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Where Biofortification Works and Where the Chain Breaks: A Critical Review of Evidence from Crop to Clinical Outcome

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ABSTRACT

Background. Biofortification breeds micronutrients into staple crops and is promoted as an agricultural solution to a medical problem. Its evidence base is usually presented as a single body supporting the approach as a whole, when it is in fact several bodies of very different strength attached to different nutrients and different rungs of a long causal chain running from plant breeding to clinical outcome.

Objective. To disaggregate that evidence by nutrient and by rung, to identify where the chain is demonstrated and where it is assumed, and to derive a framework for deciding whether a biofortified crop is the right instrument for a given deficiency.

Findings. Provitamin A biofortification has the strongest evidence. Randomised delivery trials in Mozambique and Uganda achieved adoption by 61–68 % of farmers exposed and doubled vitamin A intakes in children, with improved vitamin A status in Uganda; a controlled feeding study in which children ate 125 g of orange-fleshed sweet potato over 53 school days raised the proportion with normal vitamin A liver stores from 78 % to 87 % against no change in controls, and one Mozambican evaluation reported diarrhoea prevalence 11.4 percentage points lower in children under five and 18.9 points lower under three. Iron biofortification presents a different picture: intake rises, absorption rises — 1.9-fold in one study of iron-biofortified sweet potato — and cognitive measures improve, yet a synthesis of randomised trials of iron-biofortified rice, pearl millet and beans reported no significant effect on anaemia or iron deficiency. Zinc-biofortified wheat has shown higher zinc intakes and reduced iron deficiency in adolescent girls in a cluster-randomised trial in Pakistan.

Conclusions. The determining variables are whether the trait is visible, which governs adoption, and whether the clinical endpoint has a single nutritional cause, which governs whether a biomarker gain translates. Provitamin A satisfies both; iron satisfies neither cleanly. Biofortification should be selected nutrient by nutrient against those two questions rather than adopted or rejected as a strategy.

1. Introduction

Micronutrient deficiency is a medical condition with an agricultural cause. People are deficient in vitamin A, iron and zinc largely because the staples that make up most of their diet contain little of them, and the conventional responses — supplementation, industrial fortification, dietary diversification — all operate downstream of the field [1,2].

Biofortification proposes to act upstream instead, by breeding the nutrient into the crop. The attraction is obvious: the intervention travels through the existing seed and food system, requires no recurrent purchase by the household, reaches rural populations that industrial fortification often misses because they consume little processed food, and costs nothing per meal once the variety is in the ground [2,3].

The proposition also requires a long chain of events to hold. A variety must be bred, released, multiplied, distributed, adopted by farmers, consumed in sufficient quantity by the people who need it, absorbed from a food matrix that may contain inhibitors, and finally produce a change in a clinical outcome. Each link has been studied, and they have not been studied equally [3].

This review disaggregates the evidence along that chain and by nutrient. It is written from the position that biofortification is neither the panacea of its advocacy nor the failure its sharpest critics describe, and that the interesting question is not whether it works but for which nutrient, in which population, and at which rung the evidence currently stops.

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1.1 Scope and approach

This is a critical narrative review. Sources were identified by targeted searching and reference lists and selected to represent the range of evidence and of published disagreement rather than exhaustively. No protocol was registered and no formal appraisal instrument was applied. Quantitative findings are reported as published; the assessments in Figure 2 and Tables 2 and 4 are the author's judgement and are offered so that readers may disagree with specific placements.

2. The impact pathway

Figure 1 sets out the chain. Two features distinguish it from the pathway of a supplement or an industrially fortified food, and both are the source of biofortification's difficulties and of its advantages.

