WILEY **Birth Defects Research** THE TERATOLOGY SOCIETY EST. 1960

Total prevention of folic acid-preventable spina bifida and anencephaly would reduce child mortality in India: Implications in achieving Target 3.2 of the Sustainable Development Goals

Vijaya Kancherla [iD] | Godfrey P. Oakley Jr.

Center for Spina Bifida Prevention, Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, Georgia

Correspondence
Vijaya Kancherla, PhD, Research Assistant Professor, Department of Epidemiology, Epidemiologist, Center for Spina Bifida Prevention, Rollins School of Public Health, Emory University, 1518 Clifton Rd NE, Atlanta, GA 30322.
Email: vkanche@emory.edu

Funding information
None

Background: The potential to reduce child mortality by preventing folic acid-preventable spina bifida and anencephaly (FAP SBA) is inadequately appreciated. To quantify possible reduction in FAP SBA-associated child mortality in low- and middle-income countries, we conducted an analysis to demonstrate in India, a country with more than 25 million births and 1.2 million under-five deaths each year, the decrease in neonatal, infant, and under-five mortality that would occur through total prevention of FAP SBA.

Methods: We estimated the percent reductions in neonatal, infant, and under-five mortality that would have occurred in India in 2015 had all of FAP SBA been prevented. We also estimated the contributions of these reductions toward India's Sustainable Development Goals on child mortality indicators. We considered the overall prevalence of spina bifida and anencephaly in India as 5 per 1,000 live births, of which 90% were preventable with effective folic acid intervention.

Results: In the year 2015, folic acid interventions would have prevented about 116,070 cases of FAP SBA and 101,565 under-five deaths associated with FAP SBA. Prevention of FAP SBA would have reduced annually, neonatal, infant, and under-five mortality by 10.2%, 8.9%, and 8.3%, respectively. These reductions would have contributed 18.5% and 17.2% to the reductions in neonatal and under-five mortality, respectively, needed by India to achieve its 2030 Sustainable Developmental Goal Target 3.2 addressing preventable child mortality.

Conclusions: Total prevention of FAP SBA clearly has a significant potential for immediate reductions in neonatal, infant, and under-five mortality in India, and similarly other countries.

KEYWORDS
anencephaly, child mortality, India, mortality, spina bifida, sustainable development goals

1 | INTRODUCTION

In 1991, the Medical Research Council (MRC) study from the United Kingdom (UK) proved unequivocally through a randomized clinical trial that folic acid prevents spina bifida and anencephaly, two major disabling and often fatal birth defects (MRC Vitamin Study Research Group, 1991). By 1998, the United States had fully implemented mandatory fortification of enriched cereal grain products with folic acid and, thus reduced the combined prevalence of spina bifida and anencephaly to 0.5 per 1,000 live births (Oakley, 2009; Williams et al., 2015). Cost-benefit studies on fortification in the United States showed that the country saved $150 dollars in averted healthcare costs associated with spina bifida alone

for every $1 dollar spent on implementing the fortification program (Grosse, Berry, Tilford, Kucik, & Waitzman, 2016). Two post-fortification case–control studies showed that fortification with folic acid has prevented almost all if not all of folic acid preventable-spina bifida and anencephaly (FAP SBA), and that maternal intake of additional periconceptional folic acid supplementation did not provide further benefit in reducing the risk of these birth defects (Ahrens, Yazdy, Mitchell, & Werler, 2011; Mosley et al., 2009). Currently, about 60 countries have implemented mandatory folic acid fortification, and several have reported consistently similar reductions in the post-fortification prevalence of FAP SBA (Arth et al., 2016).

Almost all babies born with anencephaly die within a few hours after birth; the survival among those born with spina bifida is better, especially in high-income countries (Shurtleff, Luthy, Nyberg, Benedetti, & Mack, 1994). According to the Atlas of Country Resources for Neurological Disorders by the World Health Organization and the World Federation of Neurology, most low- and middle-income countries do not have adequate resources or skilled healthcare providers (e.g., neurosurgeons) to care for children with spina bifida, often leading to preventable mortality (WHO, 2004). Studies examining mortality in spina bifida-affected births reported a significantly greater risk of death compared to their unaffected counterparts, especially during childhood (Oakeshott, Hunt, Poulton, & Reid, 2010; Wang, Hu, Druschel, & Kirby, 2011). In a developed country such as the United Kingdom, 35% of those born with spina bifida died before age five (Oakeshott et al., 2010). In the United States, a population-based registry study reported the survival probability among those born with spina bifida to be about 93% up to 7 days of age, 88% up to age 1 year, and 86% up to age 5 years (Wang et al., 2011). Similar data are lacking in a majority of low- and middle-income countries. One study in rural China, with a high prevalence of spina bifida (up to 2.9 per 1,000 total births), reported 100% mortality among those affected (Moore et al., 1997).

