Evaluating the Impact of Biofortification: A Meta-analysis of Community-level Studies on Quality Protein Maize (QPM)

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Abstract— **Biofortification, or the genetic improvement of the nutritional quality of food crops, is a promising strategy to combat undernutrition, particularly among the rural poor in developing countries. However, traditional methods of impact assessment do not apply to biofortified crops as little or no yield increases are expected. Significant progress has been made to develop maize varieties with improved protein quality, collectively known as quality protein maize (QPM). Evidence for the impact of QPM at the community level, as demonstrated by randomized, controlled studies, was evaluated using meta-analysis. A new and generalizable effect size was proposed to quantify the impact of QPM on a key outcome, child growth. The results indicated that consumption of QPM instead of conventional maize leads to an 8% (95% CI: 4-12%) increase in the rate of growth in height and a 9% (95% CI: 4-12%) increase in the rate of growth in weight in infants and young children with mild to moderate undernutrition from populations in which maize is a significant part of the diet. These results are the first step in evaluating the potential economic impact of QPM by establishing and quantifying a link between use of the improved crop and nutritional outcomes. QPM can serve as a model for other biofortification efforts, and in particular, the conceptual framework and methodologies for impact assessment are directly applicable to other biofortified crops.**

Keywords— **Impact assessment, biofortification, meta-analysis.**

I. INTRODUCTION

A. Biofortification

There is increasing interest in improving the nutritional quality of food crops using conventional plant breeding or genetic engineering techniques [1, 2, 3]. This process, called biofortification, is a promising strategy to combat undernutrition in developing countries and is believed to be cost-effective [4], more sustainable than nutrition supplementation [5], and a viable complementary strategy to food fortification, which relies on central processing of food and therefore may be less accessible, particularly to the rural poor [1, 5, 6].

There have been recent biofortification efforts in several crops, with a number of products in development including orange-fleshed sweet potatoes [7] and "golden rice" [8], both with increased pro-vitamin A carotenoid content, and high-iron rice [9]. These products have significant promise in improving intakes of key nutrients in at-risk populations [4, 10, 11].

B. Quality protein maize (QPM)

In maize, much early work focused on improving protein quality [12,13]. Maize grain has poor protein quality due to deficiencies in lysine and tryptophan, two amino acids that are essential to the diets of humans and monogastric animals [14]. Conventional breeding efforts have yielded several modern maize varieties, collectively referred to as quality protein maize (QPM), which have improved protein quality and agronomic characteristics and are currently being actively disseminated, particularly in Sub-Saharan Africa [12]. As most biofortification efforts are still in early stages of research and development, QPM provides a valuable model for the development, evaluation, targeting, and dissemination of biofortified crops.

C. Impact assessment of biofortified crops

Assessing the impact of conventional improved varieties such as those from the Green Revolution is a relatively straightforward exercise, based on yield increases and rates of adoption [15]. Impact

assessment of nutritionally enhanced varieties such as biofortified maize necessarily involve the evaluation of their nutritional impact, to which traditional methods of impact assessment do not apply, as little or no yield increases are expected.

In this paper, a conceptual framework is described for assessing the impact of biofortified crops. This framework is used to evaluate the evidence for impact of QPM. Evidence of impact at the community level, as demonstrated by randomized, controlled studies, is evaluated using meta-analysis to quantify the impact of QPM on a key outcome, child growth. This analysis is needed to assess the potential impact of this technology on a broader scale. Recommendations are also made for the design of future community-level evaluations of biofortified crops.

II. METHODOLOGY

A. Conceptual framework for impact assessment

The nutritional impact of QPM, or of any biofortified crop, should be demonstrated at multiple levels [16] to make sound, evidence-based decisions on the development, targeting, and dissemination of the crop. First, the change in the nutrition composition of the crop must result in increased bioavailability of the nutrient in question when consumed by target individuals. Bioavailability refers to the fraction of an ingested nutrient that is utilized for normal physiological functions or storage [16]. This increased utilization must then result in improved outcomes among target individuals who consume the biofortified crop instead of the conventional crop.

The impact of a biofortified crop should be evaluated at the community level using both efficacy and effectiveness studies. Efficacy is "the extent to which a specific intervention, procedure, regimen, or service produces a beneficial effect under ideal conditions", while effectiveness is "the extent to which a specific intervention, procedure, regimen, or service, when deployed in the field, does what it is intended to do for a defined population" [17]. As efficacy studies are conducted under well-controlled conditions, they primarily address biological factors relating to the effect of a technology or intervention. Effectiveness studies are likely to involve less control over delivery of the technology or intervention to subjects and subjects' compliance. Therefore, external confounding factors, both biological and behavioural, are more likely to modify the effect of the technology or intervention in this type of study.