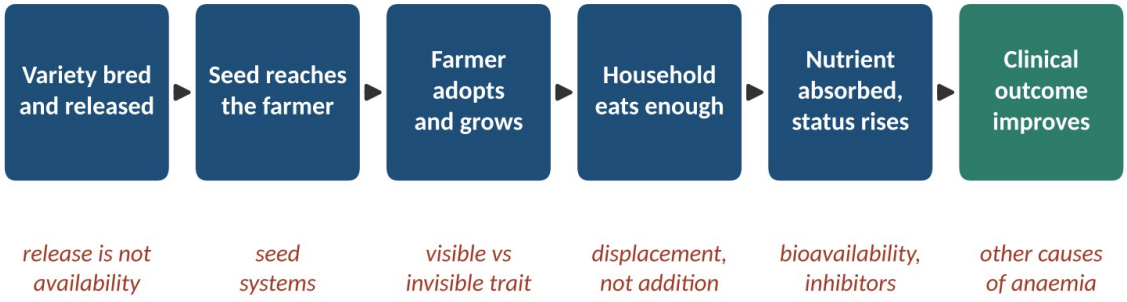


Figure 1. The chain from plant breeding to clinical outcome, with the point at which each link can fail.

First, the intervention is a crop rather than a product, so its delivery depends on seed systems, extension and farmer decision-making rather than on a factory and a distribution network. A variety that is released is not thereby available; national release lists routinely contain varieties that never reached appreciable area [1].

Second, and more consequentially, the biofortified crop must usually displace rather than supplement the conventional one. A household that adds a supplement to its diet adds nutrients; a household that adopts a biofortified variety substitutes it for the variety it was already growing, so the nutritional gain is the difference in density multiplied by the fraction of consumption that switches. Delivery research in Mozambique and Uganda documented exactly this substitution, with orange sweet potato displacing white varieties in both area and consumption [4–6]. Table 1 summarises how these features set biofortification apart from other micronutrient interventions.

Table 1. How biofortification differs from other micronutrient interventions

Feature	Supplementation	Industrial fortification	Biofortification
Delivery system	Health services	Processing industry and retail	Seed systems, extension and farming
Reaches subsistence households	Only where services reach	Poorly; little processed food is bought	Yes, by design
Recurrent cost to household	None if free, otherwise per dose	Embedded in food price	None once the variety is grown
Mechanism of gain	Addition to the diet	Addition to a purchased vehicle	Substitution for an existing crop
Dose control	Precise	Regulated and measurable	Depends on variety, soil, season and intake
Main failure mode	Coverage and adherence	Vehicle not consumed by the deficient	Adoption, displacement and bioavailability

3. Evidence by nutrient

Figure 2 summarises the strength of the evidence at each rung of the pathway for each nutrient; the sections that follow set out the basis for each assessment.

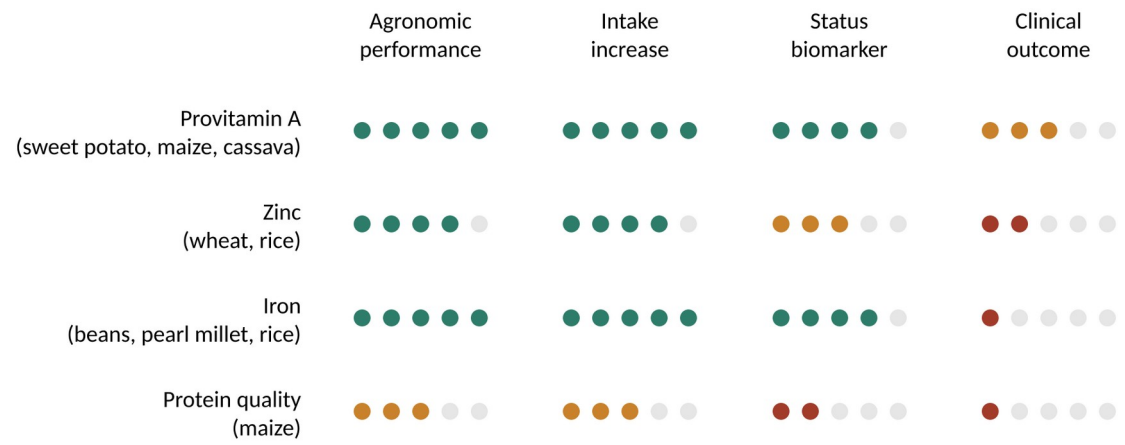


Figure 2. Strength of evidence at each rung of the pathway, by nutrient (filled dots out of five). Assessments are the author's.

