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The Unresolved Tragedy of Neural-Tube Defects in India: The Case for Folate- and Vitamin-B_{12}-Fortified Tea for Prevention

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…Thy centuries follow each other perfecting a small wild flower.

We have no time to lose, and therefore with us there is such a mad scramble for opportunities.

We are too poor to be late…

-*Rabindranath Tagore* (#64 ["Endless Time"] from the original translation of *Gitanjali* into English by Gurudev Rabindranath Tagore and preserved by his close friend William Rothenstein in the 'Rothenstein manuscript' at Harvard University).

Scenario of Neural-Tube Defects in India

Nearly 60% of children who require the services of a pediatric surgeon in India have a birth defect that warrants one or more corrective procedures. The prevalence of birth defects in India ranges from 60 to 70 cases per 1000 live births.[1] The number of babies born with Neural-Tube Defects (NTDs), which involve severe life-threatening birth defects of the brain and/or spinal cord, ranges from 4 to 8 NTDs per 1000 live births. Using data predominantly derived from tertiary centers in India, a conservative estimate is that 4.1 babies are born with NTDs per 1000 live births.[2] Based on 26-million births annually in India, this translates to well over 100,000 babies born with NTDs every single year – without accounting for an unknown number of stillbirths with NTDs. However, in two population-based (door-to-door) studies from Uttar Pradesh (U. P.),[3,4] each carried out a decade apart, the incidence of NTDs was much higher, with up to 8.2 and 7.48 babies with NTDs per 1000 live births, respectively.[3,4] The fact that there are an additional 168 districts with similar deficits in health, social, and economic development throughout North India (as found in U. P.[3,4]) suggests that the high number of babies with NTDs is a widely spread problem across India [Figure 1].

Today, the world community would unanimously agree that any disease in any country that leads to the permanent crippling of 100,000 babies every single year is, by definition, a profoundly serious endemic problem that warrants immediate attention. Thus, upon receipt of such alarming data, one can reasonably expect the highest authority of the land to prioritize the reversal of this tragic situation. This would necessitate gathering the best minds in the country together, charging them to expeditiously identify a practical solution, and then providing unlimited resources to galvanize a massive force to effect prompt corrective action. And then to reassess the results of such action over time to ensure the long-term effectiveness of this policy.

The fact is that the solution to preventing nearly three-quarters of all NTDs worldwide has been known for three decades.[5] The solution is well established, is surprisingly simple, and cheap.[6] The key is to ensure that the folate status of all women of childbearing age is optimized prior to conception[7] by administration of folic acid. In the past two decades, over 80 countries recognized the serious problem of NTDs within their borders, and adopted proactive methods to ensure that all women of childbearing age are protected (from a low folate status before conception). This has been efficiently accomplished by the fortification of staple foods (such as wheat flour) with folic acid.[8]

One might have predicted with a high level of certainty that India would have been among the first countries to pick up the gauntlet to execute a corrective action against the high incidence of NTDs, and that the highest powers in the land would galvanize forces "on a war footing" to develop focused, science-based evidence to eliminate the ongoing tragedy engulfing her most treasured resource – her women and children.

The unfortunate and troubling fact is that the Government of India has neither acknowledged the problem nor made a robust focused effort to seek a solution within the shortest possible time. This tragic inaction has permitted the birth of up to 300 babies being born with NTDs every single day, resulting in yet another 3-million more babies with NTDs born in India over the past three decades. By contrast, several other resource-limited countries implemented the solution using folate-fortified food. This "silent scandal of inaction" warrants urgent corrective action.

In this Editorial, we provide the basis for a better understanding of the magnitude of the problem, the research-based evidence for primary prevention of NTDs, and then trace how other countries strived to reduce NTDs. While acknowledging some logistical problems that may have contributed (in part) to the lack of adoption of a uniquely Indian solution (discussed below), we will highlight our own work toward a practical solution that was recently published in a respected, peer-reviewed specialty journal from the *British Medical Journal* (BMJ) group: *BMJ Nutrition, Prevention & Health*; this points to a uniquely Indian path out of this thorny problem of NTDs in India. We remain optimistic that change will happen because the light at the end of the tunnel is much more than a glimmer of hope.

