Oxygen Saturation in Childhood at High Altitude: A Systematic Review

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ABSTRACT

Background: It is well known that oxygen saturation (SpO_2), measured by pulse oximetry, decreases as altitude increases. However, how SpO_2 changes across childhood, and more specifically during sleep/wake states, at different high altitudes are less well understood. We aimed to perform a systematic review of all studies with direct SpO_2 measurement in healthy children living at high altitude (>2500 meters above sea level [masl]) to address these questions.

Methods: MEDLINE, EMBASE, and SciELO databases were searched up to December 2018. Two independent reviewers screened the literature and extracted relevant data.

Results: Of 194 references, 20 studies met the eligibility criteria. Meta-analysis was not possible due to the use of different oximeters and/or protocols for data acquisition and reporting of different SpO_2 central tendency and dispersion measures. The most relevant findings from the data were: 1) SpO_2 is lower as altitude increases; 2) at high altitude, SpO_2 improves with age through childhood; 3) SpO_2 is lower during

sleep and feeding in comparison to when awake, this SpO_2 gap between wake and sleep states is more evident in the first months of life and narrows later in life; 4) SpO_2 dispersion (inter-individual variation) is higher at younger ages, and more so during sleep; 6) In 6/20 studies the SpO_2 values were non-normally distributed with a consistent left skew.

Conclusions: At high altitude mean/median SpO_2 increases in children with aging; a significant gap between wake and sleep states is seen in the first months of life, which narrows, as the infant gets older; SpO_2 dispersion at high altitude is wider at younger ages; at high altitude SpO_2 shows a non-normal distribution skewed to the left, this bias becomes more evident as altitude increases, at younger ages and during sleep.

Introduction

Since its description in 1975, oxygen saturation (SpO_2) measured by pulse oximetry (Severinghaus, 2007) has become a routine tool in clinical practice, to the point that it has been proposed as a new vital sign (Mower et al., 1997). SpO_2 is a cheap, accessible, and portable tool used extensively in acute care, being especially important for acute respiratory infection categorization in infants and children (Lazzerini et al., 2015).

Around 140 million people worldwide live permanently at high altitude (Moore, 2001), where settlements are characterized by hypobaric hypoxia. No prior systematic review has considered normal reference data for resting daytime SpO_2 levels across childhood at different high-altitude locations, nor considered the impact of sleep and

infant feeding on SpO_2. Only through understanding normal variation can treatment thresholds be determined for acute infections such as pneumonia and bronchiolitis and chronic illness such as bronchopulmonary dysplasia, cystic fibrosis and post infectious bronchiolitis obliterans. Expected SpO_2 characteristics during sleep at high altitude are also important to interpret polysomnographic findings (Hill et al., 2016).[a]

In the decade since Subhi (Subhi et al., 2009), published a systematic review of normal SpO_2 values in high altitude resident healthy infants and children up to 12 years of age, oximeter technology has progressed. We aimed to extend and update this review to include pulse oximetry studies at high altitude across childhood, including teenagers, and taking in account the differences in wake, sleep and feeding states, especially in infants.

METHODS

We identified published studies in MEDLINE, EMBASE, and SCielo (up to December 2018) databases, using the search terms: "(oxygen saturation) AND (high altitude)" restricted to child (birth to 19 years old) without language restriction; high altitude was defined as altitude >2500 meters above sea level (masl) (Moore 2001). Studies published solely in abstract form were excluded because the methods and results could not be fully analyzed. In addition, we searched other non-bibliographic data sources such as web searching. Only studies of healthy individuals habitually living at high altitude were included. Exclusion criteria included: 1) studies limited to SpO_2 measurement uniquely during the first 24 hours of life as SpO_2 has important changes during this period (González et al.,2005); 2) data collected across a range of altitudes greater than ±50 m (for example between 3800 to 4200 masl), where it

was not possible to identify the number of individuals located at a specific altitude and, 3) studies that included children with acute or chronic cardiorespiratory disorders, chronic ill health or history of prematurity.

Data extraction and assessment of risk of bias: titles, abstracts, and citations were independently reviewed by two authors (S.U. and C.G.). Based on the full text versions, all the studies were evaluated and after obtaining full reports, eligibility was assessed. Disagreements were discussed and resolved by consensus, and, when necessary, advice was sought from the third review author (J.C-R.). The risk of bias was evaluated according to the Newcastle-Ottawa Scale (Wells GA, et al., 2011). For methodological and reporting quality a pre-specified data analysis included year, country, altitude, type of study, number of participants, age range, SpO_2 median/mean and SpO_2 dispersion measurements. The pulse oximetry device used and the duration of SpO_2 recording were also searched. We also looked at whether hemoglobin (Hb) concentration measurements were reported.