Finally, the impact of a biofortified crop should be evaluated in a broader context that, in addition to its nutritional and health effects, also investigates the agricultural, societal, environmental, and economic effects of the technology. A comprehensive impact assessment would require data on specific areas and numbers of people who suffer from nutrient inadequacies due to their consumption of the conventional crop and whose nutrient intakes would significantly increase with adoption and consumption of the biofortified crop. This assessment would therefore address two important and distinct questions. First, data on the diets of target populations should indicate risk of inadequate intakes of the nutrients in question. The improved nutritional quality of any biofortified crop is expected to have an impact by alleviating nutrient inadequacy in a target population. If there is little risk of inadequate nutrient intakes prior to its release, the technology would be expected to have little impact.

The second question that an impact assessment would answer is whether characteristics of a target region and population would allow sufficiently high adoption and consumption of the biofortified crop to have a significant impact on the adequacy of nutrient intakes in that population. Biofortified crops address a nutritional problem by introducing a new agricultural technology. The links between agriculture and nutrition that would allow the release of an agricultural technology to have an impact on the nutrition of a target population must therefore be described. The steps along these potential pathways of impact should be evaluated for factors that could modify the impact of the technology. These could include factors influencing adoption, acceptability of the crop for food preparation and consumption, nutrient losses during storage, processing, or preparation, prevalence of disease in the population, and seasonal patterns in diets or disease.

B. Evaluating the impact of QPM

For QPM, the primary target population is children under five years of age, and the primary outcomes of interest have traditionally been anthropometric measurements of growth. Clinical studies have demonstrated that the protein in QPM is more bioavailable than the protein in conventional maize (CM) [18]. Efficacy and effectiveness studies (to be reviewed below) have been conducted in several countries; however, none have been published in the peer-reviewed literature. All these studies have a common design in which children under five years are allocated into treatment groups, at least one of which receives QPM and another of which receives CM, and various outcomes, largely anthropometric, are monitored over time. The common hypothesis of these studies is that children on a QPM-based diet will have greater growth than children on a similar diet based on CM. QPM is expected to have impact if there are nutrient deficiencies as a result of poor protein quality, or specifically a lack of lysine or tryptophan, in the diet and if these deficiencies can be alleviated by substituting CM with QPM in these diets.

C. Empirical model

Meta-analysis is a statistical method to integrate the results of independent studies that address the same research question [cf. 19, 20]. For each study, a statistic, called an effect size, is calculated to quantify the effect of a treatment or intervention in a way that is interpretable and comparable across studies. A summary effect size is then calculated to quantify the overall effect of a treatment or intervention across studies.

Community-level studies on the impact of QPM were identified through literature searches and inquiries from QPM researchers and authors of QPM-related articles to identify unpublished work. Studies included in this analysis had at least two intervention groups, one which received CM and another which received QPM. Separate meta-analyses were conducted to evaluate the impact of QPM on children's growth in height and weight.

The following effect size, $\hat{\theta}_i$, was proposed to quantify the effect of QPM relative to the effect of CM on growth in height or weight in a given study *i*:

$$\hat{\theta}_i = \frac{b_{QPM_i}}{b_{CM_i}} \tag{1}$$

where b_{QPM_i} is the average growth rate in the QPM group and b_{CM_i} is the average growth rate in the CM group in study *i*. The standard error of $\hat{\theta}_i$ was approximated using the delta method [21] for all studies for which within-group standard errors of growth rates could be calculated from available data.

The summary effect size, $\hat{\theta}$, which quantifies the overall effect of QPM relative to CM, was calculated as:

$$\hat{\theta} = \sum_i w_i \hat{\theta}_i \tag{2}$$

where w_i is the weight corresponding to study *i* and $\sum_i w_i = 1$. As studies with larger sample sizes are expected to provide more precise estimates of the relative effect of QPM to CM, the w_i were proportional to the sample sizes of the respective studies. This choice gave larger weight to larger studies, as they provide more information about the summary effect size than smaller studies. Two other sets of weights were also considered, one in which all studies were equally weighted and one in which the weights were inversely proportional to the variances of the respective $\hat{\theta}_i$. The latter weights were optimal in that they minimize the variance of $\hat{\theta}$. However, they could be calculated only for those studies for which $\mathrm{var}\left(\hat{\theta}_i\right)$ could also be calculated.

