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Ariel F. Kay July 31, 2019

Association between national mandatory flour fortification legislation and anemia prevalence among children 24-59 months of age: Findings from Demographic and Health Surveys across 18 countries between 2015 and 2018

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2016

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Master of Public Health
in Global Epidemiology
2019

Abstract

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By Ariel F. Kay

Objectives: To determine whether there is an association between anemia prevalence in children aged 24-59 months and national mandatory flour fortification legislation.

Design: We conducted an ecologic analysis using retrospective, cross-sectional, population-based, multi-country Demographic and Health Surveys from 2015 through 2018. National-level flour fortification legislation was applied as individual-level exposure. Anemia was defined by hemoglobin concentrations under 11.0 g/dL. Crude and adjusted prevalence odds ratios (cPOR & aPOR) and 95% confidence intervals (CI) were estimated using logistic regression analysis, accounting for complex survey design.

Setting: Demographic and Health Surveys, conducted using two-stage sampling design, from 18 countries.

Participants: Children between 24 and 59 months of age residing in the selected countries whose mothers were interviewed and who were tested for hemoglobin (n=53,576).

Results: In countries with national mandatory flour fortification legislation, 48.72% of children were anemic compared to 45.88% in countries without such legislation. Residence in a country with mandatory flour fortification legislation was associated with a 12% increased prevalence odds of anemia among children aged 24-59 months (cPOR=1.12; 95% CI: 1.05, 1.20). However, after adjusting for potential confounding due to country of residence and interactions with urban-rural residence and education, the association was no longer significant (aPOR: 0.96, 95% CI: 0.73, 1.26).

Conclusions: Our study suggests that nationally mandated flour fortification legislation is not associated with child anemia prevalence. The cross-sectional nature of our study design limits our ability to make a causal inference; our findings are hypothesis-generating. Longitudinal studies are needed to examine fortification policy and childhood anemia.

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Conclusions: Our study suggests that nationally mandated flour fortification legislation is not associated with child anemia prevalence. The cross-sectional nature of our study design limits our ability to make a causal inference; our findings are hypothesis-generating. Longitudinal studies are needed to examine fortification policy and childhood anemia.

INTRODUCTION

Anemia is a condition characterized by a deficiency in healthy red blood cells or low levels of hemoglobin in the blood, resulting in a diminished capacity of the blood to transport oxygen throughout the body (1). The global prevalence of anemia in children aged 6-59 months has been estimated at 43%, or 273 million children (2). Children under five years of age experience the greatest prevalence and severity of anemia across all age groups in the global population, and have seen the least improvement in anemia prevalence from 1990 to 2010 (2-4). Childhood anemia has been associated with poor psychomotor development and cognitive function in infants (5-7), and with behavioral alterations (8), poor immune functioning (9, 10), impairment in intelligence (5), and reduced work capacity (11). The magnitude of morbidity associated with anemia has severe repercussions on social and economic development, with an estimated lifetime cost associated with iron deficiency anemia (IDA) in children aged 6-59 months of 8.3 million disability-adjusted life years and 24 billion USD lost in production, or 1.3% of the gross domestic product, annually (12). By 2013, IDA was the leading global cause of years lost due to disability in children and adolescents aged 0-19 years (13). Additionally, anemia disproportionately affects lower and middle income countries, with 89% of the burden in developing countries, and all-cause anemia-attributable mortality as high as 6.4% and 7.3% in Africa and Asia, respectively (14, 15).

While anemia has a multifactorial origin, the three most significant independent causes globally include iron deficiency, hemoglobinopathies, and malaria (3, 16). IDA has been attributed to approximately 42% of cases of anemia in children under 5 years of age (4). Nutritional anemias, such as IDA, may be caused from a lack of dietary diversity, poor bioavailability of iron, and from periods of high nutrient utilization, placing children at increased susceptibility as they experience periods of rapid growth (17). Risk factors associated with anemia or low hemoglobin concentrations in children include age (18, 19), sex (19), stunting (18, 19), duration of breastfeeding (18), socioeconomic status (18-20), urban or rural residence (21), iron supplementation (22), use of bed nets (23, 24), and maternal factors including anemia (20, 25), education (20), BMI (19), and additionally, human development index (26).

Food fortification is a cost-effective and widespread population intervention that does not require education or behavioral change components in order to effectively mitigate nutritional anemias (22, 27). In 2009, the World Health Organization published recommendations on wheat and maize flour fortification to provide guidance on the addition of micronutrients including iron, folic acid, Vitamin B_{12}, Vitamin A, and zinc, with updated guidelines on maize flour fortification released in 2016 (28, 29). A meta-analysis based on two randomized controlled trials of children from 6 months to eight years of age showed that consumption of fortified maize flour or its products with iron and other vitamins and minerals led to a significant reduction in iron deficiency (RR: 0.53, 95% CI: 0.40-0.69), but had no significant impact on anemia, hemoglobin concentration, or IDA compared to unfortified maize flour or its products; however, these estimations were based on very-low quality of evidence (29, 30). An additional study not included in the meta-analysis showed that fortification of maize meal in children 6-59 months of age was associated with significant increases in mean child hemoglobin concentrations of 0.87 g/dL (95% CI: 0.28-0.92, $p<0.001$) and significant reductions in anemia prevalence (-23.4%, $p<0.001$) (31).

As of 2019, 84 countries have mandatory fortification legislation, defined as requiring at least iron or folic acid fortification, for fortified wheat flour (32). Of these, 62 countries mandate fortification of wheat flour only, 15 countries mandate both wheat and maize flour, 4 mandate wheat flour and rice, 2 countries mandate wheat flour, maize flour, and rice, and 1 country mandates fortification of rice only (32). Barkley et al. found that nationally mandated fortification of wheat or maize flour was associated with a 2.4% annual reduction in the odds of anemia prevalence among non-pregnant women, however, this evaluation was not undertaken in children (26). To further elucidate the impact of nationally mandated wheat flour fortification on child anemia prevalence, Pachon et al. conducted a systematic review evaluating the effectiveness of government-supported flour fortification programs on anemia and iron status in children under 15 years of age and women of reproductive age after at least 12 months of program implementation, finding that four of thirteen subgroups of children showed statistically significant reductions in anemia prevalence from pre-to-post fortification periods (33). Overall, limited and uncertain evidence exists on the association between nationally mandated flour fortification and reductions in anemia prevalence in children aged 24-59 months.