Prevention of Neural-Tube Defects with Folate

Despite the shroud of dark clouds accompanying the birth of babies with NTDs worldwide, there were shining beacons of hope pointing a way forward in the decade before, and then in the 1990s. In 1992, a randomized controlled trial from Hungary[10] demonstrated conclusively that the first occurrence of NTDs could be prevented if prospective mothers consumed a little less than a milligram of folic acid daily to ensure they had sufficient folate in their body before they conceived. [6,9,10,11,12] This is because the decision on whether or not a baby develops a NTD occurs by the end of the very 1st month of conception. A year earlier, a randomized controlled trial from the Medical Research Council (U. K.) studied women who had previously given birth to a baby with NTD – this was a trial for the prevention of a recurrence of NTDs; such women have a 10-fold increased risk for having a subsequent baby with NTD. Those women treated with 4-mg folic acid daily before conception and throughout pregnancy also had a nearly 75% protection against delivery of a subsequent baby with NTD.[9] A clue to the reason for such protection comes from experimental studies in mice which show that blocking the entry of folate (via folate receptors[13,14,15]) into specialized cells that comprise the developing neural-tube predictably leads to NTDs;[16,17] conversely, overcoming this block with excess folate (that passively enters cells to reverse the block) allowed for normal neural-tube closure.

The best confirmation on the extent of protection of first occurrence of NTD comes from a China–US collaborative project – a massive community interventional trial on the prevention of NTDs with folic acid among 247,831 women of reproductive age.[11] This study clearly demonstrated that periconceptional supplementation with only 0.4 mg of folic acid per day can reduce NTD risk by as much as 81%.[11] Of added significance, the level of protection by folic acid was greater in those regions where there was a higher problem with low-folate status.[11](Parenthetically, because low folate and Vitamin-B_{12}status is so common among Indian women, as discussed below, it can be predicted that closer to 90% of folic acid-preventable NTDs can be achieved by a robust program to improve folate and Vitamin-B_{12}status among all Indian women. Kancherla and Oakley suggest that this can lead to prevention of over 115,000 Indian babies born with NTDs each year[18]).

Folate Fortification of Food – Experience from the West

Knowledge of the importance of sufficient folate in the mother prior to conception being protective (so very early in the developing baby) did not immediately translate into a dramatic reduction in NTDs even in the West. The reasons were threefold: first, the average woman's diet in the USA was not sufficiently rich in folate to reduce the risk of having babies with NTD. Second, over one-half of all pregnancies are not planned so there was the problem of poor timing in consumption of folate tablets prior to conception. Third, most women do not like the idea of taking vitamin tablets throughout the childbearing age. Instead, they much rather preferred to have such vitamin supplements premixed with staple foods. Since wheat flour is prepared centrally in large roller mills in the USA and uniformly distributed throughout the country, it was chosen as an ideal food vehicle for fortification with folic acid (note: "folate" is the salt of folic acid). As a consequence, by January 1998, the US Food and Drug Administration (FDA) mandated the fortification of flour with folate (140 μg of folic acid added for each 100 g of flour) to prevent NTDs.[5,7] This led to a markedly improved serum folate concentration in the population receiving folate-fortified flour,[19] and has also substantially reduced the first occurrence of NTDs. Curiously in Canada, a reduction of births with ventricular septal defects (lay-persons terminology: "a hole in the heart") was also noted;[20] this is not entirely surprising because folate is essential for the normal functioning of embryonic and fetal cells that are responsible for developmental closure of many midline structures (apart from the neural tube).[21] Thus, among the many neural-crest cells, some are also responsible for ventricular septal closure.[21]

The entire saga related to the discovery of the role of folate in the prevention of NTDs and its successful implementation in several countries resulting in a documented reduction of NTDs is clearly one of the major success stories of preventive medicine in this century.

The Unaddressed Problem of Neural-Tube Defects in India

The overwhelming success in both USA and Canada with folate fortification of wheat flour for the prevention of NTDs led to extension of this practice globally to include over 80 countries that have mandated folate fortification of industrially milled cereal grain. However, this has not been an easy task for India because of some (admittedly) unique and interrelated stumbling blocks that have coalesced to thwart progress in the prevention of NTDs in India.

