron supplements from four months of age or earlier improves iron status in infant populations at risk of iron deficiency and iron deficiency anaemia and is associated with improvements in mental and motor development. Iron supplementation should continue until adequate iron-containing complementary foods are introduced in the diet, at around 6-9 months in remote communities. Supervised administration of iron by dedicated health practitioners at home or in the community would improve adherence. This evidence review provides support for early commencement of preventative oral iron supplementation to prevent anaemia in populations at risk. Oral iron supplementation in infancy is a stop gap measure to prevent the consequences of anaemia and should be complemented with prevention strategies that address underlying causes.

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Appendices

A – Summary of feedback from CARPA discussion groups

B – Oral iron supplementation trials in infants from 0 to 4 months of age

Appendix A: Summary of feedback from CARPA discussion groups

Child and Youth Health Strategy Unit, NT Department of Health

1. Background

The Centre for Remote Health regularly publish a suite of manuals designed to support good clinical practice in primary health care in Central, Northern and remote Australia. The manuals are produced for health care workers – including Doctors, Aboriginal Health Workers, Remote Area Nurses, Midwives, Nurse Practitioners, and Allied Health Professionals. The key manual is known as the Central Australian Rural Practitioners Association (CARPA) Standard Treatment Manual (STM), which provides protocols and procedures in plain language for health care workers to follow.

The new edition of the Standard Treatment Manual (CARPA) is planned to be released sometime after August 2017. In the new edition, there are significant changes to anaemia management that includes the administration of oral iron to all breastfed infants aged 4-6 months in remote NT. Iron is to be administered daily, or at a minimum, twice weekly. This change will have a significant impact on service delivery.

A meeting was convened on Thursday 27 April to determine the NT's response to this change and if agreed upon, how best to implement the new guidelines. The meeting included General Managers from TEHS and CAHS, as well as representatives from CAAC, AMSANT and Sunrise. The main outcomes from this meeting included:

- Agreement to develop an implementation plan for the introduction of oral iron to children aged 4-6 months of age
- Agreement on establishing a working group with representatives from the different organisations to develop the implementation plan
- Agreement that an evaluation framework should be developed alongside the implementation plan to assess the impact of introducing oral iron.

The Primary Health Care General Managers from each region indicated their support for a series of workshops to be held in a timely manner across each region to seek feedback from staff around this change. Consultations were undertaken with Health Services from Top End (Darwin, Katherine, Nhulunbuy) and Central Australia (Alice Springs, Tennant Creek). These workshops were facilitated by Menzies School of Health Research and the Child Youth Health Strategy Unit (DoH).

Workshop attendees included representatives from government and non-government health services, including: A/Director of Medical Services, Operations Manager, District Managers, Outreach Managers, Paediatricians, Pharmacists, Child Health Nurses, Health Centre Managers, Strong Women Coordinators, Aboriginal Health Worker Coordinators, Aboriginal Health Workers, Primary Health Care Educators, Policy Officers, Professional Practice Nurses, Public Health Physicians, Medical Officers, Public Health Nutritionists, Continuous Quality Improvement Facilitators and Remote Area Nurses.
Total number of workshop attendees are outlined below:

Region Date	Darwin 24th May	Alice Springs 25th May	Nhulunbuy (VC) 23rd June	Katherine 5th July	Tennant Creek 6th July
Attendees	14	15	13	9	17

The Menzies School of Health Research have also proposed a NHMRC partnership project to the Northern Territory Director of Medical Services and the heads of Aboriginal Community Controlled Organisations to undertake an evaluation. The evaluation would assist in determining whether the administration of oral iron has an impact in reducing anaemia prevalence.

CARPA 7th Edition protocol for anaemia (weak blood) in children

The new CARPA guidelines (7th Edition) state:
From around 4 months

- Give supplementary oral iron to all breastfed babies — 1mL (6mg elemental iron) per dose
    - Once a day if possible
        - Provide 2 weeks supply at a time — review uptake after 2 weeks
    - OR give daily dose twice a week under supervision in clinic or community by same (dedicated) staff member
- Check Hb at 6 months
    - If normal — stop supplement and promote age appropriate food
    - If low — start treatment regime — see Table 2.2

3. Key themes of discussions at workshops

The new guidelines were introduced to representatives at the workshops along with a brief overview of available evidence to support this change. Attendees were encouraged to discuss how the new guidelines could be implemented in their regions and communities. An opportunity was also provided to discuss any concerns and issues with the new guidelines and in how they would be implemented.

