

Assessment and Management of Anemia in a Population of Children Living in the Indian Himalayas: A Student-Led Initiative

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ABSTRACT

OBJECTIVE: To determine the prevalence and etiology of anemia among school-aged children in Spiti Valley, India, and implement an appropriate management plan.

METHODS: Hemoglobin (Hb) levels were measured in 382 children (3 to 18 years old) living in the Indian Himalayas for three consecutive years. Blood smears from the 200 most severe cases of anemia were analyzed. Iron treatments were provided for three months, and hemoglobin levels were measured after six weeks.

RESULTS: Pre-treatment, 88.4% were anemic in 2007, 78.3% in 2008, and 71.3% in 2009. Analysis of the hemoglobin concentration curve over the three years demonstrated an overall shift to the right. Blood smear results showed that 57% of the samples displayed normocytic, normochromic red blood cells; 30% were hypochromic only; and 11% hypochromic, anisocytic. Post-iron treatment prevalence of anemia was found to be 82.9% in 2007, and 84.9% in 2008.

CONCLUSION: There is a significant prevalence of anemia in the Spiti Valley children, which is multifactorial in etiology. A three-year evaluation of Hb levels combined with interventions addressing linked causes of anemia, such as iron supplementation, deworming, and enhanced nutrition through greenhouses, have demonstrated a significant year-to-year improvement in anemia. The hypochromic anisocytic anemia suggests iron deficiency or thalassemia. The normocytic normochromic anemia may be due to 1) mixed iron, B12, and folate deficiencies from a low animal protein and fresh vegetable diet in winter months; 2) early iron deficiency; or 3) genetic adaptation in oxygen transport at high-altitude. Due to the multifactorial nature of the anemia, an integrated prevention and treatment approach is warranted. Future goals include administration of iron, multivitamins, and zinc supplements, improvements in water and sanitation, and evaluation of the impact of greenhouses on anemia status.

KEYWORDS: *anemia, hemoglobin, children, iron treatment, Spiti Valley*

INTRODUCTION

Anemia is a global health issue that has significant consequences for individual health and socioeconomic development. Anemia is defined by serum hemoglobin (Hb) concentrations below a recommended threshold value (Table 1). This results in insufficient oxygen delivery to tissues and organs.^{1,2} According to the World Health Organization (WHO), children are especially vulnerable and exhibit high rates of anemia.³ Childhood anemia is associated with poor health and impaired cognitive development, leading to reduced

“**The most common cause of anemia in developing nations is iron deficiency.**”

academic achievement and work productivity in adulthood.⁴⁻⁷ Several studies have demonstrated that determining iron status and providing adequate supplementation is an effective means of prevention and management of childhood anemia.⁷⁻⁹ The purpose of this study is to determine the prevalence and etiology of anemia in the students attending the Munsel-ling boarding school in Spiti Valley, India and to implement a suitable management plan.

Under the supervision of a family physician, this study

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was conducted by the University of British Columbia (UBC) Global Health Initiative (GHI). This was in collaboration with the Rinchen Zangpo Society for Spiti Development, a local community non-governmental organization (NGO) that, in 2006, invited the GHI to develop health improvement programs for the Munsel-ling school. The school is located in the town of Rangrik in the Spiti Valley. This desert-mountain valley in the Indian Himalayas lies at an altitude of 3700–4500 meters and has a population of approximately 10,000, who are predominantly of Tibetan ancestry.¹⁰ Residents of the remote Spiti Valley are exposed to environmental stressors in the winter months when the temperature ranges from -5 to -35°C, and severe snowfalls occur.¹⁰ These environmental factors, in addition to the mountainous terrain, create barriers for growing fruits and vegetables, herding animals, importing food, accessing essential supplies, and severely limit sustainable access to health care. Accordingly, Spitian children likely have deficiencies of iron, folate, zinc, and vitamin B12 in their diet.³ Another stressor is chronic exposure to high altitude, which may lead to lower Hb saturation and reduced oxygen delivery to body tissues as suggested by a study of exposure to high altitude.¹¹ Two recent analyses of genome-wide sequence variations in high-altitude Tibetans compared to non-Tibetan lowlanders found that Tibetans carried higher frequencies of two hypoxia-related gene variants, EPAS1 and EGLN1.^{12,13} Due to all these aforementioned factors, it is important to test Hb concentration and oxygen saturation in this population. It is also essential to determine the etiology of anemia in the students before implementing a treatment plan. The most common cause of anemia in developing nations is iron deficiency.³ Other causes of anemia may include other micronutrient deficiencies, infections, such as malaria, hookworms, or schistosomiasis, inherited conditions, such as thalassemia, and other chronic diseases.¹² We hypothesized that there would be a high prevalence of iron deficiency anemia in the Munsel-ling school children and that dietary folate and vitamin B12 deficiency might contribute to the burden of illness. If our hypothesis is valid, then our approach to anemia management must be multifaceted and include consideration of factors such as crop diversity, education, water, and sanitation, as well as nutrient supplementation.