A $100(1-\alpha)\%$ bootstrap percentile confidence interval [22] was then calculated for $\hat{\theta}$ based on 5000 resamples. An asymptotic $100(1-\alpha)\%$ confidence interval (CI) for $\hat{\theta}$ was also calculated by:

$$\hat{\theta} \pm z_{100\left(1-\frac{\alpha}{2}\right)} SE\left(\hat{\theta}\right) \tag{3}$$

where $z_{100\left(1-\frac{\alpha}{2}\right)}$ is the $100\left(1-\frac{\alpha}{2}\right)$th percentile of the standard normal distribution and

Table 1 Overview of eight available studies analyzing the impact of QPM on child growth

Study	Study year	Duration of study (months)	Form of treatment	Age at baseline (months)	Data on height	Data on weight	Reference
Ghana 1	1993-1994	12	Seed	4-23	yes	yes	Akuamoa-Boateng 2002
Ghana 2	1994-1995	12	Dough	4-15	yes	yes	Akuamoa-Boateng 2002
Ghana 3	1998-2000	12	Dough	4-9	yes	yes	Akuamoa-Boateng 2002
Ghana 4	2001	7	Dough	4-6	yes	yes	Akuamoa-Boateng 2002
Ethiopia	2002-2003	9	Seed	most under 24	yes	yes	Akalu 2005
India	1975-1976	6	Meal	18-30	yes	yes	Singh 1977; Singh et al. 1980
Mexico	2001-2002	14	Grain	most under 60	no	yes	Morales Guerra 2002
Nicaragua	2005	3.5	Meal	12-60	yes	yes	Ortega Alemán et al. 2006

$SE\left(\hat{\theta}\right) = \sqrt{\sum_i w_i^2 \operatorname{var}\left(\hat{\theta}_i\right)}$. A CI for $\hat{\theta}$ calculated in this latter way could only be based on studies for which $\operatorname{var}\left(\hat{\theta}_i\right)$ could be calculated. Sensitivity of the summary effect size to the influence of individual studies was explored by calculating summary effect sizes and bootstrap percentile confidence intervals while excluding one study at a time from the analysis.

III. RESULTS

A. Relevant studies

The eight identified studies [23-28] used in this analysis were conducted in Sub-Saharan Africa, Asia, and Latin America and involved infants and children under 5 years of age, reflecting the primary target group for QPM (Table 1). Most subjects were under 24 months at baseline, a critical age range for growth faltering [29]. Most studies provided prepared but uncooked dough, grain, or seed at the household level, rather than meals fed to the child. In these studies, any observed impact of QPM on child growth may therefore be a combination of biological factors and of behaviors and practices in the household. The children were drawn from populations in which maize was a staple food. Based on their average heights and weights at baseline, children in these populations exhibited mild to moderate undernutrition. The results of the meta-analyses can be generalized to populations of children with similar characteristics.

B. Effect sizes for height and weight

Rates of growth in height among children receiving QPM or CM and the associated effect size for each study are given in Table 2. In the study designated "Ghana 1", children receiving CM grew an average of 0.83 cm/month over the duration of the study, while children receiving QPM grew an average of 0.88 cm/month. The relative growth rate between the QPM and CM groups is the effect size for a given study. The effect size of 1.07 for the Ghana 1 study indicates a 7% increase in growth rate for height in the QPM group compared with the CM group. For the seven studies for which height data were available, all but the Ethiopia study had a faster growth rate in the QPM group, as indicated by effect sizes that are greater than 1.

Rates of growth in weight among children receiving QPM or CM and the associated effect size for each study are given in Table 3. In the Ghana 1 study, children receiving CM grew an average of 0.20 kg/month, while children receiving QPM grew an average of 0.19 kg/month. The effect size of 0.96 for this study indicates a 4% decrease in the growth rate for weight in the QPM group compared with the CM group. For the eight studies for which weight data were available, all other studies showed a faster growth rate in the QPM group, as indicated by effect sizes greater than 1.

Growth rates may vary among studies for several reasons including faster growth rates among younger children and greater noise in measured outcomes among studies of small sample size or shorter

Table 2 Rate of growth in height among children receiving quality protein maize (QPM) or conventional maize (CM) and the effect size for each study, calcuated as the relative growth rate of the QPM group compared with the CM group.

Study [a]	CM			QPM			Effect size	
	Growth rate (cm/month) b_{CM}	SE	N	Growth rate (cm/month) b_{QPM}	SE	N	Estimate (b_{QPM}/b_{CM})	SE
Ghana 1	0.83	0.06	40	0.88	0.05	43	1.07	0.10
Ghana 2	1.03	0.06	39	1.23	0.06	39	1.19	0.09
Ghana 3	1.01	0.01	156	1.09	0.01	161	1.08	0.02
Ghana 4	1.04	0.03	246	1.11	0.03	240	1.07	0.05
Ethiopia	0.99	- [b]	51	0.95	- [b]	51	0.96	- [b]
India	0.81	0.12	35	0.93	0.07	32	1.16	0.19
Nicaragua	0.35	0.19	24	0.58	0.36	24	1.66	1.37

[a] Mexico study did not have height data.