Overwhelmingly, the majority of representatives perceived this change in guidelines as inherent with risk. It was suggested that if supplementation was to occur, this should happen in concert with other complementary and more sustainable approaches that focus on preventing maternal anaemia, and be linked to a monitoring system to determine whether supplementation continues to be needed.

Table 1 below provides a summary of the key issues raised at the workshops by representatives, along with the risks and suggestions for mitigation.
If the CARPA recommendation is implemented by NT Health, Table 2 outlines decisions that will need to be made. Table 3 proposes an action plan along with key stakeholders who will need to be involved.

Table 1: Key issues raised at workshops around new CARPA guideline for anaemia

Issue reported	Discussion	Risks	Mitigation

1. Concern about the limited evidence which supports the recommendation	-Each site highlighted concerns that there was insufficient evidence to support such a significant change to the guidelines. Particularly around whether dosing and timeframes are sufficient (is less than in other published studies)	-Poor and inconsistent implementation	- High level support for the change - Clear presentation of available evidence and benefits - Highlight importance of the evaluation to inform practice
2. A perceived lack of focus on preventing maternal anaemia	-All sites were concerned that there was a disproportionate focus on childhood anaemia and questioned why more wasn't being done to prevent maternal anaemia	-Infants may already be anaemic by 4 months -May act as a policy barrier and prevent other approaches	-Strengthen and build on existing strategies around maternal anaemia, especially in the 3rd trimester -Workshop what additional maternal strategies are needed
3. No care plans or systems in place to manage this CARPA recommendation	-Staff highlighted that there will need to be a PCIS/Communicare "preventative iron care plan" using a similar framework to the existing Anaemia Care Plans, which are used to treat anaemia. Discussion that there will need to be two Care Plans for a) Staff administered iron, and b) Family/Carer administered	-Without a care plan, it's likely that there will be disparate approaches and methods of documentation across regions and communities	-Form a working group and develop PCIS care plans -Assist in developing similar Communicare systems
4. Imposition on staff time (competing demands)	-Concerns from staff about time investment required to deliver/provide iron in a community setting	-Staff will not administer iron, but will provide to families (which is known to be less effective due to decreased adherence)	-Highlight number of children for follow up (this is low) -Assessment of the additional time required for staff to f/u x 1 infant and estimate additional workload based on these numbers -May require advocacy for additional FTEs.
5. Lack of clarity around recommendation	-There is very limited detail in the protocol and open to different interpretation	-Likely to result in confusion and different methods if further guidance is not provided	-Need a policy document or guideline to step practitioners through this CARPA change and provide direction around issues raised (see Table 2)

6. Side effects for iron replete children	-Concerns were voiced from Aboriginal staff that PHC centres, Child Health and Aboriginal staff will lose "trustworthiness" from the community if side effects are perceived to be linked to preventative iron supplementation	-Strong Women Workers highlighted "cultural concerns" relating to blame if infants became sick after iron was provided. SWW did not want to be involved in providing iron (but were happy to assist with education)	-Could include a FAQ in PGC document outlining around why iron is being provided, the benefits vs risks (for risks, need accurate assessments of likelihood, severity, etc), potential side effects. Highlight and support parents/carers right to refuse
7. Key messaging around why only breast fed babies require supplementation and why babies using infant formula are excluded	-Concerns were raised that health are promoting "breast is best", however it is only breastfed babies needing iron supplements.	-Potential for confusion around optimal nutrition for babies (which is breast milk) without clarification.	-Important to clarify and standardise key messages and how staff should approach this issue
8. Interpretation of the guideline where mixed feeding methods are used (e.g. exclusively breast fed vs some breast milk vs infant formula fed, etc)	-Discussion about "what are the cut offs?" Should we use American Academy of Paediatrics Guidelines? (key reference provided to support recommendation)? These recommend that iron is provided to all infants 4-6 months unless infant receives >50% intake from infant formula)	-Without clarification, there is potential for infants to be included or excluded based on staff preferences, rather than infant requirements	-Clear definitions for inclusion/exclusion in the PGC document. -Need to review literature around iron in infant formula and variability between formulas (e.g. appear to range from 4-12 mg), how much is absorbed, Upper Limit (UL)?
9. Risks of providing a (potentially fatal) quantity of oral iron to families	-Discussion around what constitutes an acceptable amount of iron to provide families	-Potential for toxicity if high quantity of iron is ingested	-Consult with pharmacy. Determine whether two weeks is an acceptable quantity
10. Difficulties administering oral iron to a 4-6 month infant	-Concerns around safety and practicalities of providing a thin liquid to 4-6 month infants. Child health nurses have suggested this could be difficult – especially for families e.g. tongue extrusion reflex	-Health professionals or families may not be able to successfully administer iron	-Paediatric speech pathologist to review proposal -Staff training if the need is determined
11. Obtaining consent – opt in vs opt out	-Discussion around whether it was more appropriate for parents and carers to provide consent and "opt in". This could help shift perceptions and empower families to make a choice rather	-Potential for families to feel pressured to provide iron to their infant with the outcome that iron is not provided to infants	-Develop key messages in PGC document to explain why iron is needed at this age and the right of the family/carer to opt in/out

