# Addressing the challenges of anaemia in the Andean region

**Workshop report**

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The Academy of Medical Sciences

**National Academy of Sciences, Peru**

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## Workshop report, January 2021

## Contents

# Executive summary

**Anaemia affects more than 1.5 billion people globally. It has disproportionate impacts in low- and middle-income countries and on vulnerable populations such as children, women of reproductive age and pregnant women. As well as short-term harms, its effects on child development have long-term implications for health and economic wellbeing.**

Anaemia results from an insufficiency of red blood cells needed to deliver oxygen to meet the metabolic needs of all the body's tissues. There are many possible causes of inadequate red blood cell number, including lack of iron, a component of oxygen-carrying haemoglobin in red blood cells. Indeed, low haemoglobin levels are generally used as an indicator of anaemia and the condition is frequently treated by iron supplementation.

However, it is likely that around half of all cases of anaemia are not caused by iron deficiency, but by alternative factors such as infection or inflammation, which can limit iron availability for red blood cell production, or by other causes unrelated to iron. Since iron supplementation has the potential to have harmful impacts, there is growing interest in ensuring it is used appropriately for those with identified iron deficiency or at high risk of deficiency.

In addition, a growing understanding of iron metabolism and iron homeostasis is providing new insights into how anaemia can be triggered. In particular, research has highlighted the pivotal role of a liver peptide, hepcidin, as the master regulator of iron metabolism. In Andean regions, physiological adaptations to high-altitude living and low oxygen levels add further complexity to the regulation of iron and the development of anaemia.

In the 1960s, the World Health Organization (WHO) developed guidelines for the diagnosis of anaemia based on haemoglobin levels. These included adjustments for factors such as age and sex, but also took into account the fact that haemoglobin levels vary with altitude. However, little work has been done to validate these thresholds among people living at high altitude, leading to concerns that anaemia is being over-diagnosed in these populations. This could be exposing populations to unnecessary and potentially harmful interventions, and also diverting resources away from other important public health challenges.

In January 2021, the UK Academy of Medical Sciences and the National Academy of Sciences, Peru, jointly organised a two-day workshop to discuss these issues. Through plenary presentations and breakout sessions, workshop participants identified a range of priority research questions that need to be answered to ensure a more evidence-based approach to the challenge of anaemia in the region.

**Causes and contributory factors**: Participants identified a need to gain a deeper understanding of how distal risk factors (such as poverty) and proximal risk factors (such as nutrition, infections, inflammation and hypoxia) interact to influence the risk of anaemia at high altitude. A key question is around the proportion of cases that are due to iron deficiency and are therefore theoretically treatable through iron supplementation.

**Mechanisms of iron homeostasis and anaemia**: More information is needed on iron metabolism in high-altitude Andean populations, as well as on how other factors such as iron sequestration related to infection influence the risk of anaemia. Other important questions include how iron metabolism changes in such populations with age and at key stages of life such as pregnancy, and the implications this has for the risk of anaemia.

**Diagnosis of iron deficiency**: If haemoglobin levels are still to be used to diagnose anaemia, there is a need to identify more appropriate thresholds to diagnose iron deficiency in Andean populations. Haemoglobin is a poor indicator of iron status, since there are other causes of low haemoglobin concentration, and individuals may be iron deficient without being anaemic. More appropriate thresholds need to be developed and validated across different age groups in high-altitude populations.

There is also the potential to incorporate specific markers of iron status (such as ferritin and hepcidin, accounting for the confounding effect of inflammation) into diagnostic criteria; new approaches such as dried blood spot analysis could be developed for harder to reach populations.

**Consequences of anaemia**: Participants identified a need to determine whether functional readouts might replace or complement use of haemoglobin testing in the diagnosis of anaemia. A better understanding of the consequences of mild anaemia at altitude would help to determine whether interventions are necessary in this group. More information is needed on the impact of anaemia on vulnerable populations, such as pregnant women at high altitude, and on the consequences of anaemia in pregnancy on the life-long health of offspring and their susceptibility to disease.

**Treatment and prevention**: Participants discussed the need to identify the most appropriate dosing schedules given new knowledge of iron homeostasis, as well as the potential for alternative treatment approaches such as intravenous iron administration. More information is also needed on the potential detrimental effects of iron supplementation on the gut microbiome. Multiple practical questions remain to be answered, including the relative advantages of supplements and fortification of foodstuffs, the best sources of iron for interventions, and the key factors underpinning the effectiveness of intervention programmes. Furthermore, treatment approaches not focused on iron should also be evaluated, in particular identifying and addressing causes of inflammation.

**Methodologies**: A range of approaches that could be taken to address these questions were identified. They included analysis of data from routine health and demographic surveys, as well as in-depth studies of risk factors in high-altitude populations, including phenotypic and genotypic studies of iron metabolism in the context of high-altitude hypoxia. Collaborations – both within the Andean region, and with other high-altitude areas – were seen as important to generate comparative data. Engagement with communities was identified as vital to secure support for research and to ensure that communities have an opportunity to shape research studies.

Anaemia is one of the world's greatest public health challenges, but the extent to which it affects Andean populations is uncertain, as are its causes. Given the potential direct and indirect harms associated with unnecessary treatment, it is essential that ways are found to provide a clearer picture of the levels, causes and consequences of anaemia at high altitude, the need for treatment, and the best ways to deliver such treatment.

# Introduction

**In 2013, anaemia affected an estimated one in four of the world's population.[1] Globally, anaemia is responsible for nearly 9% of total disability, with the burden of anaemia falling mainly on low- and middle-income countries. Limited progress has been made since the 1990s despite wide recognition of its harmful impacts, particularly on children and pregnant women, and multiple public health campaigns.**

Anaemia is a recognised public health challenge in Latin America. Despite some successes in combating the condition, anaemia rates remain high in many settings, particularly in the Andean regions of Ecuador, Bolivia and Colombia and other high-altitude areas of Central and South America.

