FOLATE TASK TEAM

# LABORATORY CAPACITY BUILDING FOR FOLATE ASSESSMENT TO STRENGTHEN NTD PREVENTION

*KNOWLEDGE BRIEF*

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## *ABOUT THE FOLATE TASK TEAM*

*The Folate Task Team comprises a group of global experts and partners under the leadership of Nutrition International (NI) through GTS (Global Technical Services), all joined together to identify priority actions to reduce folate-sensitive neural tube defects, build laboratory capacity for the assessment of folate status, support research in this critical area and to facilitate access to folate-related knowledge products.*

*Nutrition International's Global Technical Services team drives continuous improvements in the quality of our programs and enables the efforts of global partners, providing technical leadership, gathering evidence and generating data, and developing innovative products and services. Our ground-breaking work is helping Nutrition International have a stronger and more meaningful impact, because it contributes to and supports policies informed by sound science and best practices. We will continue to move forward with proven methods – while exploring new approaches, forging meaningful technical partnerships, and sharing knowledge through relevant products and services – to nourish life around the world.*

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# INTRODUCTION

Neural tube defects (NTDs) are a group of severe birth defects—which include spina bifida  and anencephaly —that affect the development of the brain and spine in a fetus. In 2015, an estimated 260,100 birth outcomes were affected by NTDs around the world.[1] Of these, an estimated 57,800 resulted in stillbirths and 117,900 in under-five deaths. Scientific evidence has shown that a majority of NTDs result from an insufficiency of folate  in the mother prior to conception. The World Health Organization (WHO) recommends that at the population level, red blood cell folate concentrations should be above 906 nmol/L to prevent NTDs.[2] An insufficiency of folate below this level can result in a NTD occurring within the first 28 days of a pregnancy, often before a woman knows she is pregnant and when it is too late late for any remedial actions. Women of reproductive age (WRA) must have sufficient folate levels at least three months prior to a pregnancy to prevent NTDs.  Interventions such as mandatory large-scale food fortification with folic acid improve a population's folate status without requiring dietary change and greatly reduce the risk of NTDs, as has been shown in every country that has successfully implemented such a program.[3]

The majority of NTD-affected pregnancies occur in low- and middle-income countries in Asia and Africa where there is no fortification and little surveillance on folate status or NTD-affected pregnancies.[1,3] In 2018, the Micronutrient Forum published a Roadmap for Action with eight technical reports to serve as a guide to harmonize global NTD prevention efforts.[4] This Roadmap recommended that governments implement triple surveillance to monitor:

1. Folate status of the population
2. Birth outcomes
3. Resulting impact on society.[5]

As the first step in triple surveillance, the Roadmap highlighted that it is essential for laboratories around the world to conduct a harmonized assessment of folate status in the population, so that results can be comparable across laboratories and countries. Currently, the scarcity of high quality data hinders many governments from taking action to prevent NTDs.[6] A recent systematic review focusing on assessing folate status in WRA worldwide found that between 2000-2014 there were 45 relevant surveys conducted in 39 countries. Of these, only 11 surveys assessed folate. Furthermore, there were different methods used to assess folate status and few of the surveys complied with the current recommendation issued by the WHO to measure red blood cell folate by means of a microbiological assay.[7]

The Folate Task Team at Nutrition International (NI) has partnered with the Nutritional Biomarkers Branch at the Centers for Disease Control and Prevention, National Center for Environmental Health, Division of Laboratory Sciences (CDC) and the CDC Foundation (CDCF) to implement a laboratory capacity building project. This follows the recommendation found in the Roadmap for Action, as detailed in the published *Framework for laboratory harmonization of folate measurements in low- and middle-income countries and regions.*[7] This report suggests the identification and training of select regional laboratories to perform measurement of red blood cell folate applying a “harmonized” microbiological assay (MBA), utilizing common key reagents and a standardized technique.

