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Association between National Mandatory Flour Fortification Legislation and Anemia Prevalence Among Non-Pregnant Women of Reproductive Age: A Difference in Differences Approach

By

Kelsey Anne Rondini

Master of Public Health

Global Epidemiology

Vijaya Kancherla, PhD, MS

Committee Chair

Helena Pachón, PhD, MPH

Committee Member

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Kelsey Anne Rondini

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An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master in Public Health in Global Epidemiology

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Abstract

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Background: Anemia remains a public health concern for nearly one-third of the global population. Food fortification has shown to be a cost-effective, evidence-backed method to alleviate nutritional deficiencies, and recent literature indicates it may be a successful intervention to reduce anemia prevalence among non-pregnant women of reproductive age. Our multinational analysis attempted to determine if mandatory fortification policies have been effective in reducing anemia prevalence.

Methods: We utilized Demographic and Health Survey data from five countries: two with mandatory fortification legislation (exposed, including Nepal and Uganda) and three without (control, including Armenia, Ethiopia, and Haiti). We combined individual-level anemia status and covariates with country-level indicators before and after mandatory fortification policies were implemented and applied a difference in differences approach to estimate the differences in anemia prevalence between exposed and control countries, including means, odds, and corresponding confidence intervals (CIs).

Results: Our analysis included 68,484 non-pregnant women of reproductive age (WRA), with an average weighted anemia prevalence of 33.59% and 31.31% in pre- and post-fortification surveys, respectively. We found a decrease in anemia prevalence (mean difference estimate: -1.78, 95% CI: -2.93, -0.64) among countries with mandatory fortification policies (compared to not), between the time period before and after policy implementation, after controlling for age, body mass index, urban/ rural residential status, highest education level, oral contraceptive use, Human Development Index classification, and malaria endemicity.

Conclusions: Our results suggest a lower anemia prevalence among non-pregnant WRA after the implementation of mandatory fortification policies. Future research should expand this analysis to include more countries, across larger time periods, with an emphasis on incorporating accurate biomarker measurements to control for unmeasured confounders. Particular attention should also be paid to the individual- and/or household-level consumption of fortified products.

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CHAPTER I

BACKGROUND

Global Burden of Anemia

With decreases in red blood cell counts and cellular oxygen transport, symptoms of anemia manifest through fatigue, weakness, lethargy, and difficulty concentrating. These symptoms can directly impact work productivity and childhood development.[1,2] Anemia does not discriminate by demographic factors – it has been documented in both high- and low-income countries, among both sexes and various age groups,[1] and is classified as a moderate to severe public health concern in 142 countries globally based on greater than 20% prevalence.[5,6] In response to this continued global pervasiveness of anemia, the World Health Assembly announced in 2012 a call for a 50% decrease in anemia among WRA by 2025.[5]

Anemia, a condition defined by decreased functional hemoglobin or low levels of red blood cell mass, is commonly associated with global increases in morbidity and mortality. Anemia affects nearly one-third of the world's population, with its highest burden seen in women of reproductive age and young children. Figures have estimated a global prevalence of almost two billion individuals, with low- and middle-income countries accounting for approximately 90% of all anemia-related burdens. Causes of anemia range from genetic conditions to nutritional deficiencies, with iron-deficiency anemia as the predominant cause of anemia worldwide.[1,2] However, the proportion of anemia due to iron deficiency varies greatly by region, country, and subpopulation.[3] Recognizing and understanding the etiology and severity of individual anemia disease are essential, as interventions vary in efficacy by cause.[2,4]

The global burden of anemia is measured in numerous population-level surveys, including country-specific prevalence and disability measurements (most commonly years lived with disability [YLD]).[1] In 2013, anemia among all age groups contributed to approximately 62 million YLDs and 8% of all nonfatal health losses, a figure larger than morbidity associated with asthma, diabetes, and cardiovascular disease combined. Researchers admit this figure is likely an underestimate of anemia's true impact, but does provide insight to anemia's direct and indirect effects on life and productivity worldwide and within population groups.[1]

Etiology of Anemia

The etiology of anemia is multifactorial and complex, varying greatly depending on geographic location, sex, and age group. Significant burden is seen in sub-Saharan Africa and Southeast Asia, where severe anemia disease is geographically concentrated.[1] Women and children (both sexes, particularly under age 10 years) have historically experienced a disproportional burden of anemia, as anemia can be exacerbated during menstruation, pregnancy, immediately following childbirth, and times of cognitive development.[7] Estimates indicate while global anemia prevalence is approximately 27%, prevalence among non-pregnant women of reproductive age (WRA), pregnant women, and children are closer to 29%, 38%, and 43%, respectively.[8] Gender disparities are observed throughout adulthood, with most pronounced differences between men and women aged 20 through 34 years.[7]

Studies have shown anemia to be influenced by a number of individual- and country-level factors. Age, a common confounder in exposure-disease relationships, has been positively associated with anemia, as older women (40 – 49 years) have displayed higher odds of anemia than younger women (15-19).[9] Alternately, body mass index (BMI) has shown mixed associations with anemia. In one study, Chinese women of higher BMIs (most notably obese women) measured higher hemoglobin levels than their underweight counterparts and showed lower odds of anemia.[10] However, in another population-based study, there was no difference of odds of anemia between normal- and over-weight participants.[11] A study of 30 sub-Saharan countries indicated a negative association between anemia status and urbanicity, suggesting living in an urban area can decrease one's odds of anemia.[12] Reasons for this difference are not entirely clear, but in some countries it could be due to fortification coverage differences in rural and urban populations.[13] Education has been identified as a possible risk factor for anemia, particularly when comparing individuals with no education to those with primary or secondary level.[14] However, this relationship is not always evident: a 2017 study with pooled data from 10 countries indicated no significant association between education level and anemia.[9] Perhaps the strongest factor associated with decreases in anemia is oral contraceptive use: a study among Tanzanian women found a 56% reduction in odds of anemia among oral contraceptive users (compared to nonusers), with this reduction continuing as one's duration of oral contraceptive use extended.[15] Other factors shown to impact anemia disease burden include income, socioeconomic status, and certain comorbidities.[7,16]