Anaemia arises when a person does not have enough red blood cells to deliver sufficient oxygen to meet the body's physiological needs. The most common method for diagnosing anaemia is through measurement of levels of haemoglobin, the oxygen-carrying constituent of red blood cells. The World Health Organization (WHO) has developed thresholds for diagnosis of anaemia that take into account factors such as age and sex. These include a further adjustment for altitude,[2] with thresholds progressively increasing above 1,000 metres. The logic behind this adjustment is that higher haemoglobin levels are required at high altitude to compensate for reduced atmospheric oxygen concentrations.
The WHO thresholds were initially developed in the 1960s and have not been updated in recent years. Although the thresholds include adjustments for altitude, there are concerns that they do not provide a reliable indicator of anaemia. In particular, for altitudes above 3,000 metres, adjustments are not based on haemoglobin measurements but are estimates based on modelling. They may also not accurately reflect variation in haemoglobin levels with age, particularly in young children; haemoglobin levels change rapidly during early childhood, but the same threshold is used for all children between 6 months and 6 years.
As a result, there are suggestions that anaemia is being over-diagnosed at altitude.[3,4,5] Studies in Peru, for example, have found that the prevalence of anaemia in infants in Puno

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[1] Kassebaum NJ & GBD 2013 Anemia Collaborators (2016). *The Global Burden of Anemia.* Hematol Oncol Clin North Am **30(2)**, 247-308. doi: 10.1016/j.hoc.2015.11.002.

[2] World Health Organization (2011). *Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity*. Vitamin and Mineral Nutrition Information System.

[3] Sarna K, *et al*. (2018). *WHO hemoglobin thresholds for altitude increase the prevalence of anemia among Ethiopian highlanders*. Am J Hematol **93(9)**, E229-E231. doi: 10.1002/ajh.25194.

[4] Sarna K, Brittenham GM & Beall CM (2020). *Current WHO hemoglobin thresholds for altitude and misdiagnosis of anemia among Tibetan highlanders.* Am J Hematol **95(6)**, E134-E136. doi: 10.1002/ajh.25765.

[5] Gonzales GF, Begazo J & Alarcón-Yaquetto DE (2020). *Suitability of Haemoglobin Adjustment to Define Anaemia at High Altitudes.* Acta Haematol **143(5)**, 511-512. doi: 10.1159/000502539.

(3,800 metres) increased from 11.3% to 94.7% after WHO's haemoglobin adjustment was applied.[6] However, only 26.5% had iron deficiency as assessed by measurement of ferritin levels.

These and other findings[7,8] suggest that the threshold adjustments are leading to a diagnosis of anaemia in many children with sufficient levels of iron and haemoglobin. This could be leading to over-treatment, for example through iron supplementation, and also absorbing resources that could be used to tackle other public health challenges.
Doubts about the true anaemia disease burden at high altitude, as well as emerging new knowledge about iron metabolism and other possible causes of anaemia, such as inflammation, have raised questions about the appropriateness of the WHO thresholds for diagnosing anaemia in Andean populations and of the need for iron supplementation programmes. In plenary sessions and breakout groups at the online workshop jointly organised by the Academy of Medical Sciences and the National Academy of Sciences, Peru, participants sought to take stock of the current state of knowledge and identify future research priorities to close key evidence gaps. The breakout groups explored four key issues: the aetiology of anaemia; whether iron supplementation is an effective treatment; haemoglobin cut-offs to define anaemia; and the impact of high-altitude physiology and adaptation on haemoglobin (summarised in Annex 1).

## The nature of the challenge

Red blood cell numbers are tightly controlled. Production of new red blood cells (erythropoiesis) takes place in the bone marrow and is accelerated at certain stages of life, such as during childhood growth or pregnancy, or after significant blood loss. Low oxygen levels at high altitude also lead to increased red blood cell numbers.
Anaemia arises when the body's demands for oxygen exceed the capacity of red blood cells to deliver it. Symptoms of anaemia include fatigue, lethargy, shortness of breath and heart palpitations. In children, anaemia can lead to growth retardation and stunting, with long-term implications for health and economic wellbeing. In pregnant women, anaemia increases the risk of stillbirth, premature delivery and low birth weight. Pregnancy complicated by anaemia can also increase the risk of cardiometabolic and renal diseases in offspring in adulthood.

## The causes of anaemia

Broadly speaking, anaemia reflects the inadequate production of red blood cells in the bone marrow, shortened red blood cell life span, or red blood cell loss during bleeding. Because of the core role of haemoglobin in red blood cell function, **iron deficiency** is typically seen as the principal cause of anaemia, with dietary iron supplementation the main treatment. However, iron deficiency is only one possible cause of anaemia (see Figure 1). In fact, only around half of all cases of anaemia can be traced back to iron deficiency.[9] Moreover, even this figure may be an overestimate. A study of the effectiveness of an iron supplementation programme to correct anaemia in Peru, for example, suggested that only around 25% of

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[6] Gonzales GF, *et al*. (2018). *Correcting the cut-off point of hemoglobin at high altitude favors misclassification of anemia, erythrocytosis and excessive erythrocytosis.* Am J Hematol **93(1)**, E12-E16. doi: 10.1002/ajh.24932.

[7] Choque-Quispe BM, *et al*. (2020). *Is the prevalence of anemia in children living at high altitudes real? An observational study in Peru.* Ann N Y Acad Sci **1473(1)**, 35-47. doi: 10.1111/nyas.14356.

[8] Gonzales GF, Tapia V & Vásquez-Velásquez C (2020). *Changes in hemoglobin levels with age and altitude in preschool-aged children in Peru: the assessment of two individual-based national databases.* Ann N Y Acad Sci Nov 4. doi: 10.1111/nyas.14520.

[9] WHO (2015). *The global prevalence of anaemia in 2011*. Geneva (Switzerland): WHO Document Production Services.

cases of anaemia in infants were due to iron deficiency.[10]

Other important causes of anaemia include **deficiencies in certain micronutrients** (such as vitamins A and B12 and folate), infections, inflammation, excessive blood loss and genetic disorders affecting red blood cells (such as sickle cell disease and thalassaemias). Many different **infections** are associated with anaemia.[11,12] For example, malarial anaemia is caused in part by destruction and enhanced clearance of red blood cells. In other situations, a pathogen and a human host engage in a 'tug of war' over scarce iron resources; if pathogens gain the upper hand, or the host sequesters iron as part of a response to deprive pathogens of iron, anaemia may result.

**Inflammation**-induced anaemia shares many features with anaemia triggered by infection, due to the involvement of immune mediators such as cytokines.[13] Inflammation may be caused by a range of factors, including obesity and exposure to environmental pollutants. In Andean regions, greater use of cookstoves and biomass fuels at altitude could plausibly affect indoor pollution, cause inflammation and increase the risk of anaemia.

