**PART 3. Proposals for Pilot and Demonstration Projects**

Updated 6 December 2022 / jpc

**INTRODUCTION**

In this document, the association between TB and undernutrition is conceptualized not as bidirectional but as a triangle with nutrition, infection[[1]](#footnote-2), and disease at the vertices. The three sides depict temporal relationships corresponding to biological mechanisms of interaction.

Disease  
is

Infection

Correspondingly, this association can be divided into three distinct stages based on the temporal relationships:

Nutrition

1. Undernutrition among people who do not yet have TB infection or disease, i.e., as a risk factor for becoming infected
2. Undernutrition among people who have TB infection but not disease, i.e., as a risk factor for developing active TB disease
3. Undernutrition among active TB patients, i.e., nutrition during the therapy of TB disease

These ideas for projects are informed as much by previous intervention trials that have not worked or that remain untested as it is by updated scientific evidence as to what might work. In other words, the proposals deliberately differ from the many highly informative trials that have failed to show a benefit from a variety of micro- and macronutrient supplements. In contrast to TB, evidence shows that nutritional support benefits patients with HIV/AIDS, and it has become an important feature of HIV programs

**THREE TYPES OF PROJECT PROPOSALS**

Based on published studies and reports summarized in Part 1 and Part 2, I propose three broad types of projects. Each one is adaptable with a range of variations, combinations, and budgets depending on the scope / scale of the intervention

1. Food as an incentive to improve adherence to treatment;

2. Food and nutritional supplements to improve treatment of active TB disease;

3. Food or nutritional support to prevent TB infection and disease;

**1. Food / nutrition support as an incentive to improve adherence to treatment**

Giving food to patients as an incentive to improve adherence to treatment is commonplace, but its effectiveness varies. Broadly speaking, this strategy had not been evaluated definitively. Some programs make food contingent on perfect or near-perfect adherence (including USAID-backed interventions in the past.) Other programs do away with this conditionality, expecting the food to keep those who most need it coming back, thereby enhancing overall adherence to treatment on average. Cash transfer and conditional cash transfer programs can be considered a variant on this strategy (reward for adherence) because patients who need food spend the money on food. Many programs already offer food or nutritional supplements to their patients because their patients are undernourished.

*Several general principles stand out (no specific order).*

* Food incentives work best for those who need food most, i.e., the poorest segments of the population.
* Food as a reward contingent on adherence to treatment is the most common model.
* Alternatively, it does not have to be; those who need food will keep coming back for it.
* Incentives must have sufficient value to alter behavior.
* "Value" differs for different patients. It does not necessarily correspond to monetary value.
* Nutritional support has the greatest impact on nutritional status among pregnant women, infants, and young children.
* It may be acceptable to target pregnant women and their infants (without giving it to other patients), because by universal standards they self-evidently deserve special consideration.
* An alternative approach would be to provide it to all patients for reasons of equity, while focusing specifically on pregnant women, infants, and young children to measure impact.
* Good nutrition, obviously, has a spectrum of benefits that we would do well to measure in terms of impact and cost-effectiveness.
* Indirect benefits should be considered, depending on specific aspects of project, including stimulating the local economy such as the agriculture sector when locally sourced foods are prioritized, food vouchers provide stimulus to food vendors as well as all of the inputs to food-related commerce. Cash transfers of course add money to the size of local economic activity.
* Extensive experience shows that food, food packages and vouchers tend to be distributed outside written program guidelines and boundaries by both providers and patients, partly for humanitarian reasons.