Populations in low-income settings, including women and children, are particularly vulnerable to the effects of severe anemia. Barkley et al. indicated in their study that a country's Human Development Index (HDI), the United Nation's measure of country-level prosperity (incorporating standard of living, life expectancy, and economic and educational opportunities), was inversely related to anemia prevalence.[16] Additionally, a number of conditions often plaguing low-income communities, including malaria and HIV/AIDS, are associated with anemia. Research indicates the prevalence of malarial anemia has increased since 1990, with malaria causing 24.7% of anemia in west sub-Saharan Africa.[7] Malaria and anemia are inexplicably intertwined: studies have indicated a protective effect of malaria interventions on moderate anemia disease.[17]

Trends in Anemia Prevalence

Studies have estimated a decrease in anemia prevalence among all age groups since 1990, from 33.3% of the world's population in 1990 to 27.0% in 2013.[1,8] When considering population growth over that same time period, however, data instead indicate a global increase in annual anemia cases. Since 1990, there has been substantial progress in decreasing anemia prevalence and disability in Asia (South, East, and Southeast, with changes in absolute YLD rates of -50.5%, -44.8%, -31.7%, respectively) and Africa (Eastern sub-Saharan, with -21.1% change in absolute YLD rates). However, limited progress is evident in western and central sub-Saharan African countries (YLD rates have increased since 1990), where anemia burden is commonly concentrated within areas of high severe malaria disease prevalence.[1] Studies have indicated gender disparities in anemia have also changed over time, with women experiencing a widening increase in disease burden, compared to men of similar age, since 1990.[17] This is particularly seen in Southeast Asia, where decreases in anemia prevalence and YLD rates were primarily seen among men.[1]

Cost-benefit of Anemia Prevention

Economists from the World Bank Group, Results from Development Institute, and 1,000 Days estimate a 50% decrease in anemia prevalence among WRA by 2025 would cost US $12.9 billion, with nearly US $2.4 billion allocated towards iron and folic acid food fortification. Meeting this target would prevent 800,000 childhood deaths and 265 million cases of anemia worldwide. The cost-benefit of investing in anemia reduction is clear - economists estimate every US $1 invested in anemia disease prevention yields US $12 in returns.[5]

Food Fortification and Anemia

Fortification is a well-known, successful method to deliver micronutrients to vulnerable populations.[18] Given the global widespread use of both wheat and maize flour, fortification of these food products is commonly used to deliver iron, folic acid, vitamin B12, vitamin A, and zinc,[19] with 97 countries participating in either voluntary or mandatory flour fortification.[20] While mandatory fortification policies set national standards for nutrients at specific levels in specific food products, voluntary fortification policies provide food manufacturers with the choice to fortify their products or not. Given variation in company policies, food distribution, and food product preferences among populations, mandatory fortification has shown to be more effective in reaching a larger population of individuals and more vulnerable groups. Health benefits from fortification are also more likely to be sustained over time when mandatory policies are in place.[21] Dietary supplementation is another method to deliver micronutrients, however, this approach relies heavily on behavioral change, whereas fortification requires no additional actions on the part of the nutrient deficient individual. Prior literature has indicated an association between flour fortification and decreases in various health conditions, including neural tube defects, iron deficiency, and anemia, when World Health Organization fortification recommendations are followed.[23–25]

Current State of National Mandatory Flour Fortification Policies

Mandatory Policy Coverage

As of January 2020, the Global Fortification Data Exchange listed 83 countries with mandatory flour fortification policies in place.[20] Of those 83 countries, 63 have legislation for wheat flour alone, 14 for wheat and maize flour, 4 for wheat flour and rice, and 2 for wheat flour, maize flour, and rice.[26]

Process of Fortification

It is important to recognize that although fortification policies have been associated with positive health effects, such policies may not translate into actual application to the household level. There are a number of barriers associated with poor coverage of national fortification measures, including issues and deficiencies in knowledge, funding, laboratory resources, and economic demand of food products.[27] Additionally, a lack of foundational documents, including legislation, standards, and monitoring guidelines, can inhibit proper fortification policy implementation.[28] Establishing a mandatory fortification policy requires collaboration among nutrition experts, regulators, legislative leaders, and industry, with an overarching understanding of the population's dietary practices and food access.[21]

Although the World Health Organization and Food and Agriculture Organization provide guidelines on fortification measures, decisions regarding whether to require (i.e., mandatory) or allow (i.e., voluntary) fortification, which nutrients to fortify, and in what amounts lie exclusively with the country-specific governing agency. There are a number of factors to consider when developing a fortification plan, including which food products are commonly accessed and consumed by populations (e.g. salt, wheat flour) and the average quantities of such food products consumed.[9,18] Common iron fortification compounds for wheat and maize flour include NaFeEDTA, ferrous sulfate, ferrous fumarate and electrolytic iron; all have displayed improvements in population iron levels and decreasing anemia prevalence.[19]

