B_{12} Deficiency in Bhutanese Refugees

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Nutrient deficiencies are a common concern for health care providers who work with resettled refugee populations. Detection of these deficiencies gives providers the opportunity to promote balanced nutrition, improve symptoms, and prevent long-term medical complications. In the case of Vitamin B_{12}, the neurologic effects of long-term deficiency can be significant and irreversible, making it particularly important to identify. In the United States, B_{12} deficiency is rare outside of the elderly, gastric surgery patients, and strict vegans. However, during my four-week rotation at the IFMC I saw multiple Bhutanese patients with histories of B_{12} deficiency and neuropathy who lacked the usual risk factors, and I became curious if this was part of a larger trend within this population. Investigation into this topic revealed that not only had this trend been studied before, but there is also some debate about how to best approach such deficiencies in refugee populations.

Vitamin B_{12} is a water-soluble micronutrient that serves as a co-factor in DNA synthesis. It is a key component in neurological processes and the production of red blood cells[1]. B_{12} occurs naturally in animal source foods like eggs, meat, and dairy but is not present in plant sources. Intrinsic factor, a protein produced by gastric parietal cells and activated by gastric acid, is required for absorption of B_{12} in the small intestine. Therefore, typical risk factors for B_{12} deficiency are restrictive diets, malabsorptive conditions, PPI overuse, and elderly age due to gastric atrophy[2]. It typically takes years for someone to become B_{12} deficient due to the body's ability to maintain sizeable B_{12} stores. In the United States, the most common cause of B_{12} deficiency is pernicious anemia, an autoimmune condition against the parietal cells of the stomach[3]. In refugee populations however, a history of malnutrition or limited diet is the more common cause. The transient life of most refugees prior to resettlement makes them susceptible to such deficiencies, and the history of the Bhutanese refugees provides some insight to the potential origins of this problem.

Bhutanese refugees began to arrive in the United States for resettlement in 2008. Their flight from Bhutan began in the late 1980s when the Bhutanese government ceased to recognize the citizenship of those whom it deemed insufficiently Bhutanese according to restrictive ethnic criteria. This campaign resulted in the systemic and routinely violent oppression of largely Nepali-speaking ethnic minorities, leading to the migration of this community to Nepal in the 1990s[4]. The first UN refugee camp was established in Nepal in 1991 to address the refugee crisis that followed. In 2007 the U.S. was one of eight third-party countries that agreed to accept this displaced group, and has settled the largest number of Bhutanese refugees outside of Nepal[5]. As of 2015, 84,800 Bhutanese had voluntarily resettled in the United States. Many of the refugees we see in clinic today lived over a decade of their lives in a Nepalese camp, and some of the children had never known life outside a camp before arrival. While the history of our Bhutanese patients may begin to set the conditions for potential deficiency, the literature has shown that the cause is likely multifactorial, with the contributing factors varying from case to case.

Several studies have highlighted the prevalence of B_{12} deficiency in Bhutanese refugees. In 2011, a report published in the CDC's *Morbidity and Mortality Weekly Report* (*MMWR*) described an investigation into multiple reports by state health departments of symptomatic B_{12} deficiency in resettled Bhutanese. The investigation showed that insufficient levels of B_{12} (<150 pmol/L) were identified in 64% (n=99) of random blood samples collected during pre-departure medical exams in 2007-2008, 27% (n=64) of post-arrival exams from three states (MN, UT, TX) in 2010-2011, and 32% (n=60) of medical records from a health clinic in St. Paul, MN from 2009-2011[6]. An update to this report published in 2012 showed that CDC recommendations following the first report led to improved awareness and reduced deficiency rates in arriving refugees (17% in 2012, down from 38% in 2010), but that incidence was still high in this population[7]. A 2013 study published in the Australian journal *PLoS One* used the CDC's standards to determine what percentage of Australia's newly resettled (<1 year) refugee populations (n=916) was deficient, and the results showed that one-third of the resettled Bhutanese in this category lacked adequate amounts of B_{12}.