	than feel "railroaded" into complying		
12. Communicating the need to a) health centres, and b) communities	a) The workshops revealed that many staff members were not supportive of the change and further efforts and information is needed to ensure staff in community support the change b) How will community education be conducted? How will this message get out to the community? How will it be perceived?	a) Staff will not administer/provide iron b) Potential for uncertainty, partial understandings, mistrust and confusion in community settings	-Communication strategy to be developed
13. Community / health service differences in implementing the guidelines	-Differences between regions, NTG health centres vs ACCHOs regarding available resourcing. Some reported that they would not have the staffing needed to deliver iron and would thus require parents or carers to present to the health centre	-Potential for differences between communities/health services who favour staff administered vs family administered (likely to have less favourable outcomes) -Could complicate evaluating the guidelines (however differences would also allow a better understanding of which approaches were more successful)	-Clear guidelines (PGC) and systems (e.g. Care Plans) detailing preferred implementation pathways (e.g. 1. Health Professional to deliver and administer, 2. Family to present to health centre and provide to infant, etc)
14. Strategies to engage families and carers to visit health centres to collect iron or have iron administered	-Without engagement strategies, staff believed that many families/carers will not present at the health centre to collect preventative iron (this was perceived to be low on community hierarchy of needs)	-Poor community engagement and thus, implementation/effectiveness	-Address this in community engagement strategy
15. Difficulties tracking infants across different systems (e.g. PCIS, CCIS, Communicare)	-An existing risk due to poor system interconnectivity	-Infants may miss prevention doses. Very low risk of toxicity if there is double up as dose can be given daily	-Highlight appropriate strategies to clean/determine population lists -Iron administration could be linked/included in child health traffic light reports

16. Lack of educational resources on anaemia prevention	-Regions have reported a significant gap in educational resources to discuss prevention, and management of iron deficiency anaemia - A separate project has highlighted significant gaps with culturally appropriate anaemia resources	-Risk of anaemia after six months of age when iron rich solids are to be introduced – this risk is perceived to be very high	-Funding is needed for development of anaemia prevention resources (one is currently being drafted).

Other issues and considerations raised:

- The CARPA review process for this significant change was perceived to be problematic. It was highlighted that there was limited consultation in the review of the anaemia protocol.

- If the new anaemia guidelines are not implemented (as some regions are strongly advocating for), how would this occur? If NT Health do not implement this particular recommendation, how will this be communicated in practice considering an online and hardcopy version will exist?

- Concerns were raised that:
  - the timeframes for iron supplementation are inadequate (only 2 months duration). Given that timely introduction of iron rich solids remains a significant issue in the NT, should the timeframes be extended until 9 months?
  - the dosage is insufficient (particularly because it's more likely that staff will only provide 6mg twice weekly).
  - These issues were raised to the CARPA editors but it was too late to be changed.

- Staff highlighted that it will be difficult to follow up infants twice weekly (minimum requirement) and unrealistic to follow up daily.

Table 2: Policy decisions to be made and outlined on PGC *if* the CARPA recommendation is implemented