Fortifying Flour with Iron to Prevent Anemia

Existing Research

Prior research established an association between flour fortification with iron, a decrease in anemia prevalence, and an increase in ferritin levels, even when adjusting for common comorbidities including malaria endemicity, HIV/AIDS prevalence, and a country's Human Development Index (HDI).[19] This effect is not seen equally across populations, however, with specific subgroups experiencing greater alleviation of disease burden over time than others. In a systematic review of national-level data among 12 countries with pre- and post-fortification data and 20 countries with no fortification measures in place, every year of flour fortification resulted in a 2.4% decreased odds of anemia among non-pregnant women (POR: 0.967, 95% CI: 0.975 – 0.978).[16] In a similarly designed study among non-pregnant women of reproductive age from 11 countries, a multivariate analysis controlling for maternal age, body mass index (BMI), HDI, and urban/rural status resulted in a marginal protective effect between mandatory flour fortification and decreased prevalence of anemia (aOR: 0.92, 95% CI: 0.860 – 0.999).[30]

Study Aim

Although the protective effects of flour fortification on anemia prevalence have been examined through multivariate regression models in previous studies,[16,30,31] our study aims to investigate this association using a difference in differences (DID) approach. The DID approach has been used to investigate the effects of other governmental policy changes[32] and has since been adopted by public health researchers. Utilizing the DID approach allows researchers to examine the mean outcome prevalence before and after the intervention, among and between exposed and unexposed groups (hence, difference in differences).

A literature search for prior use of DID approach to examine the relationship between flour fortification and anemia status yielded only one study: utilizing national data to investigate the impact of wheat flour fortification on anemia among pregnant women in India between 2002 and 2013. Results from this study varied greatly by region and population coverage of the fortified wheat product intervention.[33]

For the current study, we hypothesize that countries with a mandatory flour fortification policy in place will experience a greater decrease in anemia prevalence after implementation of the policy, compared to countries that remain without a similar policy over the same time period. We will use nationally representative data from the Demographic and Health Surveys of selected countries to test our hypothesis using DID approach and arrive at results that will have public health and policy implications.

CHAPTER II

MANUSCRIPT

Association between National Mandatory Flour Fortification Legislation and Anemia Prevalence Among Non-Pregnant Women of Reproductive Age: A Difference in Differences Approach

Kelsey A. Rondini, Amy Chai, Helena Pachón, and Vijaya Kancherla

Abstract

Background: Anemia remains a public health concern for nearly one-third of the global population. Food fortification has shown to be a cost-effective, evidence-backed method to alleviate nutritional deficiencies, and recent literature indicates it may be a successful intervention to reduce anemia prevalence among non-pregnant women of reproductive age. Our multinational analysis attempted to determine if mandatory fortification policies have been effective in reducing anemia prevalence.

Methods: We utilized Demographic and Health Survey data from five countries: two with mandatory fortification legislation (exposed, including Nepal and Uganda) and three without (control, including Armenia, Ethiopia, and Haiti). We combined individual-level anemia status and covariates with country-level indicators before and after mandatory fortification policies were implemented and applied a difference in differences approach to estimate the differences in anemia prevalence between exposed and control countries, including means, odds, and corresponding confidence intervals (CIs).

Results: Our analysis included 68,484 non-pregnant women of reproductive age (WRA), with an average weighted anemia prevalence of 33.59% and 31.31% in pre- and post-fortification surveys, respectively. We found a decrease in anemia prevalence (mean difference estimate: -1.78, 95% CI: -2.93, -0.64) among countries with mandatory fortification policies (compared to not), between the time period before and after policy implementation, after controlling for age, body mass index, urban/ rural residential status, highest education level, oral contraceptive use, Human Development Index classification, and malaria endemicity.

Conclusions: Our results suggest a lower anemia prevalence among non-pregnant WRA after the implementation of mandatory fortification policies. Future research should expand this analysis to include more countries, across larger time periods, with an emphasis on incorporating accurate biomarker measurements to control for unmeasured confounders. Particular attention should also be paid to the individual- and/or household-level consumption of fortified products.

Introduction

Anemia, a condition characterized by the lack of functional hemoglobin, is estimated to impact nearly two billion individuals globally.[1,2] Women of reproductive age and children are particularly vulnerable to morbidities associated with anemia, as the condition is exacerbated during times of menstruation, pregnancy, immediately following birth, and cognitive development. Anemia remains a moderate to severe public health concern in 142 countries, where population estimates exceed 20%.[5,6] While global prevalence of anemia has marginally decreased since 1990, there has been an overall increase in annual anemia cases over this same time period.[1,8] In response to these trends, the World Health Assembly announced a call for a 50% decrease in anemia among women of reproductive age by 2025, effectively preventing 800,000 childhood deaths and 26.5 million cases of anemia worldwide.[5]

Economists believe reaching this goal would cost nearly US $12.9 billion, and recommend allocating US $2.4 billion of that towards iron and folic acid fortification.[5] Fortification is a well-known, successful method used to deliver micronutrients and alleviate nutritional deficiencies,[18] with 97 countries currently participating in a voluntary or mandatory flour fortification program.[20] Flour fortification has previously been associated with decreases in anemia prevalence[16,30,31] and increases in ferritin levels,[24] when adjusting for known covariates. However, methods used to conduct these analyses and conclusions drawn from them are often limited by the data collection's cross-sectional design, with results differing by country and population groups.[33,34]

Our study aims to further investigate this relationship using a difference in differences approach.[32] We hypothesize non-pregnant women of reproductive age living in countries with mandatory flour fortification policies will experience a greater decrease in anemia prevalence between the time period before and after policy implementation, compared to those living in countries without such policies over the same time period.