**2. Food and nutritional supplements to enhance treatment of active TB, reduce lung damage and prevent relapse**

*General principles*

* To date, nutritional supplements in general have failed to alter the clinical trajectory and outcomes of TB treatment, although individual studies have found modest benefits that are not consistent across studies.
* The following have been studied and failed to improve TB-specific outcomes or interim outcomes:  overall diet including subanalysis of its components, high energy supplements, arginine-rich proteins, vitamins D / A / zinc / selenium alone and in combinations, and multimicronutrients.
* Reasonable, science-based explanations for these results are described in the narrative below, but the general principles are these:
  + In 90% of people, the immune system is effective in killing or containing small numbers of bacilli. Active TB disease manifests when the immune system fails to contain the infection.
  + The drugs kill the vast majority of germs (>99.999%), not the immune system, so the impact of nutritional support may be slight compared with the bactericidal activity of chemotherapy.
  + Perhaps the “wrong” nutrients, populations, and outcomes have been studied based on incomplete understanding of the science—“wrong” in the sense that the studies had negative results.

**3. Nutritional support to prevent TB infection and disease.**

*General principles*

* Based on observational data, undernutrition is a powerful risk factor for incident TB disease, but not for incident TB infection.
* Thus, one would expect the greatest likelihood of success with interventions to prevent TB disease.
* Until better biomarkers become available, preventive strategies would require large numbers of beneficiaries to measure an impact because only 1/3-1/2 of closely exposed individuals become demonstrably infected and, on average, 1/10 of those will progress to active TB over the next 2 years (1/10 in well-nourished populations, more in undernourished populations).
* In combination with preventive treatment, nutritional support has been associated with reduced rates of IPT failure, i.e., lower incidence of TB among those who take or took IPT.
* Vitamin D, despite evidence it activates macrophages, has not worked in trials for reasons that become apparent from more recent understanding of its effect on the immune response in vivo.
* From a high-altitude perspective, some have posited that nutrition seems to affect TB incidence in that better nutrition reflects socioeconomic development (i.e., raising the overall standard of living).
* This suggests a population-based intervention may be effective as an alternative or complement to a targeted intervention.

**PROJECT IDEA #1 - TB TREATMENT and PREVENTION**

As the lowest hanging fruit, I might propose an intervention that combines all three aspects into a potentially efficient, practical mechanism. The group at highest risk for both incident and prevalent TB disease are close contacts of infectious TB cases. Household contacts may be easier to reach because the index TB patient is already “in the system.” The TB program is already “in the household.” Contact investigations - as a generalization - often find 25% to 50% of household members to be infected. To the extent these household members are underweight, their risk of developing active TB is far higher than those with normal body weight. Thus, providing nutritional support to the family would mitigate nutrition-attributable risk, and it could be an incentive for the patient because it’s not only for himself but for his household; an impoverished household needs food.

Food / nutrition incentives to promote adherence to treatment have been implemented widely, but evaluated poorly. Existing evidence is mixed regarding effectiveness of food incentives to promote adherence, partly because implementation often lacks fidelity to program guidelines or rules. Culturally competent, effective incentive programs based on social theory and science could be designed taking into account in pragmatic terms the success and failures of the past. Such programs would do best to focus on those in greatest poverty, to primarily engage women as providers, and to focus on pregnant women and young children. The prevalence of undernutrition in parts of India, Africa, and SE Asia are high enough that most households of lower income TB patients will include individuals with significant degrees of undernutrition, especially among children. The nutrition intervention (food) could be provided to patients and their households, for example, as long as the patient remains in treatment plus a “bonus” of 6-12 months after completing treatment to prevent relapse and maintain the family’s immunity during this highest incidence period.

In summary, the intent would be to:

* Provide nutritional support to TB patients to increase both adherence and relapse-free cure
* Improve nutritional status of their household contacts to prevent them from getting TB (plus many other benefits of better nutrition).

*Nutrition for treatment of active TB*

1. Vitamin C. In terms of specific nutritional interventions for TB treatment, based partly on what has not worked and what has not been tried in the past, four potential interventions are described based on indirect evidence. First, a series of studies by William Jacobs laboratory in New York demonstrate that high dose vitamin C for TB patients enhances the effect of TB chemotherapy potentially leading to faster sputum conversion or shorter durations of treatment. Vitamin C has been studied in phase III human clinical trials for other conditions (e.g., cancer, upper respiratory infections) that proves its safety. Thus a powerful precedent and knowledge-base already exists.