MATERIALS AND METHODS

This study protocol received ethics approval from the UBC Clinical Research Ethics Board. All students at the school (boarders or non-boarders) were eligible for enrolment into the study, and this convenience sample formed a population-based inception cohort. The cohort size varies insignificantly across the three years mostly due to new student enrolment, the majority of which are preschool children ages three to five years. Including student turnover from year-to-year allows for a more realistic assessment of anemia prevalence in this population. This also results in more conservative statistical estimates of effect size.

A cursory qualitative needs assessment at Munsel-ling school was completed in 2006, identifying three domains (health, water, and sanitation) as requiring urgent intervention. Three subsequent visits by the GHI team (2007–2009) allowed for enrolment and follow-up in this study. In 2007, health screens

and baseline Hb measurements were completed between June and August. A three month iron supplementation program was initiated with assistance provided by the local school healthcare worker. A second health screen was conducted in 2008 (June–August). Hemoglobin levels were measured, and peripheral blood smears were completed on the 200 most severely anemic. Iron supplementation was re-initiated for an additional the months. To improve efficiency for this treatment cycle, the school healthcare worker and senior students (grade 10) were trained to distribute iron tablets daily. In June 2009, a third health screen and Hb measurements were conducted for all students. Additionally, a Canadian registered dietician assessed dietary intake for a typical child's diet.

Health Screens

The health screen consisted of 1) Hb measurements, 2) qualitative assessment of parasitic infestations, 3) vision and hearing examination, and 4) a dental screen. All medical students were trained to complete the health screens through pre-departure educational sessions with the supervising physician.

Hemoglobin Measurement

Hemoglobin levels were measured for all students attending Munsel-Ling School. In 2007 and 2008, Hb levels were measured at two time points (pre-treatment/June and post-treatment/August). In 2009, Hb levels were only measured at one time point (pre-treatment/June only) due to unanticipated school closure. Finger-prick blood samples were obtained for each child using lancets and loaded into the HemoCue β -Hemoglobin Photometer to determine Hb levels. The HemoCue was calibrated on-site using a control sample. Upon returning to Vancouver, the HemoCue was validated for accuracy against a laboratory-grade analytical analyzer at the British Columbia Children's Hospital (BCH) for 10 specimens with Hb concentrations of 77–178 g/L. Descriptive statistics showed good correlation between the two instruments with a random error of 2.5% (data not published). A diagnosis of anemia was determined using the WHO definitions for anemia (age, gender, and altitude specific) (Table 1). Due to limited resources, we were unable to perform any medical laboratory analysis such as red blood cell distribution width (RDW) and mean corpuscular volume (MCV).

Blood Smears

Two hundred peripheral blood smears were performed in June 2008 (pre-treatment) on the most severe cases of anemia. Fingertip pinprick blood samples were obtained for 120 females and 80 males. The gender specific sample size was determined based on discussions with a hematologist and clinical researcher at St. Paul's Hospital in Vancouver who suggested a greater sample size for females than males as there is an established higher prevalence of anemia in menstruating females.¹⁴ Samples were smeared onto glass slides, preserved in methanol, and morphologically analyzed by a hematopathologist in New Delhi.

Nutritional Assessment

Using WHO standard weights, heights, clinical signs, and

symptoms, children were assessed for stunting, micronutrient deficiency, and anemia.¹⁵ A nutrition analysis of the school meals was conducted using a weekly menu, food stock records, and Daily Recommended Intake (DRI) values.¹⁶

Treatment

In 2007 and 2008, ferrous sulfate was provided to the school children six days per week for three months. Dosages were adherent to WHO recommendations: 30 mg/day of elemental iron for children under 13 years and 50 mg/day for those over 13 years.³ The intake of the iron was supervised by the teachers of each classroom to ensure compliance. In 2009, iron supplementation was intended but could not be implemented due to disruption in school attendance by a unique religious event that resulted in an unprecedented extended school holiday. Due to limited resources, folate and vitamin B12 supplements were not administered. However, other sustainability projects to reduce micronutrient deficiencies, such as greenhouses, were implemented.

