Response to Dr. Tarqui-Mamani's letter to the Editor

Measuring the effects of the Peru's national folic acid fortification program—differing methods, same goal

We would like to give a heartfelt thanks to Dr. Tarqui-Mamani for her diligent efforts to decrease neural tube defects (NTD) in Peru.

We recognize that differences between studies may occur, and that it is possible that the differences found between Dr. Tarqui-Mamani's NTD data (as stated in her letter) and our study, "Peru's national folic acid fortification program and its effect on neural tube defects in Lima," (1) could be due to a difference in methods. Moreover, we recognize there are limitations to epidemiology studies employing the *International Classification of Diseases, 10th edition* (ICD-10) (2). Limitations of under-reporting are due to a lack of space on data forms; omissions by coders; and diagnoses made in hospital, but not included on discharge records; whereas limitations of over-reporting occur when the diagnosis made by the clinician or entered by a clerk is selected in error (3). Concordance of ICD-10 to actual disease incidence can range from 56%–98% in other studies, with the majority showing under-reporting (not over-reporting) of the actual disease by the ICD-10 data (4–7). Overall, in large patient-number studies, under- and over-reporting errors may have less impact when measuring trends, since error rates would be expected to remain generally constant.

Measuring diseases that occur in the 0.5–2 per 1 000 range is difficult. One to two additional random cases in a year can change a rate by 30% or more. This is especially true when measurements are taken at only one site (e.g., the studies in Peru and Brazil (1, 8), giving random variation a more dramatic impact. We currently do not know whether NTDs in Peru are under- or over-reported by ICD-10 databases. While reviewing charts to identify errors can be helpful, it is impractical in studies involving thousands of patients. Thus, large studies must ultimately rely on electronic records and databases.

In studies of congenital defects, it is important to use *total* births (live and stillbirths). Studies by Tarqui-Mamani and colleagues (9) give an NTD rate as 13.6/10 000 (all subsequent NTD rates given as per 10 000) and a range of 11.2—17.9 (10). These papers seem to indicate that live births were being used as the denominator, since live births were mentioned 10 times and total births (live plus still) were not mentioned. Measuring total births is important because 22.3% of all NTDs can be stillbirths (11)—as found in the large Latin American database, Estudio Colaborativo Latino Americano de Malformaciones Congénitas (ECLAMC)—and these would not be counted in a live-birth-only data set.

If Tarqui-Mamani and colleagues are using live births as the denominator in their study, and we adjust for total births by adding 22.3%, their pre-fortification study's range becomes 13.7–21.9. This overlaps with our range of 16.6–22.1, and our average rate of 19.7 (1), showing no significant difference.

Tarqui-Mamani and colleagues' post-fortification letter states an average rate of 8.7. If we again adjust for total births, the post-fortification rate becomes 10.7. The decrease reported in Dr. Tarqui-Mamani's letter is 36%, while our data showed no significant post-fortification change (1). Unfortunately, the range and confidence intervals are not stated in her letter, and thus, we cannot determine the statistical difference between our studies. We believe larger studies, at multiple sites, are the best way to determine the overall effect of Peru's fortification program.

We find the data from our study methods to be credible because: (a) it is consistent with the ECLAMC South American data covering over 130 000 *total* births per year, where in 1999–2003, the overall NTD rate was 20.3, and in 2004–2008, it was 17.0 (11); (b) the numbers are close to those of neighboring Chile, where Hertrampf and colleagues found a pre-fortification rate of 17.1 (12); (c) the numbers are similar to those of a preliminary study we carried out with similar ICD-10 search strategy at Hospital Edgardo Rebagliati Martins, in Lima, where the prevalence was 20.1 in 2004 and 20.5 in 2008 (13); (d) there is a prior precedent of a study in Brazil (8) where folic acid fortification was below WHO-recommended levels and showed no significant NTD rate change; and (e) the coding system remained constant during the study period, and there was no reason to suspect a change in entry error rates. Lastly, while serum folate levels in other countries doubled or tripled post-fortification, with levels increasing to a range of 25.6–37.2 ng/ml range (14, 15), the only published post-fortification data on serum folate levels in Peruvians, show levels have remained low, with 22% under 5.38; 69% in the 5.38–15.19 range; and only 9% over 15.22 ng/ml (16). While this is a small study of an older Peruvian population, it is expected that universal fortification would have roughly equal effect throughout a population. This suggests that current folate intake remains suboptimal in Peru.

All these points highlight three issues larger than methodology. First, all data show that NTD rates in Peru remain above the achievable rate of prevention of 5.0 (17). Regardless of which method is preferred, there is a 75%–400% epidemic of NTD in Peru; yet, Peru's fortification law remains the fifth lowest in the world. Much more can and should be done to achieve folic acid consumption above the WHO-recommended 400 mg/day for every woman of childbearing age. This may be achieved in Peru through additional fortification of wheat flour (at least up to WHO recommended levels), and through fortification of rice, as is done in Costa Rica, getting folic acid to those whose primary source of carbohydrate is not wheat flour. Second, measurement needs to be ongoing and continuous. Measurements of folic acid levels in fortified food products, measurement of serum folate levels among women of childbearing age, and measurement of NTD rates throughout Peru are all needed to track

fortification's impact. Third, very large data sets are needed to accurately determine trends in rare preventable diseases. Ideally, Peru would have a national congenital disease registry, with accurately archived regional and national data, and would share this data with others, such as ECLAMC and the International Clearinghouse for Birth Defects (ICBD), ensuring improvements are achieved and maintained.

Peru is at an exciting time in its history, transitioning from developing to developed country. As this happens, it is also undergoing a neonatal healthcare shift, from solving problems caused by asphyxia and infection, to those caused by birth defects. We recognize the excellent work by Dr. Tarqui-Mamani and other capable and influential health professionals who are examining these shifts and are working to prevent these devastating illnesses. We applaud work being done to improve electronic data collection, its affordability, reliability, accuracy, and data mining capabilities. We stand united with all parents, physicians, and legislators who are currently working to quantify NTDs throughout Peru, and who are working towards complete fortification of flour and rice with folic acid so that more of the country's children may run and play, free from the ravages of this preventable disease.

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