# KEY MESSAGES

- In 2015, there were an estimated 260,100 NTD-affected pregnancies worldwide, which resulted in 57,800 stillbirths and 117,900 deaths of children less than five years of age.
- Low- and middle-income countries in Asia and Africa suffer the highest levels of NTDs per live birth.
- Mandatory large-scale food fortification of staple foods with folic acid has successfully reduced NTD prevalence in all countries that have implemented the intervention.
- Determining the folate status of WRA in a population is critical to inform the need for interventions to reduce NTDs.
- Measuring red blood cell folate concentration using a standardized microbiological assay to achieve comparable results across countries provides the best assessment of folate status.

# WHAT WE KNOW

## *Harmonization of Assessment Technique*

Until now, laboratories around the world have conducted folate status assessment using a variety of techniques, making it difficult to ensure quality of results, compare outcomes or determine the extent of folate insufficiency among the population. Harmonization of the assessment by a standardized technique and common key reagents assures comparable data across laboratories and over time.[7]

A critical aspect to harmonization of the assay is to define which technique to undertake so that laboratories around the world—including those in low resource settings—can conduct the assay, be confident in the results and provide comparable data. There are three main techniques for assessing folate, including the MBA, protein-binding assays and chromatographic assays. In 2015, the WHO recommended the MBA as the most accurate and reliable laboratory method to assess folate status in red blood cells (RBC).[2] Additional advantages of the folate MBA, particularly for low resource settings, are that the assay is relatively inexpensive and requires small sample volumes and simple instrumentation. A disadvantage of this technique is that it is lengthy due to a 40-hour incubation to allow the microorganism to grow in response to folate levels in the sample. Alternatively, protein-binding assays suffer from lack of comparability across platforms and sometimes even within a platform. Chromatographic assays are expensive and complex. Training on the MBA is suitable for laboratory capacity building because the assay can be used in low resource settings and can be readily harmonized.

Having comparable and accurate results on population folate status will help countries make the right decisions to develop and monitor nutrition intervention policies, such as mandatory food fortification with folic acid. After a baseline is conducted, it is recommended that a follow-up national survey be undertaken between one and two years after the intervention. Further follow-up should occur on average every five years afterwards to maintain surveillance of the folate status in the population and allow for any adjustment needed on the fortification levels of the food vehicle.[7] Ensuring a globally harmonized assessment of folate status allows for surveillance of the risk of NTDs around the world. It also supports a global effort to reduce the risk of NTD-affected pregnancies.

## *A Regional Approach*

Population surveys to assess folate status do not occur on an annual basis. Due to the periodic nature of surveys, as mentioned above, maintaining the laboratory proficiency on the folate MBA is difficult and the assay may have to be re-established every time a survey is conducted. To provide a continuous stream of samples to the laboratory, a regional approach is recommended where fewer laboratories serve the needs of many countries. For this, a few laboratories from each WHO region (African Region, South-East Asia Region, Eastern Mediterranean Region, Region of the America, European Region, and Western Pacific Region) would have to be trained and proficient in the folate MBA. They could then serve as resource laboratories to measure folate samples from different countries.

A typical survey of WRA may consist of 1,000-2,000 samples.[7] An average laboratory with one analyst is able to undertake roughly 10,000 samples per year. A given country will not have enough samples per year to justify maintaining its own folate laboratory. Instead, a fee-for-service regional approach will remove this burden from many countries while still allowing them to have access to reliable folate analysis.

One of the potential barriers to the regional approach is the motivation for countries to allow their samples to be shipped abroad for analysis, but there are ways to overcome this. For example, institutions may be motivated to send the samples together with laboratory personnel to gain insight into the generation and interpretation of results. In addition, brokering by an internationally recognized institution, which may serve as an umbrella organization for this network of regional laboratories, could facilitate the process.