3.1 Provitamin A: the case that holds

Orange-fleshed sweet potato is the crop on which the approach was established and it remains the strongest case at every rung [7].

Efficacy. A controlled feeding study in which primary school children consumed 125 g of boiled, mashed orange-fleshed sweet potato over 53 school days raised the proportion with normal vitamin A liver stores from 78 % to 87 %, while the white-fleshed control group showed no improvement and a decline from 86 % to 82 % [8]. Provitamin A maize has been shown to improve total body vitamin A stores in children in Zambia [9], and provitamin A cassava to improve vitamin A status in Kenyan schoolchildren [10].

Effectiveness at scale. Randomised delivery experiments in Mozambique and Uganda produced adoption by 61–68 % of farmers exposed to the project and doubled vitamin A intakes among children, with improved vitamin A status among children reported in Uganda [4,5]. Two intervention models differing substantially in training intensity and cost produced comparable impacts, which is a practically important finding for programme design [6].

Clinical outcome. An evaluation in Mozambique reported diarrhoea prevalence 11.4 percentage points lower among children under five consuming orange-fleshed sweet potato, and 18.9 points lower among children under three, with shorter episodes [11]. This is the rung at which most biofortification evidence stops, and it is reached here.

Taken together the provitamin A chain is demonstrated from breeding to a clinical endpoint, which no other biofortified nutrient can presently claim.

3.2 Iron: where the chain breaks

Iron biofortification has been studied as carefully as provitamin A and the result is different in an instructive way (Figure 3) [12]. Intake rises with adoption. Absorption rises measurably: a study of iron-biofortified sweet potato in Malawi and potato in Peru reported a 1.9-fold increase in total iron absorption from the biofortified sweet potato [13]. Functional measures improve, with a randomised trial of iron-biofortified beans in Rwanda demonstrating improved cognitive performance in women of reproductive age [14], and trials of iron beans and pearl millet reporting gains in haemoglobin and total body iron in Rwanda and Maharashtra [15,16].

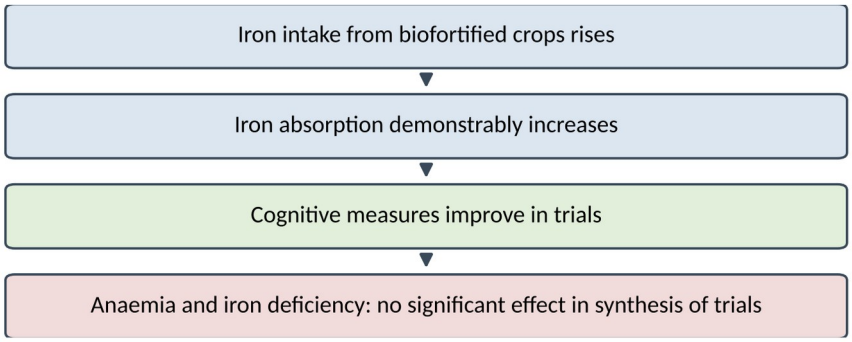


Figure 3. The iron biofortification evidence, rung by rung.

At the final rung the evidence does not follow. A synthesis of randomised trials of iron-biofortified rice in the Philippines, pearl millet in India and beans in Rwanda reported no significant effect on anaemia or on iron deficiency outcomes, while confirming the improvements in cognitive function [17]. That is not a null result at every level; it is a result that holds at four rungs and stops at the fifth. Table 2 sets out the candidate explanations.

Table 2. Why an absorbed-iron gain may not appear as less anaemia

Explanation	What it implies	Assessment
Anaemia in these populations is not solely iron-deficiency anaemia	Malaria, inflammation, haemoglobinopathies and other deficiencies contribute	Strong; the most likely principal reason
The absolute increment in absorbed iron is small relative to requirement	Even a 1.9-fold absorption gain from a low base may be insufficient	Plausible and quantifiable in principle
Phytate and polyphenol inhibitors in the same matrix limit the gain	Bioavailability is matrix-dependent, not density-dependent	Well established mechanistically
Trials were underpowered for a haematological endpoint	Absence of significance is not absence of effect	Possible; sample sizes were set for biomarkers
Baseline iron status was better than assumed	Little room to improve in replete participants	Reported in some trial populations

The first row is the one that matters for policy and it is not a criticism of the crop. Where anaemia is substantially caused by malaria, chronic inflammation or genetic haemoglobin disorders, an intervention that supplies iron cannot resolve it, and the failure is one of instrument selection rather than of the instrument. A programme that adopts iron beans expecting to reduce anaemia in a high-malaria setting has misdiagnosed the problem, and would have misdiagnosed it equally had it chosen iron supplementation.