It has been almost 30 years since we learned that folic acid prevents spina bifida and anencephaly, yet our progress in preventing FAP SBA and associated mortality has been slow. Many of the low- and middle-income countries have yet to require fortification (Arth et al., 2016). Based on a large number of births, 10- to 20-fold higher prevalence of FAP SBA compared to countries with effective folic acid fortification policies, and a significantly high risk of mortality among those born with spina bifida and anencephaly, implementing evidence-based prevention strategies in low- and middle-income countries could make an important contribution toward reducing child mortality associated with these birth defects (Atta et al., 2016; Castillo-Lancellotti, Tur, & Uauy, 2013, Darmstadt et al., 2016).

Sustainable Development Goal (SDG) Target 3.2 proposes, "By 2030, end preventable deaths of newborns and children under five years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-five mortality to at least as low as 25 per 1,000 live births" (Murray, 2015; Sustainable Development Goals, 2015). To illustrate the importance of prevention of FAP SBA in attaining the SDG Target 3.2 in low- and middle-income countries, we conducted an analysis on prevention of FAP SBA and its impact on child mortality in India.

In the year 2015, India recorded ∼26 million live births and 1.2 million deaths under age five, contributing to 20% of global child deaths. To achieve its SDG target of having no more than 25 under-five deaths per 1,000 live births by year 2030, India would need to accelerate its childhood mortality prevention efforts by two- to three-times the current annual rate of reduction (You et al., 2015). The South East Asia Regional Office of the World Health Organization has specified that a large proportion of current neonatal deaths in India can be directly attributed to birth defects (WHO, 2015). To date, no state in India has permanently instituted mandatory folic acid fortification of centrally processed staples to prevent FAP SBA.

The aim of our analysis was to estimate: (1) the annual percent reduction in the rates of neonatal, infant, and under-five mortality that could occur through total prevention of FAP SBA and (2) the proportional contribution of FAP SBA prevention toward achieving the SDG for child mortality reduction.

2 | METHODS AND MATERIALS

We utilized latest available data from multiple sources on vital indicators including number of live births and child mortality statistics to estimate our findings for the year 2015.

Selected indicators and their data source are described below.

2.1 | Birth prevalence of spina bifida and anencephaly in India

Previous studies provide adequate support for our assumption of anencephaly and spina bifida prevalence in India to be 2.5 per 1,000 live births each, and their combined prevalence to be 5.0 per 1,000 live births. This assumption is based on the following supporting literature on combined prevalence of spina bifida and anencephaly among livebirths in India. The 2006 Global Report on Birth Defects by the March of Dimes, based on modeled estimates, reported the prevalence to be 4.7 per 1,000 live births in India (Christianson, Howson, & Modell, 2006). A recent meta-analysis from

India reported a prevalence of 4.1 per 1,000 total births, including live and stillbirths in the numerator and denominator (95% CI = 3.1, 5.4) (Bhide, Sagoo, Moorthie, Burton, & Kar, 2013). Several historic estimates point to an average prevalence of 5.0 per 1,000 births. McMahon and Yen described an unrecognized epidemic of spina bifida and anencephaly among live births in the mid-1930s in Boston and Providence, United States, where prevalence peaked at 5.0 per 1,000 births, with an equal proportion of spina bifida and anencephaly cases (MacMahon & Yen, 1971). In addition, a population-based surveillance of 28 week and older pregnancies in Belfast, Ireland, between 1964 and 1968 reported a live and stillbirth prevalence of neural tube defects to be 8.7 per 1,000 total births, also with an equal representation of both defects (Elwood & Nevin, 1973). More contemporary estimates from robust surveillance studies in northern China (including outcomes in pregnancies of at least 20 weeks' gestation) and the Newfoundland province in Canada (live births, stillbirths, and elective terminations of pregnancies due to fetal anomalies) report the prevalence to be 5.0 to 10 per 1,000 total births (Berry et al., 1999; De Wals et al., 2007).

2.2 | Method of estimating child mortality reduction through folic acid programs in India

We utilized country-specific data reported by the 2015 United Nations Inter-Agency Group for Child Mortality Estimation (IGME)—Levels and Trends in Child Mortality Report (United Nations, 2015) to record the total number of live births in India, and the three child mortality indicators including rates of: (1) neonatal mortality; (2) infant mortality; and (3) under-five mortality. Using above information, we estimated the annual absolute number of deaths in the neonatal, infant, and under-five age categories. We then estimated the number of preventable cases of spina bifida and anencephaly by subtracting the achievable baseline prevalence of all cases that are non-folic acid preventable (0.5 per 1,000 live births) from the total prevalence (5.0 per 1,000 live births). Thus, the FAP SBA in India was estimated to be at least 4.5 per 1,000 live births (Figure 1).