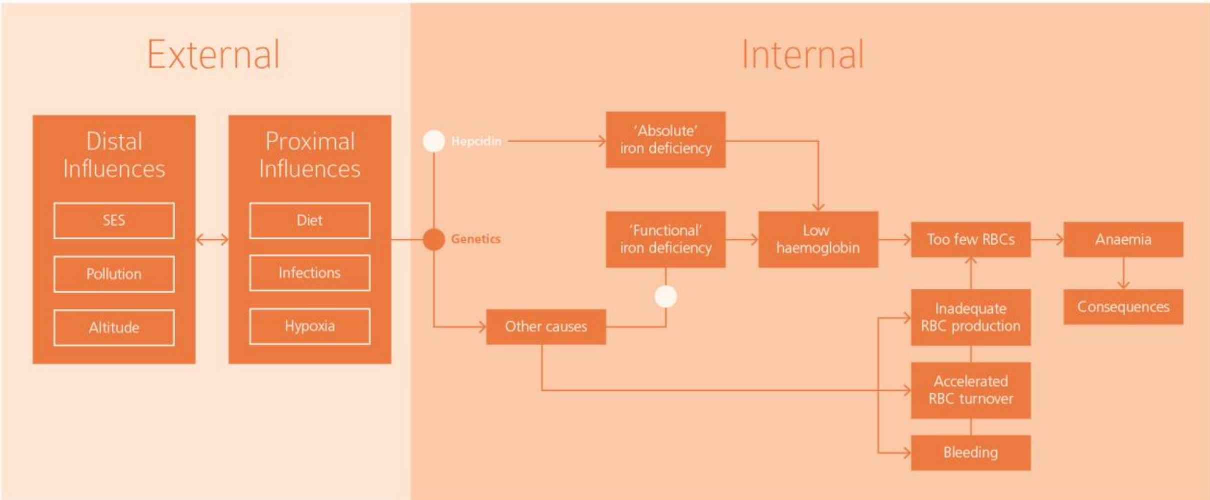


*Figure 1: Routes to anaemia. Multiple environmental factors can lead to anaemia. Their impact will be dependent on multiple genetic factors. Anaemia ultimately results from inadequate numbers of red blood cells (RBCs), which may reflect inadequate dietary availability of iron ('absolute' deficiency'), or restricted access to iron ('functional' deficiency), or iron-independent mechanisms. Hepcidin has a key role in regulating the availability of iron, so is of fundamental importance to iron-associated anaemia. SES; socioeconomic status.*

[10] Choque-Quispe BM, Paz V & Gonzales GF (2019). *Proportion of anemia attributable to iron deficiency in high-altitude infant populations*. Ann Hematol **98(11)**, 2601-2603. doi: 10.1007/s00277-019-03823-7.

[11] Darton TC, *et al*. (2015). *Rapidly Escalating Hepcidin and Associated Serum Iron Starvation Are Features of the Acute Response to Typhoid Infection in Humans*. PLoS Negl Trop Dis **22;9(9)**, e0004029. doi: 10.1371/journal.pntd.0004029.

[12] Prentice AM, *et al*. (2019). *Respiratory infections drive hepcidin-mediated blockade of iron absorption leading to iron deficiency anemia in African children*. Sci Adv **5(3)**, eaav9020. doi: 10.1126/sciadv.aav9020.

[13] Nemeth E & Ganz T (2014). *Anemia of inflammation.* Hematol Oncol Clin North Am **28(4)**, 671-81, vi. doi: 10.1016/j.hoc.2014.04.005.

## Iron homeostasis

Iron is an essential mineral. As well as being a core component of haemoglobin, it also has other important cellular roles. However, iron is also potentially highly reactive and therefore hazardous, so it is tightly regulated in the body. Iron is obtained from dietary sources but is also carefully managed internally, for example through recycling of ageing red blood cells.

New research is providing new insights into iron metabolism that could have significant implications for the diagnosis and management of anaemia. In particular, this work has revealed the central importance of **hepcidin**, a peptide hormone produced by the liver, as a master regulator of iron metabolism. Hepcidin promotes degradation of the iron transporter, ferroportin, which is highly expressed in the duodenum and on iron-recycling macrophages.[14] Hepcidin is therefore the key factor controlling the availability of iron in the body – even with plentiful iron in the diet, high levels of hepcidin (as seen in inflammation) will block uptake in the gut and promote iron sequestration in macrophages, leading to a state of 'functional' iron deficiency that cannot be corrected by additional dietary iron.

Production of hepcidin is regulated, positively and negatively, by a range of factors. An increase in iron levels in the body stimulates hepcidin production, acting as a negative feedback mechanism. Infection and inflammation also enhance hepcidin production, reducing iron uptake. By contrast, iron deficiency, low oxygen levels (hypoxia)[15] and the need to increase red blood cell production[16] have the opposite effect, reducing hepcidin synthesis and promoting iron uptake.

The role of hepcidin in iron homeostasis is being elucidated in increasing detail. However, less is known about the mechanisms of iron homeostasis at high altitude. Hypoxia triggers a range of short-term and longer-term physiological changes that promote survival at high altitude, which include changes to iron metabolism. Work in high-altitude populations has also identified genetic adaptations that may promote survival at high altitude.[17] An example is the *EPAS1* gene in Tibetan populations, which acts to lower haemoglobin levels.[18] There is also some evidence of genetic adaptations affecting metabolism in Andean populations,[19,20] although little is known about how genetic factors might influence iron metabolism or the risk of anaemia.

## Diagnostic criteria

These factors have led to uncertainty about the reliability of haemoglobin-based approaches for diagnosing anaemia at high altitude and the need for iron supplementation to address it. **The Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia**

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[14] Billesbølle CB, *et al*. (2020). *Structure of hepcidin-bound ferroportin reveals iron homeostatic mechanisms*. Nature **586(7831)**, 807-811. doi: 10.1038/s41586-020-2668-z.

[15] Sonnweber T, *et al*. (2014). *Hypoxia induced downregulation of hepcidin is mediated by platelet derived growth factor BB*. Gut **63(12)**, 1951-9. doi: 10.1136/gutjnl-2013-305317.

[16] Kautz L, *et al*. (2014). *Identification of erythroferrone as an erythroid regulator of iron metabolism*. Nat Genet **46(7)**, 678-84. doi: 10.1038/ng.2996.

[17] Beall CM (2014). *Adaptation to high altitude: phenotypes and genotypes*. Annu Rev Anthropol **43**, 251–72.

[18] Simonson TS, *et al*. (2015). *Adaptive genetic changes related to haemoglobin concentration in native high-altitude Tibetans.* Exp Physiol **100(11)**, 1263-8. doi: 10.1113/EP085035.

[19] Bigham AW, *et al*. (2014). *Maternal PRKAA1 and EDNRA genotypes are associated with birth weight, and PRKAA1 with uterine artery diameter and metabolic homeostasis at high altitude*. Physiol Genomics **46(18)**, 687-97. doi: 10.1152/physiolgenomics.00063.2014.

