

Childhood and Adolescent Anemia Burden in India: The Way Forward

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The burden of anemia in Indian children, based on capillary blood sampling, is believed to be profound and worsening (67.1%) according to the successive National Family Health Surveys (NFHS). This might be an overestimate. The recent Comprehensive National Nutrition Survey of Indian children, that used venous blood sampling, found only less than half (30.7%) the NFHS prevalence, of which only one third was due to iron deficiency (ID). Unfortunately, the apparently worsening NFHS anemia burden estimate has been interpreted as an inadequacy of the present iron supplementation policy. This has led to additional iron supply through mandatory rice fortification. However, the lack of efficacy of iron supplementation appears inevitable, if the true prevalence of iron deficiency anemia is only about 10%. Thus, etiology is a critical consideration when devising appropriate and effective prevention policies. Future policies must focus on precision, thoughtfulness, restraint, and community engagement.

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THE PRESENT

Current Prevalence and Causes of Anemia in India

The most influential surveys to describe the state of anemia in Indian women of reproductive age (WRA) and children (6-59 months) have been the different rounds of the National Family Health Survey (NFHS), conducted every 5-10 years. In the most recent of these surveys, from NFHS-4 in 2015-2016 [1], to NFHS-5 in 2019-2021 [2], the prevalence of anemia has been high, but changing in an apparently adverse manner from 53.2% to 57.2% in WRA and 58.6% to 67.1% in children. This has been a matter of concern and debate. These NFHS surveys, though conducted with a granularity that could quantify anemia at the district level, were nevertheless limited methodologically (see below for uncertainties) and did not investigate the specific etiologies of anemia. Without this knowledge, it has been erroneously assumed that the predominant or sole cause of anemia in India is dietary iron deficiency (ID). Thus, most policy initiatives focus on iron, without any specific knowledge of national prevalence of ID.

This knowledge lacuna was filled by a recent national survey of Indian children aged 1-19 years, called the Comprehensive National Nutrition Survey (CNNS), conducted between 2016 and 2018 [3]. This unique survey investigated not only the prevalence of anemia, which on average was about half (30.7%) of that estimated by the NFHS, but also its specific causes, by assessing venous

blood biomarkers that reflected the body status of different erythropoietic nutrients. Examples of these measured markers are serum ferritin for iron status, C-reactive protein for inflammation (which affects ferritin concentrations and allows for filtering out children who had infections or inflammation), serum folate, vitamin B₁₂ and vitamin A concentrations for their respective status [3]. All these have diagnostic cut-offs that indicate deficiency (or the presence of inflammation for CRP).

In an analysis of the CNNS anemia etiology [4], it was shown that in children aged 1-4 years, only 36% of anemia was due to ID, while 19% was due to folate and vitamin B₁₂ deficiency, and the rest was due to other causes. In older primary school children, only 16% of anemia was due to ID, while 24% was due to folate and vitamin B₁₂ deficiency, and the rest was due to other causes. In adolescent children, only 21% of anemia was due to ID, while 25% was due to folate and vitamin B₁₂ deficiency, while the rest was due to other causes. In effect, the CNNS has shown us that a lack of dietary iron is not the major cause of anemia in India, especially in older children, and that other causes, including inflammation, may be more important, and should be considered when going forward.

THE UNCERTAINTIES

Is the Prevalence of Anemia Really High, and Is Micronutrient Deficiency Really Profound and Pervasive in India?

With these extraordinarily high and persistent NFHS

anemia rates, there are uncertainties. Is anemia prevalence really that high? Is it possible that such a high baseline prevalence could have stubbornly resisted the effects of iron supplementation for decades? One possibility for a lack of response to supplementation is false-positive anemia diagnosis, or that ID prevalence was wrongly presumed to be overly high, from the very beginning.