The cognitive findings deserve to be taken seriously on their own terms rather than treated as a consolation. If iron biofortification improves cognitive performance without shifting haemoglobin, that is a meaningful outcome and it suggests the relevant deficiency was functional rather than haematological [14,17]. It also means anaemia prevalence is the wrong indicator by which to monitor such a programme, which is nonetheless the indicator most national surveys collect.

3.3 Zinc

Zinc biofortification sits between the two. Cluster-randomised trials of zinc-biofortified wheat in rural Pakistan have shown higher zinc intakes and reductions in iron deficiency among adolescent girls consuming the biofortified flour [18], and zinc-biofortified wheat and rice have been shown feasible agronomically [1].

The evidence is thinner at the status and outcome rungs than for provitamin A, and zinc carries a specific assessment difficulty that iron and vitamin A do not: there is no well-validated, sensitive biomarker of zinc status, so demonstrating that a zinc intervention has worked is harder than demonstrating that it was delivered, and population prevalence of deficiency must itself be estimated indirectly [19]. Reviews of the field consistently identify this as a constraint on the evidence rather than a finding about the crops [1,3].

3.4 What distinguishes the successful case

Two variables separate provitamin A from the rest, and neither is about the nutrient content of the crop (Figure 4).

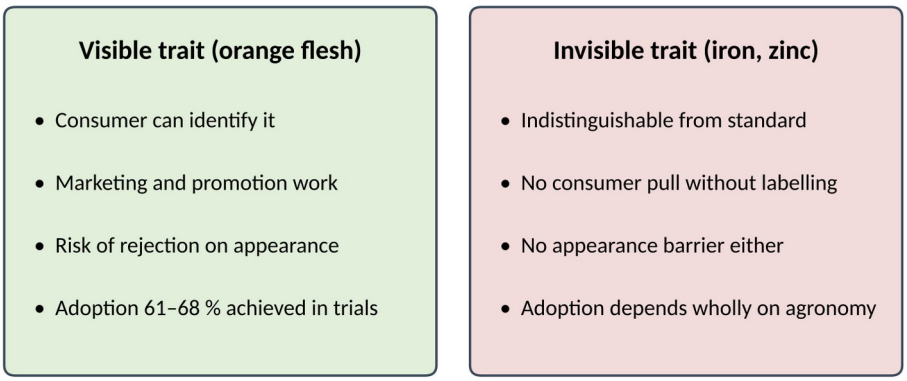


Figure 4. Trait visibility and what it changes about adoption.

Trait visibility. Provitamin A crops are visibly different — orange flesh where consumers expect white. Iron and zinc biofortified crops are indistinguishable from their conventional counterparts. Visibility cuts both ways: it creates a risk of rejection on appearance, and it makes promotion, identification and consumer choice possible at all. The Mozambique and Uganda experience shows that where the nutritional message is credible and yields are comparable, visibility becomes an asset, with adoption reaching 61–68 % [4–6]. For an invisible trait there is no consumer pull to mobilise, and adoption rests entirely on agronomic performance and seed availability.

Causal specificity of the endpoint. Vitamin A deficiency has essentially one nutritional cause, so raising vitamin A intake raises vitamin A status and improves vitamin A-dependent outcomes. Anaemia has many causes, so raising iron intake may leave it unmoved. An intervention that supplies one nutrient can only resolve a condition caused by the absence of that nutrient, and the more multifactorial the endpoint, the weaker the expected effect regardless of how well the agricultural part works. Table 3 applies both variables to each nutrient–crop combination.