[20] Brutsaert TD, *et al*. (2019). *Association of EGLN1 gene with high aerobic capacity of Peruvian Quechua at high altitude*. Proc Natl Acad Sci USA **116(48)**, 24006-24011. doi: 10.1073/pnas.1906171116.

**(BRINDA)** project[21] has sought to address this issue by collating data from national and subnational nutritional surveys of children and women of child-bearing age to provide insights into the nutritional and non-nutritional causes of anaemia in different locations. Data analyses have revealed considerable heterogeneity in the causes of anaemia, dependent on factors such as environmental setting, population group, infectious disease burden and the prevalence of other causes of anaemia.[22] Analysis of BRINDA data has also raised questions about the validity of the WHO threshold adjustments for altitude.[23]

In Latin America, an analysis of demographic and health survey data in Bolivia has also raised questions about the significance of iron deficiency in anaemia.[24] Anaemia levels in young children are reported as above 40%, and above 60% at high altitude. Between 1998 and 2016, anaemia levels dropped slightly at medium and low altitudes, but increased at high altitude – reaching 74% in 2016. A number of risk factors for anaemia were identified, but none were specifically associated with anaemia at high altitude. These patterns are particularly striking given the active programme of nutritional interventions in Bolivia.

Some programmes have achieved a reduction in anaemia levels. Chile, for example, reduced anaemia levels in young children from 18.8% in the mid-1970s to 4% in 2012, at least in part through the provision of iron-fortified milk by the National Complementary Feeding Program.[25] More generally, however, progress has been limited. In some cases, iron supplementation programmes have had minimal impacts on the prevalence of anaemia even when adherence to interventions has been very high.

In Peru, several studies have raised doubts about the altitude adjustment. In the city of Puno, 3,800 metres above sea level, 66% of young children were judged to have anaemia on the basis of adjusted thresholds, but only 4.8% when unadjusted thresholds were used. There was little correspondence between haemoglobin levels and measures of total body iron.[26] In addition, data from national surveys indicate that increasing haemoglobin levels are seen at lower altitudes than 1,000 metres, suggesting that anaemia may actually be being underestimated at low altitudes. They also show significant variation with age, arguing that thresholds should cover narrower age bands than at present.[27]

## Understanding iron deficiency in the Andean context

When looking at different causes of anaemia, there has been growing interest in the use of different markers to assess iron deficiency and anaemia. Several indicators of iron status are available, including ferritin. However, confounding by inflammation presents a challenge, meaning iron status assessment must be interpreted in association with inflammatory markers such as C-reactive protein (CRP) and alpha-1-acid glycoprotein.

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[21] Suchdev PS, *et al*. (2016). *Overview of the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) Project.* Adv Nutr **7(2)**,349-56. doi: 10.3945/an.115.010215.

[22] Chaparro CM & Suchdev PS (2019). *Anemia epidemiology, pathophysiology, and etiology in low- and middle-income countries.* Ann N Y Acad Sci **1450(1)**, 15-31. doi: 10.1111/nyas.14092.

[23] Sharma AJ, *et al*. (2019). *Reexamination of hemoglobin adjustments to define anemia: altitude and smoking.* Ann N Y Acad Sci **1450(1)**, 190-203. doi: 10.1111/nyas.14167.

[24] Cordero D, *et al*. (2019). *Anemia in Bolivian children: a comparative analysis among three regions of different altitudes.* Ann N Y Acad Sc **1450(1)**, 281-290. doi: 10.1111/nyas.14038.

[25] Mujica-Coopman MF, *et al*. (2015). *Prevalence of Anemia in Latin America and the Caribbean.* Food Nutr Bull **36(2 Suppl)**, S119-28. doi: 10.1177/0379572115585775.

[26] Choque-Quispe BM*, et al. (2020). Is the prevalence of anemia in children living at high altitudes real? An observational study in Peru*. Ann N Y Acad Sci **1473(1)**, 35-47. doi: 10.1111/nyas.14356.

[27] Gonzales GF, Tapia V & Vásquez-Velásquez C (2020). *Changes in hemoglobin levels with age and altitude in preschool-aged children in Peru: the assessment of two individual-based national databases.* Ann N Y Acad Sci. doi: 10.1111/nyas.14520.

A longer-term possibility could be monitoring of hepcidin levels. For example, there is some evidence from Africa that levels of hepcidin could be used to determine whether anaemia was caused by iron deficiency.[28,29] One trial in Africa evaluated the use of hepcidin screening to guide iron interventions for women during pregnancy, but outcomes were inferior to the WHO recommendation of universal daily iron supplementation.[30]

The growing understanding of iron metabolism, particularly the role of hepcidin in controlling iron uptake from the gut, could also have important implications for **dosing schedules**. Spacing iron dosing to alternate days, for example, may lead to more efficient take-up of iron by negating the inhibitory effects of hepcidin triggered by supplementation.[31,32] There is also interest in using **alternative delivery mechanisms** in pregnancy, such as intravenous iron infusion,[33] to circumvent the hepcidin 'blockade' on uptake from the gut and to avoid the gastrointestinal side effects that limit adherence to oral treatments.

## The potential downsides

The emerging picture suggests that, if anaemia is in reality less common than currently reported, and if it is caused by iron deficiency less often than thought, population-level iron supplementation programmes are likely to be of limited effectiveness. Furthermore, such programmes could represent poor use of healthcare resources that could be better deployed to tackle other public health challenges. In addition, there is potential for iron supplementation to have adverse effects. In some settings, for example, it is associated with an increased risk of infection (particularly from malaria).[34]

A further reason to reduce unnecessary use of iron supplementation is because of its potential impact on the **gut microbiome**. The contribution of the gut microbiome to multiple aspects of human health is now well established. Gut bacteria contribute to iron homeostasis, competing for limited supplies of iron and inhibiting iron uptake from the gut.[35] The impact of iron supplementation on the gut microbiome is not fully understood, but it has the potential to disturb microbial ecosystems and there is some evidence of detrimental impacts.[36,37]

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[28] Pasricha SR, *et al*. (2014). *Expression of the iron hormone hepcidin distinguishes different types of anemia in African children*. Sci Transl Med **6(235)**, 235re3. doi: 10.1126/scitranslmed.3008249.

[29] Bah A, *et al*. (2017). *Serum Hepcidin Concentrations Decline during Pregnancy and May Identify Iron Deficiency: Analysis of a Longitudinal Pregnancy Cohort in The Gambia*. J Nutr **147(6)**, 1131-1137. doi: 10.3945/jn.116.245373.