[b] Ethiopia study did not have within-group standard errors.

Table 3 Rate of growth in weight among children receiving quality protein maize (QPM) or conventional maize (CM) and the effect size for each study, calcuated as the relative growth rate of the QPM group compared with the CM group.

Study	CM			QPM			Effect size	
	Growth rate (kg/month) b_{CM}	SE	N	Growth rate (kg/month) b_{QPM}	SE	N	Estimate (b_{QPM}/b_{CM})	SE
Ghana 1	0.20	0.02	40	0.19	0.02	43	0.96	0.11
Ghana 2	0.24	0.02	39	0.24	0.02	39	1.00	0.09
Ghana 3	0.19	0.00	157	0.21	0.00	160	1.10	0.04
Ghana 4	0.35	0.01	246	0.38	0.01	240	1.10	0.04
Ethiopia	0.14	- [a]	52	0.16	- [a]	53	1.11	- [a]
India	0.21	0.02	35	0.26	0.03	32	1.23	0.17
Mexico	0.25 [b]	0.07	32	0.50 [b]	0.06	35	1.97	0.60
Nicaragua	0.05	0.13	24	0.23	0.13	24	4.27	10.53

[a] Ethiopia study did not have within-group standard errors

[b] Weight was measured in physical development (percentage of the median weight of a reference population of the same age) instead of kg.

duration. In the meta-analyses, the studies from Nicaragua and Mexico were conservatively treated as outliers, given their large effect sizes and associated standard errors compared with the other included studies. These two studies were also distinguished from the other included studies by their small sample size, wide range of ages among the study participants, and, in the case of the Nicaragua study, short duration.

C. Summary effect sizes for height and weight

Summary effect sizes and confidence intervals for growth in height and weight were determined using the three weighting methods and two confidence interval methods on the main data set with and without outliers (Table 4). The summary effect sizes and bootstrap confidence intervals based on the main data

Table 4 Summary effect sizes and confidence intervals for growth in height and weight. Three weighting methods and two confidence interval methods were evaluated on the main data set with and without outliers.

			Main data set [a]		Main data set + outlier [b]	
Outcome	Weighting method	CI method	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Height	Sample size	Bootstrap	1.08 (1.04, 1.12)	0.0014	1.10 (1.05, 1.22)	0.0002
	Equal	Bootstrap	1.09 (1.03, 1.15)	0.0037	1.17 (1.05, 1.35)	0.0004
	Optimal [c,d]	Bootstrap	1.08 (1.07, 1.16)	0.0000	1.08 (1.07, 1.16)	0.0000
	Optimal [c,d]	Asymptotic [d]	1.08 (1.05, 1.12)	0.0000	1.08 (1.05, 1.12)	0.0000
Weight	Sample size	Bootstrap	1.09 (1.04, 1.12)	0.0019	1.14 (1.06, 1.32)	0.0002
	Equal	Bootstrap	1.08 (1.02, 1.15)	0.0073	1.21 (1.03, 1.48)	0.0010
	Optimal [c,d]	Bootstrap	1.09 (1.00, 1.11)	0.0187	1.09 (1.01, 1.11)	0.0121
	Optimal [c,d]	Asymptotic [d]	1.09 (1.04, 1.14)	0.0001	1.09 (1.04, 1.14)	0.0001

[a] Main data set includes 6 studies from Ghana, Ethiopia, and India.

[b] For height, the outlier is the Nicaragua study; for weight, the outlier is the Mexico study.

[c] Inversely proportional to the variance of the effect size.

[d] Excludes the Ethiopia study because the variance of its effect size could not be estimated.

set with weights proportional to sample sizes were considered the main results on the effect of QPM on child growth. The results indicate that consumption of QPM instead of CM leads to an 8% (95% CI: 4-12%, p = 0.0014) increase in the rate of growth in height and a 9% (95% CI: 4-12%, p = 0.0019) increase in the rate of growth in weight in infants and young children with mild to moderate undernutrition from populations in which maize is a significant part of the diet. The comparable results for height and weight suggest that for the populations represented by these studies, the effect of QPM is largely an effect on growth in height, with the increase in growth in weight reflecting the increased growth in height.