2. n-3 PUFA. The anorexia and cachexia of TB are part of an overall catabolic state driven primarily by the immune system’s production of cytokines and cytolytic agents such as tumor necrosis factor (called “cachexin” when it was first discovered). Nutritional support at this stage is like trying to fill a tub with water with an open drain at the bottom. A severely catabolic patient cannot gain weight regardless of calorie and protein intake. Consequently, dietary interventions have been largely futile. Effective treatment gradually shuts off the catabolic state and the cytolytic inflammatory state enabling the patient to gain weight and replenish their deficits. In other words, the best treatment for these patients’ wasting is HRZE. Patients nutritional status naturally improves when their TB treatment is effective. That said, nutritional support can ensure full, balanced nutritional rehabilitation and promote tissue repair. What if the nutrition interventions targeted the root problem, not its downstream consequences? This would be the equivalent of closing the drain. Diets or supplements rich in omega-3 polyunsaturated fatty acids (n-3 PUFA) have an anti-inflammatory effect used routinely in clinical practice to treat autoimmune diseases such as rheumatoid arthritis and psoriasis. n-3 PUFA can be delivered through the diet or as a supplement. The theory is that it will cool down the destructive inflammatory response, leading to faster resolution of symptoms, faster weight gain, and possibly faster resolution of radiographic changes. Reducing inflammation may limit lung damage and improve recovery. In HIV-infected TB patients, it may help limit immune reconstitution inflammatory syndrome (IRIS). It would probably not increase sputum conversion or faster time-to-sputum culture conversion which are function of the anti-TB drugs, not of the immune response. The big advantage is this may be the only dietary / macro-nutrient intervention that has not been disproven. It is also entirely safe, practical, cheap.

3. Healthy lipids. Third, *M.tb.* in vivo preferentially use lipids for energy for metabolism and replication. In a lipid-rich environment, *M.tb.* accumulate and store lipids in cytoplasmic vacuoles large enough to see by microscopy. At the same time, in a lipid-rich environment their replication rate decreases to a near standstill at the far end of the spectrum. The process has been studied down to the level of specific mycobacterial genes and regulators. These findings are consistent with the well-documented, stepwise decrease in TB risk among individuals who are overweight and obese. On the other hand, individuals who are underweight have very little body fat relative to those with BMI in the normal range. In lipid scarce environments, *M.tb.* switches to carbohydrate and protein metabolism for energy and replicates faster. Thus, a lipid-based hypothesis may provide a more cogent explanation for the inverse association between TB risk and BMI than a protein-based hypothesis. These two macronutrients should be evaluated in combination as well. Following this science, the nutritional intervention, therefore, would focus on providing enough healthful fats to patients and their families. This approach naturally dovetails with n-3 PUFA.

***NB:*** These may sound promising, but as noted previously published studies of dietary / nutritional interventions have shown little benefit in terms of TB treatment outcome. It’s not because they are ineffective: weight gain and nutritional status improve better than controls. In some studies, chest x-rays have improved faster, but not standard TB-specific metrics such as sputum culture conversion, cure/completion, treatment failure, relapse, or death. In terms of tempering expectations, it would be hubris to assume one’s own project would succeed where others have not, so trying different nutrients and measuring different outcomes than what has been tried before may be central to success: reducing relapse, reducing lung damage, improving adherence to treatment, reducing TB incidence in contacts.

*Nutrition for TB Prevention*

For prevention of TB, nutrition interventions are a wide open field because they hardly have been tried even though indirect evidence suggests this is where they may be most effective. Protein calorie nutritional status as reflected by BMI is an important determinant of TB risk. Certain lipids may bolster immune surveillance and immune effector mechanisms, while recent data suggest vitamins A and E deficiencies increase the risk of TB disease.

1. Balanced protein-energy. Given the risk of TB associated with low BMI, balanced protein-energy nutritional support to those at risk of TB, enough to gain weight (increase BMI>18.5), should help prevent TB. This means >2000 to >3000 kcal daily dietary intake plus >1g/kg of complete protein per average adult. This “balanced diet” approach appeals to common sense. As a supplement to the regular household diet, the proportion of these daily calories that would need to be provided would depend on the extent of their average daily consumption without the supplement.