Methods

Demographic and Health Surveys (DHS)

We utilized nationally representative, cross-sectional survey data from the Demographic and Health Surveys (DHS) Program. Given the two-stage cluster sampling methods of DHS,[35] sampling weights were applied to ensure individual data were representative of country estimates. We received permission to access DHS data, collected every five years, from a total of 24 countries.[30] To be included in the study, countries needed DHS survey (including anemia) data before and after 2011, our fortification legislation change year of interest. We examined each country's available datasets and included countries that met the following criteria: 1) DHS data from 2005-2006, 2) DHS data from 2015-2017, and 3) anemia prevalence information for both survey years. We selected 2005-2006 as this is the last survey period before 2011, and 2015-2017 as it is the earliest survey period after 2011. To avoid any country-level confounding by year of policy change, our exposed group only included countries which enacted fortification legislation in 2011. We used these years (2005-2006 and 2015-2017) so that the period before and after fortification was not variable in our analysis for countries studied. In total, our analysis included DHS data from five countries: two with mandatory fortification legislation for flour fortification with several nutrients that contribute to hemoglobin synthesis (e.g. iron, copper, zinc, folate, and vitamins B12, B2 (riboflavin), B6, B1 (thiamin), A, and E)[36] (Nepal and Uganda) and three without such mandatory flour fortification legislation (Armenia, Ethiopia, and Haiti).

Study Design

Our study population included non-pregnant women of reproductive age (WRA, defined as between 15 and 49 years of age) in the selected countries (Nepal, Uganda, Armenia, Ethiopia, and Haiti) which met our study criteria detailed in the previous paragraph. Since individual-level consumption of flour products is not collected by DHS, our study relied on the assumption that all individuals in mandatory fortification countries consumed such fortified products, while individuals in non-mandatory fortification countries did not. Our sample included individuals with anemia classification (Not Anemic or Mild, Moderate, or Severely Anemic) or altitude-adjusted hemoglobin level measurement (where Hb < 12 g/dl is considered anemic). Biologically implausible hemoglobin levels (Hb < 4 or Hb > 18 g/dl) were set to missing, and those observations were kept if they had anemia classification data; otherwise, they were dropped. Our final sample contained 68,488 non-pregnant WRA with anemia status information. Our method is displayed in **Figure 1**.

In the DHS datasets provided, adjusted hemoglobin levels were classified as followed: “Severely Anemic” (4 < Hb < 8 g/dl), “Moderately Anemic” (8 < Hb < 11 g/dl), “Mildly anemic” (11 < Hb < 12 g/dl), and “Not Anemic” (Hb ≥ 12 g/dl). For our analysis, we dichotomized anemia status to anemic (where Hb < 12 g/dl) or not anemic, providing a binary outcome variable.

Primary exposure variable information, defined as having a mandatory fortification legislation policy or not, was gathered from the Global Fortification Data Exchange (GFDx).[20] Countries were categorized as being exposed if they enacted mandatory fortification legislation in 2011. Besides Haiti, all control countries lacked any form of mandatory fortification legislation. Since Haiti passed legislation in 2017, after the 2015-2016 DHS survey was conducted, it was still included as a control country in the analysis.

Covariates of interest were determined from previous literature,[9–12,15–17] and included age (categorized as 15-19, 20-34, and 35-49 years for descriptive purposes, and kept continuous for the analysis), body mass index (BMI, categorized as “Underweight” (<18.5 kg/m^2), “Normal Weight” (18.5 – 24.9 kg/m^2), “Overweight” (25 – 29.9 kg/m^2), and “Obese” (>30 kg/m^2) for descriptive purposes, and kept continuous for the analysis), urban/rural status of residence (kept binary), highest education level (classified in four categories: “No Education,” “Primary Education,” “Secondary Education,” and “Higher Education”), oral contraceptive use (dichotomous yes or no, where yes is exclusively oral contraceptive pills and no includes no or other birth control methods), country-specific human development index (HDI, continuous, assigned for each year of DHS),[37] and country-level malaria endemicity (dichotomous yes or no, assigned for each year of DHS).[38]

Statistical Analysis

All analyses were conducted in SAS 9.4, using DHS survey weights to provide country-, exposure level-, and year-specific prevalence of anemia. We examined the difference in differences (DID) parallel trends assumption by plotting weighted anemia prevalence of exposed (mandatory fortification countries) and control (non-mandatory fortification countries) groups at both DHS time points (**Figure 2**). Surveys conducted between 2005-2006 were considered as pre-fortification, and surveys conducted between 2015-2017 were considered as post-fortification data sources. Since the trend lines were subjectively determined to be parallel, the assumption was declared met.

Following the parallel trends assumption test, we conducted a simple DID analysis[39] to examine the effect of mandatory fortification country assignment on anemia prevalence. DHS guidelines were followed, including the application of standard weights, to ensure results could be generalized to the survey respondents' country level. To present estimates on an additive scale, the following logistic regression model (both unadjusted and adjusted for covariates) was used to estimate the difference in differences effects at the means:

$$Y_i = \alpha + \beta E_i + \gamma t_i + \delta(E_i \cdot t_i) + \varepsilon_i$$

where Y is the outcome (1 if anemic, else 0), E is exposure group (1 if mandatory legislation countries, else 0), α is the model's intercept, β is the exposure-specific effect, γ is the time-specific effect, δ is the true effect of mandatory fortification legislation, and ε is the random error term.

Covariates in the model were selected based on *a priori* criterion using a comprehensive literature review. Both an unadjusted model and a model adjusted for known confounders of the fortification-anemia relationship were built. A logistic regression was run on both models to determine parameter estimates for confounding variables and to ensure these estimates were similar to existing literature.