Issue	Discussion	Risks	Mitigation
1. Is iron to be provided to infants in communities with zero prevalence or very low rates of anaemia?	-Should preventative iron be provided to communities that don't have a significant anaemia problem? If yes, what is the messaging? If no, what are the cut-offs? For how long do rates need to be "low"? etc	- Side effects for iron replete children?	-Clear policy guideline weighing up benefits and risks
2. What is the target population?	-Does the CARPA guidelines pertain to all infants in remote areas? i.e. Indigenous and non-Indigenous. Available data on	-Assumptions that non-Indigenous infants do not also have high anaemia rates. Available data suggests that anaemia is also	-Ensure CARPA recommendation is made universal i.e. for non-Indigenous and Indigenous children

	anaemia prevalence (e.g. East Arnhem South communities) suggests that this measure should apply to ALL infants 4-6 months	impacting non-Indigenous children at high rates	-May need to be moderated by vulnerability/risk factors
3. Mixed feeding methods – what are the cut-offs?	-Decision around how much infant formula needs to be given (as a percentage of intake) before iron supplementation is ceased	-Children receiving any infant formula will not receive iron	-Determine appropriate cut-offs and clarify in policy guidelines
4. Safe storage of iron	-Needs to be below 250C and not easy for children to access	-Iron toxicity -Spoilage	-Clear guidelines around storage (pharmacy to advise)
5. Checking Hb at six months (not four months)	-Discussion that families may want their child's Hb checked before iron is administered. Need to develop a position on this (i.e. test if asked or not, but if yes, are results valid? What are reference ranges?)	-Families may refuse if infant's iron levels cannot be assessed	-Review whether Hb test at 4 months is valid. If so, what are reference ranges?
6. Develop a position for infants who start iron late	For example, for a child who starts at 5 months, would they receive 1 or 2 months of iron?	-If they start late, they may not receive full course of preventative iron	-Clear position around infants who start late

Table 3: Proposed action plan *if* implementation is to proceed

What	Details	Who	When
1. Feedback discussions from workshops to GMs, CHO, CMO, CNO, ACCHOs and await decision re implementation	-Organise face-to-face meeting -Internal memo (DoH) to brief executive (ED SSPP, CHO and CE) on change	-Child Health Nutritionist (CYHSU)	-Done
2. Develop PCIS preventative iron care plan (will need to provide to ACCHOs for incorporation into Communicare)	Care plan will need to factor in: -Obtaining consent from family/carer -Prompt before infant is 4 months to prepare family	-Chair will need to be elected for development of care plans. Should involve: PPNs, PCIS staff, CHN, Child Health Program Support Officer.	-ASAP (if preventative iron is to be implemented as per CARPA)

	-Be able to track infants moving between communities -Show how (e.g. PHC staff or family) and how much iron was administered	CYHSU will provide support.	
3. Public awareness campaign of new prevention guidelines and development of promotional resources. *This was highlighted at each workshop as critical for successful implementation*	-Feedback at each workshop that this was critical to help explain the need to the community and PHC staff. Benefits need to be outlined clearly to ensure community and staff are on board with change -Health promotion materials could include: posters, flipcharts, apps, -Idea also discussed to have a "pack" for each infant requiring preventative iron treatment, which might include: small bottles, syringes (draw up if possible and marked/labelled), educational resource)	-Strategic advisory committees to decide on the need and the opportunity/cost of resource investment. Funding will be required for development of resources and promotional materials. Corporate Communications could develop these if prioritised	-ASAP
4. Evaluation working group	-Need to understand differences in treatment outcomes due to circumstances of pregnancy, differences with compliance etc	-TK (Menzies) to lead -Will need representatives from different health organisations/regions	-Medium term
5. Policy or guideline (NTG) needed to accompany CARPA guideline. Will detail how NTG health services are to implement the guideline and manage risks	-Needs to include a brief outline of evidence -May include a FAQ section, key messages, communication strategy, delivery methods (e.g. within health centre, outside health centre, by HP, family/carer). -Should address risks to be managed: key messaging, supply of iron, storage at home/clinic, syringe usage and disposal, managing	-CYHSU to lead in collaboration with working group *(time limited)*	-ASAP

	transient clients/communication between clinics		
6. Staff training and resources	-Training is needed for administration and to ensure staff are delivering consistent information. -Materials/resources are needed that are targeted and appropriate to the context	-CYHSU will help coordinate framework for the training package -Operational teams to develop content and assist with resource development	-Short term

Recommendations

1. Communicate decision to a) support, or b) not support, the new CARPA anaemia guidelines

2. If supported, it is recommended that:

a. there is a temporary hold-off until a governance process is in place around implementation and evaluation;

b. an additional in-depth literature review of the evidence is undertaken. The literature review should include considerations around implementation