We applied known age-specific mortality probabilities to estimate the number of neonatal, infant, and under-five deaths associated with FAP SBA in India. However, data on mortality associated with spina bifida and anencephaly are lacking in most low- and middle-income countries, including India. Among studies that were available, we examined mortality statistics from a population-representative surveillance in Ireland for births between 1976 and 1987 (Sutton, Daly, & Kirke, 2008). For our analysis, this period in Ireland was assumed to be comparable to the current demographic and socio-economic profile of India. In Ireland, a majority of

infants with anencephaly were stillborn or died shortly after birth, and those born with spina bifida had a mortality probability of 25% within the first 28 days of birth, about 50% by age one, and 75% by age five (Sutton et al., 2008).

3 | RESULTS

In the year 2015, UNICEF reported a total of 25,794,000 live births in India. The neonatal, infant, and under-five mortality rates were 27.7, 37.9, and 47.7 per 1,000 live births, respectively (Table 1). At a combined spina bifida and anencephaly prevalence rate of 5.0 per 1,000 live births, we estimated that about 128,970 births were affected by these two defects in 2015, and that folic acid interventions could prevent 116,073 (90%) of those cases, which were occurring at a prevalence of 4.5 per 1,000 live births (Figure 1).

Applying mortality probabilities from previous studies, we estimated all babies born with anencephaly (including those resulting in stillbirths) constituted one half of all cases ($n = 58,037$), and would have died within the first week of their life. Among babies born with spina bifida ($n = 58,037$), about 75% ($n = 43,527$) would have died within five years of age, contributing ∼15,000 deaths to each of the neonatal, infant, and under-five mortality categories. Overall, in the year 2015, we estimated a total of 101,564 FAP SBA-associated deaths in India by the time the child reaches age five (Table 1).

3.1 | Annual percent reduction in the rates of neonatal, infant, and under-five mortality that could occur through total prevention of FAP SBA

3.1.1 | Neonatal mortality

The percent of cases that die within the first 28 days of life accounts for 100% for anencephaly and 25% for spina bifida. In 2015, India's neonatal mortality rate was 27.7 per 1,000 live births (uncertainty interval [UI] = 24.0–31.6 per 1000 live births). If we were to prevent all FAP SBA, it would avert 72,546 neonatal deaths associated with anencephaly and spina bifida. This would reduce the neonatal mortality rate from the current rate of 27.7 per 1,000 live births to 24.9 per 1,000 live births (UI = 21.2–28.8 per 1,000 live births). Holding all else constant, this would account for a reduction of 10.2% (UI = 8.9%–11.7%) in the neonatal mortality rate (Table 2).