We then used a difference in differences estimator to determine the effects (percent change in anemia prevalence) of exposure (mandatory fortification legislation) at each time point. This estimator, a non-identity link with non-local means (NLMeans) macro, in turn applied an inverse link function to the four log odds estimates of the logistic regression (exposed at time 1, exposed at time 2, unexposed at time 1, and unexposed at time 2) and output the difference in difference contrasts, thereby calculating a difference in differences of means between the two groups.[40]

Results

Information regarding country-specific mandatory fortification status, flour(s) fortified, nutrient(s) included, WRA sample size, anemia prevalence, HDI, and malaria endemicity (yes or no) for each DHS year are provided in **Table 1**. Descriptive findings of individual- and country-level characteristics before the 2011 fortification period are presented in **Table 2**, including characteristics for the total sample and stratified by fortification group (of note, since this is before fortification, although groups are labeled as countries who fortify or do not, no countries at this time point have enacted mandatory fortification policies). Finally, **Table 3** presents the same characteristics as **Table 2** after mandatory fortification policies have been established.

Between 2005 and 2006, the pre-fortification period, weighted anemia prevalence among WRA ranged from 35.85% to 39.10% in exposed countries (Nepal and Uganda), 24.16% to 45.49% in control countries (Armenia, Ethiopia, and Haiti) (**Table 1**), and 33.59% overall (**Table 2**). Likewise, in the post-fortification period (2015-2017), weighted anemia prevalence ranged from 30.95% to 40.51% in exposed countries (Nepal and Uganda), 13.50% to 48.82% in control countries (Armenia, Ethiopia, and Haiti) (**Table 1**), and 31.31% overall (**Table 3**). Average HDI in the pre-fortification period was 0.47 among fortification (exposed) countries and 0.50 among control countries. In the post-fortification period, average HDI was 0.55 among exposed countries and 0.57 among control countries (data not shown). All countries were malaria endemic, except for Armenia, during the post-fortification survey period.

In a logistic regression analysis among individual- and country-level covariates, we found a positive association between anemia status and maternal age, maternal education level (no education v. secondary education), and oral contraceptive nonuse, and a negative association between anemia status and body mass index (BMI), urban v. rural residential status, maternal education level (no education v. higher education), HDI, and malaria non-endemicity (**Table 4**). We found an association between anemia status and the main exposure (fortification status) and time of survey (pre- or post-fortification period) in the multivariate logistic regression model after controlling for potential confounders (**Table 4**).

Our adjusted DID analysis showed a decrease in odds and mean anemia prevalence among WRA between fortification and non-fortification countries, prior to and after the fortification period, controlling for potential covariates. Overall, fortification countries in the pre- versus post-fortification period displayed 11% decreased odds of anemia (aOR: 0.89, 95% CI: 0.83 – 0.96) and 2% decreased mean of anemia prevalence (mean DID estimate: -1.78%, 95% CI: -2.93% – -0.64%), compared to non-fortification countries between 2005 and 2017 after controlling for age, BMI, urban v. rural residential status, maternal education level, oral contraceptive use, HDI, and malaria endemicity (**Table 5**).

Discussion

Through our difference in differences approach, with nationally representative DHS and fortification data, we found 11% decreased odds of anemia and 2% decreased mean anemia prevalence among WRA in countries with mandatory fortification legislation between 2005 and 2017, compared to countries without such legislation over the same time period. Our results suggest mandatory fortification legislation, in the countries we examined, shows a beneficial effect in reducing anemia prevalence among women of reproductive age. Besides Armenia, these countries were especially high burden with respect to anemia prevalence with notable population sizes. Thus, the benefits from fortification are noteworthy in terms of the number of women reached in absolute numbers.

The DID approach is commonly used in econometrics, particularly when assessing whether a new policy or law was effective. To our knowledge, this is the first multinational application of the DID approach to assess the impact of fortification policies on anemia status. While we did find a prior study utilizing the DID approach to examine anemia and fortification among pregnant women in various Indian States,[33] our study focuses on non-pregnant WRA in a variety of nations and geographic settings. Further research is needed to determine if our reported effects are seen on an even larger scale, beyond the scope of countries included in our study.

There were a number of strengths and weaknesses to our approach. The cross-sectional nature of Demographic and Health Surveys often limits the ability to develop causal inferences in data analysis. By utilizing the difference in difference approach, and controlling for confounding, we were able to avoid this limitation and assess policy impacts on individual-level health outcomes. A DID approach provides strong evidence to interpret the relationship between anemia and mandatory fortification policies, building on prior approaches that rely on regression model estimates of cross-sectional data.

While our analysis did see a difference in average prevalence and odds of anemia, we only assessed effects of policy change among countries with legislation passed in 2011 with data from five years before and after the enactment period. As such, our sample only consisted of two countries with mandatory fortification legislation and three countries without. Dropping countries from our analysis due to different policy enactment years and missing DHS data limits the generalizability of the results. Future studies that include more countries, and properly address differences in year of policy change, would exhibit better external validity. Further, the countries included in our study are only representative of similar lower- to middle-income countries. More research is needed to determine if similar relationships exist in upper middle- and high-income countries.

In any analysis, there is a potential for confounding. Our analysis is vulnerable to confounding at two points of note, the first being participants' hemoglobin measurements and subsequent classifications of anemia. Given the cross-sectional nature of DHS, and historical discrepancies in field laboratory techniques used to measure hemoglobin levels,[41] it is possible measurements may be imprecise or incorrect, leading to outcome misclassification in our study. Second, our study only controlled for certain covariates – other confounders of the mandatory fortification-anemia relationship were not examined and could impact both the direction and magnitude of our results. This was the case specifically with individual HIV and malaria status, as standard DHS datasets do not provide access to these biomarker data. While we attempted to control for malaria using country-level endemicity status, this measurement limits our analysis as it does not provide information on the individual level, like covariates measured during DHS. Our analysis only controlled for variables included in standard DHS survey collection, and therefore cannot be interpreted as inherently unbiased.