[30] Bah A, *et al*. (2019). *Hepcidin-guided screen-and-treat interventions against iron-deficiency anaemia in pregnancy: a randomised controlled trial in The Gambia.* Lancet Glob Health **7(11)**, e1564-e1574. doi: 10.1016/S2214-109X(19)30393-6.

[31] Stoffel NU, *et al*. (2017). *Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials.* Lancet Haematol **4(11)**, e524-e533. doi: 10.1016/S2352-3026(17)30182-5.

[32] Stoffel NU, *et al*. (2020). *Iron absorption from supplements is greater with alternate day than with consecutive day dosing in iron-deficient anemic women.* Haematologica **105(5),** 1232-1239. doi: 10.3324/haematol.2019.220830.

[33] Neogi SB, *et al*. (2019). *Safety and effectiveness of intravenous iron sucrose versus standard oral iron therapy in pregnant women with moderate-to-severe anaemia in India: a multicentre, open-label, phase 3, randomised, controlled trial*. Lancet Glob Health **7(12)**, 1706-e1716. doi: 10.1016/S2214-109X(19)30427-9.

[34] Mwangi MN, Prentice AM & Verhoef H (2017). *Safety and benefits of antenatal oral iron supplementation in low-income countries: a review*. Br J Haematol **177,** 884–895.

[35] Das NK, *et al*. (2020). *Microbial Metabolite Signaling Is Required for Systemic Iron Homeostasis.* Cell Metab **31(1)**, 115-130.e6. doi: 10.1016/j.cmet.2019.10.005.

[36] Zimmermann MB, *et al*. (2010). *The effects of iron fortification on the gut microbiota in African children: a randomized controlled trial in Cote d'Ivoire.* Am J Clin Nutr **92(6)**, 1406-15. doi: 10.3945/ajcn.110.004564.

[37] Paganini D & Zimmermann MB (2017). *The effects of iron fortification and supplementation on the gut microbiomeand diarrhea in infants and children: a review.* Am J Clin Nutr **106(Suppl 6)**, 1688S-1693S. doi: 10.3945/ajcn.117.156067.

# Key research questions

**Given this emerging picture, workshop participants identified an urgent need to generate a clearer picture of the true burden of anaemia in Andean populations and its causes, to develop better methods of diagnosis, and to identify more appropriate approaches to treatment that better reflect the epidemiology, causes and mechanisms of anaemia at high altitude. The workshop identified the following as critical areas where more research is needed to address these issues.**

## Causes and contributory factors

Delegates suggested that there was a need to understand the causes of anaemia at high altitude in order to determine how it should be addressed. One key question is around the proportion of cases linked to iron deficiency, as these are the ones where treatment with iron supplementation would be appropriate. However, it is also important to understand the contributions made by non-dietary influences on iron metabolism such as infection and inflammation.

A further important issue identified by participants was the need to determine how contextual factors affect the risk of anaemia. The Andean region has contrasting environmental surroundings, including large urban conurbations, rural areas and jungle, and coastal regions, each of which could have an impact on anaemia risk. More generally, there is a need to understand the pathways through which distal risk factors, such as environmental surroundings and poverty, contribute to the development of anaemia.

A major programmatic challenge is to determine how the most important contributory factors can be identified in particular settings, so that appropriate interventions can be applied.

## Mechanisms of iron homeostasis and anaemia

Participants noted that high-altitude physiological adaptations could affect iron metabolism and other factors influencing the risk of anaemia. Some of these adaptations may reflect homeostatic responses to low oxygen levels. Others may stem from inherited changes that enhance survival at high altitude. Potentially, these latter changes could be identified through genetic approaches, and would provide insights into key physiological pathways involved in the adaptation to altitude.

Of particular significance is the interplay between physiological adaptations to altitude and iron homeostasis, particularly hepcidin. These are already known to be intimately intertwined, with hypoxia typically triggering changes that reduce hepcidin production and increase iron take-up.

Other important questions include how iron metabolism changes with age in children and how this affects the risk of anaemia. Pregnant women are at particular risk of anaemia, and there is a need to understand how iron metabolism changes during pregnancy at altitude and how this might influence fetal development.

## Diagnosis of iron deficiency

At the moment, measurement of haemoglobin levels is the most practical and widely used technique for diagnosing anaemia. While this remains the case, participants suggested that there was a need to revisit the thresholds that determine iron deficiency and anaemia at altitude and across different ages.

A key challenge is how new thresholds would be developed. One possibility might be to identify those people whose haemoglobin levels are abnormally low compared with the population average. Using a cut-off of two standard deviations below average, for example, anaemia rates in Peruvian children living above 4,000 metres are 5% compared to 66% using WHO thresholds.[38]

It would be important for pilot studies to be carried out at a local or country level to validate revised thresholds and their ability to provide an accurate assessment of anaemia at high altitudes.

With anaemia potentially having multiple causes, there was also interest in differential diagnosis to distinguish between possible contributory factors. A more precise understanding of causes could be used to make the case for alternative approaches to treatment and prevention.

The use of alternative markers to assess iron deficiency and anaemia could also be explored, including ferritin and inflammatory markers, and potentially also hepcidin. However, measurement of hepcidin is technically more challenging. There would also be a need to standardise testing (for example, testing at specific times of day). There is some interest in using dried blood spot samples to measure hepcidin levels, which could offer a more practical alternative to blood sampling in remote regions.

Participants also suggested that grading the severity of anaemia might have potential in identifying those in need of treatment. It is currently not clear whether mild anaemia has significant implications for health at altitude.

## Consequences of anaemia

Monitoring of haemoglobin levels provides a convenient assessment of anaemia, but participants stressed that the implications for health may not be straightforward to determine. It was suggested that more attention should be given to understanding the functional consequences of anaemia at altitude. A further important question is whether different causes of anaemia have different functional consequences.

Other key areas include the consequences of anaemia in vulnerable populations such as

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[38] Ocas-Córdova S, Tapia V & Gonzales GF (2018). *Hemoglobin Concentration in Children at Different Altitudes in Peru: Proposal for [Hb] Correction for Altitude to Diagnose Anemia and Polycythemia.* High Alt Med Biol **19(4)**, 398-403. doi: 10.1089/ham.2018.0032.

pregnant women and the implications for the health of the mother, fetus and newborn, as well as the risk of longer-term conditions in offspring. In addition to increasing the risk of fetal death, preterm birth and intrauterine growth restriction, perinatal iron deficiency has been associated with long-term cardiovascular complications in adult offspring, including hypertension and susceptibility to renal injury. The risk of cardiovascular morbidity and mortality is also elevated in women who had anaemia in pregnancy.