## *Building Capacity of Laboratories*

In order to select laboratories to serve as regional resource centres, a number of selection criteria are proposed. These include experience and proficiency in performing the folate MBA, the capability to direct purchase expendable chemicals and laboratory supplies, infrastructure (including access to reliable electrical power and other equipment), and the ability to analyze samples from other countries. Additional criteria are mentioned in the article *Framework for laboratory harmonization of folate measurements in low- and middle-income countries and regions.*[7]

While developing this project, the Folate Task Team and the CDC team noted the importance of approaching capacity building as hierarchy of needs, including 1) structures, systems and roles, 2) staff and infrastructure, 3) skills, and 4) tools, as described by Potter and Brough.[8] These four categories of need feed iteratively into each other such that, for a capacity building project to be successful, it should address all levels of the hierarchy to support the project.

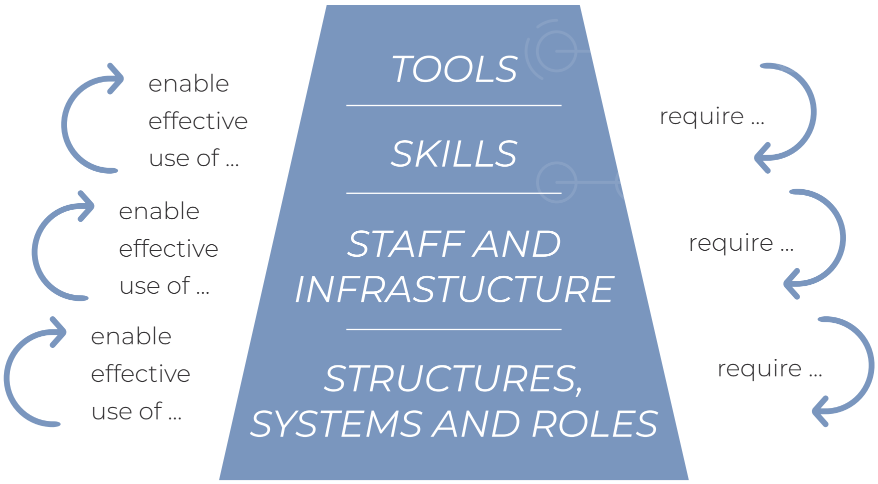


Fig.1. Potter, C. & R. Brough. 2004. Systemic capacity building: a hierarchy of needs. Health Policy and Planning. 19(5): 336 – 345.

By designing the capacity building project following this guiding framework, the project has been able to provide support to the laboratories at all four levels. Tools were addressed by the CDC/CDCF training team who produced eight training posters, a detailed training manual and a 25-minute training video. The skills of the technicians were developed through the training program, and the trainers observed a significant increase in proficiency by technicians after completion of the program. For each country, two laboratory staff were selected for training, including one experienced laboratory analyst and a laboratory team leader, to retain knowledge in the laboratory while mitigating the risk of staff turnover. Staff and infrastructure needs were supported by the acquisition of critical supplies necessary for running the folate MBA, and the structures, systems and roles will be supported through the creation of a network of regional laboratories and an umbrella organization to manage this relationship.

In parallel to this project, the CDC is also developing a MBA kit that will support staff and infrastructure in the hierarchy of needs. This ready-to-use kit contains key components to the assay such as quality control materials, the microorganism, folate calibrator, and other pre-aliquoted reagents that need to be added to the growth medium at the time of preparation.[7] The CDC will also design a performance verification program that addresses the tools category of the capacity building pyramid, and is essential to ensuring the sustainability of the project through the maintenance and documentation of proficiency by the laboratories.