Meta-analysis was not performed due to the variation between studies in oximeter devices, protocols and the central tendency (e.g. mean/median) and dispersion measures (e.g. standard deviation, interquartile range, 5^{th}/95^{th} percentile) to report SpO_2 values.

Using original source data from the Rojas-Camayo study (Rojas-Camayo et al., 2018) the SpO_2 values from the first quartile were compared with those from the second to fourth quartiles grouped using RV 3.6.1 (July 2019 version) software. The comparison was made for three altitude levels (2,500, 3,600 and 5,100 masl) and for two age groups (1-5 and 6-17 years old). Statistical differences were determined

using the T test when the Shapiro-Wilk test showed a p-value<0.05, otherwise the Mann Whitney test was used.

RESULTS

One hundred and ninety-four studies were retrieved from the databases, of which 20 were eligible for inclusion (Figure 1). Most of the studies (n=14) came from the South America Andean region (Peru=4, Bolivia=4, Colombia=3, Ecuador=2, Argentina=1); three studies were from China, two from the USA, and one from Nepal. Seventeen studies reported SpO_2 data during wakefulness, (Alduncín et al., 2005; Beall 2000; Duenas-Meza et al., 2015; Gamponia et al.,1998; Hill et al., 2016; Huicho et al., 2001; Lozano et al.,1992; Mattos et al., 2005; Nicholas et al., 1993; Niermeyer et al.,1993; Niermeyer et al., 1995; Ramírez-Cardich et al., 2004; Rojas-Camayo et al., 2018; Torres et al.,1999; Schult et al., 2011; Shrestha et al., 2012 and Weitz et al., 2007). Nine studies reported SpO_2 data during sleep (Hill et al., 2016; Dueñas-Meza et al., 2015; Gamponia et al.,1998; Niermeyer et al.,1993; Niermeyer et al., 1995; Ramírez-Cardich et al., 2004; Torres et al.,1999; Ucrós et al., 2015 and Ucrós et al., 2017); four studies reported data in infants during feeding (Gamponia et al., 1998 Niermeyer et al., 1995; Ramírez-Cardich et al., 2004 and Torres et al., 1999;) and one study when infants were crying (Gamponia et al., 1998). One study was published in a Colombian journal not identified by the search but was known by the authors (Torres et al., 1999). All studies were cross-sectional, except one, which had a longitudinal component (Duenas-Meza et al., 2015). The total number of SpO_2 records sampled in these 20 studies were 6877 during wakefulness, 923 during

sleep, and 528 in infants during feeding. The pulse oximetry device used and the sampling protocols were diverse (Table 1). The quality assessment of most studies was high with a low risk of bias.

Studies in the wake and sleep states

The results of studies for SpO_2 during the wake state are shown in Tables 2, 3 and 4 across three different geographic regions. Sleep data are shown in Table 5. The most relevant findings are as follows: diurnal awake SpO_2 is lower as altitude increases (for illustrative data see Figure 2) and is lower at the same altitude during sleep and infant feeding in comparison to the wake state; in younger children the range of normal diurnal SpO_2 increases with increasing altitude, so for example, varying by 5% in children aged 1 to 5 years at 2500 masl, in comparison with 12% in the same age group at 5100 masl, with this phenomenon being more marked during sleep. At high altitude SpO_2 increases with age and a significant gap between wake and sleep states occurs in the first months of life and narrows as the age increases, for example, Hill et al report that at 3700 masl, the median difference in infants 6 to 10 months old between the wake vs. sleep stage is 6%, compared to 3% between the ages of 13 to 17 years (Hill CM.,[b] et al. 2016) (Figure 3). SpO_2 dispersion at high altitude is wider at younger ages (for illustrative data see Figure 4), and SpO_2 peak values are attained at older ages as altitude increases.

Studies during infant feeding and crying

Five studies analyzed SpO_2 during feeding in infants up to five months of age at high altitude (Table 6). The data show a SpO_2 decrease between 0.2% to 6% when wake and feeding states are compared, with a mean decrease of -2.2%. Only one study reported SpO_2 differences in infants when crying compared to quiet wakefulness (Gamponia et al., 1998); this study included 19 infants 0 to 5 months of age at 4018 masl, and noted a 0.8% decrease in median SpO_2 in crying infants.