For a yearly school-wide anti-helminthic program (2007-2009), a single 400 mg dose of albendazole (Albenza®) was provided to every student. Children that demonstrated infestation by the observation of worms in stool were provided a second 400 mg dose, two weeks after the first dose.

Statistical Analysis

All statistical analyses were comparisons of means between two

groups, and hence two-sample t-tests were employed throughout. In the determination of Hb levels over the three years, a Bonferroni correction for multiple comparisons was applied where the threshold of significance is $\alpha/n=0.05/3$. Therefore we employed a threshold p-value of 0.0167 for all t-tests. We treated missing raw data to be missing at random.

RESULTS

Health Screens

The study population of Munsel-ling school students (ages 3–18 years) from 2007–2009 demonstrated a significant increase in mean Hb levels from 130.3 g/L ($\sigma = 18.6$) in 2007 to 141.1 g/L ($\sigma = 15.4$) in 2009 ($p = 6.713 \times 10^{-10}$). Comparing year-to-year differences, an increase was noted between years 2007 and 2008 ($p = 0.001$) as well as years 2008 and 2009 ($p = 0.003$). The mean Hb levels for female and male subjects are represented in Table 2. The distribution curve for Hb levels is slightly skewed to the right (Figure 1). While both males and females show increases in Hb levels 2007–2009, the increase is more significant in males ($p = 4.338 \times 10^{-8}$ versus $p = 0.001$). However, the year-to-year increase in Hb for females from 2007–2008 and from 2008–2009 are not statistically significant ($p = 0.043$ and 0.351 , respectively). For males, the year-to-year increase in Hb is statistically significant both from 2007–2008 ($p = 0.0095$) and 2008–2009 ($p = 0.0022$). Anemia prevalence was found to be 88.4% in 2007 ($n=379$),

Table 1. Age, sex, and altitude specific threshold values for the diagnosis of anemia according to the WHO and CDC recommendations.¹⁷ Altitude adjustment for an elevation of 3700 m consisted of the addition of 30 g/L of Hb to each strata cut-off except in pregnant women where there is a 20 g/L addition.

Age (years)	Sex	Hemoglobin	Adjusted for altitude
< 5	Male or female	110	<140
5–11	Male or female	115	<145
12–14	Male or female	120	<150
>15	Female (<i>non-pregnant</i>)	120	<150
>15	Female (<i>pregnant</i>)	120	<140
>15	Male	130	<160

Table 2. Characteristics of the Munsel-ling School students as derived from assessment of the health screens. Definition of height and weight below the 3rd percentile was calculated using Indian growth charts.¹⁵

Variable	2009 Screen	2008 Screen (June)	2007 Screen
No. of Children	416	384	379
Age, Mean (SD), Years	10.2 (4.0)	10.2 (3.4)	9.8 (3.4)
Sex, Male, n (%)	213 (51.2%)	199 (52.0%)	202 (53.4%)
Hb, mean (SD), g/L	138.0 (15.4)	134.6 (17.6)	130.3 (18.6)
Hb (females), mean (SD), g/L	135.1 (13.8)	133.6 (17.6)	129.9 (16.8)
Hb (males), mean (SD), g/L	140.8 (16.5)	135.6 (17.6)	130.6 (20.0)
Anemic, n (%)	295 (71.3%)	299 (78.3%)	321 (88.4%)
Height < 3rd percentile, n (%)	72 (17.3%)	66 (17.1%)	117 (30.9%)
Weight < 3rd percentile, n (%)	11 (2.6%)	53 (13.8%)	39 (10.3%)
Relevant disease present at screening, n (%)	11 (2.7%)	16 (5.6%)	-
Worms (<i>reported by children at screening</i>)	11 (2.7%)	16 (5.6%)	-