## *Training video*

A critical contribution to the training was the production of a training video. The project's second cohort of laboratory trainees were able to study the training video prior to attending the training program, which significantly improved pre- and post-training comprehension, as assessed through written evaluations. In addition, the availability of the training video reduced the in-person training schedule from two weeks to five days. This significantly lowered the cost of the training for both the CDC and NI, and reduced the amount of time laboratory technicians had to be away from their laboratories. The training video is available on the CDC Foundation website:
**https://www.cdcfoundation.org/programs/capacity-building-folate-measurement**

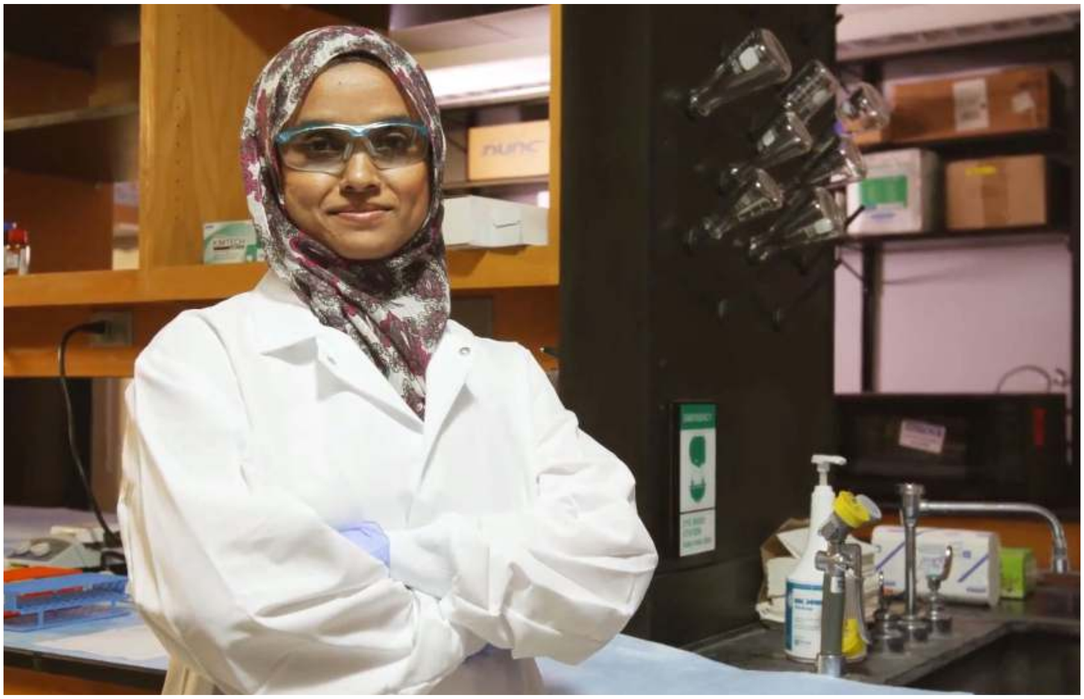


Photo credit: CDC Folate Microbiologic Assay Training Video

## *Folate task team webinar – Using laboratory folate status assessment to strengthen NTD prevention*

On March 4, 2019, the Folate Task Team hosted a webinar to commemorate the annual World Birth Defects Day. Speakers included Homero Martinez from the Folate Task Team Secretariat and Christine Pfeiffer, Team Lead for the laboratory project and Chief of the Nutritional Biomarkers Branch, Division of Laboratory Sciences at the CDC National Center for Environmental Health. Trainees from cohorts one and two who participated in the training project were also able to share their experiences. This included Renuka Jayatissa, Department Head at the Nutrition Medical Research Institute in Colombo, Sri Lanka and Kehkashan Begum, Manager of the Nutrition Research Laboratory in Karachi, Pakistan. To watch this webinar, please visit the Folate Task Team web page, **https://www.nutritionintl.org/folate-task-team/**

# WHAT'S NEXT

## *Network of Regional Laboratories and Umbrella Organization*

The Folate Task Team plans to build a network of resource laboratories that other countries can rely on to conduct the assay on a fee-for-service basis. This network would include laboratories previously trained or experienced in the folate MBA, in addition to the ones trained under this project. Sustaining this network will require the support of an umbrella organization to coordinate activities, support communication between laboratories and governments, and facilitate continuing education opportunities between member laboratories.[7] This organization will also work with governments to assist in the logistics of shipping their specimens to the regional laboratory. The Folate Task Team and the CDC will collaborate to identify and select this umbrella organization.