Studies reporting ethnicity and gender influences

Three studies reported the influence of ethnicity and sex on waking SpO_2 variables. One study in Tibet at 3200 masl (Weitz et al., 2007) reported a significant sex by-ethnicity interaction in 15-19 yr-olds, such that Tibetan females had higher SpO_2 values than Tibetan males, but among Chinese Han born at this high altitude, males had higher SpO_2 values than females (the Han population originate from lowland plains in Eastern China). A study from Peru at 4100 masl found no differences in SpO_2 values between males and females, but children from the Nuñoa ethnicity had higher SpO_2 levels in comparison with children from Tintayá and Marquirí ethnicities (Huicho et al., 2001), all ethnicities being highlanders. Finally, a study at 3800 masl reported that Tibetan 5-9-yr-olds had significantly higher SpO_2 values than Han children did at the same age (Niermeyer et al., 1995).

Statistical distribution

In 12/20 studies a normal distribution was assumed by the authors who reported mean values, but without specification of the statistical test used to reach this conclusion. In 2/20 a non-normal distribution can be deducted from the data, but the

statistical bias is not known; in 6/20 studies a left skewed non-normal distribution was found (Hill et al., 2016[a]; Hill et al., 2016[b]; Rojas-Camayo et al., 2018;Torres et al., 1999; Ucrós et al., 2015, Ucrós et al., 2017). A review of the source data from studies by Hill and Rojas-Camayo confirmed that the data distribution has a negative bias. In Figure 5, the SpO_2 left skewed distribution at different altitudes and ages is shown. In Figure 6 the increase in the difference between percentile 5^{th} and percentile 95^{th} as altitude increases, can be seen reflecting how the left bias is more evident as altitude increases.

The comparison of SpO_2 values from the first quartile with those from the second to fourth quartiles grouped, using data from the Rojas-Camayo study, indicated statistically significant differences in all altitude/age groups analyzed (Table 7).

Hemoglobin concentration measurement

Hemoglobin (Hb) concentration was only measured in two studies (Mattos et al., 2005 and Ramírez-Cardich et al., 2004). Oxygen carrying capacity was not calculated in any of the studies.

DISCUSSION

To the best of our knowledge, this is the first systematic review to examine the influence of high altitude on SpO_2 across childhood from 0 to 19 years of age. It builds on data published by Subhi (Subhi et al., 2009), which was limited to six studies above 2500 masl (rather than the 19 included here), and to pre-adolescent children. Furthermore, we included data on infants when feeding and report key differences between wake and sleep states.

Data provided by this review show that SpO_2 at high altitudes increases through childhood; this phenomenon was highlighted by Beall (Beall 2000) who reported that at altitudes between 3800-4200 masl, SpO_2 peak values were attained by 11 years of age and were 7% higher than values in young infants. The SpO_2 improvement with age can be viewed as a marker of physiological adaptation or "SpO_2 maturation" (Hill et al., 2016)[b]; interestingly SpO_2 maturation is not a phenomenon exclusive to high altitude and is also seen at sea level (Schulter et al., 2001). In addition, the present review shows that inter-individual variability in SpO_2 is higher at younger ages (Figures 3, 4 and 6). This point was also noted by Beall (Beall 2000) and has been observed in subsequent studies (Duenas-Meza et al., 2015). This inter-individual variation increases with altitude and is more marked during sleep (Figures 3, 4 and 6) (Duenas-Meza et al., 2015; Hill et al., 2016; Ucrós et al., 2015; Ucrós S et al., 2017) and during feeding in young infants (Torres et al., 1999; Niermeyer et al., 1993; Niermeyer et al., 1995). In consequence at altitudes >2500 masl, SpO_2 treatment thresholds may change depending on sleep-wake or feeding status, especially in young infants.

The lower SpO_2 values during sleep are normal in children, even at sea-level (MacLean et al., 2015[1]), and could be related with drops in respiratory rate and functional residual capacity, as well as, and increase in upper airway resistance (Marcus 2001). What emerges from the present review is that the SpO_2 gap between wake and sleep stages is notable at high altitude. The explanation for lower SpO_2 values during feeding in infants is less certain; a recent study in infants, aged 2 weeks-3 months with cardiac disease, showed significant desaturation (mean -2.8%)

during feeding but no drop in a healthy age-similar control group (Miranda et al., 2019). The lower baseline SpO_2 values in the infants with cardiac disease are similar to those seen in Andean infants at the threshold of high altitude; this suggests that minor perturbations in ventilation associated with infant feeding may become critical when baseline SpO_2 is lowered. As it is known, from the O_2 dissociation curve, at high altitude mild changes in P_aO_2 induce significant SpO_2 drops (Chernick V, West JB., 1990).