In this study, we aimed to determine whether anemia prevalence in children aged 24-59 months differed between countries that implemented mandatory wheat or maize flour fortification legislation versus countries that did not have mandatory wheat or maize flour fortification legislation.

METHODS

Study Population

Datasets for this secondary data analysis were obtained from 19 nationally representative cross-sectional surveys conducted by The Demographic Health Survey (DHS) Program and in-country partners, although one survey from Malawi was later excluded as it did not meet the criteria of our exposure variable. Included countries with mandatory flour fortification legislation were Benin, Burundi, Jordan, Nepal, Senegal, South Africa, Tanzania, Uganda, and Zimbabwe; countries with no mandatory flour fortification legislation included Albania, Angola, Armenia, Ethiopia, Haiti, Maldives, Myanmar, Tajikistan, and Timor-Leste. Only publically available standard and continuous DHS surveys that conducted anemia testing in children and employed the most recent DHS-VII recode were eligible for inclusion. DHS recode files are created in order to standardize data across countries in a given DHS phase for comparison, including standardized variables and definitions, coding, weighting, and exclusion criteria (34). Child recode datasets were downloaded from each eligible country and concatenated into one large file for analysis. The concatenated dataset included all observations from each country for children under 5 years of age; however, we restricted our analysis to children 24 to 59 months of age. All children between 24 and 59 months of age residing in the selected countries whose mothers were interviewed and who were tested for hemoglobin were eligible to be included in the analysis. DHS surveys utilize a two-stage probability sample design allowing each survey to be representative at the national, regional, and residential level, with thorough sampling procedures described elsewhere (35). All individual-level data were de-identified prior to accessing the datasets. We were granted permission from the DHS Program to access DHS data files for each country used in this analysis.

Study Design

We applied an ecological approach to analyzing retrospective, cross-sectional, population-based, multi-national data by assuming that each child residing in a country with a national mandatory wheat or wheat and maize flour fortification legislation consumed fortified wheat or maize flour or their byproducts, while children residing in countries without such flour fortification policies did not consume any fortified wheat or maize flour or their byproducts. The presence of national mandatory wheat or wheat and maize flour fortification legislation was attributed to each child based on their country of residence. In order to conduct this analysis, we pooled all eligible surveys to conduct an individual-level meta-analysis (36).

Outcome Variable

Our main outcome of interest was child anemia status. In DHS surveys, hemoglobin testing is routinely conducted in children aged 6 to 59 months to estimate population-based childhood anemia prevalence (37, 38). Hemoglobin data was collected according to DHS protocol by trained enumerators using the Hemocue® Hb 201+ or 301+ system, with the full protocol detailed elsewhere (37, 39).

Hemoglobin concentrations were categorized according to cut-offs determined by the DHS program and based on WHO-recommended guidelines (37, 38). Among children 6-59 months of age, anemia was defined by DHS as none (≥11.0 g/dL), mild (10.0-10.9 g/dL), moderate (7.0-9.9 g/dL), and severe (<7.0 g/dL). For our analysis, we created a dichotomized variable for child anemia status categorized as yes (<11.0 g/dL) or no (≥11.0 g/dL).

Further, DHS datasets reported hemoglobin concentrations that were adjusted for residential altitudes greater than 1000 meters (40). Altitude adjustments are needed to account for variation in oxygen saturation of the blood, as higher altitudes result in lower oxygen saturation, and higher hemoglobin levels, of the blood (41). We preserved DHS-established altitude adjustments in our analysis. We also excluded biologically implausible child observations if adjusted hemoglobin concentrations were less than 4.0 g/dL or greater than 18.0 g/dL (41).

Primary Exposure Variable

Data on the primary exposure, i.e., country-level status of national mandatory wheat or wheat and maize flour fortification legislation, were extracted from the Global Fortification Data Exchange (GFDx), along with information on the date of mandate, the type and quantity of nutrients required by the policy, and the fortification quality (42). For the current study, we created a binary exposure variable based on whether a country had national mandatory wheat or maize flour fortification legislation. At least one flour type, wheat or maize flour, had to be mandated in order for a country to be classified as having fortification legislation. Ethiopia was the only survey that had voluntary fortification of wheat flour and was classified as not having mandatory fortification legislation for wheat or maize flour.

Among countries with mandatory fortification legislation, the duration of time spanning from the last day of DHS survey collection to the time when the national mandatory wheat or maize flour legislation took effect was calculated. Previous literature has defined the post-fortification period as occurring 12 months after fortification implementation (33). If DHS survey data collection in a country ended prior to reaching the post-fortification period, the country was defined as being in the pre-fortification period and classified in this analysis as not having had the national flour fortification legislation, as was the case with Haiti (43). Further, if DHS survey data collection spanned the pre-and-post-fortification periods, the survey was excluded from analysis, as was the case with Malawi (44). After excluding Malawi, a total of 18 surveys from unique countries were included in this analysis: 9 surveys had national mandatory wheat or wheat and maize flour fortification legislation, while 9 countries did not have national mandatory wheat or wheat and maize flour fortification.

Covariates

Based on an extensive literature review, we included the following covariates in our analysis.