Appendix B: Oral iron supplementation trials in infants 0 to 4 months of age

Study	Setting	Sample size (*n*)[i] and attrition	Age at randomisation (months)	Age outcomes assessed (months)	Intervention duration (months)	Intervention (mg elemental iron)	Supervision & adherence	Outcome measures (anaemia, ID, IDA definitions)	Results	Conclusions	Considerations
Aydin et al., 2017[1]	Turkey, Istanbul University, Cerrahpasa Medical Faculty, well child outpatient clinic	150 R 112 C Attrition = 25.3%	4	9	5	2mg/kg/day ferrous sulfate (Fe^{2+}) Or ferric polymaltose – (Fe^{3+}) Dose adjusted at monthly visits.	Unsupervised. Relied on verbal histories from parents about compliance and assumed 100% compliance	Iron status Adverse effects (ID = Hb > 110 g/L + TS < 16%; IDA = Hb < 110 g/L + ID)	**Iron status:** Hb, hematocrit, PF and TS all significantly increased in both groups from 4 to 9 months ($P < 0.001$), while only MCV significantly increased in the ferrous sulfate group ($P < 0.001$). Comparing OIS interventions at 9 months, the ferrous sulfate group had significantly higher Hb ($P < 0.001$), hematocrit ($P < 0.001$), MCV ($P < 0.0025$) and TS ($P < 0.001$) than the ferric polymaltose group. There was no difference in PF between groups. There was no significant difference in ID or IDA prevalence between the ferrous sulfate group (30.3%; 5.8%) vs ferric polymaltose group (41%; 19.2%) at 9 months. **Adverse effects:** side effects were comparable between groups with 34.8% of infants having adverse effects such as diarrhoea, constipation, vomiting and tooth staining	Iron markers of infants supplemented with ferrous sulfate were significantly higher and ID and IDA rates were significantly lower than the ferric polymaltose group at 9 months. Authors recommended increasing period of supplementation to 12 months as ID & IDA prevalence remained high (~15% after OIS)	No placebo or control group (all Turkish infants received OIS from 4 months) Study underpowered to detect differences in ID and IDA 18 infants excluded who developed IDA (Hb <95g/L)
Bora et al., 2019[2]	India Hospital setting in Northeast, population predominantly rural and low SES	200 R 180 C (100 infants from anaemic mothers Hb <100g/L and non-anaemic mothers) Attrition = 10.0%	0 (36 hrs after birth)	6	6	2 mg/kg/day ferrous ascorbate (10mg/mL) Or placebo	No supervision	Iron status Motor development Adverse effects (ID = Hb > 110 g/L + SF < 12 µg/L; IDA = Hb < 110 g/L + ID)	**Iron status:** Infants receiving OIS had 7% higher Hb (103.7 ± 9.3 g/L) than infants not receiving iron (97.0 ± 9.4 g/L, p < .0001). Serum ferritin was also 55% higher in the OIS group (133.9 ± 52.4 ng/L) versus no-iron group (78.1 ± 42.0 ng/mL, p < .001). There were no significant differences in ID or IDA at 6 months between groups **Motor development:** Motor development was closer to age-appropriate norms (5.83 ± 0.69) than the group not receiving iron (5.18 ± 1.35, p < .01). **Adverse effects:** There were no significant differences in parental reports of diarrhoea, vomiting or respiratory illnesses between any of the OIS groups or placebo groups	Supplementation of iron from the second day after birth improved iron status and motor development at 6 months in term infants at risk for early iron deficiency (mothers Hb < 100 g/L) compared with the no iron-supplementation group	Very high prevalence of anaemia (Hb < 110g/L) in the population at baseline. 85% of eligible mothers for the study were anaemic at time of delivery. 27% of infants (40% among infants of anaemic mothers) had ID at birth (cord SF < 75ng/mL). All neonates received early umbilical cord clamping less than 30 seconds after birth At 6 months, prevalence of ID and IDA very low in OIS and placebo groups (elevated CRP not controlled for)