2. n-6 PUFA. In contrast to n-3 PUFA, n-6 PUFA have an immune-boosting or pro-inflammatory effect that may bolster immune surveillance and the immune response to initial infection, eliminating inhaled mycobacteria before TST-conversion. Similarly, this effect may enhance mycobacterial killing or stasis after the onset of adaptive immunity as well. Thus, for household members in whom active disease has been ruled out, n-6 PUFA may prevent the progression of the initial infection to TST-conversion to active disease.

3. Micronutrients. Recent evidence from Peru provides striking evidence that deficiencies of vitamins A and E increased the risk of incident TB 10- and 5-fold, respectively. These micronutrient deficiencies can be addressed together with low BMI. They could be delivered either as supplements or as part of a diet rich in healthy fats and therefore fat-soluble vitamins A and E.

**PROJECT IDEA #2 - TARGET PREGNANT WOMEN AND YOUNG CHILDREN**

These interventions can be applied to various target populations. Nutrition programs have been most effective (in terms of improving nutritional status) for pregnant and lactating women, their infants, and young children. Therefore, it makes sense that nutritional interventions to reduce TB morbidity and mortality will have the highest likelihood of success by targeting these same groups. To the extent that the TB program provides services to reproductive age women, pregnant/lactating women, infants and young children, the program could implement many of the proven interventions by either integrating into TB services (given the right infrastructure and personnel and budget) or alternatively through collaboration with community-based nutrition centers, agents or resources. In addition to the macro- and micronutrients detailed above, the effects of iodine, iron, folate, and zinc are so well-established that they should be included because the marginal cost is minimal and the health benefits, substantial. Impact increases as poverty increases. Three different strategies suggest themselves as detailed below in the implementation / platforms section. First, from the TB program perspective, a project might provide nutritional support specifically to pregnant women and young children in their care. Second, the program could provide nutritional support more broadly to TB patients, but measure treatment outcomes in pregnant women and young children. A third strategy, this one to prevent TB, would be to provide nutritional support to pregnant women and young children in impoverished communities through existing international or local food aid programs, measuring TB incidence as an outcome. Any of these could be adapted to the patient-and-household model described above.

**PROJECT IDEA #3 - TARGET MDR TB**

The benefits of nutritional support may be small relative to the massive bactericidal effect of chemotherapy, killing >99.99% of bacilli within days to weeks. In order to detect a benefit, it makes sense to look at situations where chemotherapy is relatively less effective or where the immune system is relatively more important. Historically, chemotherapy has been much less effective against MDR-TB, requiring 3-6 months for sputum culture conversion and consistent weight gain versus 1-2 months for drug-susceptible TB. Globally, cure rates average <60% for MDR-TB and <30% for XDR-TB versus >85% for drug-susceptible TB. Because the drugs are less effective and treatment much longer, the immune system may play a relatively larger role in highly drug-resistant TB. Thus, the necessity of cooling down the destructive inflammatory response (n-3 PUFA) and enabling healing to begin supported by balanced protein-energy nutrition. These statistics may change, however, with the advent of BPaL, so these comments are conditional on MDR-TB treated with either of the WHO-recommended regimens, the 9-month / 7-drug short regimen or the 20-22 month long 5-drug (similar to STREAM-1). The benefits may be modest, e.g., boosting cure rates from 80% (trial conditions) / 75% (program conditions) by an additional 5%. A comparative intervention would require >2500 people to detect this difference as being statistically significant.