First, the conventional Indian diet poses serious risks for prospective mothers. This stems from the fact that the average Indian diet is relatively monotonous and does not contain sufficient folate or Vitamin B_{12}. Indeed, there is a high incidence of dietary low-folate and low-Vitamin-B_{12}status (estimated in two-thirds to three-quarters of Indian women), and among vegetarians as well as nonvegetarians in India;[22,23] in fact, the diet among professed nonvegetarians is more accurately described as "near-vegetarian." Since Vitamin $B_{12}$is essential for folate to function properly in all cells,[7,24] any plan to supplement Indian women with folate must include sufficient Vitamin B_{12}. However, despite knowledge of the widespread problem of folate and Vitamin-B_{12}deficiency in India,[23] there has not been a sufficiently strong response to effect meaningful change to the status quo. The Government of India does have a program for weekly distribution of supplements containing a combination of iron-folic acid tablets (composed of 100-mg elemental iron and 500-µg folic acid) with the hope of improving the iron and folate status of women of childbearing age. However, in practice, adolescent and young women that we have encountered have uniformly admitted to poor compliance (adherence) in taking these tablets regularly; this is invariably triggered by the well-known side effects of oral iron on the gastrointestinal system. A significant clue to the high incidence of iron and folate deficiency can be deduced in data from Dibrugarh, Assam, where only 15% of women actually completed a course of iron-folate tablets given them;[25] this is not likely to be different throughout India, and probably contributes to the high incidence of anemia and NTDs in Assam (Personal Communication: Professor Hemonta Kr. Dutta, Pediatric Surgeon, Assam Medical College). Finally, the fact that there are hundreds of millions of women of childbearing age in India with a low Vitamin-B_{12}status has not yet been meaningfully addressed by the Government of India.

Second, there are several inherent logistical problems that preclude the successful deployment of centrally-processed folate-fortified flour to reach all Indian women to prevent NTDs. For example, after folate fortification of flour centrally in large roller mills for milling cereal, which usually occurs in larger cities, folate-fortified flour must be widely distributed to reach populations living in the smallest towns, villages, and hamlets throughout India. This poses insurmountable challenges for India, where 70% of the population live in over 650,000 villages, cereal grain is more often grown and purchased locally, and flour is prepared by small-scale millers in towns and villages; this effectively bypasses any need by the local population for centrally-processed folate-fortified flour. This predicts that India is unlikely to achieve a robust folate-food fortification program solely using wheat flour. Currently, in addition to folate-fortified wheat flour, rice and salt are also being examined as food vehicles. However, the success of the utility of each of these food vehicles will necessarily be restricted by the extent to which each of these fortified foods is efficiently distributed and eventually consumed by women living in the smallest hamlets of India. In this context, it should also be noted that Indians actually consume several types of whole grains, which largely depends on geographic and climactic conditions that permit the growth of one or more grains in a given region; such grains include wheat (*gehu*), rice (*chawal*), pearl millet (*bajra*), finger millet (*ragi*), sorghum (*jowar*), and corn/maize (*makka*). Thus, even within a single large state, because of the predilection for purchasing grains locally, there may be different forms of grains consumed by a single family. This fact can potentially complicate, confound, and crimp the widespread utility of folate- and Vitamin-B_{12}-fortified wheat flour (or rice) by Indians. An additional challenge relates to the visual (organoleptic) properties conferred on these foods by the yellow color of folate and the red color of Vitamin B_{12}. Indeed, the broad challenge in identifying a common food-based vehicle that is acceptable to all Indian women of every geographic, social, economic, cultural, ethnic distinction (whose diet is dictated by these very differences) is a formidable one.