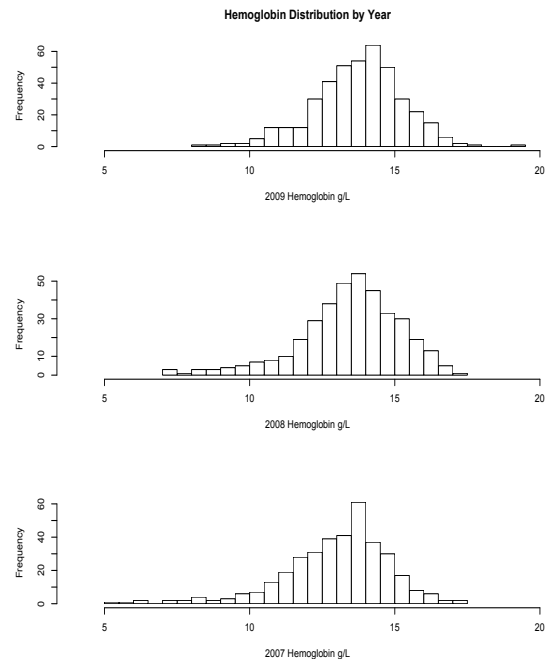


Figure 1. Frequency distribution of hemoglobin concentrations in the Munsel-ling school children (2007, n=379; 2008, n=384; 2009, n=416).

78.9% in 2008 (n=384), and 71.3% in 2009 (n=416). In 2008, the prevalence of anemia in males (76.4%, Hb = 136.8 g/L) was observed to be lower than in females (81.5%, Hb = 134.1 g/L) (Table 2), although the difference is not statistically significant (p = 0.26). Looking across all years, the prevalence of anemia decreases in males with age, while in females, it increases up to the age of 10 and then tends to decrease.

Due to small sample sizes within each subgroup, we also performed a visual inspection. Boys of all age levels had consistently improved throughout the three study years as had girls aged 3-10 years. Girls aged 11-18 years have not demonstrated a consistent improvement in their Hb concentrations (Figure 2). The prevalence of anemia in the age groups of three to seven years was comparable between males and females at 86.1% and 85.2%, respectively (Figures 2 and 3). Between the ages of eight and 10, a difference was noted in the prevalence of anemia between genders (76.4% in males and 85% in females). This became more pronounced between the ages of 11 and 16 (69.2% in males and 75.9% in females).

Based on WHO guidelines, if a population of children demonstrates

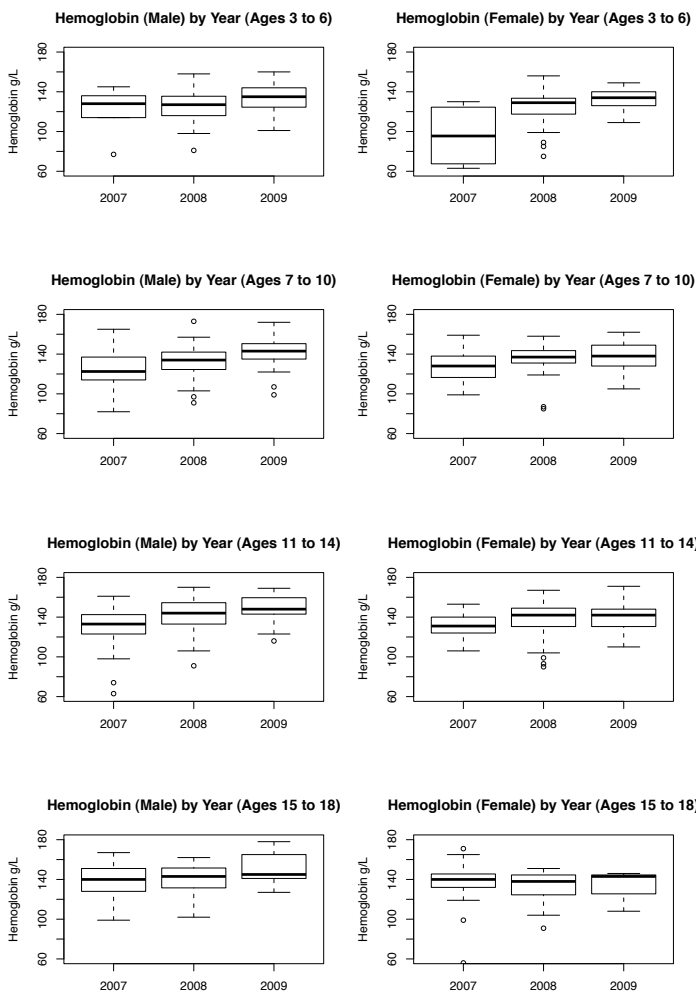


Figure 2. Box-plots representing hemoglobin levels in all Munsel-ling School children from 2007–2009 divided evenly into four age groups to facilitate analysis. The solid center line represents the median, the box is the inter-quartile range, and the circles represent outliers.