Multiple factors consistent with the history of this group could contribute to this trend. Diets low in animal source foods and limited access to supplements predispose a population to deficiency. While traditional Bhutanese cuisine includes a variety of meats[8], it is reasonable to question whether such nutritionally high-value foods were consistently available to a group facing socioeconomic oppression and active exclusion in their home country. The *PLoS One* study defined food insecurity as a common factor for all refugees, and that "the inability to ensure basic nutritional needs of the populations…has emerged as one of the pressing

problems resulting from, and in turn reinforcing, political instability in many refugee-source countries". The authors analyze the link between chronic food insecurity in developing source countries and high rates of B_{12} deficiency in newly resettled populations. Using the Maplecroft Food Security Index, Bhutan received a "moderate" food insecurity rating but Iran, which had just as many deficient in its sample as Bhutan (one-third) was rated "low", and Afghanistan, with only one-quarter of its population deficient, received an "extreme" food insecurity rating by this same index[9] (Figure 1). Despite the absence of a linear correlation between these two data sets, overall access to nutrient-rich foods cannot be overlooked as a potential cause of long-term deficiency.

After migration to Nepal but before the UN camps were established, conditions for the Bhutanese refugees were poor due to lack of clean water, disease, and limited resources in their makeshift settlements along the Mai River[10]. Malnutrition was the norm and disease was widespread. Epidemiologic studies of *H. pylori* infection in Bhutan and Nepal present evidence of high prevalence in these countries[11,12], and the rural conditions with poor sanitation also increased the risk of infection, independent of geography. In the CDC's first *MMWR* report, five of six B_{12}-deficient refugees who presented to the St. Paul clinic with GI symptoms tested positive for *H. pylori*, as compared to one of four in the non-deficient group[13]. *H. pylori* has been linked to B_{12} deficiency independent of the gastric atrophy it causes, with some evidence that the organism itself may bind the vitamin[14] and prevent its absorption, which could be yet another cause for deficiency in endemic areas.

Once the UN camps were established, conditions improved and a daily diet was provided through food rations. According to a 2014 report, standard rations provided by UNHCR and the World Food Programme consisted of "rice, lentils, chickpeas, vegetable oil, sugar, salt, and fresh vegetables"[15], a diet that lacks animal source foods. Multivitamin supplements were reserved mostly for young children or pregnant women, and the popularity of a locally produced food fortified with micronutrients called 'Unilito' varied greatly. Purchase of additional foods at markets outside the refugee camps required local currency, a limited resource for refugees. In fact, the 2012 *MMWR* update proposed that along with an increased awareness of B_{12} deficiencies, improving B_{12} levels in pre-departure samples correlated with increased remittances as family members who had already departed the camps resettled overseas. All things considered, the CDC's assessment as late as 2014 was that in the camps "vegetarianism is relatively rare (6%) but frequency of meat consumption is low"[16]. An increasing awareness of this issue produced attempts to identify and correct B_{12} deficiencies in refugee populations. The UN World Food Program and UNHCR began providing 1-gram micronutrient powder sachets within the camps, each containing 0.9 micrograms of B_{12} (the recommended daily amount for adults is 2.4 mcgs[17]). As a result, B_{12} levels in pre-departure samples improved by 5% as stated above in the 2012 *MMWR* update. Despite these improvements, the adapted meal preparations and personal tastes that likely developed over years of standard camp rations may persist even after resettlement, and B_{12} deficiency along with it.

After resettlement, refugees may continue to face nutritional challenges. The *PLoS One* study points out that whatever the initial cause, it is not safe to assume that deficiencies will correct simply from exposure to varied foods in resettlement countries. Lack of awareness, cultural habits, adaptive dietary preferences, and continued food insecurity due to poverty after resettlement may all play roles in continued deficiencies. For this reason, it is as important to inform newly arrived populations about B_{12} deficiency as it is identify those who require treatment.

Since the publication of these reports, steps have been taken to address this trend, but some debate remains about whether or not screening tests are necessary. In 2011 the CDC recommended that all Bhutanese refugees receive counseling about nutrition and supplemental vitamin B_{12} for at least 30 days (at least 500-1000 mcg daily[18]), and that only symptomatic patients have their levels checked[19]. Treatment with parenteral B_{12} or high-dose oral supplements was recommended for those with insufficient levels, along with an investigation into the source of the deficiency. According to this plan, levels are checked only when symptoms present, with the implication that subclinical deficiency will either resolve with nutrition or present clinically before significant neurological damage occurs.