It is also important to recognize the effectiveness of flour fortification on anemia status is entirely dependent on intervention uptake.[33,42,43] We were not able to control for this in our analysis and, given variation in flour intake, fortification compliance, and coverage,[33,34] these are likely to influence the impact of fortification legislation.

Future nationally representative surveys (DHS or otherwise) should attempt to include HIV and malaria biomarkers with individual-level fortified product consumption data, to better assess the impacts on anemia status. Additionally, a more accurate measurement system to record hemoglobin levels, and thereby properly classify anemia status, is needed to increase confidence in any relationships observed.

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Tables and Figures

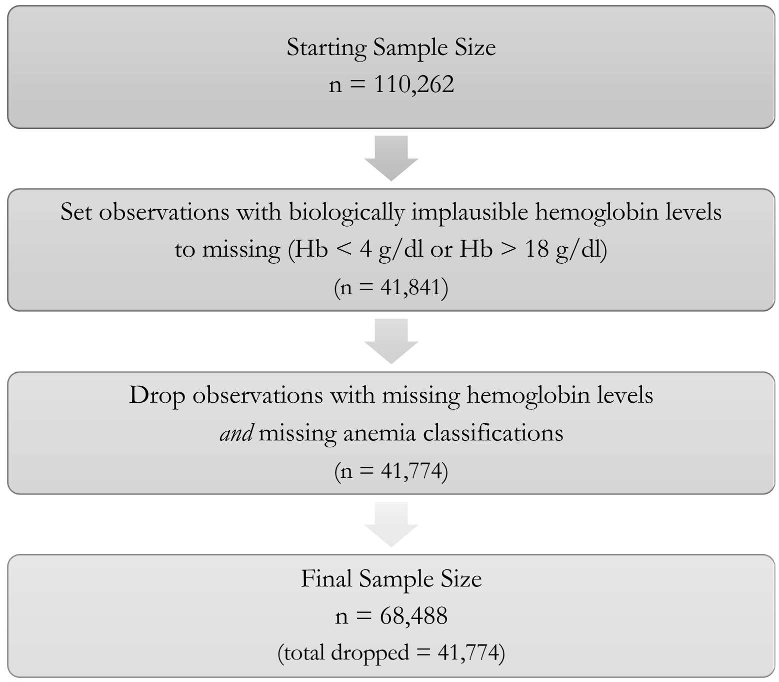

Figure 1. Sample selection method for difference in differences analysis of mandatory flour fortification policies on anemia prevalence.

Table 1. Description of countries included in analysis, including those with (n = 2) and without (n = 3) national mandatory fortification legislation†

Country	Estimated Population, Women of Reproductive Age (15 – 49 years) ‡	Year Mandatory Fortification Legislation	Flour(s) Fortified	Nutrient(s) Included in Fortification Standard	DHS Year	WRA (n) ††	Weighted Anemia Prevalence % (95% CI)††, §	HDI*	Malaria Endemicity‡‡
Nepal	9,029,000	2011	Wheat	Folate (B_9), iron, vitamin A	2006	10,041	35.85 (34.91, 36.78)	0.484	1
					2016	6,134	40.51 (39.28, 41.74)	0.572	1
Uganda	10,939,000	2011	Wheat, maize	Folate (B_9), iron, niacin, riboflavin, thiamin, vitamin A, vitamin B_6, vitamin B_{12}, zinc	2006	2,477	39.90 (37.97, 41.82)	0.447	1
					2016	5,397	30.95 (29.71, 32.18)	0.520	1
Armenia	746,000	-	None	None	2005	5,957	24.16 (23.07, 25.25)	0.694	1
					2015-2016	5,646	13.50 (12.60, 14.39)	0.750	0
Ethiopia	28,513,000	-	None	None	2005	5,489	26.19 (25.04, 27.34)	0.346	1
					2016	13,436	23.20 (22.50, 23.91)	0.460	1
Haiti‡‡	3,062,000	(2017)	(Wheat)	(Folate (B_9), iron, vitamin B_6, vitamin B_{12}, zinc)	2005-2006	4,908	45.49 (44.10, 54.51)	0.454	1
					2016-2017	9,003	48.82 (47.79, 49.85)	0.499	1

†Fortification policy details obtained from the Global Fortification Data Exchange, 2020.[20]

‡United Nations Population Division, World Population Prospects: 2020 Estimates, including both pregnant and non-pregnant women of reproductive age.[44]

††Data accessed from country-specific Demographic and Health Survey (DHS) for numbers of non-pregnant women of reproductive age (WRA) participants.[35]

‡‡Wheat flour fortification became mandatory in Haiti after the 2016-2017 DHS was conducted.[20]

§Weighted anemia prevalence per DHS sampling methodologies.[35]

*Human Development Index (HDI) is a single measure of national human development (ranging from 0 to 1, with 1 being the highest level of human development) that incorporates gross national income, expected years of schooling, and life expectancy. HDI values were gathered for DHS years, and were averaged if a DHS spanned over multiple years.[37]

‡‡Information on malaria endemicity was accessed via the World Health Organization's 2011 World Malaria Report, where 0 indicates not endemic and 1 indicates endemic.[38]

CI: Confidence Interval
DHS: Demographic and Health Survey
HDI: Human Development Index
WRA: Women of Reproductive Age (non-pregnant)

Table 2. Descriptive statistics of non-pregnant women of reproductive age (WRA, 15-49 years) before mandatory flour fortification study period, by country policy status, Demographic and Health Surveys (2005-2006, n = 28,872)