The estimated summary effect sizes and confidence intervals were robust to alterative formulations of weights and methods for calculating the confidence interval. The outlying Mexico and Nicaragua studies generally had little effect on the summary effect size, as their study characteristics resulted in the studies having relatively low weights in the meta-analyses. Inclusion of the outliers did increase the width of confidence intervals obtained from bootstrapping; however, in all cases, a significant positive effect of QPM on growth was observed. Sensitivity to studies in the main data set was also evaluated by leaving one study out at a time and repeating the meta-analyses. However, the results again were robust to the inclusion or exclusion of individual studies.

IV. DISCUSSION

A. Use of results to assess economic impact

Methods have been developed to evaluate the ex ante economic impact of biofortified crops by estimating an improved crop's impact on disability-adjusted life years (DALYs) in target populations [4, 11]. These methods require an established link between improved nutrient intakes and nutritional or health outcomes. In this analysis, we quantify an effect of improved protein quality, achieved through higher levels of essential amino acids in maize, on child growth. Growth faltering is a significant problem throughout the developing world [29, 30], and its impact on performance and productivity throughout the life course has been documented [31]. The results in this paper are the first step in evaluating the potential economic impact of QPM by establishing and quantifying a link between use of the improved crop and nutritional outcomes.

B. Proposed effect size and use of bootstrap

In meta-analyses of two-group studies to assess a treatment effect, the difference between the mean responses in the two groups, rather than their ratio, is typically used as the effect size [32]. This difference of means may be standardized using the pooled within-group standard deviation. However, in the studies under consideration here, the difference of means could depend on study duration and age of children in the study. If there is a positive effect of QPM on child growth, studies of longer duration may have larger mean differences between the two treatment groups. Likewise, as growth rates decrease with age, studies with older subjects may have smaller mean differences. In addition to its meaningful interpretation as a relative growth rate, the effect size developed for this analysis removes the effect of child age and study duration in the comparison of QPM relative to CM. It also did not depend on any within-treatment standard errors. This new effect size can be used in a wider range of applications whenever the relative rate or percent change of an outcome in a treatment group compared with a control group has a meaningful interpretation.

The use of bootstrapping to construct a confidence interval for the summary effect size also offered several advantages. It was not necessary to know within-group standard errors for all studies or to approximate variances of individual effect sizes. Also, unlike the asymptotic confidence intervals considered in this study, the bootstrap percentile confidence intervals took into account between-study variation as well as within-study variation. In these meta-analyses, variation among studies is expected as the included studies represent different populations, ages, and cultures with different diets, child feeding practices, and other factors.

C. Methodological recommendations for future studies

The experience from the efficacy and effectiveness studies on QPM to date allows the formulation of several recommendations for future community-level evaluations of QPM or other biofortified crops. These studies should distinguish between efficacy and effectiveness, i.e., they should follow a methodology that separates the biological and non-biological effects of the biofortified crop. For a new biofortified crop, an efficacy study should be conducted prior to an effectiveness study to quantify the biological impact of the improved crop prior to evaluating the impact of other potentially confounding factors in the household or community. Monitoring of potential confounders in effectiveness studies will be useful to assess the impact of a new crop. Total food intake, not limited to foods made with the biofortified crop, is particularly important, as the biofortified crop will primarily have impact if a target individual consumes foods with improved nutritional quality in an otherwise nutritionally deficient diet.

Community-level studies can be randomized at the individual, household, or community level. The level of randomization affects the statistical power of the study and should be considered when determining the sample size and data analysis plan. Particularly in the case of community-level studies on QPM, other outcomes besides anthropometry should be considered as biofortified foods could have benefits beyond improved growth. These studies should be double-blinded whenever possible to minimize bias. Appropriate ethical practices, standard for human subjects research, should also be followed. In particular, approval by an institutional review board and informed consent from all participating subjects (or their guardians) should be obtained prior to the commencement of a study.

V. CONCLUSIONS

This is the first systematic review of efficacy and effectiveness studies on a crop that has been genetically improved for nutritional quality. Meta-analyses of these studies indicate a positive effect of QPM on growth of young children. Specifically, consumption of QPM instead of CM varieties leads to an 8% (95% CI: 4-12%) increase in the rate of growth in height and a 9% (95% CI: 4-12%) increase in the rate of growth in weight in infants and young children with mild to moderate undernutrition in populations where maize is a significant part of the diet. These results were robust to alternative methods of determining the summary effect size and its statistical significance and can be used to estimate the potential impact of the technology on target populations. QPM

can serve as a model for other biofortification efforts, and in particular, the conceptual framework and methodologies for impact assessment are directly applicable to other biofortified crops.

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