Tea – A Uniquely Indian Universal Food Vehicle for Fortification with Folate and Vitamin B_{12}

We postulated that tea, the most common beverage of choice after water, met all the criteria as an ideal, contextually appropriate, food vehicle for fortification with folate and Vitamin $B_{12}$to replenish ~500-million girls and women in India. Most of the 1200-million kg of tea grown annually is largely processed in tea plantations from four states of India – Assam, West Bengal, Tamil Nadu, and Kerala. Moreover, the vast majority of Indians from every geographical area within India – from megacities to the smallest towns, villages, and hamlets – consume at least one cup of tea from one of these regions every day. Therefore, tea retains a unique role by being a common "food" that is consumed despite the otherwise extremely diverse food preferences of Indians. Moreover, both Vitamin $B_{12}$and folic acid are heat stable at the temperatures used to make hot tea; do not change the color, taste, or aroma of tea; and are nontoxic, with prompt excretion of any excessive vitamin intake in the urine. Like high-grade folate and Vitamin B_{12}, the vitamin-fortified tea would also exhibit a long shelf life at room temperature when stored in dark containers that tea leaves are traditionally stored in.

The immediate challenge was to experimentally show that tea is an efficient vehicle for fortification with these vitamins. We had confirmed that nearly all 60 young women (who were nursing students at a college in Sangli, India) had low-folate status and nearly two-thirds had a low-Vitamin-B_{12}status, similar to that of women in the nearby city of Pune.[26] Accordingly, in another group of 43 young Indian women (nursing and homeopathy students in Sangli) with borderline or low-vitamin stores, [26] we determined if consumption of a single daily cup of tea prepared from teabags that were individually fortified with both these water-soluble vitamins could lead to a rise in serum folate and Vitamin B_{12}within 2 months. The "experimental group" was divided into two subgroups to receive tea from teabags fortified with two strengths of vitamins: 1-mg folate plus either 0.1-mg or 0.5-mg Vitamin B_{12}per teabag (containing 2 g of tea); one teabag was used per cup of tea. There was another small "control group" for comparison who received unfortified (mock-fortified) tea. We subsequently documented that daily use of vitamin-fortified tea for 2 months led to significant rises in their serum folate and Vitamin-B_{12}levels, and hemoglobin concentration, which signified a clinical response; by contrast, there were insignificant changes in women using daily unfortified tea.[26]

As noted above, the key to prevention of over three-quarters of NTDs lies in raising the serum folate and Vitamin-B_{12}level of Indian women prior to conception. Therefore, the fact that vitamin-fortified tea raised the serum folate level in 34 of 36 women in 2 months,[26] and also improved Vitamin-B_{12}levels in a dose-dependent manner, suggests that tea is an efficacious vehicle to rapidly replenish folate and Vitamin B_{12}in Indian women of childbearing age. In practical terms, a recent study has suggested that folate replenishment could ultimately help prevent over 115,000 babies with NTD in India each year.[18] Moreover, with a reduction of folate- and Vitamin-B_{12}- deficiency-induced anemia in Indian women, and additional evidence highlighting the importance of folate for fetal brain development, this could ensure long-lasting benefits on improved social interactions and scholastic achievement in their children; this coupled with other robust data showing the benefits of sufficient folate (and Vitamin B_{12}) in preventing strokes and Alzheimer's disease promises additional benefits to *all* adult Indians.([26] and References therein)

Thus, our paper, in the nutrition-focused specialty journal of the BMJ – *BMJ Nutrition, Prevention & Health*, in June 2021, pointed a way forward to eliminate folate and Vitamin-B_{12}deficiency in India;[26] this paper can be accessed at: https://nutrition.bmj.com/content/4/1/293.

The Logical Next Steps

1. Since our study using vitamin-fortified tea was a first-of-its-kind preliminary study in humans,[26] we will pursue a rigorous Phase III placebo-controlled randomized controlled trial format to confirm the capability of full-dose replacement doses of folate and Vitamin-B_{12}(in vitamin-fortified teabags and vitamin-fortified loose tea) to normalize the folate and Vitamin-B_{12}status and

improve hemoglobin among both urban and rural Indian women under various levels of monitoring. Such studies will also need to determine the optimum duration of the intervention to positively impact all subjects. Another second set of formal studies will be needed to determine the optimum dose (and duration) of vitamin-fortified tea required to maintain normal serum levels as women continue to consume their usual low folate and Vitamin-B_{12}diets.