**PROJECT IDEA #4 - POPULATION LEVEL: TARGET HIGH-RISK COMMUNITIES USING GEOGRAPHIC INFORMATION SYSTEMS (GIS) AND LOCAL KNOWLEDGE**

Use GIS to identify communities with the highest incidence of TB overlaid with measures of poverty and nutritional status which are likely to overlap greatly with TB incidence. For a population-based approach, partner with an existing nutrition / food aid endeavor or social welfare agency or charity to raise the nutritional status of the community, measuring TB incidence as one of several outcome measures. Measure these outcomes specifically in young children and reproductive age women. Could USAID partner with ”SUN” (Scaling Up Nutrition) or with “1000 Days” mitigate undernutrition among young children and their pregnant/lactating mothers in one city, province, or country? Could USAID partner with Zero TB Cities, to mitigate malnutrition in one metro area as a demonstration project for combatting TB and also for many other benefits to health, growth, physical and mental development. For a TB program- or clinic-based approach, one would work in the clinics and dispensaries in those communities applying any of the strategies described in preceding paragraphs.

**IMPLEMENTATION IDEAS / POTENTIAL PLATFORMS**

In the past, the global enterprise of providing food / nutrition for people in poverty enterprise has been relatively separate from the global professional community that works on TB control / prevention / treatment. A matrix of these distinct domains can be approached from either direction. Nutrition projects and programs could be matrixed with TB programs in 2 ways, either bringing those nutrition interventions into TB programs, or bringing TB prevention into nutrition interventions.

*From the TB program perspective:*

For example, many of the interventions require talking with the individuals repeatedly, measuring their height and weight, examining them for signs of nutritional deficiency, educating them and counseling them about nutrition, recording this information. Some would involve distributing micronutrients in the form of tablets, capsules, powders, liquids, or ready to use foods. These are precisely the type of activities in which TB medical officers, nurses and outreach workers engage on a daily basis except focused only on TB prevention and treatment. TB nurses, case workers, and others normally meet with patients regularly, observe or examine them, teach patients and contacts about TB, and administer their medications.

Adding Nutritional Assessment, Counseling and Support (NACS, USAID’s systems approach to providing nutrition *standard of care*) would at least double the amount of time personnel would need to spend with each patient, meaning it would require roughly doubling or tripling the number of personnel. They can include nutrition in their assessment, counseling and teaching and, for patients, including micronutrients with DOT. Most do already to some extent because patients naturally have questions about what they should/shouldn’t eat. They monitor patients’ weight at every visit. They can monitor children’s height and weight in the same way. They can identify and refer (assist in treatment of) severe or moderate acute malnutrition. DOTS workers or TB case workers could administer any or all of the micronutrient supplements, ensuring they were taken. They can provide macro-nutritional supplements (they often do already) — a kilo of rice, a kilo of lentils, a liter of healthy cooking oil per week for the patient and his or her household. They could technically do all these things in the sense that it would fit naturally into many of the existing work flows, but it would require increased human resources, infrastructure, material support and management/monitoring. It would require doubling or tripling the number of TB nurses and community workers, for example, and training them, so that each one could spend time on nutrition-specific activities. Naturally, TB care providers also interact with providers in other sectors of the health system as well as with their clientele.

Extending such nutrition services to the prevention of TB among household and family contacts of TB patients would require much more emphasis than is typical in LMIC on active contact tracing (including home visiting), testing for quiescent and subclinical TB infection, and preventive treatment. Preventive treatment is become much more practicable as a consequence of one- and three-month regimens for HIV-infected and HIV-negative individuals with LTBI. This is one of the ways in which a nutrition-focused intervention could stretch and strengthen TB programs in new ways, growing the contact investigation / TB screening / TB prevention limb. This would also reduce TB morbidity.

*From the nutrition program perspective*

One would implement evidence-based, proven effective nutrition interventions, striving to implement them exceptionally well. One would concentrate on nutrition interventions that would be expected on theoretical grounds to provide the greatest resistance to TB (& other infectious diseases), i.e., to support to immune system and host defenses (specific micronutrients, balanced protein-energy, and either n-6 PUFA or n-3 PUFA (depending on the goal)). As part of a careful monitoring and evaluation process, one would look at TB morbidity and mortality in the target populations—young women, pregnant and lactating women, infants and young children—in the intervention programs or communities (districts, households) compared with historical experience in those programs, compared with programs/communities that have not yet implemented those interventions, and ideally with different interventions in different communities to learn what works and what does not work. Adding the perspectives of public health science and common sense, one would measure impact on non-TB morbidity and mortality that would be expected to respond to these nutrition interventions. This suggests that other program areas may be interested in collaborating or cosponsoring.