3.1.2 | Infant mortality

The percent of FAP SBA cases that die within the first year of life accounts for 100% for anencephaly and 50% for spina
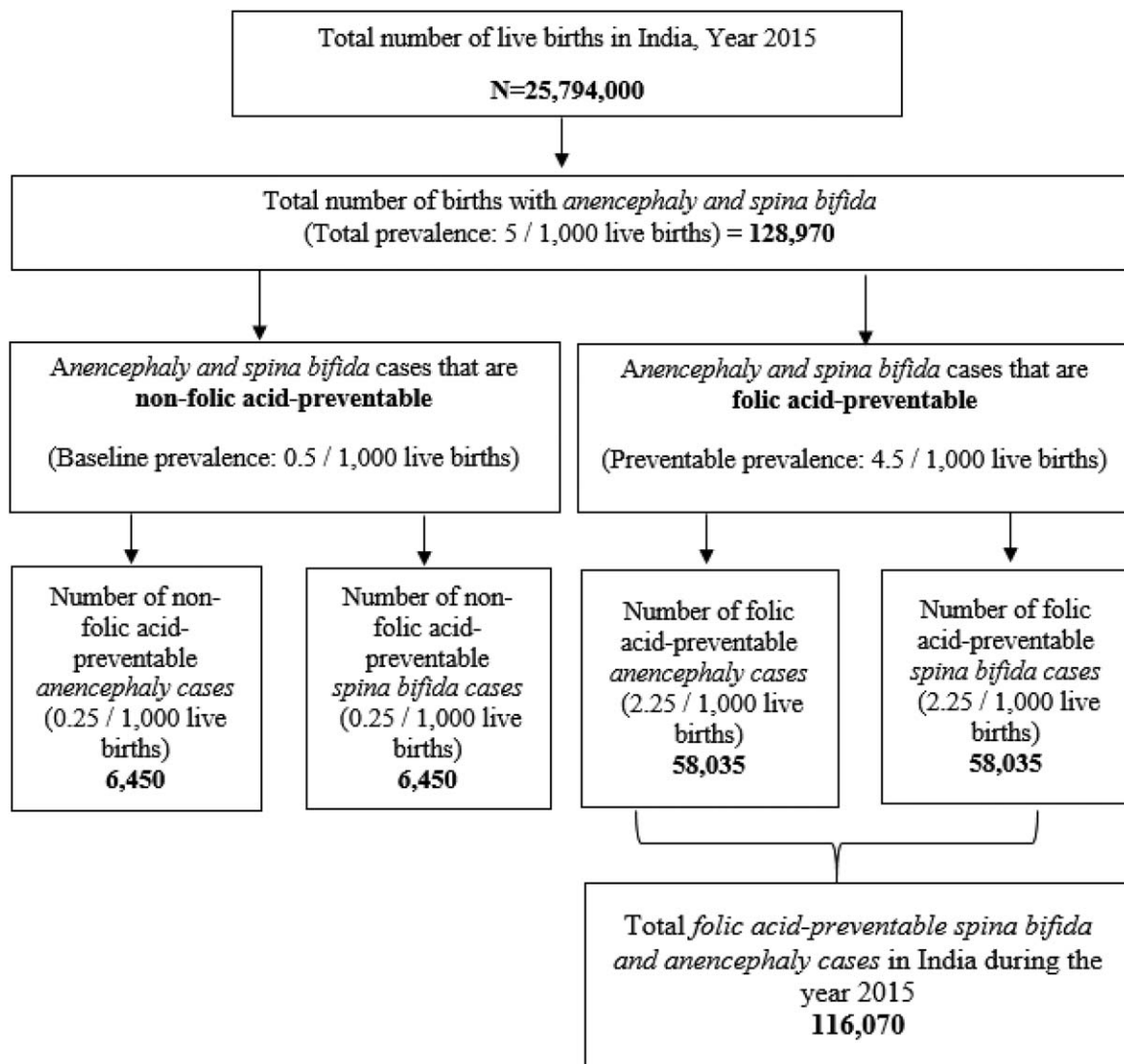
FIGURE 1 Estimated births with folic acid-preventable spina bifida and anencephaly in India, Year 2015 (rounded to nearest 5th)

bifida. In 2015, India's infant mortality rate was 37.9 per 1,000 live births (UI = 34.1–41.8 per 1,000 live births). Total prevention of FAP SBA would prevent about 87,055 infant deaths (58,037 deaths due to anencephaly and 29,018 deaths due to spina bifida). This would reduce the infant mortality from 37.9 per 1,000 live births to 34.5 per 1,000 live births (UI = 30.7–38.5 per 1,000 live births), a reduction of 8.9% (UI = 8.1%–9.9%) in the infant mortality rate (Table 2).

3.1.3 | Under-five mortality

The percent of FAP SBA cases that die by age five years is 100% for anencephaly and 75% for spina bifida. Total prevention of FAP SBA can avoid up to 101,564 deaths associated with these defects among children under age five years. In the year 2015, the under-five mortality rate in India was 47.7 per 1,000 live births. Preventing FAP SBA would have reduced the under-five mortality to 43.8 per 1,000 live births

(UI = 38.5–49.4 per 1,000 live births), contributing to 8.3% reduction (UI = 7.4%–9.3%) (Table 2).

3.2 | Proportional contribution of FAP SBA prevention toward achieving the SDG for child mortality reduction

To reach its SDG target for neonatal mortality of 12 per 1,000 live births from the current level of 27.7 per 1,000 live births, India should achieve a reduction of 15.7 per 1,000 live births. Similarly, to achieve its SDG target for under-five mortality from the current level of 47.7 per 1,000 live births to 25 per 1,000 live births, there should be a reduction of 22.7 per 1,000 live births. As shown in our analysis, preventing FAP SBA would reduce neonatal and under-five mortality estimates to 24.8 and 43.7 per 1,000 live births from the current levels of 27.7 and 47.7 per 1,000 live births, respectively. Thus, the proportional contribution of FAP

TABLE 1 Indicators and measures of child mortality, and prevalence of, and mortality associated with spina bifida and anencephaly in India, year 2015