Proportion of Population with Anemia

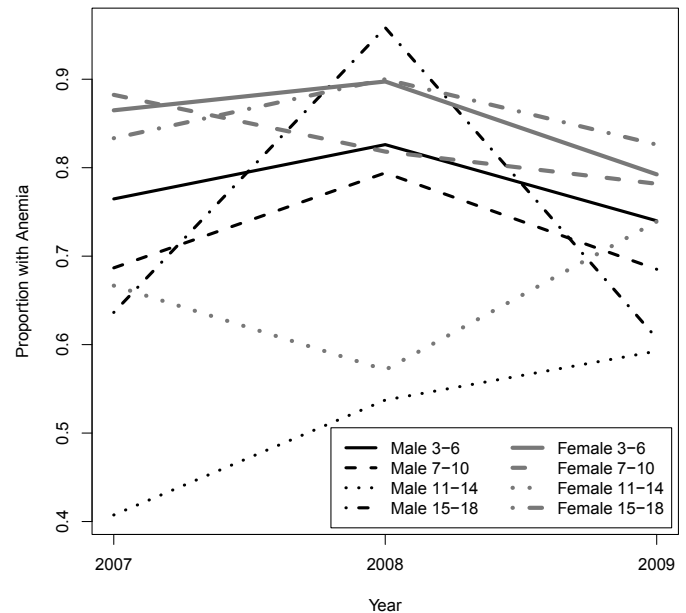


Figure 3. Pre-treatment anemia prevalence in the Munsel-ling school children.

a prevalence of anemia exceeding 40%, mass iron supplementation should be provided to all children.³ Accordingly, all the Munsel-ling school students were treated with iron supplementation. The post-treatment Hb levels measured in August 2007 indicated a prevalence of anemia of 82.9% and in August 2008 of 84.9%. No treatment was implemented in 2009.

Other components of the health screen included documenting cases of intestinal worm infestation and recording growth parameters. 16 students (5.6%) reported seeing worms in their stools in 2008, while only 2.6% reported worms in 2009. The helminth infection reporting rates were likely under-reported due to the subjective nature of the responses. Given the visible presence of worms in the drinking water, most students are likely infected with helminths. The percent of students under the 3rd percentile in weight decreased from 10.3% in 2007 to 2.6% in 2009. A similar reduction was observed for the percent of students under the 3rd percentile in height (30.9% in 2007 to 17.3% in 2009).

Blood Smears

Peripheral blood smear results (Table 3) consist of morphological descriptions of RBCs based on microscopic visualization. Fifty-seven percent (57%, n=200) of the blood smears showed a normochromic normocytic morphology. Isolated hypochromia was found in 30% of the samples. Another 11% were both hypochromic and anisocytic, while 2% of the smears were described as having multiple morphologies, including hypochromia, microcytosis, and/or macrocytosis.

Nutritional Assessment

The combined nutrition and health screen found that 20% of the population showed signs of micronutrient deficiency, and 20% are stunted based on WHO growth guidelines.¹⁵ The dietary assessment conducted through observations at mealtime and

Table 3. Microscopic description of red blood cell morphology as seen on peripheral blood smears in the 200 most severely anemic Munsel-ling school children.

Description of RBC morphology on Peripheral Blood Smear	No. of smears (n = 197)	% of smears
Normocytic normochromic	112	57
Hypochromic only	60	30
Hypochromic anisocytic	22	11
Other (includes samples with combined hypochromia, microcytosis and/or macrocytosis)	3	2

monthly purchasing log assessments showed student meals were adequate in calories and carbohydrates but inadequate in dietary fat, high biological value (HBV) protein, iron, folate, zinc and B12 in comparison to dietary reference intake (DRI) values.¹⁶ A report of this analysis will be used by the Indian NGO that runs Munsel-ling School to lobby the state government for more school food funding.