Child Characteristics: We categorized child age into three categories: 24-35.9 months, 36-47.9 months, and 48-59.9 months. Child sex was classified as either male or female. DHS provided data on child height-for-age z-scores based on the 2006 WHO standards, so we created a dichotomous variable that defined stunting as <-2 standard deviations below the reference mean (45). Information on breastfeeding status was categorized in our dataset as: "ever breastfed, but not currently breastfeeding," "never breastfed," and "still breastfeeding." One survey collected information on the duration of breastfeeding in months rather than as a categorical variable, so we recoded that survey such that all children whose breastfeeding duration was less than their age were considered "ever breastfed, but not currently breastfeeding," and children whose duration of breastfeeding was equal to 0 were classified as “never breastfed.” Children whose age equaled the duration of breastfeeding (n=2), whose values were flagged by DHS as implausible (n=1), or whose response was “don’t know” (n=1) were excluded from variable-specific analyses. Data on child consumption of iron pills, sprinkles with iron, or iron syrup in the 7 days prior to the survey were collected, with possible answers including: no, yes, or “don’t know.” All responses of “don’t know” were excluded from variable-specific analyses. Information on the type of mosquito bed net(s) the child slept under the night prior to the survey was available, with possible answers including: “no net,” “only treated nets,” “both treated and untreated nets,” and “only untreated nets.” Due to the small number of children who slept in both treated and untreated nets in the night prior to the survey, we recoded this variable to make it dichotomous: “no bed net use” or “any bed net use,” where “any bed net use” was defined as the child sleeping under any treated, untreated, or both treated or untreated bed nets.

Maternal Characteristics: Maternal education was classified as: no education, primary only, secondary only, or higher education. We created a dichotomous variable for maternal anemia based on adjusted hemoglobin values: yes (<12 g/dL) or no (≥12 g/dL); however, all women whose hemoglobin values were outside of 4.0-18.0 g/dL or who reported being pregnant were excluded from variable-specific analyses (37, 38, 41). Maternal body mass index (BMI) was characterized as: underweight (<18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25 – 29.9 kg/m^2), and obese (>30 kg/m^2) (46).

Other Characteristics: Residence was defined as either urban or rural. The DHS-created wealth index for rural and urban residence variable was a within-country variable created by splitting all interviewed households into five quintiles and taking residence into account (34). The United Nations Human Development Index (HDI) ranges in value from 0 to 1, with higher HDI scores representing higher levels of human development (47). HDI data specific to the year that DHS data collection started in each country was extracted for each country from the United Nations Development Programme Human Development Reports. HDI was categorized into four categories: low (<0.550), medium (0.550-0.699), high (0.700-0.799), and very high (≥0.800) (47). For descriptive purposes, country-specific surveys were categorized by level of significance of anemia as a public health problem by applying the following thresholds to anemia prevalence: <5% (no public health problem), 5–19.9% (mild public health problem), 20–39.9% (moderate public health problem), and ≥40% (severe public health problem) (48).

Statistical Analysis

All analyses were conducted in SAS 9.4 and used DHS sample design weights to account for complex survey design, following DHS guidelines (40, 49). Using weighted frequency procedures, we calculated the prevalence of anemia in each country and obtained 95% confidence intervals using the Taylor series linearization method for variance estimation. We conducted bivariate analyses to describe associations between possible covariates and national flour fortification legislation status and anemia status, independently. In order to account for the complex survey design, Rao-Scott Chi square tests were performed to test the significance between groups at $\alpha = 0.05$. We calculated crude prevalence odds ratios (cPOR) and 95% confidence intervals (CI) using unconditional logistic regression for the associations between fortification legislation and child anemia status, as well as with each of the possible covariates. Multivariable logistic regression was conducted for adjusted estimates, where all covariates were considered as possible effect measure modifiers, except country, which was examined as a potential confounder. We used this approach based on review of the literature. Each covariate was assessed for interaction using the likelihood ratio test and evaluated for collinearity. Standard collinearity assessment was incompatible with complex survey procedures in SAS 9.4, so we evaluated collinearity using correlation matrices. Based on collinearity assessment, HDI was unable to be considered in the fully adjusted model as it was perfectly predicted by country. All significant interaction terms were included in a fully parameterized model that accounted for fixed effects by country. We proceeded to conduct backwards elimination to create a reduced multivariable model, which included fixed effects by country and interaction with mandatory fortification legislation by wealth index, residence, and maternal education. Since wealth index was highly associated with both residence and maternal education, we dropped wealth index from the adjusted model. Our final reduced model used to estimate adjusted PORs (aPOR) and 95% CIs controlled for fixed effects by country, included interaction terms between mandatory fortification legislation and residence and mandatory fortification legislation and maternal education, and incorporated the lower order variables from the included interaction terms.

This study received a human subjects research exemption by the Emory University Institutional Review Board.

RESULTS

A total of 4,688 children residing in countries with mandatory flour fortification legislation and 4,702 children residing in countries without mandatory flour fortification legislation were excluded from analyses a priori due to missing adjusted hemoglobin values. Seventy-seven children were additionally excluded due to biologically implausible hemoglobin values. Our final dataset included information from 53,576 children across 18 countries between the years of 2015-2018. Out of the 18 included countries, nine countries implemented mandatory flour fortification legislation; among these, five countries mandated both wheat flour and maize flour, and four countries mandated wheat flour only (Table 1). None of the countries mandated fortification of maize flour only.

Overall, country-specific anemia prevalence among children ranged from 9.77% (95% CI: 7.22, 12.32) in Armenia to 65.40% (95% CI: 63.25, 67.55) in Benin. Pooled anemia prevalence, by mandatory fortification legislation status of countries, was significantly higher among countries with mandatory wheat or wheat and maize flour fortification legislation (48.72%; 95% CI: 47.74, 49.70) compared to countries with no mandatory national flour fortification legislation (45.88%; 95% CI: 44.55, 47.21) (p=0.0009) (Table 2).

The significance level of anemia as a public health problem was worse among countries with mandatory fortification legislation, as seven countries reached levels indicative of a severe public health problem, defined as anemia prevalence of at least 40%, and two countries reached levels indicative of a moderate public health problem, defined as anemia prevalence between 20-39.9%. Among countries without mandatory flour fortification policies, five countries experienced levels of anemia prevalence indicative of a severe public health problem, while two countries reached anemia prevalence thresholds indicative of a moderate and mild, defined as anemia prevalence between 5-19.9%, public health problem, respectively (Table 2).