Indicators	Measures (UI)
Annual live births[a]	25,794,000
UNICEF/UN-IGME child mortality indicators (for all causes)[a]	
Neonatal mortality (0–28 days of life) [27.7/1,000 live births] (UI: 24.0–31.6)	714,494 (619,056–815,090)
Infant mortality (<1 year of age) [37.9/1,000 live births] (UI: 34.1–41.8)	977,593 (879,575–1,078,189)
Under-five mortality (<5 years of age) [47.7/1,000 LB] (UI: 42.4–53.3)	1,230,374 (1,093,666–1,374,820)
Total number of cases of spina bifida and anencephaly	
Anencephaly	
Total number of cases observed at birth prevalence of 2.5/1,000 live births = (25,794,000 × 2.50)/1,000	64,485
Preventable cases with folic acid at birth prevalence 2.25/1,000 live births = (25,794,000 × 2.25)/1,000	58,037
Spina Bifida	
Total number of cases observed at birth prevalence of 2.5/1,000 live births = (25,794,000 × 2.50)/1,000	64,485
Preventable cases with folic acid at birth prevalence 2.25/1,000 live births = (25,794,000 × 2.25)/1,000	58,037
Child mortality averted by total prevention of FAP SBA (number; rate per 1,000 LB)	
Neonatal mortality: 100% FAP anencephaly (n = 58,037) + 25% FAP spina bifida (n = 14,509)	72,546 [24.9/1,000 live births]
Infant mortality: 100% FAP anencephaly (n = 58,037) + 50% FAP spina bifida (n = 29,018)	87,055 [34.5/1,000 live births]
Under-five mortality: 100% FAP anencephaly (n = 58,037) + 75% FAP spina bifida (n = 43,527)	101,564 [43.8/1,000 live births]

[a]Estimates generated by the UN Inter-Agency Group for Child Mortality Estimation (IGME) in 2015. Downloaded from http://data.unicef.org [http://www.childmortality.org/files_v20/download/IGME%20report%202015%20child%20mortality%20final.pdf] (Retrieved May 1, 2017).

FAP, folic acid-preventable; SBA, spina bifida and anencephaly; SDG, Sustainable Development Goals; UI, uncertainty intervals; UNICEF, United Nations International Children's Emergency Fund; UN-IGME, United Nations Inter-Agency Group for Child Mortality Estimation.

SBA prevention toward achieving India's SDG goal is 18.5% (UI = 14.3%–23.2%) (i.e., 2.9 out of the 15.7 deaths per 1,000 live births) for neonatal mortality, and 17.2% (UI = 13.8%–22.4%) (i.e., 3.9 out of the 22.7 deaths per 1,000 live births) for under-five mortality (Table 2).

4 | DISCUSSION

We have shown that if India were to prevent all FAP SBA, there would be an important and immediate reduction in neonatal, infant, and under-five mortality rates. The intervention can produce a remarkable reduction in the mortality rates that has a potential to drive India toward its SDG Targets for year 2030. The goal of total prevention of FAP SBA is challenging. But, India has a successful history of reaching challenging public health goals in the past, rolling out programs that eradicated smallpox and eliminated polio. This simple analysis in India demonstrates the importance of preventing FAP SBA not only to eliminate preventable cases of these severely disabling birth defects, but also to reduce associated child mortality. Our estimates provide a strong rationale to increase the likelihood that India pursue the goal of total

prevention of FAP SBA, and achieve reductions in neonatal and under-five mortality associated with FAP SBA. Our analysis in India can also be applied to other countries considering effective folic acid interventions to achieve rapid reductions in their child mortality to reach their SDGs.

An important limitation of our analysis is lack of information on all pregnancy outcomes. The denominators in our analyses included only live births for assessing prevalence. We know that a large proportion of cases with anencephaly result in stillbirths (Elwood, 1970). But stillbirths, and their causes, are not tracked in any of the global mortality estimates (Lawn et al., 2011). Allagh et al. (2015) showed hospital-based stillbirths associated with anencephaly are rarely tracked in India, leading to their underestimation (Allagh et al., 2015). Bhide et al. (2013) reported stillbirth prevalence of spina bifida and anencephaly, but had an overall sample of just 51 cases; the spina bifida and anencephaly associated stillbirth prevalence was presented as 1.7 per 1,000 total births. Sutton et al. (2008) reported that 12% of all cases of spina bifida and anencephaly resulted in stillbirths. Due to variation and paucity of data, we were unable to determine stillbirths associated with spina bifida and anencephaly in India. For our analysis, we assumed stillbirths

TABLE 2 Annual percent reduction in child mortality and proportional contribution of FAP SBA prevention towards achieving the SDG for child mortality reduction in India, year 2015