2. It follows that because over three-quarters of Indian women have a low folate and Vitamin-B_{12}status,[26] there will necessarily need to be two strengths of vitamin-fortified tea: One strength of tea that is fortified with a higher full therapeutic daily dose of both vitamins (for rapid replenishment of depleted or deficient stores) will be required for almost all Indian women for at least 2–4 months initially. Then, women can switch to a second strength of vitamin-fortified tea that is fortified with a much lower (maintenance) daily dose of vitamins to allow them to maintain their folate and Vitamin-B_{12}status at optimum levels. This maintenance dose will require a minimum of 400 μg of folate per 2 g of tea to ensure that a single cup of tea daily is sufficient to maximally reduce the risk of folate-responsive (preventable) NTDs – as recommended and subsequently verified[6,20] by the U. S. Public Health Service. As noted above, both folate and Vitamin $B_{12}$are not toxic, and any excess vitamins consumed in tea will be promptly excreted.[26] However, there is a great danger and risk from using suboptimal fortification doses of vitamins because the consequence will be a predictably persistent risk of NTDs. Thus, the authorities must carry out periodic re-assessments of the efficacy and effectiveness of any dose of vitamins used for fortification (of any food vehicle chosen) to ensure that it improves folate and Vitamin-B_{12}status and prevents NTDs in India.[27]
3. We will also need to study women from another Indian State, who have a distinctly different diet from women in Sangli, to help confirm that the efficacy of vitamin-fortified tea rises well above other dietary–cultural–social and ethnic differences that influence diet. Plans are being drawn out to carry out similar randomized controlled trials in the heart of a large population of underprivileged women who work in tea plantations. Indeed, any plan aspiring to use tea as a fortification vehicle to reach half a billion Indian women must necessarily be located in Assam, where one-half of all India's tea is generated. Additional consultation with the Tea Board of India and the renowned Tocklai Tea Research Center in Jorhat, and other Government agencies (such as the Food Safety and Standards Authority of India and the National Institute of Nutrition) will be required to discuss issues related to scaling up the fortification of tea within tea

factories. This is a necessary prelude to planning future clinical trials designed to confirm the effectiveness of vitamin-fortified tea in reducing the incidence of NTDs in Indian women.

Cost-Effectiveness in Prevention of Neural-Tube Defect with Vitamins

A 2016 study from the Centers for Disease Control and Prevention (USA) pointed to the lifetime costs incurred in taking care of a single baby with NTD in the USA at approximately $791,900, or $577,000 excluding caregiving costs.[28] At the current exchange rate of Rs 74 for $1, this will translate to a total cost of Rs 5,85,34,000 per baby. Even assuming medical costs in India to be one-tenth or even one-hundred times less than that of the USA, this is still a very large expense for an average primary wage earner of the family in India making Rs 372 every day.[29] Hence, if over 100,000 babies are born each year in India, how much will the lifetime medical costs, as well as other caretaking costs, for these children be? Moreover, there are the intangible costs incurred by each baby with NTDs in terms of physical, mental, and emotional suffering; in addition, there is also significant emotional, psychological, mental, and spiritual suffering for parents of an afflicted child. Their own financial troubles invariably spill over to affect the nutrition of the entire family. Finally, to allow both parents to work outside the home, the burden of caring for an affected infant can often fall on siblings which can impinge on their own educational opportunities. By comparison, the net cost of vitamin fortification (of foods like tea) with relatively cheap folic acid and Vitamin B_{12}will be far smaller.[28] Such questions merely need to be asked to make the case on the overall cost savings by vitamin fortification of tea more meaningful and essential for India.

An Example of a Successful Response to Reduce the Risk of Neural-Tube Defects

How the USA responded to reducing the annual births of <5000 babies with NTDs is an instructive example.[30] Hence, the moment the solution to preventing the first occurrence of NTDs with folic acid was published in 1992, within the same year, the U. S. Public Health Service recommended that all women who were capable of becoming pregnant should consume 400 µg of folic acid daily to prevent NTDs. And a mere 6 years later, after realizing that folic acid tablets led to poor compliance among women of childbearing age, the FDA mandated that sufficient folic acid must be mixed into wheat flour to ensure that all American women are protected from the risk of giving birth to babies with NTDs.[5,7] Important follow-up studies then identified that Hispanic women were not sufficiently being protected from NTDs because their staple food was corn flour derived (and not wheat flour). This led to a corrective action to include folic acid fortification of corn flour to resolve this oversight. Such a focused sequence of actions is an excellent blueprint for the successful control of NTDs.