A further practical question is whether functional assessments can be used to refine diagnosis of anaemia, provide a more nuanced picture beyond haemoglobin levels and guide more targeted treatment.

## Treatment and prevention

Participants identified a range of important unanswered questions related to the treatment and prevention of anaemia. For example, the growing understanding of iron metabolism, particularly the role of hepcidin in controlling iron uptake from the gut, could have important implications for dosing schedules. Alternative delivery mechanisms, such as intravenous iron, could also be explored. Furthermore, participants raised whether targeting the causes of infection/inflammation could be effective in combating anaemia by relieving hepcidin-mediated iron restriction, and noted that this should be investigated further.

One reason to reduce the use of iron supplementation is because of its potential impact on the gut microbiome. The role of the gut microbiome in many aspects of human health is now well established, including its involvement in iron homeostasis. Very little is known about the effects of supplementary iron on the microbiome in high-altitude populations.

Many practical issues also exist. The relative advantages and disadvantages of iron supplementation and fortification remain open to debate, and the most appropriate sources of iron for supplementation/fortification in the region remain to be determined. There may be opportunities to engage with local food industries and processing plants to generate large quantities of iron-containing products safely, and to explore region-specific sources of iron such as dried llama meat.

There is also a need to identify the factors that contribute to successful supplementation and fortification programmes. Some countries have achieved significant reductions in the prevalence of anaemia and several studies have described effective interventions in the Latin American and Caribbean regions.[39] Research is also needed on how to integrate new markers for anaemia and iron deficiency programmatically.

## Methodologies

Workshop participants identified a range of approaches that could be used to answer some of these priority questions. Countries in the region typically have well-organised national demographic and health surveys that provide an important source of data, as well as opportunities to add new measures to explore associations between haemoglobin levels, anaemia, and other health and socioeconomic indicators.

More specific questions would need to be addressed through working directly with affected

[39] Iglesias Vázquez L, et al. (2019). Prevalence of Anemia in Children from Latin America and the Caribbean and Effectiveness of Nutritional Interventions: Systematic Review and Meta-Analysis. Nutrients 11(1), 183. doi: 10.3390/nu11010183.

populations. Longitudinal cohort studies would provide an opportunity to track changes over time, to explore the longer-term impacts of iron deficiency and/or anaemia. Genetic studies could be used to provide insight into adaptations to high altitude and shed light on the metabolic pathways contributing to susceptibility or resilience to anaemia, although genetic contributions are likely to be small. Regional collaborations could enable comparable data to be collected on populations in different countries. There is also potential to use implementation and operations research to explore factors contributing to successful programme development.

Participants also highlighted the importance of community engagement with high-altitude populations, to ensure local support for research activities. Such work could also identify health and social issues of importance to local communities, so that studies address other local priorities as well as anaemia. Such research could underpin the development of more integrated services for populations that are often highly disadvantaged. How best to engage with communities at altitude is a further important research priority.

# Conclusion

**Globally, anaemia is a major cause of disability. Although high levels of anaemia have been identified among populations living at high altitude in the Andes, it remains unclear whether this reflects a true disease burden or stems in large part from the adjustments in diagnostic thresholds recommended by the WHO.**

There is an urgent need to address this uncertainty. Use of iron supplementation to treat anaemia is not without risks, so its unnecessary use needs to be minimised. In addition, if anaemia is not such a major public health challenge, it may be absorbing resources that could be more productively deployed elsewhere.

The research questions outlined here provide the first step towards a research agenda that could reduce some of the current uncertainty. Closing evidence gaps could ensure that interventions are targeted at those most in need, use the most effective approaches and minimise unnecessary harm to vulnerable populations.

# Annex 1: Breakout group summaries

## Breakout group 1: Aetiology and diagnosis of anaemia

**What are the potential causes of anaemia, and how might these be differentiated diagnostically?**

- Haemoglobin concentration: considered as a bioindicator rather than a biomarker.
- Anaemia severity should be considered when discussing interventions.
- There are many potential causes of anaemia and they can be context-specific, varying from region to region.
- We need to have differential diagnoses and investigate further than just haemoglobin.
- Need to refine socioeconomic proxies and variables in understanding anaemia, causes of inflammation – many risk factors may be relatively homogenous within specific contexts.
- There is a need to collaborate on more focused regional studies and then unify them – cost is a potential barrier to this.
- Factors associated with anaemia can include:
    - Socioeconomic status
    - Malnutrition
    - Water quality
    - Iron deficiency
    - Nutritional deficiencies
    - Infection
    - Inflammation: important to understand causes of inflammation – e.g. obesity, pollution, parasites?
    - Malaria (not prevalent in much of the region)
    - Practices of high-altitude populations – e.g. solid fuel burning, effect of coca leaf chewing?
    - Sickle cell disease
    - Double burden of disease – obesity
    - Life stage: infancy, pregnancy, women of reproductive age

**What are the current challenges associated with assessment of iron status?**
**Practical/logistical challenges**

- Cultural barriers – attitudes to providing blood samples.
- There could be greater inclusion via community outreach from universities and NGOs to raise participation and to consider citizen perspectives where there has been a history of mistrust.
- Access to remote populations, and logistics for meaningful sample analysis (especially low sample volumes from infants).
- Cost of assessing more refined iron biomarkers.

- Balancing large population-based surveys with specific studies for understanding nuances.

**Technical challenges**

- Role of inflammation – need to consider acute and chronic inflammatory markers (CRP/AGP), and ideally to include both in surveys.
- How should corrections for inflammation be applied?
- Are current cut-offs sensitive and specific?
- Different methods produce different results: need for assay standardisation, e.g. hepcidin, sTfR.
- New approaches: blood spot assays?

**How can recent insights into iron biology influence approaches to anaemia-control strategies?**

- Collaborative projects are needed, e.g. focusing on mediators of inflammation and the effects on iron status and anaemia.
- We need to understand which indicators would be optimal (and practical) for population studies.
- Hepcidin is regulated by many systems so understanding the impact of this in more detail across different settings and different life stages is required.