Indicators	Measures (UI)
Annual percent reduction in the rates of neonatal, infant, and under-five mortality that could occur through total prevention of FAP SBA	
Neonatal mortality: (neonatal deaths due to FAP SBA/all neonatal deaths) = (72,546/714,494)	10.2% (8.9%–11.7%)
Infant mortality: (infant deaths due to FAP SBA/all infant deaths) = (87,055/977,593)	8.9% (8.1%–9.9%)
Under-five mortality: (under-five year deaths due to FAP SBA/all under-five year deaths) = (101,564/1,230,374)	8.3% (7.4%–9.3%)
Proportional contribution of FAP SBA prevention towards achieving the SDG for child mortality reduction	
Neonatal mortality:	
Neonatal mortality rate achievable through folic acid interventions = [Total number of neonatal deaths post-folic acid interventions / total live births] = [(714,494 − 72,546) / (25,794,000)]	24.8/1,000 livebirths (21.2–28.8)
Difference between observed neonatal mortality (year 2015) and achievable neonatal mortality from folic acid interventions = [27.7/1,000 live births] – [24.8/1,000 livebirths]	2.9/1,000 livebirths
Proportional contribution of preventing FAP SBA to SDG on reducing neonatal mortality = [27.7/1,000 live births (observed) – 12/1,000 live births (SDG Goal)] = 15.7/1,000 live births = [2.9/1,000 live births (with folic acid interventions)/15.7/1,000 live births (needed reduction for SDG)]	18.4% (14.3%–23.2%)
Under-five mortality:	
Under-five mortality rate achievable through folic acid interventions = [Total number of under-five deaths post-folic acid interventions / total live births] = [(1,230,374 − 101,564)/(25,794,000)]	43.8/1,000 livebirths (38.5–9.4)
Difference between observed under-five mortality (year 2015) and achievable under-five mortality from folic acid interventions = [47.7/1,000 live births] – [43.8/1,000 livebirths]	3.9/1,000 livebirths
Proportional contribution of preventing FAP SBA to SDG on reducing under-five mortality = [47.7/1,000 live births (observed) – 25/1,000 live births (SDG Goal)] = 22.7/1,000 live births = [3.9/1,000 live births (with folic acid interventions)/22.7/1000 live births (needed reduction for SDG)]	17.2% (13.8%–22.4%)

FAP, Folic acid-preventable; SBA, spina bifida and anencephaly; SDG, Sustainable Development Goals; UI, uncertainty intervals.

associated with anencephaly to have occurred in the neonatal period. This method is similar to the technique utilized by birth defects surveillance programs when reporting birth prevalence of anencephaly and spina bifida (total live- and stillbirths affected by the birth defect divided by live births only) (Williams et al., 2015). The denominator used in our estimation procedure did not include stillbirths as they are not reliably tracked in India (Bhide et al., 2013). A recent systematic analysis by Blencowe et al. (2016) reported that India has the highest number of stillbirths in the world ($n = 592,000$), and that the overall prevalence of stillbirths varies significantly worldwide with countries in the South East Asian region having an average of 25 stillbirths per every 1000 live and stillbirths combined. Their review also pointed out that prevalence estimates of stillbirths in developing countries were mostly determined based on retrospective household surveys and were an undercount. Without accounting for stillbirths in the denominator, the estimates

we used for the prevalence and mortality for spina bifida and anencephaly may overestimate our findings on achievable prevention of FAP SBA prevalence and associated child mortality. We opine that even if there were a million stillbirths in India each year, accounting for them in the denominator would slightly reduce the prevalence of anencephaly to the most extent (as large proportion of anencephaly-affected fetus are misclassified as neonatal deaths), but would not alter the overall results significantly. Additionally, anencephaly- and spina bifida-affected pregnancies that result in still births are often underreported, which results in an underestimate of total prevalence of these defects. If this phenomenon is true in India, it can counterbalance the overestimate of prevalence we discussed earlier by not including stillbirths in the denominator. A robust surveillance of all pregnancy outcomes can help overcome limitations in the assessment of prevalence and mortality associated with spina bifida and anencephaly. Results from our analysis should be interpreted as best estimates available with current data, and

have a potential for improvement as better data become available in the future.

The main strength of our analysis is the application of recent knowledge on preventable cases of spina bifida and anencephaly. A non-folic acid preventable spina bifida and anencephaly prevalence in populations has been established by Crider et al. (2014) which is approximately 0.5 per 1,000 births (baseline). Any prevalence above this baseline is shown to be preventable in many countries through mandatory fortification of staples (Atta et al., 2016; Williams et al., 2015). We applied this information in our analysis for estimating the number of FAP SBA in India, a similar approach followed in our previous publication on preventable cases of SBA worldwide (Arth et al., 2016). Developing countries have high baseline prevalence of spina bifida and anencephaly reaching up to 5 per 1,000 births (Christianson et al., 2006). We show in our analysis that a prevention percent can be variable, with higher reductions in countries with a high baseline prevalence of spina bifida and anencephaly and where nutritional deficiencies are significantly higher compared to developed countries, and thus increase the risk of spina bifida and anencephaly several folds.

Mandatory fortification of staples with folic acid would be a cost-effective and efficient primary approach for addressing FAP SBA (Atta et al., 2016; Grosse et al., 2016). Fortification can be implemented quickly in urban and semi-urban areas where a majority of women of reproductive age eat centrally processed wheat and rice. As a second strategy, India's Public Distribution System, which provides subsidized food to the poor, could be considered for distribution of fortified wheat flour and rice instead of un-milled grains. Third, technologies that facilitate fortification of staples at small-scale or home-based mills may find success in rural areas. Finally, high-cost, targeted folic acid supplement pill programs for women of reproductive age may be needed in hard-to-reach pockets of the country.