## *Include Other Micronutrients: Vitamin B12*

As the capacity building project unfolds, there can be several advantages to engaging the network of trained laboratories to conduct other micronutrient determinations. In particular, given the similar biochemical pathways that folate and vitamin $B_{12}$ share, it would be advantageous to assess these two micronutrients in the same laboratories. Similar to the folate MBA, there is also a MBA to determine vitamin $B_{12}$.  Accordingly, the sharing of similar supplies and equipment between these two assays reduces the need for additional resources and training. Determination of other micronutrients that may increase the value-added nature of the laboratory network will be considered in the future.

## *Food Fortification with Folic Acid*

Once a population survey is complete and the identification of folate levels categorized as insufficient occurs, interventions to address the concern for NTDs must be considered. Food fortification with folic acid is an effective, low-cost intervention that can reach large portions of a population. There are multiple factors that contribute to the success of a fortification program, including 1) that it is mandatory with coexisting quality assurance mechanisms in place, and 2) that the food vehicle selected is consumed by the majority of the population. Please refer to the Folate Task Team advocacy brief *The importance of folic acid food fortification to prevent neural tube defects* (**https://www.nutritionintl.org/resources/advocacy-brief-folic-acid-food-fortification/)** for more information.

# TAKE AWAY MESSAGES AND ACTIONS

## *For Decision-Makers*

- A harmonized assessment of folate status in the population will allow results to be comparable across laboratories and countries, which will help determine the occurrence of NTDs in a population and guide decisions regarding what interventions to implement.
- The WHO recommends using the red blood cell microbiological assay as the most accurate and reliable laboratory method to assess folate status.
- A fee-for-service regional approach to folate assessment is practical for many countries, as they will not conduct enough health surveys to warrant having their own folate laboratory. Instead, they can ship their samples to their regional laboratory and pay for this service to ensure they are receiving quality results. Once the folate status of the population has been assessed, decision-makers can decide the best intervention strategy to reduce the incidence of folate insufficiency in their country.
- Mandatory large-scale food fortification with folic acid has reduced the occurrence of NTDs in countries that have implemented successful programs since the 1980s.

### *For Laboratory Technicians*

- The WHO recommends using the red blood cell microbiological assay as the most accurate and reliable laboratory method to assess folate status.
- At the population level, a red blood cell folate concentration of 906 nmol/L is optimal for NTD prevention.
- The Folate Task Team hosted a webinar, “Using laboratory folate status assessment to strengthen NTD prevention”, reviews the importance of having a harmonized assessment technique and the CDC training being undertaken. Please watch at **https://www.nutritionintl.org/what-we-do/nteam/folate-task-team/**
- The Folate Microbiologic Assay Training Video is also available on the CDC Foundation’s website for your use: **https://www.cdcfoundation.org/programs/capacity-building-folate-measurement**

# ACKNOWLEDGEMENTS

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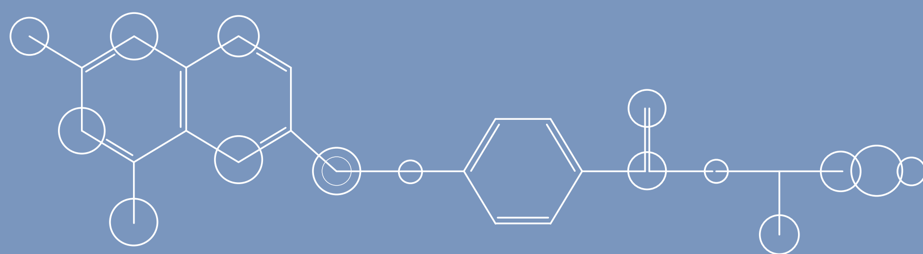

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