Therefore, it is important to consider if the estimates of anemia or ID prevalence are inflated in India. There are at least two reasons to believe this is correct:

Blood Sample

The first reason is the way in which blood is sampled for Hb estimation. In the influential NFHS surveys, capillary blood from a finger prick is used to measure its Hb concentration [1,2]. An important study from Uttar Pradesh, on almost 1000 women who agreed to simultaneous sampling of capillary and venous (antecubital vein) blood, with immediate measurement of both blood samples on the same point-of-care instrument, showed that capillary blood had a lower hemoglobin (Hb) concentration than venous blood, by about 1 g/dL [5]. This meant that the anemia prevalence, measured by venous blood was 35.2%, about half that measured by the capillary blood sample (59.2%) in the same women. This is the best evidence available for a direct comparison between capillary and venous blood, since issues like different instrumentation for different blood samples, and long and differential wait times for analysis, plague other comparative studies.

Hemoglobin Cut-off

The second reason to think that anemia prevalence might be overestimated, is that the diagnostic Hb cut-off may be wrong, or too high. A higher cut-off will result in more anemia being diagnosed, as the average Hb value in the Indian WRA population [6] is close to the current Hb cut-off that is suggested by the WHO [7]. The problem is that the WHO Hb cut-off is based on a statistical examination of the Hb distribution in Western healthy populations (the cut-off is taken as the 5th percentile of this normal distribution). However, even within the USA, there are differences in Hb distributions in healthy black and white populations surveyed in the National Health and Nutrition Examination Survey [8]. Therefore, there is good reason to believe that the Hb distribution might be left-shifted in healthy Asian populations, for example. If so, this would result in a lower Hb cut-off. In a rigorous examination of healthy children from the CNNS, based on a very large number of filters for socio-economic status and biomarkers for adequate nutritional status among others, the 5th percentile of the Hb distribution for boys and girls aged 1-

19 years, was 1-2 g/dL lower than the WHO prescribed cut-off [9]. A similar phenomenon has been observed in an analysis on preschool children and WRA involving 25 low-middle income countries [10]. Using the India-specific cut-offs for children [9] in the original CNNS sample, would lower the national anemia prevalence substantially, by two-thirds.

Effectively, the correction of both these problems (the type of blood sampling and the Hb cut-off used) might reduce the anemia prevalence to less than 20% but confirming this will need prospective national surveys with venous blood, as well as consensus on the need for population-specific Hb cut-offs, with the implicit recognition that one-size-does-not-fit-all.

Iron Requirement

Finally, iron deficiency in India has been overestimated in terms of the daily requirement metric. In part, this was due to the substantially higher iron requirements that were previously suggested for Indian WRA, of 20-30 mg/day [11,12]. This requirement, when conflated with the Indian vegetarian diet containing 8.5 mg iron/1000 Kcal of energy, suggested that most Indians would have inadequate iron intake, and therefore, high prevalence of iron deficiency (ID). However, this is an overestimate, and the present correct daily iron requirement for WRA, defined in 2020, is 15 mg/day [13], met in a diet of 1750 Kcal/day, and easily attainable from normal diverse diets. The final proof of a lower-than-expected ID prevalence lies in empirical data, which are available from the CNNS [14]. ID prevalence was about 30% in children, and even lower (11-15%) in primary school children and adolescent boys [14]. The patterning of ID (measured as CRP adjusted serum ferritin) was also counterintuitive, in that it was higher in urban children, and in the higher wealth quintiles, despite adjustment for relevant confounders. The utilization of iron to form Hb was therefore relatively ineffective in the poorer children, possibly due to residual biological effects of earlier infections and deficiencies of additional hematopoietic nutrients [14]. This provides credence to the need for multiple nutrients (diverse food) rather than single chemical nutrient initiatives and simultaneous attention to combating inflammation, including through improved water supply and sanitation.

THE FUTURE: THE WAY FORWARD

Delink nutrient supplementation policies to simple anemia prevalence

The prevalence of anemia (however high or low that may be) cannot be attributed to a single nutrient deficiency and should not be translated into a supplementation policy for that alone. Anemia is multifactorial in etiology, and single

nutrient supplementation policies must be delinked from simple anemia prevalence estimates. For example, it is now well known that iron deficiency is not the common cause for deficiency anemia in India; it is only one cause. Other erythropoietic nutrients like vitamin B₁₂, folate and protein are also important. Hereditary anemias like thalassemia or sickle cell anemia are prevalent in certain parts of India. Hygiene and the environment [15], including air pollution with PM_{2.5} [16], may be other contributing factors. A holistic approach is required, instead of fragmentary initiatives. Thus, policy initiatives that target specific nutrients like iron in response to a general survey of anemia, without any knowledge of cause, or any knowledge of whether dietary iron is inadequate, is a knee-jerk reaction. Given that nutrients in excess can be dangerous, this is unjustified, and there is a need for precision. A careful and measured consideration of all the facts at hand is required, and if the facts are unavailable, then relevant surveys are required.