## Breakout group 2: Is iron supplementation a safe and effective treatment in this population?

**Is providing non-haem iron a risky intervention in children <2 years of age?**

- Magnitude of risk should be considered primarily, as currently same dose of iron is given to all children.
- Dose of iron should be categorised according to severe, moderate or mild anaemia.
- Different types of iron should be considered, dependent on age.
- A study in peri-urban Lima has confirmed studies in Africa that iron supplementation has an impact on the microbiome of children, with increased prevalence of enteric pathogens.
- Cause of anaemia – is it diet or disease?
- Fortification is seeing positive effects with less risk.
- Incorporating supplements in food, e.g. sprinkles, is considered less easy to be fully adopted and maintained.
- Iron absorption is often blocked in population groups with inflammation. No clear study on the prevalence of inflammation in the Andean region.
- Supplementation should be mandatory in children who are truly iron deficient. But we do not have easy ways to identify them.
- Education of families and communities is absolutely key for any programme to be successful.

**What is the effect of non-haem or haem iron on gut microbiota?**

- Initially more data on the effect of different types of iron on microbiota are required. Haem iron is expected to cause less disruption to the microbiome, but studies are needed.
- Haem iron mixed with food is a very easy way to incorporate in the diet.
- Dietary sources of haem iron are expensive in Peru and the Andean region.

- There has been success with different ways to increase intake of haem iron, like making powder of dry meat in rural Andean areas, mixing it with other food ingredients, with high acceptability. But this approach needs to be made universal.
- Cultural, social and economic issues should be considered when developing these types of interventions.
- Research into use of blood products is required, dependent on the area. For example, using blood from animals living in mining areas has been shown to be contaminated with heavy metals from water pollution.
- Lyophilised blood or alternative methods of industrial production of haem iron needs high safety controls. Increased demand is also important. Currently no major programme is buying these products for any social programme.
- Haem iron has better absorption, but implementation is an issue.
- A food-based intervention has been developed using a novel iron compound (IHAT).
- Uptake in families of interventions with non-haem iron is better if the children like the supplement they take and the programme has been developed with strong community and social participation.

**Trade-off between haem vs non-haem iron supplementation in young children: absorption vs potential side effects in non-malaria-endemic regions.**

- Hard data in different populations looking at effects at low and high altitude are needed.
- Logistically there is no easy access to haem iron. It needs to be de-contaminated and processed correctly.
- Consideration should be given to the use of dried blood products, as there is no need to adhere to cold chain regulations.
- Peruvian meat suppliers, if given cohesive support, could harness this area.
- Interventional, controlled, prospective studies are needed using different types of haem and non-haem iron in different populations to develop evidence for policy in the region.

**Safe and effective iron supplementation schemes in young children in LMICs**

- Not ready to give a universal recommendation on what to use to correct iron-deficient anaemia in children, more so in high altitude areas.
- Benefit over risk is the overriding factor. Impact studies in young children are needed to document the real physiological benefit of correcting mild iron-deficient anaemia.
- A cohort study in the city of Puno, followed prospectively to assure compliance with all Ministry of Health of Peru nutrition guidelines, increased haemoglobin levels only by 0.2 g. The perception of the investigator was that they did not need iron supplements.
- The efficacy for sulphate balance depends on how anaemic an individual is.
- More research is needed, evaluating iron status, inflammation, and adjusting for several covariates of importance, such as dietary intake and diet quality.
- No matter which intervention is selected, it is important to develop education and communication strategies, with community participation and culturally sensitive messages.

**Some conclusions**

1. Not ready to make specific recommendations for young children at this time. More studies are needed.
2. Importance of diet, including diet quality, was stressed.
3. Haem iron supplementation programmes seem promising, requiring more studies, with good and safe manufacturing plants.
4. Non-haem iron supplementation needs revisions, particularly on dosing, as well as the interaction with gut inflammation. No discussion on its use in iron-depleted children.

5. Iron fortification is another important strategy that needs further impact evaluation.
6. Important to do case studies of countries such as Chile that have eradicated the problem of iron-deficiency anaemia.

## Breakout group 3: Haemoglobin cut-off to define anaemia in low- and high-altitude countries

**What is the biological/physiological explanation of the current haemoglobin threshold for anaemia diagnosis?**

- WHO anaemia thresholds for sea level which are then adjusted for altitude (curve).
- The data do not take into account current understanding of the pathophysiology of anaemia or physiological responses to different environments.
- Clinical features are not considered in any model for diagnosis, for example the assessment of inflammation.

**What would be the pros and cons of changing the current haemoglobin threshold for anaemia diagnosis, including the impact on the governmental policies and strategies to fight anaemia?**

- Pros
    - WHO data are not representative of a normal population when studied in the current real world and over-estimate the prevalence, particularly at lower altitudes.
    - Data show a significant shift in 2007, which is well after when the WHO reference values were last updated. Changing the data now would make the thresholds more relevant and checking it every year would be best practice.
    - Linear adjustments for altitude are arguably more representative and could be used in future diagnosis thresholds.
    - Within the WHO thresholds, there is no adjustment for locality type, e.g. city vs mountainous area.
    - Opportunity to identify thresholds with a higher specificity and sensitivity than the current thresholds.
    - Haemoglobin levels alone are not a good marker; reviewing how anaemia is diagnosed more broadly would be useful.
    - Currently resources are used to treat people who are not anaemic and are non-responsive to iron therapy. This is a waste and can cause harm.

- Cons

Consensus would be needed on a number of factors, for example:

- Whether linear corrections should be made.
- Whether clinical features should be considered.
- Which data set should be used as a reference point?
- Whether only healthy subjects should be considered in a data set.
- Whether geographic factors such as mountain regions vs city living be adjusted for.
- How regularly data should be updated.
- The standard of mathematic modelling required to make data robust.

The right interventions to manage anaemia are not established.

**Which new biomarkers would be suitable for a better anaemia diagnosis?**

- Actual data: 95% reference interval for sea level with a correction for altitude with regression (linear).
- Specific data for the region and type of setting (e.g. jungle), tested for sensitivity and specificity.
- Clinical markers.

## Breakout group 4: High-altitude physiology and adaptation: impact on haemoglobin

**What elements of the physiology of the oxygen homeostasis and iron homeostasis pathways are most relevant to haemoglobin concentration?**

- This question may pose a false dichotomy because hypoxia-inducible factors (HIFs) are the master regulators of oxygen homeostasis and iron homeostasis is embedded within. Examples include *EPO, HAMP, TFN.*
- We may not be able to associate a particular trait as reflecting *either* adaptation to hypoxia or iron homeostasis. Erythropoietin and hepcidin concentrations illustrate this.
- Consider conceptualising iron homeostasis as an adaptation to high-altitude hypoxia.
- Blood and plasma volumes and red blood cell mass influence haemoglobin concentration.