Shortly after the CDC's report, the Minnesota Department of Health went a step further by implementing B_{12} screening for every Bhutanese refugee upon arrival (Appendix A). Treatment and a work-up for cause was consistent with the CDC's guidance, but included the additional recommendation to consider *H. pylori* testing in this group. This screening approach assigns more urgency to subclinical deficiency and opts to treat as early as possible. This approach was also evident in the Australian *PLoS One* study which required the screening of all newly settled refugees, reporting that despite evidence of high deficiency rates, "Vitamin B_{12} is not part of most recommended screening protocols for newly arrived refugees". Based on the available literature, there are several reasons why this may be the case.

Although the results of the studies discussed above

are convincing within each study population, the body of literature on this topic is not yet large enough to show that low B_{12} on arrival leads to clinical symptoms in a significant percentage of the total population. This is challenging to overcome because no single resettlement site produces a sample size large enough for its data to be easily generalized to the larger population. Also of importance is the fact that none of the data so far has shown that screening in this population has led to improvements in long-term health. Additionally, although the particular combination of risk factors in the Bhutanese experience may put these refugees at a higher risk of deficiency, the individual risk factors detailed above are not unique to them. In the absence of a cause specific to this population, screening only the Bhutanese may cause the medical community to overlook similar needs in other refugee populations. Finally, there is the question of whether or not testing serum levels of B_{12} is an effective screening test in the first place. The *PLoS One* study discusses the argument that serum B_{12} is less sensitive than testing methylmalonic acid (MMA) and homocysteine which would detect more cases. In practice, however, serum B_{12} is thought to be more practical due to availability and lower short-term costs. Other routine screening measures such as CBC analysis to look for macrocytosis and anemia have had "weak correlation in the literature" with B_{12} deficiency[20], making MCV and hemoglobin less reliable indices for its detection. As a result, there is not yet a consensus on whether serum B_{12} screening is the answer to this problem. Further research across multiple sites or the use of cohort studies would help make the case for universal screening in this population.

In the interim, providers can use the above study results, knowledge of the Bhutanese refugee experience, and clinical observation at their sites to test and treat as necessary. The CDC's emphasis on nutritional education could be easily implemented at the clinician level. A specific emphasis on B_{12}-rich foods could be reinforced with all Bhutanese refugees through counseling at initial visits. Shopping aids could be provided to help non-English speaking refugees identify appropriate foods at the supermarket (Appendix B). Providers should have increased vigilance for clinical manifestations of B_{12} deficiency such as peripheral neuropathy, confusion, ataxia, or depression, and should be prepared to test levels as part of the work-up. Once a deficiency is identified, investigation into the source through a dietary history, inquiries about current food security, and the potential for *H. pylori* or malabsorptive disorders should be explored. As far as asymptomatic screening, it seems most clearly appropriate in pregnant or breastfeeding mothers, in light of the high risk that B_{12} deficiency can pose to fetal development and newborns[21]. It is also reasonable to consider screening patients already being treated for *H. pylori* infection, since there is a known association between the two in endemic areas. As for treatment, B_{12} replacement therapy consistent with AAFP recommendations (Figure 2) should help achieve timely correction.

Today, the success of resettlement for Bhutanese refugees is clear. In 2007, 108,000 refugees were living in seven UN camps. In 2015, UNHCR and the International Organization for Migration reached the milestone of 100,000 Bhutanese refugees resettled to third-party countries, with less than 18,000 remaining in the last two camps[22]. Through resettlement, these individuals and families have been given the opportunity to start new lives free from the threats they faced in their home country. But relocation is difficult, and success in resettlement has much to do with the support available in their new homes, which includes a network of medical and social providers whose mindfulness about the refugee experience can help identify needs that are uncommon in the domestic population. It is the initial awareness of health providers that identified B_{12} deficiency in the Bhutanese, and as a result of the investigations that followed, refugee populations have become less susceptible to micronutrient deficiencies over the past ten years. Likewise, a continued sensitivity to the risk factors associated with the flight histories of each refugee group can help prevent the past lives of refugees from continuing to affect their health even after resettlement.