**POTENTIAL OBSTACLES AND SOLUTIONS**

1. For nutritional interventions with TB patients, the biggest obstacle is the consistently disappointing outcomes among randomized controlled nutritional intervention trials. In other words, a substantial body of available evidence does not support the expectation that nutritional interventions with TB patients would have a substantial impact on their TB treatment outcomes. In part this is because TB treatment for drug-susceptible disease is highly effective. It’s hard to improve upon.

Response: Find common structural and procedural elements as to why they haven’t worked and develop novel strategies and tactics accordingly. Try science-based interventions and strategies that have not yet been tried—different nutrients/combinations, different delivery platforms, measure different outcomes (lung damage, relapse). Interventions will require sufficient resources and must strive for assiduous implementation. Focus on patients in which chemotherapy is relatively less effective, i.e., MDR or any RR-TB because in the impact of nutritional interventions may be relatively larger or more apparent. Focus on populations in which nutritional interventions predictably have greater impact—those living in extreme poverty, pregnant women, infants and young children.

2. Vitamin C is tricky largely because of its history with popular fads alleging that vitamin C benefits everything from the common cold to cancer, including prominent scientists like Linus Pauling, giving credibility to these claims.

Response: One advantage is that vitamin C is entirely benign as an intervention—there is virtually no down side. Another advantage is that there are solid theoretical reasons and preclinical data supporting a serious initiative. A third advantage would be the novel strategy: vitamin C potentiates the effect of first line anti-TB drugs. It makes first line drugs more effective. That means it could potentially shorten treatment, for example, from 6 to 5 months, without any other change. Could it shorten 3HP or 4R for prevention? Could it shorten Study 31 from 4 mos to 3 or 3.5 mos? This is the novelty and the reason it deserves investigation.

3. For nutritional interventions in those with LTBI or those exposed to TB for the purpose of prevention, the biggest obstacle is there is no substantial precedent and no direct evidence because it has not been adequately tried.

Response: Design, implement, and evaluate interventions in high risk groups, e.g., household contacts and family contacts, in immunocompromised individuals. Focus on populations in which nutritional interventions predictably have greater impact—those living in extreme poverty, pregnant women, infants and young children.

4. An important premise here is that it is not practicable to provide nutritional support services to some clients or patients and not others who may also be in need. This is the reef on which “food incentive” programs have shipwrecked consistently. It simply goes against humanitarian nature to offer food to selected hungry TB patients and not to others. Implementation does not stay within protocol boundaries.

Response: Focus on populations in which food and nutrition supplements are predictably more effective—communities with a high prevalence of extreme poverty or food insecurity, pregnant women and their infants and young children. Food incentives are less effective in changing the behavior of people who have enough to eat. While it may not be practicable to withhold food from selected clients for reasons of equity, the proportion in whom food / nutritional support has no impact could be seen as “losses due to friction” or inefficiencies in the system that are accounted for in the planning. These inefficiencies will be minimized by targeting the right populations.

5. At the population level, first, population level nutrition interventions have not focused on TB. Population level nutrition interventions have been an enormous undertaking since at least the 1950s and 1960s, eventuating in WFP, FAO, as well as the corresponding departments in WHO, WB, USAID/USG and many governments, UNICEF, Red Cross, philanthropies, NGOs, and innumerable local organizations. Repeated evaluations have demonstrated that not all food aid, not all population food programs have a measurable benefit (famines excluded).

Response: Effectiveness has been consistently demonstrated in certain population groups, especially reporoductive age women, pregnant / lactating women, and their young children. At the same time, a core of effective programs has been articulated, and the evidence has been published. None of these focus on TB. Among infectious diseases, HIV, malaria, pediatric diarrhea, measles benefit from nutritional interventions. Otherwise, nutrition-sensitive but not nutrition-specific programming can have an important direct or indirect effects, including better agricultural stocks and practices, treating anemia, deworming, food fortification, empowering and education girls and women.