Bivariate analyses were conducted to assess associations between national mandatory fortification legislation status and covariates of interest. All covariates, except for child age and wealth index, were associated with residence in a country with national mandatory fortification policy (Table 3). Our bivariate analyses also revealed significant associations between individual child anemia status and all covariates of interest (Table 4).

To better evaluate the effect of nationally mandated flour fortification policy on anemia prevalence in children aged 24-59 months, we conducted unadjusted and adjusted logistic regression analyses. In the unadjusted logistic regression model, residence in a country with mandatory fortification legislation was associated with a 12% increased prevalence odds of anemia among children aged 24-59 months (cOR=1.12; 95% CI: 1.05, 1.20). Collinearity assessment and backwards elimination revealed that type of residence and maternal education, independently, modified the relationship of the effect of mandatory fortification legislation on the prevalence odds of child anemia. In multivariable logistic regression, after adjusting for fixed effects by country and effect measure modification by residence type and education, the association between residing in a country with mandatory flour fortification policy and child anemia was no longer significant (aPOR: 0.96, 95% CI: 0.73, 1.26) (Table 5).

DISCUSSION

By linking pooled, individual-level child anemia status from 18 nationally representative, cross-sectional DHS surveys with information on nationally mandated flour fortification legislation status, we aimed to evaluate the association between nationally mandated wheat or wheat and maize flour fortification legislation on anemia prevalence in children aged 24-59 months of age. We found that residing in a country with mandatory flour fortification policy was associated with an increased prevalence odds of anemia in the target group; however, this association lost significance after controlling for country and effect measure modification by residency type and maternal education.

The choice of food vehicle, such as staple foods, processed foods, and condiments, for fortification plays a critical role in optimizing the potential impact on anemia prevalence. A review by Das et al. found that hemoglobin levels improved significantly in fortified processed foods and fortified staple foods, but the risk of anemia was significantly reduced only from consumption of fortified processed foods (50). Similarly, another systematic review with meta-analysis suggested that fortification of wheat or maize flour is not significantly associated with reductions in child anemia (30). However, existing evidence has proven inconsistent, with four of 13 subgroups of children assessed for changes in anemia prevalence following government-supported flour fortification implementation experiencing significant reductions in anemia prevalence (33). Taken together, our findings align with previous literature suggesting that anemia prevalence may not be significantly reduced by consumption of fortified staple foods, such as wheat and maize flour, regardless of whether a national legislation policy was in place.

Variability in design and implementation of flour fortification programs across countries may have resulted in ineffective, suboptimal national fortification programs being grouped with effective and optimally designed national fortification programs, thereby underestimating the possible measure of association of a well-implemented national flour fortification policy. Based on review of efficacy studies on iron-fortified foods and evaluation of wheat flour fortification programs in 78 countries, Hurrell et al. concluded that most flour fortification programs would have little impact on national anemia prevalence, as seen in our findings, due to the use of non-recommended, low-bioavailability forms of iron compounds in fortification programs (51). In fact, fortification programs in only nine of 78 countries were anticipated to positively improve population-level iron status (51). Of the countries whose flour fortification policies were evaluated in the study by Hurrell et al., five of these were also included in our analysis. Among these five countries, the country of Jordan was the only one with an implemented legislation policy judged to have an expected positive impact on iron status in the population.

Further, among countries with a nationally mandated flour fortification policy included in our analysis, the proportion of fortified flour, population coverage, quantity and type of added micronutrients, and choice of iron compound varied across countries and by type of flour. For example, the proportion of wheat flour fortified in a given country ranged from 20% in Burundi to 100% in both Senegal and Uganda (42). Despite a national mandatory policy to fortify maize flour, the proportion of maize flour fortified in Burundi, Tanzania, and Uganda was estimated to be 0% (42). Population coverage of fortified flour has also been shown to vary by region and country (52). Among countries included in this analysis, Uganda achieved 11% population coverage of fortified wheat flour and 92% coverage of fortified maize flour, while Senegal achieved approximately 82% population coverage of wheat flour (42). A 2019 study comparing national wheat and maize flour fortification standards with WHO-recommended guidelines in 73 countries with mandatory fortification revealed that 63% of country standards included at least one of the WHO-recommended compounds for national wheat and/or maize flour fortification; however, WHO-recommended fortification levels of iron, zinc, and vitamin B_{12} were met in less than 50% of national standards (53). In summary, the Hurrell et al. and Bobrek et al. studies support our findings and suggest that national fortification programs need to revise their flour fortification guidelines in order to effectively implement programs and achieve a meaningful population-level effect on iron status (51, 53).

Interestingly, the significance level of anemia as a public health problem was most concerning among countries with mandatory fortification legislation. Particularly if country-specific childhood anemia prevalence is correlated with anemia prevalence in the general population, it may be possible that countries with higher childhood anemia prevalence are more inclined to institute national fortification policies to address this public health issue, compared to countries where anemia among children is not seen as a significant public health problem. Future studies may benefit in further exploring this observation.

This is the first study to evaluate the effect of nationally mandated wheat or wheat and maize flour fortification legislation on child anemia prevalence using multi-national, pooled individual-level child anemia data from DHS surveys. Due to the sampling design utilized by DHS, each country survey was nationally, regionally, and residentially representative. By pooling data across all eligible countries, we were able to analyze individual-level child anemia data, rather than using country prevalence, and create a large sample size of 53,576 children between 24 and 59 months of age; both of these considerations could be expected to improve the statistical precision of our estimate. Most of the DHS data collected was based on self-report or recall; however, verification of information was conducted when possible, and the testing of biomarkers, including height, weight, and hemoglobin concentrations, was administered by trained enumerators.

Our analysis included several limitations due to its cross-sectional and ecological approach, in which we attributed national-level fortification policy to individual-level consumption of fortified wheat or wheat and maize flour. Since we used an ecological approach, most covariates, except for country, were associated only with child anemia and not with national-level flour fortification policy, thereby limiting our ability to adjust for possible confounding variables. Given the cross-sectional design, we are unable to infer a causal relationship between residing in a country with a mandatory flour fortification policy and prevalence of child anemia.