Conclusion

An impartial assessment of the track record of those charged with optimizing the nutritional health of Indian women and children must lead to the conclusion that the response to prevention of NTDs has been wholly unsatisfactory. The Government of India's response in blatantly ignoring the distressing problem of NTDs is unacceptable. The lack of accountability for developing a comprehensive and cohesive strategy for prevention of NTDs over the past three decades is deeply disturbing, and it will be the purview of medical historians to unravel the basis for this tragedy. There is also an ever-present danger that Indian policy-makers and health-care leaders who are not active in practice (and therefore do not see the suffering of toddlers and children with NTDs with any regularity, and have never had to look into the eyes of the mothers who care for them) may continue to view this entire topic of prevention of NTDs with skepticism, and deem it a low priority. However, such a callous disregard for human life, when left unchallenged, can devolve into a progressive downward spiral in values that eventually rests comfortably and ossifies into a fatalistic belief that nothing can be done. The deafening silence of the Indian media on the many facets of NTDs in India also defies explanation – one can only speculate a serious dearth of high-quality Indian journalists specializing in news on science.

In stark contrast, the massive and highly successful Pulse Polio immunization campaign established by the Government of India (to eliminate poliomyelitis, another crippling disease that is of a far lesser magnitude than NTDs) points to a high degree of competence – and a triumph of India's finest leaders in policy-making, logistics, and implementation. This Editorial is written in the hope that India can rise to the challenge to do the same with prevention of NTDs, especially because a contextualized solution using a daily hot cup of vitamin-fortified tea promises to be within reach of all Indian women.

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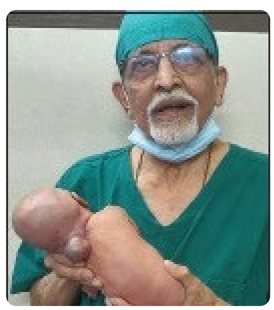
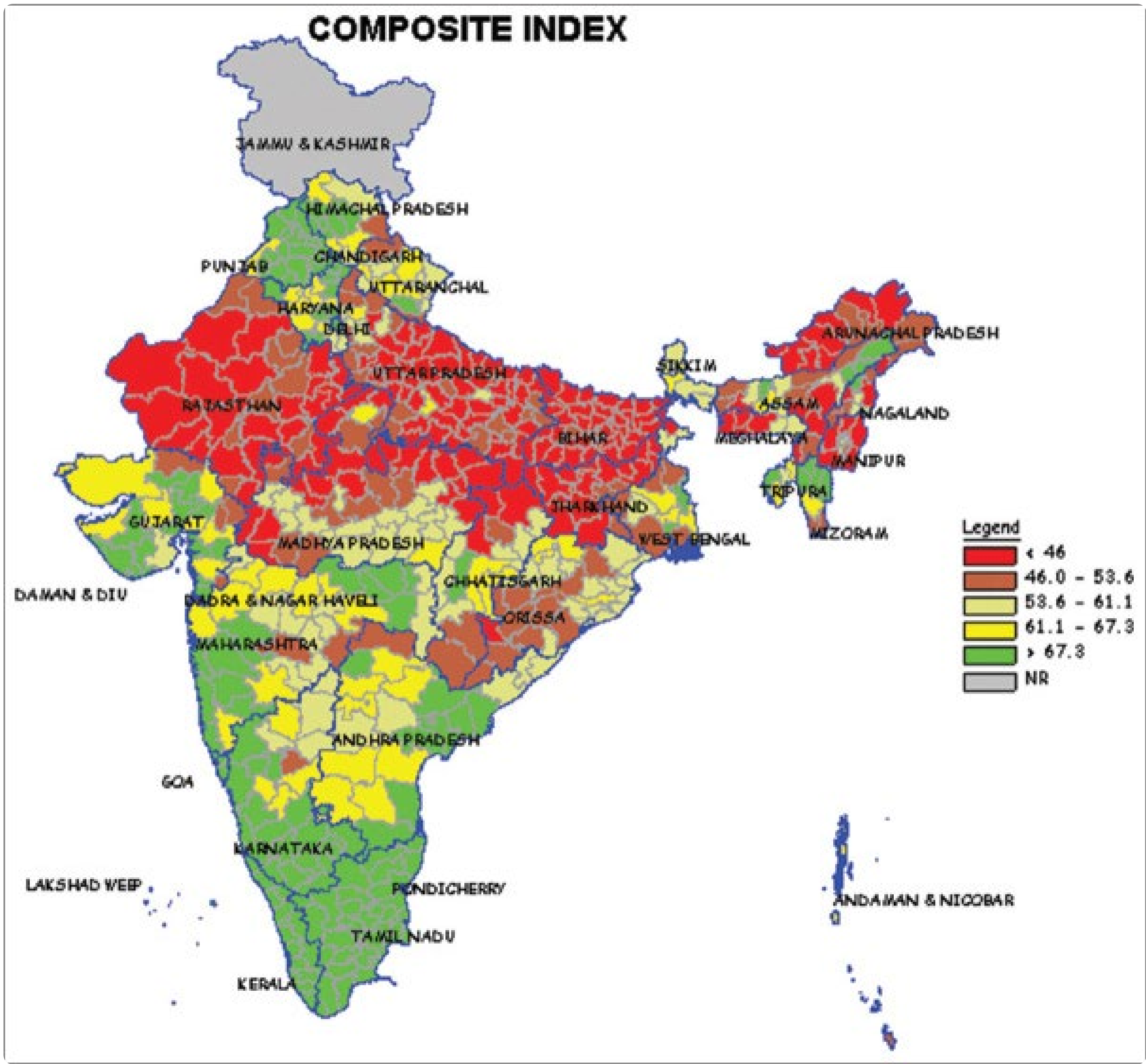
Figures and Tables