Table 3. The two determining variables, applied

Nutrient and crop	Trait visible?	Endpoint causally specific?	Evidence reaches
Provitamin A, sweet potato	Yes, orange flesh	Yes, vitamin A deficiency	Clinical outcome
Provitamin A, maize and cassava	Yes	Yes	Status biomarker and visual function
Zinc, wheat and rice	No	Partly; biomarker is weak	Intake and partial status
Iron, beans, millet and rice	No	No; anaemia is multifactorial	Absorption and cognition, not anaemia

4. A framework for selection

The framework in Figure 5 is ordered so that the questions most often decisive come before the one most often asked. Whether the crop contains more of the nutrient is established by breeding and is rarely the constraint; whether the deficiency has the cause the crop addresses, and whether the crop will be adopted and eaten in place of something else, usually are.

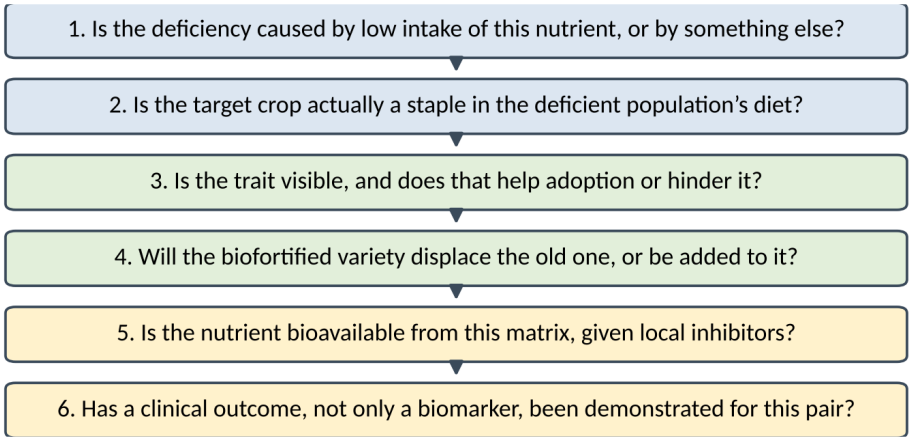


Figure 5. Six questions to ask before committing to a biofortified crop.

Table 4. The framework applied to three cases

Question	Provitamin A sweet potato in a vitamin A-deficient population	Iron beans where anaemia is malarial	Zinc wheat in a wheat-staple population
Is the deficiency caused by low intake of this nutrient?	Yes	Partly at best	Plausibly
Is the crop a staple for the deficient group?	Yes in the target areas	Yes	Yes
Does trait visibility help or hinder?	Helps, once promoted	Neutral; invisible	Neutral; invisible
Will it displace or be added to the old variety?	Displaces, documented	Displaces	Displaces
Is the nutrient bioavailable from this matrix?	Yes	Limited by phytate	Limited by phytate
Has a clinical outcome been demonstrated?	Yes	Not for anaemia	Not yet
Overall	**Proceed**	**Reconsider the endpoint**	**Proceed with realistic monitoring**

The middle column of Table 4 is the practical use of the framework. It does not conclude that iron beans are worthless; it concludes that anaemia is the wrong outcome to promise and the wrong indicator to monitor, and that a programme justified on cognitive or functional grounds with appropriate measurement would be defensible where one justified on anaemia reduction would not.

4.1 Cost and comparison

Where biofortification works it appears to work cheaply. Orange-fleshed sweet potato combined with community nutrition education has been costed at approximately US$15–20 per disability-adjusted life year saved, which falls well inside conventional thresholds for a highly cost-effective intervention [7].

That figure should be read with two cautions. It is derived from the successful case, and applying it to nutrients whose chain stops earlier would be unwarranted. And it includes the nutrition education component, which the Mozambique and Uganda experiments suggest could be delivered less intensively at similar effect — the two models differing in training intensity produced comparable impacts [6] — so the cost of the delivered intervention is itself a variable rather than a constant.