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Figure 1:

Benson J, Phillips C, Kay M, et al. Low vitamin B12 levels among newly-arrived refugees from Bhutan, Iran and Afghanistan: A multicentre Australian study. *PLoS One*. 2013;8(2):e57998. doi: 10.1371/journal.pone.0057998 [doi].

Table 1. Top ten source countries for refugees in the Australian off-shore resettlement program and risk of food insecurity.

	2010		2011	
	Top ten refugee-source countries, Australian off-shore humanitarian intake [37]	**Risk of food insecurity [38]**	**Top ten refugee-source countries, Australian off-shore humanitarian intake [39]**	**Risk of food insecurity [40]**
1	Burma	Moderate	Iraq	Low
2	Iraq	Low	Burma	Moderate
3	Bhutan	Moderate	Afghanistan	Extreme
4	Afghanistan	Extreme	Bhutan	Moderate
5	Congo (DRC)	Extreme	Congo (DRC)	Extreme
6	Ethiopia	Extreme	Ethiopia	Extreme
7	Somalia	Extreme	Sri Lanka	Moderate
8	Sudan	Extreme	Iran	Low
9	Liberia	Extreme	Sudan	Extreme
10	Sierra Leone	Moderate	Somalia	Extreme

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Table 2. Country of origin of refugees and Vitamin B12 results.

Country of origin	**Total number of refugees**	**Vitamin B12 level**			**Median Vitamin B12 level**	**Interquartile range for B12 levels**
		<150 pmol/L	**150 – 240 pmol/L**	**>240 pmol/L**		
		n (%)	**n (%)**	**n (%)**		
Afghanistan	159	39 (24.5)	61(38.4)	59 (37.1)	207	150, 291
Bhutan	196	61 (31.1)	82 (41.8)	53 (27.0)	188	137.5, 249
Burma	113	2 (1.8)	8 (7.1)	103 (91.2)	412	312, 532
Iraq	70	14 (20)	27 (38.6)	29 (41.4)	216	164, 308
Iran	48	14 (29.2)	17 (35.4)	17 (35.4)	176	145.5, 255.5
Sri Lanka	23	0	5 (21.7)	18 (78.3)	315	242, 373
Horn of Africa[1]	104	11 (10.6)	37 (35.6)	56 (53.9)	250.5	187, 338
Central Africa[2]	145	5 (3.5)	23 (15.9)	117 (80.7)	374	282, 510
West Africa [3]	13	0	1 (7.7)	12 (92.3)	492	399, 701
East Africa[4]	32	3(9.4)	6 (18.8)	23 (71.9)	355.5	236.5, 440
Other[5]	13	2 (15.4)	2 (15.4)	9 (69.3)	267	208, 288

[1]Includes: Somalia, Ethiopia, Eritrea.
[2]Includes: Congo (DRC), Rwanda, Burundi.
[3]Includes: Sierra Leone, Liberia.
[4]Includes: Sudan, Kenya.
[5]Includes: Bangladesh, Pakistan, China (Uyghur), India, Zimbabwe.
doi:10.1371/journal.pone.0057998.t002

Figure 2:

Oh R, Brown DL. Vitamin B12 deficiency. *Am Fam Physician*. 2003;67(5):979-986

View/Print Table

TABLE 4

Schedule for Vitamin B_{12} Therapy

ROUTE OF ADMINISTRATION	INITIAL DOSAGE	MAINTENANCE DOSAGE
Oral	1,000 to 2,000 mcg per day for one to two weeks	1,000 mcg per day for life
Intramuscular	100 to 1,000 mcg every day or every other day for one to two weeks	100 to 1,000 mcg every one to three months