Stop Unbalanced Policy Initiatives

Even if a single nutrient policy is initiated, over-enthusiastic and muscular implementation, instead of measured and precise steps, is an unbalanced approach that is unlikely to yield any dividends. It is important to recognize that single policy approaches, including the layering of identical interventions [17], also have their own dangers. For example, universal and mandatory iron supplementation and/or fortification, which could result in excess iron intake and body stores, can increase the risk of diabetes or dyslipidemia [18], or oxidative risk to those with hereditary anemias, even with heterozygous traits [19,20], or the risk of an adverse composition of the micro-biome in children who eat iron fortified food [21]. There will be severe penalties that will be paid by those subjected to these unbalanced policies. A simpler way to filter out ineffective (and potentially unbalanced) approaches, is to simply examine systematic reviews of the efficacy of the intended policy initiative. An example is with rice fortification, where a systematic review of all trials performed with fortified rice on humans, concluded that it is unlikely to prevent anemia in the population [22]. That should have given some pause.

Give Food a Chance: It is the Most Pragmatic Way Forward

A case in point for food, is the recent finding that cessation of the mid-day-meal during the one-year COVID lockdown, in 2020-2021, resulted in an increase in anemia prevalence in South Indian school children; yet the prevalence of iron deficiency did not increase during this period in these children. This demonstrates the importance of a mixed diet supplying multiple erythropoietic micronutrients [23].

Thus, whole food approaches will be better and safer for children. However, it is often stated that the only way forward is to supplement or fortify food staples with chemical nutrients, rather than the more difficult but logical food-based approach. These chemical approaches are touted as ‘practical and pragmatic’, ‘short-term’ and eventually, ‘complementary to diverse diets’. Nothing is further from the truth: these are slogans for technological solutions that do not benefit the real stakeholders, or the children, who only need simple but diverse diets, delivered with precision. Indeed, the fortification of staple foods with chemicals might be antithetical to dietary diversity, as populations are educated to eat only that fortified staple.

Do Not Forget the Environment

Going back to the analysis of anemia in the CNNS data [4], the largest proportion of its prevalence in primary school children (almost half), and pre-school children and adolescents (about one third) was of ‘other’ unknown causes, including inflammation. That is, these causes were other than nutrient deficiency. Subclinical inflammation is an important cause of anemia, due to many reasons, including reduced erythropoiesis due to cytokine effects on the bone marrow, reduced iron absorption, and reduced erythrocyte survival time [24]. While it is difficult to unequivocally prove the efficacy of specific sanitation measures, for a variety of reasons, negative associations between anemia and improved sanitation have been observed [25], suggesting that poverty alleviation, with improvement of hygiene, pollution [15,16] and adequate prevention and treatment of childhood infections, is a critical part of reducing childhood anemia prevalence.

CONCLUSIONS

The future for anemia prevention policies is one of thoughtfulness, precision, restraint, and community engagement through education. Thoughtfulness and restraint go together, through rigorous review of the evidence available. They lead to the inevitable conclusion that it is time to implement precision in public health, since the etiology of anemia is multi-factorial and varies geographically and temporally. Initiatives to implement precision in public health are underway in India, for example, with the Screen and Test approach for prevention and treatment of anemia [26].

Precision will avoid the universal and mandatory one-size-fits-all interventional approach, with its risk of many harms, including economic and ethical dimensions [27]. Multi-sectoral involvements and actions are required, instead of the popular and ever-present lament and focus on iron, as if a single nutrient could offer a silver bullet. In the near future, point-of-care devices must be developed

to enable specific etiological diagnoses of anemia, to define appropriate interventions at the individual level. This individual approach to public health, will have a positive, multiplicative effect on anemia. At all costs, current methods and metrics must be improved, and thoughtful restraint applied, such that unnecessary panic, and reactionary knee-jerk policies do not occur.

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