DISCUSSION

The findings of this study confirm that there is a high prevalence of anemia in the Munsel-ling students. The three month course of iron supplementation for all school children in 2007 and 2008 proved beneficial, reducing anemia prevalence by 9.5% from 2007 to 2008 and then by 7.6% from 2008 to 2009. This supports iron deficiency as a contributing cause to the anemia. However, a reduction in the occurrence of anemia was lower than anticipated since iron deficiency anemia should be more rapidly reversed with iron therapy.¹⁸⁻²¹ A similar study in Pune, India documented a prevalence of anemia of 66%, which dropped to 30% following wide-scale treatment with iron for eight weeks.²⁰ This suggests that the anemia in the students at Munsel-ling may be compounded by other factors such as micronutrient deficiencies, infections, and inherited conditions. Some studies have suggested that with continued daily administration, iron absorption could decrease due to fatigability of the intestinal mucosa.^{19,22-25} One study reports that absorption from a single dose of iron reduces from 30–40% on the first day to as low as 3–6% after a few days of continuous daily administration.²³ This recent evidence implies that biweekly or weekly iron supplementation may have superior effectiveness in the management of anemia and is worth considering as a future directive of this project.

Although the iron supplementation was provided annually over the course of three months, the students continued to consume a low iron diet for the remainder of the year. Education on nutrition and iron deficiency was not provided to the families as they did not have the resources to adjust their diet. Consequently, greenhouses were funded by GHI to improve nutrition at the boarding school. The Center for Disease Control states that one of the reasons the worldwide prevalence of anemia has not been reduced is because typical interventional programs assumed that there is a single cause of anemia.⁹ They recommend improving the assessment of the status of the anemia to enable appropriate treatment programs that address linked causes.

To plan effective anemia intervention in the Munsel-ling students,

peripheral blood smear analysis was performed to determine the true etiology of the disease.²⁵⁻²⁸ The majority of smears (57%) demonstrated a normochromic normocytic morphology. One explanation for these findings is that the anemic children suffer from mixed nutritional deficiencies. With iron only deficiency, a hypochromic microcytic appearance is characteristic whereas with folate or vitamin B12 deficiency, macrocytosis is observed. If all three deficiencies coexist, normochromic normocytic cytology is a possible outcome.²⁸ A second explanation for normocytic normochromic anemia is early iron deficiency whereby there is still a sufficient concentration of normal RBCs in the circulation, outnumbering any microcytes in the blood sample. A third explanation involves genetic adaptation documented in inhabitants of high altitude. Since the 1970s, several reports described relatively low Hb concentration among Tibetan high-altitude natives compared to newcomers and have raised the question of a genetic influence on the physiology of oxygen transport.^{12,13,29-35} A study in Tibetan children living at high altitude found the mean Hb concentration to be lower than the expected altitude adjusted mean concentration, and the population distribution was Gaussian.²⁹ The normality of the population curve, together with a mixed distribution analysis, led the authors to conclude that either the whole population should be considered anemic because they submit to the same living conditions or that Tibetans react differently to high altitude and adapt without increasing their hemoglobin; our study exhibited similar findings. Figure 1 shows a Gaussian distribution of the Hb concentrations that is skewed to the right. Most students have borderline Hb concentrations with a mean between 130 and 140 in the three study years. The normality of the hemoglobin distribution suggests that a genetic adaptation may exist in these Tibetan descendants; however, the slight rightward skewing of the Hb levels over the subsequent three years suggests that factors other than genetics, such as nutritional deficiencies, may be contributing to the anemia. It is worth noting that the majority of school children look healthy overall with no complaints of fatigue, weakness, pallor, or shortness of breath and thus are not symptomatic from their low Hb concentrations. Provided that the Hb levels are due to genetic adaptations, then the anemia prevalence measured in this study may be an overestimate, and the Centre for Disease Control guidelines for altitude-adjusted hemoglobin ranges used to define anemia may not be applicable to this population.¹⁷ It was beyond the scope of this study to confirm genetic adaptations for decreased Hb. Given that the study population showed improvement in Hb levels, iron supplementation should be continued according to the guidelines for the altitude-adjusted hemoglobin ranges used to diagnose anemia.