Another major limitation of our study includes the assumption that children who reside in a country with mandatory national flour fortification legislation consumed fortified wheat or wheat and maize flour, or its byproducts. Many studies elucidate flaws in this assumption, suggesting that child consumption of wheat or maize flour varies substantially by age, country, and type of residence (54-56). The WHO-UNICEF Technical Expert Advisory Group on Nutrition Monitoring, along with other global nutrition organizations, have recommended the inclusion of household fortification coverage indicators in DHS-8, including consumption patterns and coverage of fortifiable wheat flour and food vehicles (57). This update to the DHS questionnaire would allow future analyses to overcome inherent limitations of an ecological study design by linking individual-level fortified food consumption with individual-level anemia status information. In the absence of robust data on fortification coverage in the country as well as individual-level data on fortified flour consumption, context-specific consumption patterns should be analyzed and accounted for in future studies to better assess the true measure of association.

While hemoglobin concentrations are used to characterize the prevalence of anemia in populations and can be used to draw inferences about population-level iron status, hemoglobin measures alone cannot distinguish IDA, one type of nutritional anemia, from other anemias (38). IDA has been attributed to approximately 42% of cases of anemia in children under 5 years of age (4). Additional biomarkers should be collected to differentiate IDA from nutritional anemias unrelated to iron, infectious diseases, such as malaria, hookworm, and schistosomiasis, or hemoglobinopathies (38). Individual-level biomarkers for HIV status and inflammation would also aid in improved population estimation of anemia prevalence (58, 59). Since standard and continuous DHS surveys do not routinely collect HIV or malarial status in children 24-59 months of age, we were unable to adjust for these in our analyses. Among included countries, only four of 18 countries had no endemic malaria, with only one non-malaria endemic country implementing mandatory flour fortification legislation. Consequently, we were unable to control for country-specific endemic malaria status as was done in a previous effectiveness study on nationally mandated flour fortification policies (26). Overall, a number of unaccounted-for variables may be masking the true effect of mandatory flour fortification legislation on child anemia prevalence.

Our study adds to the limited and uncertain literature evaluating the effectiveness of mandated flour fortification programs on anemia prevalence in children, and suggests that nationally mandated flour fortification legislation is not associated with child anemia prevalence. Countries should improve the design and implementation of their fortification programs to optimize program effectiveness. Meanwhile, efforts to mitigate anemia should remain multifaceted to address the diverse disease origins and should incorporate both population-level and individual-level strategies, including the improvement of dietary diversity and environmental health, treatment of infectious diseases, iron supplementation, and better access to health care.

Our findings are hypothesis-generating and should be explored by future studies. To overcome the limitations of the presented analysis, future studies should account for differences in context-specific consumption patterns and characteristics, including coverage, of each country's fortification program in order to more accurately describe the effect of nationally mandated flour fortification programs on child anemia prevalence. Future studies may also benefit from measuring and adjusting for anemia-related biomarkers, utilizing a longitudinal analysis design that allows for causal inference, and incorporating child-level data on consumption of fortified flour.

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TABLES

Table 1. Nutrients in wheat and maize flour fortification, year of mandate, and flour fortification quality by country and type of flour among selected countries with mandatory fortification legislation, Global Fortification Data Exchange (42) , 2019

	Wheat Flour				**Maize Flour**			
Country	**Nutrient**	**Quantity (mg/kg)**	**Year Mandated**	**Quality***	**Nutrient**	**Quantity (mg/kg)**	**Year Mandated**	**Quality***
Benin	Iron	60.00	2010	90%	N/A	N/A	N/A	N/A
	Folate (B_9)	2.50						
Burundi	Zinc	88.00	2015	20%	Niacin (B_3)	30.00	2015	0%
	Niacin (B_3)	60.00			Zinc	29.00		
	Iron	30.00			Iron	20.00		
	Thiamin (B_1)	9.80			Thiamin (B_1)	6.50		
	Riboflavin (B_2)	6.60			Vitamin B_6	5.00		
	Vitamin B_6	6.50			Riboflavin (B_2)	4.00		
	Folate (B_9)	2.30			Folate (B_9)	1.20		
	Vitamin A	1.00			Vitamin A	1.00		
	Vitamin B_{12}	0.02						
Jordan	Niacin (B_3)	35.00	2008	90%	N/A	N/A	N/A	N/A
	Iron	33.97						
	Zinc	20.08						
	Calcium	14.15						
	Vitamin B_6	3.62						
	Riboflavin (B_2)	3.60						
	Thiamin (B_1)	2.89						
	Folate (B_9)	1.52						
	Vitamin A	1.50						
	Vitamin B_{12}	0.01						
	Vitamin D	0.01						

Table 1 (continued)

	Wheat Flour				Maize Flour			
Country	**Nutrient**	**Quantity (mg/kg)**	**Year Mandated**	**Quality***	**Nutrient**	**Quantity (mg/kg)**	**Year Mandated**	**Quality***
Nepal	Iron	60.00	2011	20%	N/A	N/A	N/A	N/A
	Folate (B_9)	1.50						
	Vitamin A	1.00						
Senegal	Iron	60.00	2009	100%	N/A	N/A	N/A	N/A
	Folate (B_9)	2.50						
South Africa	Iron	35.00	2003	40%	Iron	35.00	1972	80%
	Niacin (B_3)	23.68			Niacin (B_3)	25.00		
	Zinc	15.00			Zinc	15.00		
	Vitamin B_6	2.63			Vitamin B_6	3.13		
	Thiamin (B_1)	1.94			Thiamin (B_1)	2.19		
	Vitamin A	1.79			Vitamin A	2.09		
	Riboflavin (B_2)	1.78			Folate (B_9)	2.00		
	Folate (B_9)	1.43			Riboflavin (B_2)	1.69		
Tanzania	Niacin (B_3)	57.50	2011	54%	Zinc	22.50	1975	0%
	Iron	40.00			Iron	15.00		
	Zinc	40.00			Folate (B_9)	1.50		
	Thiamin (B_1)	10.00			Vitamin B_{12}	0.01		
	Vitamin B_6	6.50						
	Riboflavin (B_2)	5.75						
	Folate (B_9)	3.00						
	Vitamin A	1.75						
	Vitamin B_{12}	0.02						