**What do we know about the relationship between haemoglobin concentration and indicators of good health and function at high altitude?**

- We should assess the appropriateness of haemoglobin concentration cut-offs using physiological readouts and functional tests.
- In Peru, both very low and very high haemoglobin levels are associated with poor pregnancy outcomes measured as stillbirths and small-for-gestational age babies. Among Tibetans, exercise and reproductive success are best at 'low-altitude' levels of haemoglobin.
- Birth weight decreases with increasing altitude; any influence of iron homeostasis is unknown. At low altitudes, iron supplementation appears to reduce chance of low birth weight. Consider assessing iron homeostasis and birth weight at various altitudes by examining birth weight centiles and incorporating maternal health records.
- Other opportunities for studies include neurodevelopment, academic performance, physical work output, taking into account confounding sociocultural and economic factors.

**How might those elements modify indicators of iron status?**

- Hepcidin levels – need to define 'normal', as at present normal range considered 2–55. Note that hepcidin studies ideally collect samples at same time each day (before eating in morning).
- Excessive erythrocytosis (EE) and chronic mountain sickness (CMS) are evidence of loss of adaptation to hypoxia. What is the role of iron status or the consequence for iron homeostasis?
- Pulmonary hypertension characterises hypoxic stress in the Andes. Iron supplementation can dampen this response for acutely exposed individuals. Is there an association among Andean highlanders? There is none among Amhara highlanders in Ethiopia.

**What do we need to learn to understand the how and why of the differences in oxygen and iron homeostasis among the various high-altitude populations?**

- Is iron homeostasis the same at all altitudes and for various subgroups, particularly those under additional stress such as reproduction, growth or exercise?
- Full understanding of the effects of iron supplementation at all stages of life.
- Contributions of inflammation and diet as well as cultural factors such as coca chewing.
- Properly define anaemia with revised functionally-based cut-off values for anaemia in relation to geographic or other factors.
- Use genomics to identify informative pathways, interactions and phenotypes.
- Take advantage of existing datasets and ongoing health surveys.

# Annex 2: Participant list

**Dr Virginia Abello Polo**, Facultad de Medicina, Fundación Universitaria de Ciencias de la Salud, Bogotá, Fundación Universitaria de Ciencias de la Salud, Bogotá

**Dr Roberto Accinelli**, High Altitude Research Institute, Peru

**Dr Ana Maria Aguilar Liendo**, Universidad Mayor de SanAndres, La Paz, Bolivia

**Dr. Ricardo Amaru Lucana**, Bolivia

**Amy Anderson**, Department of Anthropology, University of California Santa Barbara, US

**Juan Pablo Aparco Balboa**, Instituto Nacional de Salud, Lima, Perú

**Dr Andrew Armitage**, University of Oxford, UK

**Professor Sarah Atkinson**, KEMRI-Wellcome Trust Research Programme and Department of Paediatrics, University of Oxford, UK

**Dr Rosario Bartolini**, Instituto de Investigación Nutricional, Peru

**Dr Cynthia Beall**, Case Western Reserve University, USA

**Dr Jose Begazo**, Peru

**Fern Brookes**, Academy of Medical Sciences, UK

**Lidia Sofía Caballero**, Universidad Nacional del Altiplano Puno

**Hayley Carr**, Academy of Medical Sciences, UK

**Dr. Dante Chumacero Del Castillo**, Bolivia

**Hilary Creed-Kanashiro MPhil**, Instituto de Investigación Nutricional, Peru

**Dr Miguel Dávila**, PAHO Peru

**Professor Carlos Alberto Delgado Bocanegra**, Universidad Nacional Mayor de San Marcos (UNMSM) and Instituto Nacional de Salud del Niño (INSN), Lima

**Dr Achsah Dorsey**, University of Massachusetts, Amherst, USA

**Jane Ellis**, Academy of Medical Sciences, UK

**Dr Wilma B Freire**, Universidad San Francisco de Quito, Quito, Ecuador

**Dr Diego Gaitán**, Colombia

**Professor Max Gassmann**, University of Zurich, Switzerland

**Professor Dino Giussani**, University of Cambridge, UK

**Dr Cynthia Gonzales-Castañeda**, Universidad Peruana Cayetano Heredia, Peru

**Dr Gustavo F. Gonzales**, National Academy of Sciences, Peru

**Claire Gorby**, Academy of Medical Sciences, UK

**Alex Hulme**, Academy of Medical Sciences, UK

**Michelle Jimenez**, UNICEF, Peru

**Professor Mairead Kiely**, School of Food and Nutritional Sciences, University College Cork, Ireland

**Dr Claudio Lanata**, National Academy of Medicine, Peru

**Professor Heimo Mairbäurl**, Translational Lung Research Center Heidelberg, German Center for Lung Research, University Hospital Heidelberg, Germany

Professor Francisco Mardones, Chile

**Dr Elaine McCarthy**, School of Food and Nutritional Sciences, University College Cork, Ireland

**Professor Miguel Angel Méndez Silva**, Universidad San Francisco de Quito

**Dr Sophie Moore**, Kings College London, UK

**Dr Martina Muckenthaler**, Germany
**Dr César V. Munayco**, General Directorate of Epidemiology, Ministry of Health, Peru
**Dra Alejandra Nunez de la Mora**, Universidad Veracruzana, México
**Professor Manuel Olivares, Chile**
**Professor Mary E. Penny**, Instituto de Investigación Nutricional, Peru
**Professor Lucilla Poston FMedSci**, Kings College London, UK
**Dr Jose L San Miguel**, Instituto de Investigación en Salud y Desarrollo (IINSAD), Facultad de Medicina, Universidad Mayor de San Andrés
**Dr Tatum Simonson**, University of California, San Diego, USA
**Andrea Sosa Moreno**, University of Michigan, USA
**Dr Nicole Stoffel**, ETH Zurich, Switzerland
**Professor Parmi Suchdev**, Emory Global Health Institute, USA
**Dr Yibby Forero Torres**, Coordinadora de Nutrición del Instituto Nacional de Salud de Colombia, Colombia
**Dra Maria Elena Ugaz**, UNICEF, Peru
**Cinthya Vásquez-Velasquez**, Universidad Peruana Cayetano Heredia
**Dr Samuel Verges**, Grenoble Alpes University, Grenoble, France
**Wilfredo Villamonte Calanche**, Centro Multidisciplinario de Investigación en Medicina Materno Perinatal de Altura Universidad Andina del Cusco, Peru
**Dr Nelly Zavaleta**, Instituto de Investigación Nutricional, Peru

The Academy of Medical Sciences

Academy of Medical Sciences
41 Portland Place
London, W1B 1QH
+44(0)20 3141 3200

info@acmedsci.ac.uk
www.acmedsci.ac.uk

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