Ravindra M. Vora

Figure 1



A Map of the Indian Government's National Commission on Population Report (Government-of-India, http://populationcommission.nic.in: 80/mapbased.htm) National Commission on Population Report (accessed August 4, 2004) highlights the composite index of major health, social, and economic indices, which paints a detailed portrait of the general state of the health of various communities within the many States of India. The composite index employed 12 variables including population growth, births, deaths, safe water and sanitation, female literacy rates, child marriage, fertility, family planning, sex ratio, immunization, access to skilled obstetric care, and connection to other villages via paved roads. (See legend on the Right of the Map for color codes that signify the composite index score of each region studied throughout India). Balrampur district (located just above the alphabets 'SH' in UTTAR PRADESH), in the northeastern side of the most populous North Indian State of Uttar Pradesh of ~200 million, borders Nepal, and shaded in Red, is at the very bottom of the list of the Government of India's health–social–economic–composite index. This district, which had a composite index <46, had the highest incidence of neural-tube defects (up to 8.2 per 1000 live births).[3] There are an additional 168 districts, primarily in North India, with comparable composite index values as Balrampur district, consistent with widespread and serious deficits in health, social, and economic development throughout North India. Footnote to Map:

This Map, which was originally accessed from the Government of India's National Commission on Population Report in 2004, was used (and referenced) in the Discussion section of the Lancet paper[3] to provide a wider context to the work on neural-tube defects in India. This map was later accessed in May 2006 and referred to on the topic of folate deficiency and neural-tube defects in a supplement published in the American Journal of Clinical Nutrition (Antony AC. In utero physiology: Role of folic acid in nutrient delivery and fetal development. Am J Clin Nutr 2007;85:598S-603S) following a National Institutes of Health (USA)-sponsored conference at Baylor University, Texas, USA. This Map and related data were inexplicably removed from the website sometime after these publications, and no one in the Indian Ministry of Health has responded to repeated requests for clarity on this important work. Hence, it is retained to accompany this Editorial for both historical value and as the only available map on this topic that was originally generated by the Government of India.