**POTENTIAL FOR IMPACT**

There are two distinct types of impact: the impact on TB incidence and the impact on TB treatment and outcomes. Neither can be guaranteed because of the relatively extensive history of ineffective programs in the past. Learning from their mistakes, however, building on advances in science, implementing high-quality projects that test novel approaches with the right resources and partnerships, I would expect the impact on TB incidence to be measurable and significant in a sample of 4000-5000 participants assuming a 50% reduction in incidence compared with no intervention, 9000-10,000 participants assuming a 33% reduction in incidence, and 18,000-20,000 given a 25% reduction in incidence. For comparison, the effect of LTBI preventive treatment is estimated to decrease incidence by 60% to 90% depending primarily on adherence.

In terms of impact on TB treatment and outcomes, the effect of chemotherapy is so high (>85% globally, not including relapses), that it’s hard to improve upon it, but a creative and diligent food-incentive-for-adherence program could conceivably reduce non-adherence from 8-10% to <5%, for example, if it were to be implemented in deeply impoverished areas/population groups, food insecure areas or population groups and time periods of extraordinary food insecurity. Nutrition interventions described here could potentially reduce the duration of treatment, measurably reduce residual lung damage and respiratory disability, and reduce relapse rates.

There may also be a third type of impact, more oriented to the future, the impact of knowledge gained and leadership. Considering the aplastic overlap between the undernutrition-TB domain and the effective nutrition interventions domain, the question naturally arises about the extent to which USAID GTB would be interested in including research, operations research, or translational science into its programming. Numerous interventions appear promising based on science and reason but have not yet been evaluated in demonstration projects, controlled intervention trials, or other comparative studies.

**BULLETED SUMMARY AND RECOMMENDATIONS**

* Target the households of TB patients first and high incidence neighborhoods or communities second focusing on those in the most impoverished areas or groups with the least food security.
* Pilot 3 interventions for TB prevention:
  + a. Vitamins A & E for TB prevention, ideally in a factorial design
  + b. Balanced protein-energy with energy from healthy fats
  + c. n6-PUFA, either as a supplement or dietary component
* Pilot 3 interventions for TB treatment:
  + a. Vitamins C
  + b. n3-PUFA, either as a supplement or dietary component
  + c. Balanced protein-energy with energy from healthy fats
* Target groups:
  + Household contacts of TB patients,
  + Pregnant women and young children,
  + Highly impoverished / food insecure communities or population groups.
* Within TB programs,
  + Staff up and train up to add nutrition component that will reach broader populations served by TB programs: cases, contacts, those at risk,
  + Integrate into TB services or link with community nutrition centers / workers
  + Consider vouchers for local vendors.
  + Consider cash transfers / conditional cash transfers.
  + Implement NACS universally.
* Population-wide (districts, jurisdictions) implement effective nutrition interventions measuring TB incidence (and other morbidity) as an outcome.
  + Compare intervention sites with sites having different intervention, e.g., school-based nutrition programs or management of severe acute malnutrition or moderate acute malnutrition. Stepped wedge design gets all sites all interventions over time.

1. There is also a brief period between the first moment a M.tb. bacillus lands in the lung and the subsequent development of immunological memory characterized as TST-conversion or IGRA-conversion, generally on the scale of weeks. Our methods of detecting infection are blind to this period, so it will not be discussed further in this document. That said, one can hypothesize that innate immune effector mechanisms most active at this stage are optimized by having plentiful energy, proteins, lipids, and micronutrients available for the acute phase response, cellular proliferation, and signaling. Scientific inquiry into the distinction between initial infection and the development of adaptive immunity has accelerated in recent years. “Infection,” in this document, refers to latent and subclinical infection. In immunized or previously infected individuals, adaptive immunity may also be at work. [↑](#footnote-ref-2)