5. Discussion

5.1 What the evidence supports

Table 5. Summary assessment

Claim	Assessment
Crops can be bred to substantially higher micronutrient density	Established across iron, zinc, provitamin A and protein quality
Biofortified crops are adopted when promoted	Demonstrated for orange sweet potato at 61–68 % in randomised delivery trials
Adoption raises intake of the target nutrient	Demonstrated; vitamin A intakes doubled in children
Raised intake improves status	Demonstrated for provitamin A; partial for zinc; demonstrated for iron absorption
Improved status improves clinical outcome	Demonstrated for provitamin A; not demonstrated for iron and anaemia
Biofortification reduces anaemia	Not supported by synthesis of randomised trials
Biofortification is cost-effective	Supported for orange sweet potato; not established nutrient by nutrient
Biofortification reaches populations fortification misses	Plausible and central to the rationale; less directly tested

The last row of Table 5 deserves more attention than it receives. The strongest conceptual argument for biofortification is that it reaches subsistence households who buy little processed food and therefore consume little industrially fortified product [2]. That argument is about coverage rather than about efficacy, it is the one that distinguishes biofortification from cheaper alternatives, and it has been tested far less directly than the efficacy questions that dominate the literature [3].

5.2 Limitations of this review

This is a narrative review by a single author without a registered protocol, systematic search, duplicate screening or formal risk-of-bias appraisal. It concentrates on a small number of prominent trials and syntheses selected to illustrate the structure of the evidence, and a systematic review would identify substantially more primary studies, particularly for zinc and for provitamin A maize and cassava, and might place several assessments in Figure 2 and Tables 2 to 5 differently.

The assessments of evidence strength are judgements, not measurements, and the author has not examined individual participant data from any trial. Findings are reported as published and where a claim is contested both positions are given rather than adjudicated. The review does not address the agronomic sustainability of biofortified varieties, soil micronutrient status as a constraint on grain content, consumer acceptability studies in detail, seed system economics, or the regulatory and intellectual property questions surrounding variety release, each of which bears on whether a programme succeeds.

Publication and promotion bias deserve explicit mention. Much of the primary evidence originates from a small number of programmes with an institutional interest in the approach, which is common in applied nutrition and is not an accusation, but it means the balance of published findings may not reflect the balance of results obtained. The iron synthesis reporting a null for anaemia [17] is evidence that discouraging findings do reach publication; it is not evidence that all of them do.

6. Conclusion

Biofortification is not one intervention with one evidence base. For provitamin A the chain is demonstrated end to end: a controlled feeding study raised normal vitamin A liver stores from 78 % to 87 %, randomised delivery trials achieved 61–68 % adoption and doubled children's vitamin A intakes, and a Mozambican evaluation reported diarrhoea prevalence 11.4 percentage points lower in children under five. For iron the chain holds for four rungs and breaks at the fifth: absorption rises 1.9-fold, cognition improves, and a synthesis of randomised trials finds no significant effect on anaemia.

The difference is explained by two variables that have nothing to do with how much nutrient the breeders put in the seed. A visible trait can be promoted, identified and chosen, and an invisible one cannot. And an

endpoint with one nutritional cause responds to supplying that nutrient, while a multifactorial endpoint such as anaemia may not respond at all.

The practical conclusion is to stop arguing about biofortification and start selecting between biofortifications. Where the deficiency is specific and the trait is visible, the evidence supports proceeding and the costing is favourable. Where the endpoint is multifactorial, the right response is not to abandon the crop but to change what is promised and what is measured — and, before either, to establish what is actually causing the deficiency the programme intends to fix.

Declarations

Ethical approval. Not applicable. This review uses only published literature and involves no human participants, dietary data or identifiable information.

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Conflicts of interest. The author declares no conflicts of interest, financial or non-financial, in relation to the subject matter of this manuscript.

Scope disclaimer. This review appraises published evidence and does not recommend or discourage any specific variety, programme or national policy. Decisions on crop selection and nutrition programming should follow local assessment of deficiency aetiology, dietary patterns and delivery capacity.

Data availability. Data sharing is not applicable to this article, as no new data were generated or analysed. All material discussed is available in the cited published sources.

Author contributions. Ranjana Meshram (Damle) is the sole author of this work and was responsible for the conception and design of the review, literature identification and appraisal, interpretation of the evidence, preparation of the figures and tables, and drafting, revision and final approval of the manuscript. The author is accountable for all aspects of the work.

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