In conclusion, preventing FAP SBA would immediately prevent ∼100,000 child deaths in India, leading to reductions in neonatal, infant, and under-five mortality rates. We can also expect large reductions in perinatal mortality associated with FAP SBA. The prevention of FAP SBA should be given a high priority in India because it is a cost-effective, prompt, and a sustainable way to achieve about 18% and 17% of reductions needed for India to reach Target 3.2 SDGs by year 2030, for neonatal and under-five mortality, respectively. In addition, a similar strategy can be employed in all countries to reduce child mortality through effective folic acid programs such as mandatory fortification of staple foods.

CONFLICT OF INTEREST

The authors have no financial relationships relevant to this article to disclose.

ORCID

Vijaya Kancherla http://orcid.org/0000-0002-2803-8030

REFERENCES

Ahrens, K., Yazdy, M. M., Mitchell, A. A., & Werler, M. M. (2011). Folic acid intake and spina bifida in the era of dietary folic acid fortification. *Epidemiology*, *22*, 731–737.

Allagh, K. P., Shamanna, B. R., Murthy, G. V., Ness, A. R., Doyle, P., Neogi, S. B., & Pant, H. B.; Wellcome Trust-PHFI Folic Acid project team. (2015). Birth prevalence of neural tube defects and orofacial clefts in India: A systematic review and meta-analysis. *PLoS ONE*, *10*(3), e0118961.

Arth, A., Kancherla, V., Pachón, H., Zimmerman, S., Johnson, Q., & Oakley, G. P., Jr. (2016). A 2015 global update on folic acid-preventable spina bifida and anencephaly. *Birth Defects Research Part A Clinical and Molecular Teratology*, *106*(7), 520–529.

Atta, C. A., Fiest, K. M., Frolkis, A. D., Jette, N., Pringsheim, T., St Germaine-Smith, C., ... Metcalfe, A. (2016). Global birth prevalence of spina bifida by folic acid fortification status: A systematic review and meta-analysis. *American Journal of Public Health*, *106*(1), e24–e34.

Berry, R. J., Li, Z., Erickson, J. D., Li, S., Moore, C. A., Wang, H. ... Correa, A. (1999). Prevention of neural-tube defects with folic acid in China. China-U.S. Collaborative Project for Neural Tube Defect Prevention. *New England Journal of Medicine*, *341*(20), 1485–1490.

Bhide, P., Sagoo, G. S., Moorthie, S., Burton, H., & Kar, A. (2013). Systematic review of birth prevalence of neural tube defects in India. *Birth Defects and Research Part A Clinical and Molecular Teratology*, *97*(7), 437–443.

Blencowe, H., Cousens, S., Jassir, F. B., Say, L., Chou, D., Mathers, C. ... Lawn, J. E.; Lancet Stillbirth Epidemiology Investigator Group. (2016). National, regional, and worldwide estimates of stillbirth rates in 2015, with trends from 2000: A systematic analysis. *Lancet Global Health*, *4*(2), e98–e108.

Castillo-Lancellotti, C., Tur, J. A., & Uauy, R. (2013). Impact of folic acid fortification of flour on neural tube defects: A systematic review. *Public Health Nutrition*, *16*, 901–911.

Christianson, A. L., Howson, C. P., & Modell, B. (2006). *Global report on birth defects: The hidden toll of dying and disabled children*. White Plains (NY): March of Dimes Birth Defects Foundation.

Crider, K. S., Devine, O., Hao, L., Dowling, N. F., Li, S., Molloy, A. M., ... Berry, R. J. (2014). Population red blood cell folate concentrations for prevention of neural tube defects: Bayesian model. *BMJ*, *349*(29), g4554.

Darmstadt, G. L., Howson, C. P., Walraven, G., Armstrong, R. W., Blencowe, H. K., Christianson, A. L. ... Walani, S. R.; Participant Working Group of the Dar es Salaam Seventh International Conference on Birth Defects and Disabilities in the Developing World. (2016). Prevention of congenital disorders and care of affected children: A consensus statement. *JAMA Pediatrics*, *170*(8), 790–793.

De Wals, P., Tairou, F., Van Allen, M. I., Uh, S. H., Lowry, R. B., Sibbald, B. ... Niyonsenga, T. (2007). Reduction in neural-tube

defects after folic acid fortification in Canada. *New England Journal of Medicine*, *357*, 135–142.

Grosse, S. D., Berry, R. J., Tilford, J. M., Kucik, J. E., & Waitzman, N. J. (2016). Retrospective assessment of cost savings from prevention. Folic acid fortification and spina bifida in the U.S. *American Journal of Preventive Medicine*, *50*(5 Suppl 1), S74–S80.