Characteristics of WRA	Total Subjects		Countries with Fortification Policy		Countries without Fortification Policy	
	n	%*	n	%*	n	%*
Anemia†						
Yes	9,458	33.59	4,447	36.65	5,011	31.26
Age (years)						
15-19	6,500	22.59	2,849	22.70	3,651	22.51
20-34	12,978	45.23	5,844	46.46	7,134	44.28
35-49	9,394	32.18	3,825	30.83	5,569	33.21
BMI‡						
Underweight	5,206	18.14	2,726	21.77	2,480	15.36
Normal	18,474	64.46	8,621	68.19	9,853	61.60
Overweight	3,577	12.43	976	8.53	2,601	15.41
Obese	1,505	4.98	180	1.51	1,325	7.63
Urban/Rural Residence						
Urban	11,342	31.14	3,153	15.83	8,189	42.79
Rural	17,530	68.86	9,365	84.17	8,165	57.21
Highest Level of Education						
None	10,237	36.49	5,773	46.24	4,464	29.08
Primary	6,356	22.22	3,166	25.56	3,190	19.69
Secondary	10,208	33.87	3,035	24.22	7,173	41.22
Higher	2,071	7.41	544	3.98	1,527	10.01
Oral Contraceptive Use						
Yes	610	2.22	342	2.91	268	1.70

*Weighted percent due to Demographic and Health Survey sampling techniques.[35]

†Current anemia status; Hemoglobin (Hb) <12.0 g/dl.

‡BMI, Body Mass Index (kg/m^2): Underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (>30 kg/m^2).

Note: Since these data are from the pre-fortification legislation time period, although groups are labeled as countries with fortification policies and without fortification policies, no countries at this time point have enacted mandatory fortification policies.

BMI: Body Mass Index
WRA: Women of Reproductive Age (non-pregnant)

Table 3. Descriptive statistics of non-pregnant women of reproductive age (WRA, 15-49 years) after mandatory flour fortification study period, by country policy status, Demographic and Health Surveys (2015-2017, n = 39,616)

Characteristic	Total Subjects		Countries with Fortification Policy		Countries without Fortification Policy	
	n	%*	n	%*	n	%*
Anemia†						
Yes	12,792	31.31	4,184	36.04	8,608	29.41
Age (years)						
15-19	8,442	20.78	2,524	21.76	5,918	20.39
20-34	19,053	48.82	5,524	47.95	13,529	49.17
35-49	12,121	30.39	3,483	30.28	8,638	30.44
BMI‡						
Underweight	6,058	14.35	1,544	13.15	4,514	14.84
Normal	24,372	63.09	7,582	64.03	16,790	62.71
Overweight	6,349	15.67	1,800	16.82	4,549	15.21
Obese	2,743	6.89	583	6.00	2,160	7.24
Urban/Rural Residence						
Urban	16,577	39.62	5,211	45.84	11,366	37.10
Rural	23,039	60.38	6,320	54.16	16,719	62.90
Highest Level of Education						
None	9,998	26.10	2,718	22.65	7,280	27.50
Primary	11,943	29.98	4,131	35.23	7,812	27.86
Secondary	12,145	29.89	3,476	31.02	8,669	29.43
Higher	5,530	14.03	1,206	11.11	4,324	15.22
Oral Contraceptive Use						
Yes	742	1.84	293	2.58	449	1.54

*Weighted percent due to Demographic and Health Survey sampling techniques.[35]

†Current anemia status; Hemoglobin (Hb) <12.0 g/dl.

‡BMI, Body Mass Index (kg/m^2): Underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥ 30 kg/m^2).

BMI: Body Mass Index

WRA: Women of Reproductive Age (non-pregnant)

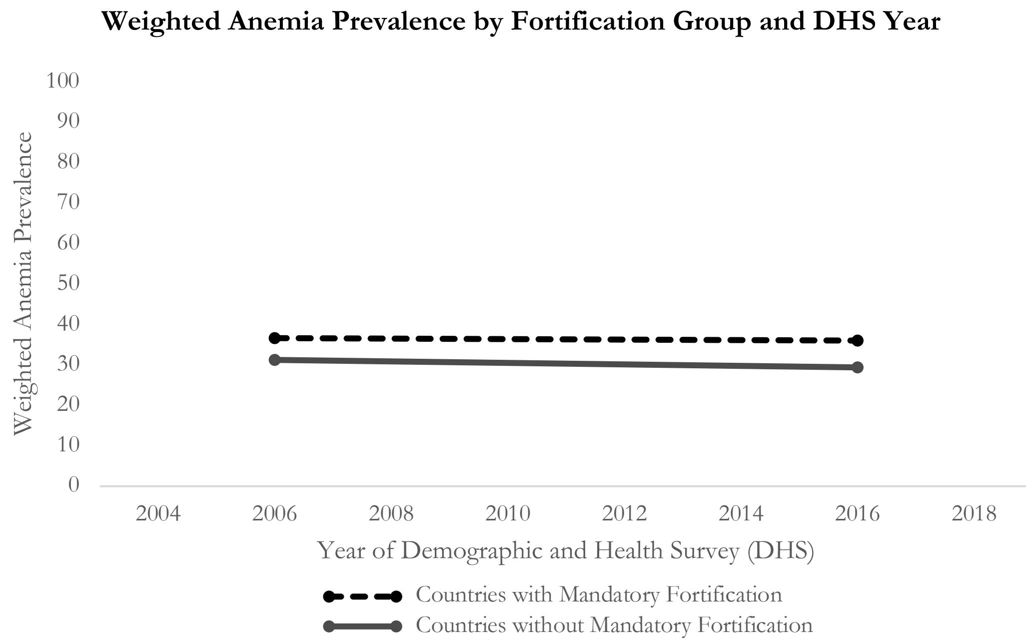

Figure 2. Weighted Anemia Prevalence (%) by fortification group (national mandatory fortification or not) and Demographic and Health Survey (DHS) year. Surveys collected between 2005 and 2006 were plotted at the 2006 time point (before fortification), and surveys collected between 2015 and 2017 were plotted at the 2016 time point (after fortification). Weighted anemia prevalence was calculated per DHS sampling methods.[35]