As for the remaining smears, 30% were found to have hypochromic cells only, which suggests either iron deficiency anemia or thalassemia.²⁵⁻²⁷ To confirm the presence of thalassemia, further investigations would be required, such as Hb electrophoresis with genetic testing, which were beyond the scope of this project. A literature review to determine the prevalence of thalassemia in the Indian Himalayas and Tibetans proved inconclusive. One study reports that thalassemia is rare in the neighboring Nepalese Himalayas.³³ Since Tibetans and Nepalese

in the Himalayas may have common ancestry, it is permissible to hypothesize that a similar low prevalence of thalassemia exists in the Spitian population.^{35,36} However, the prevalence of thalassemia is significantly high among South Asians, including certain tribes from northern India.³⁷ Inter-racial genetic mixing may have taken place in the Spiti Valley, and hence, thalassemia cannot be ruled out. Another 11% of blood smears showed both hypochromia and anisocytosis, consistent with iron deficiency anemia. Finally, 2% of smears were found to have multiple morphologies, including hypochromia, microcytosis, and/or macrocytosis. This supports the hypothesis that there are multiple contributors to the anemia.

Concurrent etiologies for the anemia may explain the decrease of 5.5% and the increase of 6% in post-treatment prevalence of anemia in August 2007 and 2008, respectively. Although folate, zinc, vitamin A, and B12 deficiencies may have contributed to the anemia, only iron and anti-helminthic treatments were provided, which may account for the suboptimal improvement observed. Another consideration is that post-treatment Hb measurements were taken earlier than planned. Measurements were taken at six weeks of treatment due to travel logistics while a three month course of treatment was provided complying with the WHO standard of care.³ Six weeks may be insufficient to elicit changes in Hb levels. It should also be noted that the anti-helminth treatment should have been effective as it was prescribed according to current Canadian practice guidelines, and hookworm infestation as a cause of anemia six weeks after albendazole (Albenza®) treatment is less likely.

An important difference in the outcomes between female and male subpopulations was a major finding. The older females (ages 15–18) did not demonstrate as great an improvement in Hb levels compared to males of the same age. This is likely due to menstrual losses and possibly due to variations in quantity of food intake between genders. Further investigation of food intake between genders and more rigorous interventions for females should be considered, including education and regular supplementation.

With low Hb concentrations and low inspired oxygen partial pressures at high altitude, it raises the question of whether oxygen saturation is sufficient to meet the body's metabolic needs. Medical Checks for Children (MCC), a Dutch NGO also involved in health care promotion at the Munsel-ling school, measured oxygen saturation in all school children in 2006 and found results to be within normal limits (data not available). Adequate oxygen saturation in the blood indicates that sufficient oxygen is being delivered to body tissues.

Considering the remoteness of the Spiti Valley and the limited expertise of the GHI members, we acknowledge some shortcomings of this study. Namely, a lack of adequate laboratory facilities and expertise prevented certain investigations from being carried out, such as ferritin levels, RDW, MCV, and stool ova and parasite testing, that would have allowed accurate diagnosis of anemia and determination of its etiology.

Despite limited resources and geographical constraints, the GHI studied the prevalence and etiology of anemia in a population of children in the Indian Himalayas and implemented an integrative management program in a collaborative, sustainable manner. In conclusion, blood smear analysis and the minimal

improvement with iron treatment suggest that anemia in the Munsel-ling children is multifactorial in nature and warrants an integrative treatment approach. Deficiencies in iron, folic acid, and vitamin B12 could all be possible causes of the anemia. The GHI's solution to the anemia problem in the Spiti Valley was comprehensive and consisted of therapeutic, nutritional, and preventative components that were adapted annually based on an expanded understanding of the study population. Aside from the therapeutic initiatives previously discussed, preventative intervention included construction of greenhouses to improve folic acid and iron levels by increasing fresh fruit and vegetable intake during the cold winter months. Treatment with albendazole (Albenza®) would not prevent recurrent parasitic infections; thus, preventative measures such as hygiene education, construction of toilet blocks, water purification, and sanitation projects were implemented.

Future goals include follow-up of the productivity and effectiveness of constructed greenhouses in addition to continuing with multivitamin, zinc, and iron supplementation as necessary. A school nurse was trained to perform annual health screens, and a

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In conclusion... anemia in the Munsel-ling children is multifactorial in nature, and warrants an integrative treatment approach.

local resident was employed to manage the greenhouses to ensure year-round access to fresh vegetables. The GHI's approach is to focus on sustainable interventions to reduce the linked causes of anemia and thus effectively meet the long-term needs of this remote, underserved community. ♪

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