Dijkhuizen et al., 2001[3]	Indonesia (Borgor District, West Java, rural setting)	239 R 177 C Attrition = 16.0% (Not including x 2 arms of ppts with zinc/iron and zinc alone)	4	10	6	10mg/day ferrous sulfate provided 5d per week Or placebo	Supervised. Trained health volunteer provided daily OIS to prevent overdosing and monitor bottles. Doses tallied to assess adherence Mean overall adherence was 86% (+/-16%) of the total intended dose. Similar for placebo and iron	Iron status Growth (Anaemia = Hb < 110 g/L; IDA = Hb < 110 g/L + PF[‡] < 12 µg/L)	**Iron status:** Iron supplemented group had significantly higher Hb, PF and significantly lower anaemia and IDA rates at 10 months than placebo OIS group: Hb = 115g/L ±10; PF = 36.8, 95% CI 19.1, 61.2; 28 infants anaemic (1 severe); 3 infants with IDA Placebo: Hb = 106g/L ±11; PF = 14.3, 95% CI: 8.1–25.3; 66 infants anaemic (6 severe); 30 infants with IDA **Growth:** no significant differences between groups (high rates of stunting in all groups) **Adverse effects:** insufficient data. One case of discolouration of teeth	Preventative OIS reduced the prevalence of IDA by 90% compared to the placebo group	Unable to determine micronutrient status at baseline High prevalence of anaemia reported in population (~66%) and growth problems (21% stunted) Trial included 4 arms, included zinc + iron and zinc alone (iron alone had better results + iron alone does not affect zinc status)
Domellöf et al., 2001[4] Dewey et al., 2002[5]	Honduras, (San Pedro Sula) and Sweden (Umeå)	263 R (142 Honduras) 214 C (118 Honduras) Attrition = 19%	4 6	6 and 9 9	5 3	1 mg/kg/day ~6-9mg/d ferrous sulfate Or placebo	Unsupervised – provided by mothers High mean adherence reported (79-99%) (based on fluid remaining in btls). Overall 24 non-compliers (drug given on <75% of study days)	Iron status Growth Adverse effects (Anaemia = Hb < 110 g/L ID defined as ≥ 2 abnormal iron measures (SF < 12 µg/L; MCV < 70 fL; ZPP > 80 µmol/mol heme IDA = Hb < 110 g/L + ID)	**Iron status:** Hb and PF significantly higher at 6 months between iron and placebo groups. For 4-9 month OIS group, Hb, PF and MCV were significantly higher at 9 months than placebo. For 6-9 month OIS group, MCV, was significantly higher than placebo at 9 months. Hb was significantly higher in Honduras only. When comparing 4-9 and 6-9 month groups, PF was significantly higher in both Honduras and Sweden groups at 9 months. There was no difference in Hb or MCV. In Honduras, IDA was significantly reduced in the 4 – 9 month OIS group at 6 months (9%) vs placebo (25%) and at 9 months (9% vs 29% respectively). In Sweden, IDA prevalence (3%) was not significantly different. **Growth:** Infants receiving OIS at 4–9 mo of age had significantly reduced linear growth and head circumference in Sweden. In Honduras, a negative effect on linear growth was evident only at 4 – 6 mo among those with initial Hb < 110 g/L. **Adverse effects:** OIS reduced the likelihood of diarrhoea among infants with Hb < 110 g/L at 4 mo. For infants with Hb > 110 g/L at 4 mo, the likelihood of diarrhoea was increased. There was no significant effect on other morbidity outcomes	OIS of term breast-fed infants from 4 – 6 months until at least 9 months improves iron status and reduces anaemia in populations where IDA is prevalent. Supplementation in populations where IDA is uncommon is not beneficial and may be harmful. Authors concluded no difference in outcomes between 4-9 and 6-9 month OIS groups	There was no correlation between maternal iron supplementation and infant iron status at 4 months (85% of Honduran mothers received OIS during pregnancy) By 4 months of age, Honduran and Swedish infants already had significantly different iron status. Honduran infants had significantly lower birth weight and larger weight gain from birth to 4 months, suggesting catch up growth [and increased iron requirements]