Table 1 (continued)

	Wheat Flour				**Maize Flour**			
Country	**Nutrient**	**Quantity (mg/kg)**	**Year Mandated**	**Quality***	**Nutrient**	**Quantity (mg/kg)**	**Year Mandated**	**Quality***
Uganda	Niacin (B_3)	60.00	2005	100%	Zinc	30.00	2011	0%
	Zinc	60.00			Niacin (B_3)	20.00		
	Iron	30.00			Iron	15.00		
	Thiamin (B_1)	9.80			Riboflavin (B_2)	2.00		
	Riboflavin (B_2)	6.60			Thiamin (B_1)	2.00		
	Vitamin B_6	6.50			Vitamin A	1.00		
	Folate (B_9)	2.30			Folate (B_9)	0.50		
	Vitamin A	1.00						
	Vitamin B_{12}	0.02						
Zimbabwe	Niacin (B_3)	50.00	1973	40%	Zinc	40.00	1973	43%
	Iron	40.00			Niacin (B_3)	25.00		
	Zinc	40.00			Iron	20.00		
	Thiamin (B_1)	9.00			Thiamin (B_1)	4.50		
	Vitamin B_6	6.00			Riboflavin (B_2)	3.00		
	Riboflavin (B_2)	6.00			Vitamin A	1.50		
	Folate (B_9)	2.00			Folate (B_9)	1.30		
	Vitamin A	1.50						
	Vitamin B_{12}	0.02						

*Flour fortification quality refers to the percentage of flour fortified in the selected country

Table 2. Prevalence of anemia and significance level of public health problem among children 24 to 59 months of age across 18 countries, by country and national mandatory fortification legislation status of wheat or wheat and maize flour, Demographic and Health Surveys, 2015-2018

Country	Total Number of Children	Number of Children with Anemia	Weighted Prevalence (%) of Anemia*	95% Confidence Interval for Prevalence (%) of Anemia*†	Public Health Problem‡
Mandatory Fortification Legislation§					
Benin‖	3,546	2,324	65.40	(63.25, 67.55)	Severe
Burundi¶	3,477	1,878	56.06	(53.73, 58.39)	Severe
Jordan‖	5,811	1,766	28.91	(26.84, 30.97)	Moderate
Nepal‖	1,372	580	43.34	(39.98, 46.69)	Severe
Senegal‖	6,132	4,167	65.22	(63.33, 67.11)	Severe
South Africa¶	550	320	58.65	(52.80, 64.50)	Severe
Tanzania¶	4,915	2,360	48.07	(45.99, 50.16)	Severe
Uganda¶	2,515	1,137	43.20	(40.50, 45.90)	Severe
Zimbabwe¶	2,702	784	28.86	(26.83, 30.90)	Moderate
Total	31,020	15,316	48.72	(47.74, 49.70)	Severe
No Mandatory Fortification Legislation§					
Albania	1,324	284	18.74	(15.75, 21.73)	Mild
Angola	3,567	2,056	57.87	(54.93, 60.80)	Severe
Armenia	908	93	9.77	(7.22, 12.32)	Mild
Ethiopia**	5,104	2,699	50.07	(46.48, 53.66)	Severe
Haiti††	3,246	1,937	60.65	(58.18, 63.11)	Severe
Maldives	1,323	596	47.58	(43.69, 51.48)	Severe
Myanmar	2,392	1,126	50.75	(47.88, 53.62)	Severe
Tajikistan	3,483	1,132	33.44	(30.78, 36.09)	Moderate
Timor-Leste	1,209	393	34.54	(30.73, 38.35)	Moderate
Total	22,556	10,316	45.88	(44.55, 47.21)	Severe

Table 2 (continued)

[*]Weighted anemia prevalences were calculated using the Demographic and Health Surveys sample design weights to account for complex survey design, following DHS guidelines (40)

[†]Confidence intervals were calculated using Taylor series linearization method for variance estimation

[‡]Country-specific surveys were categorized by level of significance of anemia as a public health problem by applying the following thresholds to anemia prevalence: <5% = no public health problem; 5–19.9% = mild public health problem; 20–39.9% = moderate public health problem; ≥40% = severe public health problem (48)

§Data on legislation status by country was extracted from the Global Fortification Data Exchange (42)

[||]Nationally mandated legislation for wheat flour fortification (42)

[¶]Nationally mandated legislation for wheat flour and maize flour fortification (42)

**Employs voluntary wheat flour fortification nationally (42)

[††]Wheat flour fortification became mandatory in February 2017, two months prior to the end of the Haiti Demographic and Health Survey data collection in April 2017 (42, 43)

Table 3. Descriptive characteristics and bivariate analyses of children 24 to 59 months of age by national mandatory fortification legislation status of wheat or wheat and maize flour across 18 countries, Demographic and Health Surveys, 2015-2018