Table 4. Adjusted logistic regression analysis for the association between flour fortification policy status and anemia† for individual- and country-level covariates among women of reproductive age (WRA, 15-49 years) in study countries, Demographic and Health Surveys (2005-2006, 2015-2017)

Characteristic	Unadjusted Model (n = 68,488) OR (95% CI)	Adjusted Model (n = 68,284) OR (95% CI)
Main Exposures		
Country Fortification Status		
No Mandatory Fortification	Ref	Ref
Mandatory Fortification	1.27 (1.21 – 1.34)	1.29 (1.22 – 1.35)
DHS Survey Period		
Pre-fortification (2006-2007)	Ref	Ref
Post-fortification (2015-2017)	0.92 (0.88 – 0.96)	1.11 (1.06 – 1.16)
Individual-Level Covariates		
Age (years)		1.00 (1.00 – 1.00)
Body Mass Index (kg/m^2)		0.97 (0.97 – 0.98)
Urban/Rural Residence		
Urban		Ref
Rural		0.86 (0.83 – 0.89)
Education Level		
None		Ref
Primary		0.96 (0.92 – 1.01)
Secondary		1.11 (1.05 – 1.16)
Higher		0.80 (0.74 – 0.86)
Oral Contraceptive Use		
Yes		Ref
No		1.54 (1.36 – 1.74)
Country-Level Covariates		
Human Development Index‡		0.94 (0.73 – 1.20)
Endemic Malaria♯		
Yes		Ref
No		0.36 (0.32 – 0.39)

†Defined as current anemia status, with a hemoglobin (Hb) level <12.0 g/dl.

‡Human Development Index (HDI) is a single measure of national human development (ranging from 0 to 1, with 1 being the highest level of human development) that incorporates gross national income, expected years of schooling, and life expectancy. HDI values were gathered for DHS years, and were averaged if a DHS spanned over multiple years.[37]

♯Information on malaria endemicity was accessed via the World Health Organization's 2011 World Malaria Report, where 0 indicates not endemic and 1 indicates endemic.[38]

Unadjusted Model includes exposure and time effects, unadjusted for covariates.

Adjusted Model additionally controls for individual- and country-level covariates.

DHS: Demographic and Health Surveys
WRA: Women of Reproductive Age (non-pregnant)
Ref: Reference Group

Table 5. Difference in differences estimates of anemia†, comparing fortification status (mandatory fortification countries and non-mandatory fortification countries) and time period (pre- or post-fortification legislation), among women of reproductive age (WRA, 15-49 years) in study countries, Demographic and Health Surveys (2005-2006, 2015-2017)

Model Assessed	**Difference in Differences**	
	Odds (95% CI)	Mean‡ (95% CI)
Unadjusted Model (n = 68,488)	1.06 (0.99 – 1.14)	1.24 (-0.27 – 2.74)
Adjusted Model (n = 68,284)	0.89 (0.83 – 0.96)	-1.78 (-2.93 – -0.64)

†Defined as a hemoglobin (Hb) level <12.0 g/dl.

‡Assessed as average weighted[35] anemia prevalence (%).

Unadjusted Model includes exposure and time effects, unadjusted for covariates.

Adjusted Model additionally controls for age, BMI, urban v. rural residential status, maternal education level, oral contraceptive use, HDI, and malaria endemicity.

WRA: Women of Reproductive Age (non-pregnant)

CHAPTER III

PUBLIC HEALTH IMPLICATIONS

Anemia continues to be a serious issue of public health concern, afflicting nearly one third of the world's population[1,2] and contributing to over 62 million years lost in death and productivity.[1] Anemia's nonfatal health losses contribute to a greater figure than asthma, diabetes, and cardiovascular disease combined,[1] affecting individuals of all genders, ages, and income levels.[7,16] While progress has been made to decrease anemia prevalence worldwide, this progress has been slow and challenges remain.[1,8] A feasible, effective solution is needed to further alleviate the morbidity and mortality associated with anemia.

Our findings have several public health implications, particularly in regard to the effectiveness of mandatory flour fortification legislation and the potential implications for fortification programs worldwide. The evidence presented in this study suggest flour fortification with nutrients that contribute to hemoglobin synthesis (e.g. iron, copper, zinc, folate, and vitamins B12, B2 (riboflavin), B6, B1 (thiamin), A, and E) decreases anemia levels among non-pregnant women of reproductive age, particularly when adjusting for factors commonly associated with increased anemia risk.

While anemia is considered a moderate to severe public health concern in 142 countries,[5,6] only 83 countries currently have mandatory fortification policies in place.[20] This study presents highly suggestive evidence of the effectiveness of such policies, indicating the societal, economic, and health benefits of investing in fortification methods to reduce anemia prevalence.

The United Nations Population Prospects estimates there are approximately 1.9 billion women of reproductive age worldwide.[44] While our analysis only examined non-pregnant WRA, a 2% reduction in anemia prevalence among all women of reproductive age would equate to over 384 million avoided cases of anemia. Further, considering baseline figures likely underestimate anemia's true health losses,[1] and reductions will largely depend on successful coverage of a country's fortification policy, there is the possibility for even greater impact amongst high-coverage areas.