Elwood, J. H. (1970). Anencephalus in Belfast: Incidence and secular and seasonal variations, 1950-66. *British Journal of Preventive & Social Medicine*, *24*(2), 78–88.

Elwood, J. H., & Nevin, N. C. (1973). Anencephalus and spina bifida in Belfast (1964–1968). *Ulster Medical Journal*, *42*(2), 213–222.

Lawn, J. E., Blencowe, H., Pattinson, R., Cousens, S., Kumar, R., Ibiebele, I., ... Stanton, C.; Lancet's Stillbirths Series steering committee. (2011). Stillbirths: Where? When? Why? How to make the data count? *Lancet*, *377*, 1448–1463.

MacMahon, B., & Yen, S. (1971). Unrecognised epidemic of anencephaly and spina bifida. *Lancet*, *1*(7688), 31–33.

Moore, C. A., Li, S., Li, Z., Hong, S. X., Gu, H. Q., Berry, R. J., ... Erickson, J. D. (1997). Elevated rates of severe neural tube defects in a high-prevalence area in northern China. *American Journal of Medical Genetics*, *73*(2), 113–118.

Mosley, B. S., Cleves, M. A., Siega-Riz, A. M., Shaw, G. M., Canfield, M. A., Waller, D. K. ... Hobbs, C. A.; National Birth Defects Prevention Study. (2009). Neural tube defects and maternal folate intake among pregnancies conceived after folic acid fortification in the United States. *American Journal of Epidemiology*, *169*, 9–17.

MRC Vitamin Study Research Group. (1991). Prevention of neural tube defects: Results of the Medical Research Council Vitamin Study. *Lancet*, *338*(8760), 131–137.

Murray, C. J. L. (2015). Shifting to sustainable developmental goals: Implications for global health. *New England Journal of Medicine*, *373*(15), 1390–1393.

Oakeshott, P., Hunt, G. M., Poulton, A., & Reid, F. (2010). Expectation of life and unexpected death in open spina bifida: A 40-year complete, non-selective, longitudinal cohort study. *Developmental Medicine & Child Neurology*, *52*(8), 749–753.

Oakley, G. P. Jr. (2009). The scientific basis for eliminating folic acid-preventable spina bifida: A modern miracle from epidemiology. *Annals of Epidemiology*, *19*(4), 226–230.

Shurtleff, D. B., Luthy, D. A., Nyberg, D. A., Benedetti, T. J., & Mack, L. A. (1994). Meningomyelocele: Management in utero and post natum. *Ciba Foundation Symposium*, *181*, 270–280.

Sustainable Developmental Goals. (2015). Sustainable Development Goals. Available at: https://sustainabledevelopment.un.org/sdgs. Accessed May 3, 2017

Sutton, M., Daly, L. E., & Kirke, P. N. (2008). Survival and disability in a cohort of neural tube defect births in Dublin, Ireland. *Birth Defects and Research Part A Clinical and Molecular Teratology*, *82*(10), 701–709.

United Nations. (2015). The United National Inter-Agency Group for Child Mortality Estimation (IGME)—Levels and Trends in Child Mortality Report, 2015. Available at: http://www.childmortality.org/files_v20/download/igme%20report%202015%20child%20mortality%20final.pdf. Accessed May 1, 2017

Wang, Y., Hu, J., Druschel, C. M., & Kirby, R. S. (2011). Twenty-five-year survival of children with birth defects in New York State: A population-based study. *Birth Defects Research Part A Clinical and Molecular Teratology*, *91*(12), 995–1003.

Williams, J., Mai, C. T., Mulinare, J., Isenburg, J., Flood, T. J., Ethen, M. ... Kirby, R. S. (2015). Updated estimates of neural tube defects prevented by mandatory folic acid fortification—United States, 1995–2011. *Morbidity and Mortality Weekly Report*, *64*(1), 1–5.

World Health Organization. (2004). The Atlas of Country Resources for Neurological Disorders, WHO and the World Federation of Neurology, 2004. Available at: http://www.who.int/mental_health/neurology/neurogy_atlas_lr.pdf?ua=1; Accessed June 11, 2017

You, D., Hug, L., Ejdemyr, S., Idele, P., Hogan, D., Mathers, C. ... Alkema, L. (2015). Global, regional, and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: A systematic analysis by the UN Inter-agency Group for Child Mortality Estimation. *Lancet*, *386*(10010), 2275–2286.

World Health Organization. (2015). Neonatal-perinatal database and birth defects surveillance. Report of the regional review meeting. Available at: http://www.searo.who.int/entity/child_adolescent/documents/sea-cah-23/en/ Accessed June 11, 2017