Friel et al., 2003[6]	Canada, Newfoundland, (St John's regional post-partum unit)	77 R 51 C (44 at 12 months) Attrition = 33.8% (42.9% at 12 months) (similar dropout rates between OIS & placebo)	1	6, 12, 13	5	7.5mg/day ferrous sulfate (~1.6mg/kg/day at 1 mo to ~1mg/kg/day at 6mo) Or placebo	Unsupervised (~2.5 months iron provided)	Iron status Mental & psychomotor development Growth Adverse effects (ID = SF < 12 µg/L; IDA = Hb < 110 g/L or HCT < 0.33 + ID)	**Iron status:** MCV at 3.5 months and Hb and MCV at 6 months were significantly higher in the OIS group (with a trend to higher PF, P = .06). No significant differences at 12 months. In the OIS group, 0% of infants had IDA at 6 months compared to 14% with IDA in the placebo group. **Mental & psychomotor development:** Supplemented infants performed significantly better on Bayley Psychomotor Development Indexes (100 ± 12) than placebo (93 ± 9) and demonstrated improved visual acuity (Z scores = 1.54 ± 1.18 vs 0.87 ± 0.79; OIS group vs placebo, respectively). There were no significant differences between groups on Mental Developmental Indexes. **Growth:** No significant differences between weight, length, or head circumference at any clinic visit **Adverse effects:** No differences in reported episodes of gastrointestinal symptoms and/or minor illnesses	OIS of term breast-fed infants prevented the natural fall in Hb and MCV that occurs between 1 to 6 months of age (by ~8g/L) No evidence of oxidative stress in the OIS group (i.e. superoxide dismutase, catalase, plasma ferric-reducing antioxidant power)	Small sample and underpowered – study terminated early due to funding (possible type II errors e.g. PF did not reach significance)
Lozoff et al., 2016[7] Angulo-Barroso et al., 2016[8]	China, Hebei Province, rural Sanhe County	730 R 633 C (*n* = 312–327/group) (Not including x 2 arms where mothers received OIS) Attrition = 13.3%	1.5	9	7.5	1 mg/kg/day iron protein succynilate Or placebo	No supervision Mothers needed to request additional iron supplements which rarely occurred Poor adherence >50% infants only received OIS before 6 months (nil after)	Iron status Motor development Growth Adverse effects (Anaemia = Hb < 110 g/L; ID defined as ≥ 2 abnormal iron measures (MCV < 74 fL; ZPP/H > 69 µmol heme/mol; SF <12 µg/L); IDA = Hb < 110 g/L + ID)	**Iron status:** Risk of anaemia (Hb < 110 g/L) was reduced by 23% in OIS group vs placebo group (RR 0.77 95% CI 0.63, 0.93); ID was reduced by 11% (RR 0.89 95% CI 0.79, 1.00). IDA risk reduced by 27% (RR 0.73 95% CI 0.58, 0.92). Iron supplementation in infancy, but not pregnancy, reduced ID risk: (RR 0.79, 95% CI 0.63, 0.98) (OIS in infancy vs pregnancy) **Motor development:** Iron supplementation in infancy (but not pregnancy) improved gross motor scores: overall, *P* < .001; reflexes, *P* = .03; stationary, *P* < .001; and locomotion, *P* < .001. Iron supplementation in infancy improved motor scores by 0.3 SD compared with no supplementation or supplementation during pregnancy alone. (Instrument used = Peabody Developmental Motor Scale – Version 2; PDMS-2) **Growth:** no adverse effects on growth overall or among infants who were iron sufficient at birth. **Adverse effects:** no differences in doctor visits/hospitalisations. More infants ID at birth saw a doctor for upper respiratory infections/fever in iron group [145/307 (47.2%) vs placebo 119/304 (39.1%)]	Iron supplementation in infancy, but not pregnancy, reduced ID risk, independent of ID status at birth. Iron supplementation in infancy, regardless of supplementation in pregnancy, improved gross motor development at 9 months.	Infants with cord ferritin <35 mg/L excluded (to prevent assigning to infants with brain ID to placebo) >60% of infants still had ID at 9 mo
Wang et al., 2012[9]	China	123 R 60 C Attrition = 51.2%	4	6	2	1 mg/kg/day iron amino acid chelate Or placebo	Not stated	Iron status Growth Adverse effects	**Iron status:** Hb levels were significantly different between OIS group and controls at six months (P < 0.05). There were no significant differences between groups in other iron markers. MCV in infant girls (77.20 ± 3.17) was significantly higher than boys (75.89 ± 3.34) **Growth:** No significant differences	Daily OIS from 4-6 months increased Hb relative to controls	Study underpowered. High attrition rate. Only abstract available in English - unable to access fulltext
Wieringa et al., 2003[10]	Indonesia Bogor District, West Java, rural setting	129 93 C Attrition = 28% (Not including x 3 arms of ppts with zinc/iron/ß-carotene, zinc/iron, or zinc/ ß-carotene)	4	10	6	Iron 10mg/day ferrous sulfate provided 5d per week Or placebo	Supervised. Village health volunteers provided OIS and monitored doses by weighing bottles Median overall compliance was 91% of total intended dose (IQR: 76–98%). No significant differences between groups	Iron status (Anaemia = Hb < 110g/L IDA = Hb < 110 g/L + PF < 12 µg/L	**Iron status:** OIS group had significantly higher Hb (118 ± 10), PF 38.2 (18.0–68.1) and significantly lower anaemia (20%) and IDA rates (5%) at 10 months than placebo (Hb = 110 ± 11, *P* < 0.01; PF = 15.2, 8.2–28.1, *P* < 0.001; anaemia = 49%, *P* < 0.001; IDA = 29%, *P* < 0.001) **Growth:** No significant differences between groups at baseline or at endpoint	Iron-supplementation from 4 months of age increased iron status and lowered rates of anaemia and IDA at 10 months of age	
Yurdakok et al., 2004[11]	Turkey (Hacettepe University Ihsan Dogramaci Children's Hospital Well Baby Clinic)	79 R 67 C Attrition = 15.2%	4	6, 7	3	1 mg/kg/day or 7 mg/kg/week ferrous sulfate (dose increased monthly) Or placebo	Unsupervised Adherence monitored by weekly household visits. Two children in iron arm considered non-compliant & removed from data analysis	Iron status Adverse effects (ID = PF < 12 µg/L (4-5 months) and PF < 10 µg/L (6-7 months IDA (4-5 months) = Hb < 95 g/L and ≥ 2 abnormal iron measures (MCV < 74 fL; SF <12 µg/L; SI < 18 µg/dL; TS < 10%); IDA (6-7 months) = Hb < 105 g/L + ≥ 2 abnormal iron measures	**Iron status:** No significant differences between groups at 6 or 7 months for Hb, MCV, TS. At 6 months, SF levels decreased in daily (27.5 ± 23.1) and control groups (31.9 ± 23.8), but did not decrease in weekly group (40.4 ± 26.6). At 7 months, SF levels significantly increased in all groups due to dietary iron sources. **Adverse effects:** side effects reported from supplementation occurred in 44.4% of infants (vomiting, decreased appetite, black stool, diarrhoea, constipation). No significant difference between daily or weekly groups.	Weekly supplementation was more effective than daily or control at reserving iron status (SF) in exclusively breastfed infants at 6 mo	Study underpowered. 200 infants required to observe differences in ID or IDA with 80% power at 5% level of significance. Healthy population. Infants or mothers with ID or IDA at baseline were excluded. Infants consumed diets with adequate iron intake at around 6 months SF appeared much higher at baseline (4 months) in control group vs iron groups