Characteristics	**Total Children**		**Mandatory Fortification Legislation***		**No Mandatory Fortification Legislation***		**Rao Scott P-Value**	**Crude POR†**	**95% CI‡**
	n	**Percent†**	**n**	**Percent†**	**n**	**Percent†**			
Child Anemia§									
Yes	25,632	47.52	15,316	48.72	10,316	45.88	0.0009	1.12	(1.05, 1.20)
No	27,944	52.48	15,704	51.28	12,240	54.12		Referent	
Age of Child (months)									
24-35.9	18,149	33.57	10,559	33.83	7,590	33.21	0.11	1.01	(0.96, 1.06)
36-47.9	17,719	33.13	10,096	32.67	7,623	33.75		0.96	(0.91, 1.01)
48-59.9	17,708	33.30	10,365	33.49	7,343	33.05		Referent	
Sex of Child									
Male	27,316	51.24	15,721	50.69	11,595	52.00	0.02	Referent	
Female	26,260	48.76	15,299	49.31	10,961	48.00		1.05	(1.01, 1.10)
Child Stunting‖									
Yes	22,355	41.27	14,861	47.06	7,494	33.35	<0.0001	1.78	(1.65, 1.92)
No	31,221	58.73	16,159	52.94	15,062	66.65		Referent	
Breastfeeding Status									
Ever breastfed, not currently	47,944	89.30	28,043	90.76	19,901	87.31	<0.0001	1.08	(0.94, 1.25)
Never	2,111	3.81	1,207	3.74	904	3.90		Referent	
Still	3,425	6.89	1,674	5.50	1,751	8.80		0.65	(0.54, 0.78)
Iron Supplements¶									
Yes	4,321	10.70	2,084	8.45	2,237	14.38	<0.0001	0.55	(0.49, 0.62)
No	39,600	89.30	25,630	91.55	13,790	85.62		Referent	
Child Bed Net**									
None	16,740	50.35	10,311	45.49	6,429	61.79	<0.0001	Referent	
Yes (treated and/or untreated)	16,961	49.65	12,976	54.51	3,985	38.21		1.94	(1.75, 2.15)

Table 3 (continued)

Characteristics	Total Children		Mandatory Fortification Legislation*		No Mandatory Fortification Legislation*		Rao Scott P-Value	Crude POR[†]	95% CI[‡]
	n	**Percent[†]**	**n**	**Percent[†]**	**n**	**Percent[†]**			
Maternal Education[††]									
None	16,897	31.38	10,521	32.96	6,376	29.22	<0.0001	Referent	
Primary	16,019	30.59	9,462	32.20	6,557	28.38		1.01	(0.90, 1.12)
Secondary	15,922	29.13	8,352	25.99	7,570	33.42		0.69	(0.60, 0.79)
Higher	4,737	8.91	2,053	8.86	2,053	8.97		0.88	(0.74, 1.03)
Maternal Anemia[‡‡]									
Yes	31,154	57.03	18,603	58.80	12,551	54.61	<0.0001	1.19	(1.11, 1.27)
No	22,422	42.97	12,417	41.20	10,005	45.39		Referent	
Maternal BMI[§§]									
Underweight	3,839	9.27	1,687	7.73	2,152	11.18	<0.0001	0.71	(0.64, 0.78)
Normal	24,210	62.33	13,414	61.73	10,796	63.08		Referent	
Overweight	7,913	19.40	4,430	20.16	3,483	18.46		1.12	(1.02, 1.22)
Obese	3,764	9.00	2,393	10.38	1,371	7.29		1.46	(1.29, 1.64)
Residence									
Urban	18,958	35.57	12,138	39.99	6,820	29.53	<0.0001	Referent	
Rural	34,618	64.43	18,882	60.01	15,736	70.47		0.63	(0.55, 0.71)
Wealth Index for urban/rural[‖‖]									
Poorest	14,832	23.01	8,476	23.45	6,356	22.41	0.51	1.04	(0.93, 1.16)
Poorer	11,492	21.66	6,657	21.22	4,835	22.26		0.94	(0.87, 1.03)
Middle	10,208	19.91	5,989	20.00	4,219	19.78		Referent	
Richer	9,142	19.04	5,354	19.06	3,788	19.01		0.99	(0.91, 1.09)
Richest	7,881	16.38	4,523	16.27	3,358	16.54		0.97	(0.86, 1.10)
Human Development Index[¶¶]									
Low	31,637	60.74	23,287	76.25	8,350	39.53	<0.0001	14.2	(12.08, 16.70)
Medium	12,573	23.26	1,922	6.31	10,651	46.45		Referent	
High	9,366	16.00	5,811	17.44	3,555	14.02		9.16	(7.62, 11.02)

Table 3 (continued)

POR, Prevalence Odds Ratio; CI, Confidence Interval; BMI, Body Mass Index

*Data on legislation status by country was extracted from the Global Fortification Data Exchange (42)

†Weighted tabulations were calculated using the Demographic and Health Surveys sample design weights to account for complex survey design, following DHS guidelines (40)

‡Confidence intervals were calculated using Taylor series linearization method for variance estimation

§Among children, anemia was defined as hemoglobin concentration <11.0 g/dL (37, 38)

||Stunting was defined as <-2 standard deviations below the reference mean, based on 2006 WHO standards (45)

¶Consumption of iron pills, sprinkles with iron, or iron syrup in the 7 days prior to the survey (34)

**Child slept under bed net the night prior to the survey (34)

††Highest education level attended by mother (34)

‡‡Among women, anemia was defined as hemoglobin concentration <12.0 g/dL (37, 38)

§§Maternal BMI was classified according to the following thresholds: underweight (<18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25 – 29.9 kg/m^2), and obese (>30 kg/m^2) (46)

|||| Within-country variable measuring household's cumulative living standard and created by splitting interviewed households into quintiles, factoring in residence (34)

¶¶Human Development Index ranges from 0-1, with 1 representing higher HDI scores. HDI is categorized as low (<0.550), medium (0.550-0.699), and high (0.700-0.799) (47)

Table 4. Descriptive characteristics and bivariate analyses of children 24 to 59 months of age by individual anemia status across 18 countries, Demographic and Health Surveys, 2015-2018