Appendix A:
Minnesota Department of Health Protocol

Recommended Protocol for Vitamin B12 Testing in Bhutanese Refugees

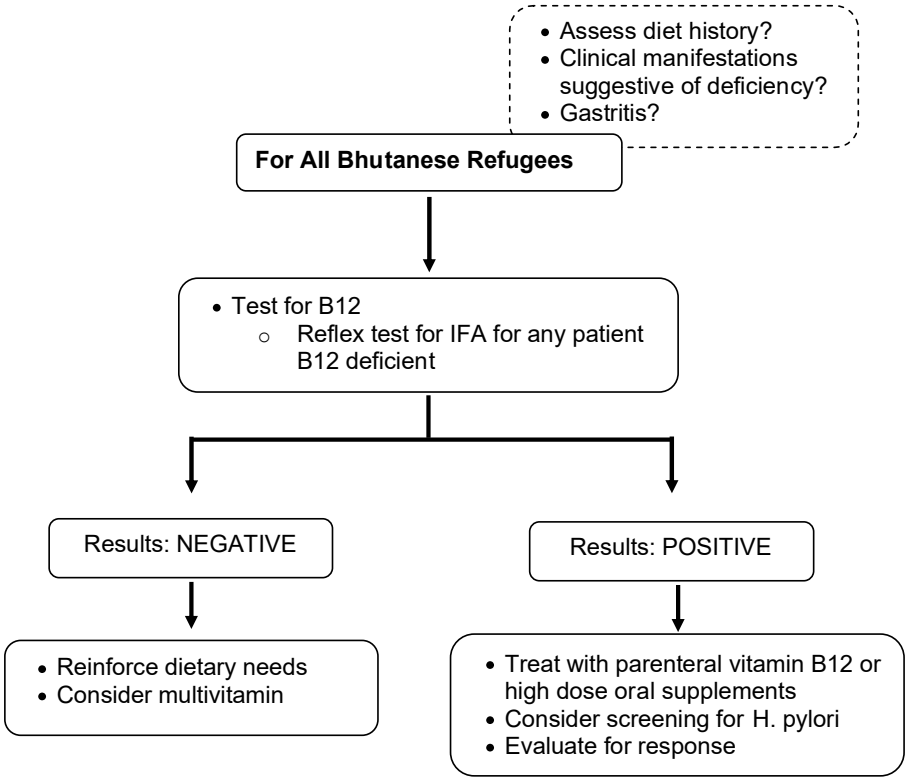
The Minnesota Department of Health recommends B12 testing for **all** Bhutanese refugees.

Note: This recommendation differs slightly from CDC recommendations (see MMWR, reference below).

MDH recommends B12 testing for all Bhutanese refugees due to these important factors:

- High pretest probability of B12 deficiency in Bhutanese
- Promote consistency in screening practice at the provider level
- Vegetarian diet has not been found to be a clear indicator of B12 deficiency.

MDH Recommended Protocol



CDC recommendations published in MMWR on March 25, 2011:
Centers for Disease Control and Prevention. Vitam in B12 Deficiency in Resettled Bhutanese Refugees - United States, 2008–2011. *MMWR* 2011;60:343-46.

Additional information:
Why Vitamin B12 Deficiency Should Be on Your Radar Screen: A Continuing Education Update
www.cdc.gov/ncbddd/b12/documents/B12-030910.pdf

MINNESOTA MDH DEPARTMENT OF HEALTH
Refugee Health Program
P.O. Box 64975
St. Paul, MN 55164-0975
651-201-5414 or 1-877-676-5414
www.health.state.mn.us/refugee

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Appendix B:
Example of a Counseling Aid and Visual Shopping Guide with Nepali Translation - for identifying common foods high in B_{12} by their store packaging.

Breakfast बर्ेअकफ़सत्

For0fied cereals चरेअल

Milk and for0fied soy मलिक, स◌ये

Eggs एगग्स्

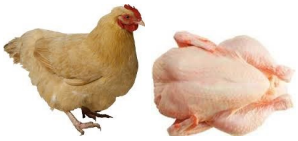
Cheese च◌ीे

Yogurt य◌ोगुर्

Lunch लचुं


Deli meat म◌त

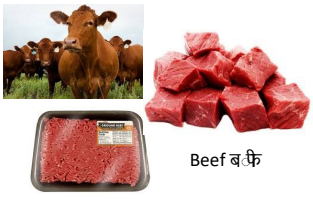

Cheese च◌ीे




Chicken चकि◌ंे

Fish फशि

Dinner दनि◌रे


Beef ब◌फ़ें


Fish फशि

Liver लविर


Clams चल◌ास्