								(MCV < 70 fL; SF <10 µg/L; SI < 30 µg/dL; TS < 12%)			
Ziegler et al., 2009[12]	United States (Department of Paediatrics, University of Iowa, Study Centre)	75 R 63 C (52 at 18 months) Attrition = 16.0%	1	5.5 (monthly visit until 12 mo, then at 15 and 18 mo)	4.5	7mg/day ferrous sulfate (in MV preparation incl Vit A, C & D) Or placebo	Unsupervised. Parents provided with 50mL bottles with droppers calibrated to provide 0.7ml (~71 doses btl). Bottles weighed each monthly visit to determine dosing. Mean daily use was 0.47g/d in the first month and 0.41g/d in the final month. Expected use was 0.3g/d.	Iron status Growth Adverse effects (Anaemia = Hb < 105 g/L; ID = PF < 10 µg/L; IDA = Hb < 110 g/L or + ID)	**Iron status:** Hb: No significant difference at any timepoint PF was significantly higher in OIS group at 4, 5.5 (adjusted & unadjusted) and 7.5 months (unadjusted), no difference at 9 months. MCV was significantly higher in the OIS group at 7.5 and 9 months. **Growth:** no significant differences between groups. Subgroup analyses showed that OIS significantly decreased weight gain of female infants from 1 to 5.5 months (19.7% change ± 5.1) compared to placebo (22.7 ± 4.6). **Adverse effects:** No significant differences in frequency of regurgitation, fussiness, colic or gassiness. Only significant difference was in number of green/black stools, no difference in consistency or total stool number.	Early supplementary iron moderately benefitted iron stores in infants for the period of treatment (until 5.5 months), but not after (by 9 months).	Small sample size, underpowered to assess if supplementation reduces ID/IDA and morbidity. Significant differences in weight/length between OIS and placebo group at baseline. Low prevalence of anaemia in population (3%)

[i]Enrolled in the trial and at primary endpoint
[‡]PF and SF are highly correlated but significant discrepancy between measures exists[13]
Hb = haemoglobin, MCV = mean corpuscular volume, TS = transferrin saturation, PF = plasma ferritin, SF = serum ferritin, HCT = haematocrit, ZPP = Zinc protoporphyrin, SI = Serum Iron
OIS = oral iron supplements
E = Enrolled and randomised at beginning of trial
C = Completed trial with data available
IQR = Interquartile range

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