Characteristics	Total Children		Children with Anemia*		Children without Anemia*		Rao Scott P-Value	Crude POR†	95% CI‡
	n	Percent†	n	Percent†	n	Percent†			
Mandatory Fortification Legislation§									
Yes	31,020	57.77	15,316	59.23	15,704	56.45	0.0009	1.12	(1.05, 1.20)
No	22,556	42.23	10,316	40.77	12,240	43.55		Referent	
Age of Child (months)									
24-35.9	18,149	33.57	10,031	38.7	8,118	28.92	<0.0001	1.83	(1.74, 1.93)
36-47.9	17,719	33.13	8,484	33.41	9,235	32.87		1.39	(1.32, 1.47)
48-59.9	17,708	33.30	7,117	27.89	10,591	38.21		Referent	
Sex of Child									
Male	27,316	51.24	13,302	52.12	14,014	50.45	0.0028	Referent	
Female	26,260	48.76	12,330	47.88	13,930	49.56		0.94	(0.90, 0.98)
Child Stunting‖									
Yes	22,355	41.27	11,377	44.16	10,978	38.65	<0.0001	1.26	(1.19, 1.32)
No	31,221	58.73	14,255	55.84	16,966	61.35		Referent	
Breastfeeding Status									
Ever breastfed, not currently	47,944	89.30	22,815	88.63	25,129	89.91	<0.0001	1.05	(0.93, 1.19)
Never	2,111	3.81	948	3.68	1,163	3.93		Referent	
Still	3,425	6.89	1,807	7.7	1,618	6.17		1.33	(1.15, 1.55)
Iron Supplements¶									
Yes	4,321	10.70	1,921	9.82	2,400	11.53	<0.0001	0.84	(0.77, 0.91)
No	39,600	89.30	19,587	90.18	20,013	88.47		Referent	
Child Bed Net**									
None	16,740	50.35	8,906	49.53	7,834	51.29	0.02	Referent	
Yes (treated and/or untreated)	16,961	49.65	9,256	50.47	7,705	48.71		1.07	(1.01, 1.14)
Maternal Education††									
None	16,897	31.38	10,309	39.54	6,588	23.99	<0.0001	Referent	
Primary	16,019	30.59	7,795	31.28	8,224	29.96		0.63	(0.59, 0.68)
Secondary	15,922	29.13	6,173	24.03	9,749	33.75		0.43	(0.40, 0.47)
Higher	4,737	8.91	1,354	5.15	3,383	12.3		0.25	(0.23, 0.28)

Table 4 (continued)

Characteristics	Total Children		Children with Anemia*		Children without Anemia*		Rao Scott P-Value	Crude POR†	95% CI‡
	n	Percent†	n	Percent†	n	Percent†			
Maternal Anemia‡‡									
Yes	31,154	57.03	16,930	64.95	14,224	49.86	<0.0001	1.86	(1.77, 1.96)
No	22,422	42.97	8,702	35.05	13,720	50.14		Referent	
Maternal BMI‡‡									
Underweight	3,839	9.27	2,011	10.66	1,828	8.14	<0.0001	1.20	(1.10, 1.32)
Normal	24,210	62.33	11,330	65.25	12,880	59.95		Referent	
Overweight	7,913	19.40	3,055	16.64	4,858	21.65		0.71	(0.66, 0.76)
Obese	3,764	9.00	1,390	7.45	2,374	10.26		0.67	(0.60, 0.74)
Residence									
Urban	18,958	35.57	7,859	31.02	11,099	39.69	<0.0001	Referent	
Rural	34,618	64.43	17,773	68.98	16,845	60.31		1.46	(1.37, 1.56)
Wealth Index for urban/rural‖‖									
Poorest	14,832	23.01	7,874	25.47	6,958	20.78	<0.0001	1.26	(1.17, 1.36)
Poorer	11,492	21.66	5,608	22.67	5,884	20.74		1.13	(1.05, 1.21)
Middle	10,208	19.91	4,774	19.6	5,434	20.19		Referent	
Richer	9,142	19.04	4,157	18.09	4,985	19.9		0.94	(0.87, 1.01)
Richest	7,881	16.38	3,210	14.17	4,671	18.39		0.79	(0.73, 0.86)
Human Development Index¶¶									
Low	31,637	60.74	17,286	68.37	14,351	53.84	<0.0001	1.38	(1.29, 1.48)
Medium	12,573	23.26	5,607	22.24	6,966	24.18		Referent	
High	9,366	16.00	2,739	9.39	6,627	21.98		0.47	(0.42, 0.51)

POR, Prevalence Odds Ratio; CI, Confidence Interval; BMI, Body Mass Index

*Among children, anemia was defined as hemoglobin concentration <11.0 g/dL (37, 38)

†Weighted tabulations were calculated using the Demographic and Health Surveys sample design weights to account for complex survey design, following DHS guidelines (40)

‡Confidence intervals were calculated using Taylor series linearization method for variance estimation

§Data on legislation status by country was extracted from the Global Fortification Data Exchange (42)

‖Stunting was defined as <-2 standard deviations below the reference mean, based on 2006 WHO standards (45)

¶Consumption of iron pills, sprinkles with iron, or iron syrup in the 7 days prior to the survey (34)

**Child slept under bed net the night prior to the survey (34)

††Highest education level attended by mother (34)

‡‡Among women, anemia was defined as hemoglobin concentration <12.0 g/dL (37, 38)

Table 4 (continued)

§§Maternal BMI was classified according to the following thresholds: underweight (<18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25 – 29.9 kg/m^2), and obese (>30 kg/m^2) (46)

‖‖ Within-country variable measuring household's cumulative living standard and created by splitting interviewed households into quintiles, factoring in residence (34)

¶¶Human Development Index ranges from 0-1, with 1 representing higher HDI scores. HDI is categorized as low (<0.550), medium (0.550-0.699), and high (0.700-0.799) (47)

Table 5. Final adjusted model evaluating the association between national mandatory flour fortification legislation for wheat or wheat and maize flour and anemia status in children aged 24-59 months across 18 countries, Demographic and Health Surveys, 2015-2018

Full Model	**Adjusted POR***	**95% CI†**
Fortification + Country + Residence + Education + Fortification*Residence + Fortification*Education	0.96	(0.73, 1.26)

POR, Prevalence Odds Ratio; CI, Confidence Interval

*Weighted tabulations were calculated using the Demographic and Health Surveys sample design weights to account for complex survey design, following DHS guidelines (40)

†Confidence intervals were calculated using Taylor series linearization method for variance estimation