In relation with lower SpO_2 values during sleep in children, it is known at sea level, that normal sleep onset prompts a fall in respiratory rate, functional residual capacity and an increase in upper airway resistance (Marcus 2001), and that small decrements in oxygen saturation (e.g 1-2%) are acceptable (MacLean et al., 2015[1]). Regarding with differences by sex, it is been found in adults aged 30 to 40 years at high altitude, higher SpO_2 levels in females than in males (Beall 2000), but similar findings are not evidenced in the pediatric literature (Huicho L et al, 2001).

An interesting question is why SpO_2 maturation occurs. It could be hypothesized that since periodic breathing (PB) is much more important at high altitude during the first months of life (Duenas-Meza et al., 2015; Ucrós et al., 2015, Ucrós et al., 2017), there could be a link between SpO_2 increase and decrease in PB with age. We found 2 studies in infants which explored this possible association. The first was carried out by Parkins et al, who exposed 34 healthy infants to a 15% oxygen environment during a mean of 6.3 hours sleep, and measured oxygen saturation, frequency of isolated and periodic apnea, and frequency of desaturation (Parkins et al., 1998). In the later published by Ucrós et al, oxygen saturation, PB and apnea indexes were

measured during a mean of 4.1 hours sleep at 2560 masl, in infants aged between 1 and 4 months (Ucrós et al., 2015). Neither study found an association between mean SpO_2 and PB. Similarly, studies carried out in adults have not found this correlation (Insalaco et al., 2012; Salvaggio et al., 1998; Ainslie et al., 2013). A second hypothesis could be related to possible changes in ventilation across childhood at high altitude, nevertheless studies undertaken by Beall on different populations do not support this theoretical mechanism; this research showed that Tibetans were more hypoxic than Aymara, despite a higher resting ventilation and hypoxic ventilatory responses (Beall et al., 1997). A third mechanism, and probably the most plausible hypothesis, is that as pulmonary pressure falls through childhood, the SpO_2 gradually increases (Penaloza and Arias-Stella., 2007). The question that would then remain is why pulmonary pressure shows such behavior in children living at high altitude.

In six studies, data explicitly demonstrated a non-normal SpO_2 left skewed distribution, meaning significant inter-individual differences in SpO_2 at a same age and altitude. This phenomena was also noted when data from an early study published in 1963 were reanalyzed; in this research oxygen saturation was measured in blood in children living around 4,400 masl (Sime et al 1963) (Figure 5). The striking feature of a left skewed SpO_2 distribution has been found consistently across different altitudes, ages and sleep versus wake states. At high altitude, the SpO_2 non-normal statistical distribution delivers a parabolic curve, which has to be differentiated from the sinusoidal oxygen dissociation curve related with the capacity

of hemoglobin to carry oxygen. This concept is illustrated in Figure 7 (Chernick V, West JB., 1990; Peñaloza D, Arias-Stella J. 2007).

We speculate that children with low steady state oxygen saturation measures during health may be at increased risk of later life chronic mountain sickness (CMS) in its different forms. These include CMS with altitude polycythemia or Monge's disease (Villafuerte et al 2016); high-altitude heart disease (HAHD) or high-altitude pulmonary hypertension which occurs without polycythemia (Aldashev et al., 2002; Kojonazorov et al 2007; Ge and Helun 2001; Reeves and Grover 2005; Xu and Jing 2009); and mixed CMS, which includes both excessive polycythemia and pulmonary hypertension–related HAHD (Ge and Helun 2001). These different kinds of progressive, life-limiting conditions, affect 5-10% of high-altitude residents in the first category (Leon-Velarde 2005), and 5 to 18% in the second one (Mirrakhimov and Strohl 2016). To the best of our knowledge childhood predictors of CMS have not been reported. The etiology of this condition is likely to be multi-factorial including genetically determined differences in erythropoiesis regulation, as demonstrated by Stobdan et al, who identified novel genes involved in high altitude adaptation in the Andes (Stobdan et al, 2017); alterations in ventilatory responses to hypoxia (Villafuerte et al, 2016); hypoxia gene expressions related with CMS (Stobdan et al, 2017; Xing G et al., 2008) and levels of mediators related with lung vascular reactivity (Aldashev et al.,2002; Kojonazarov et al., 2012). Longitudinal studies of SpO_2 across childhood would be of value in this context.

The present study has several limitations. First, different oximeter devices and/or protocols for measuring SpO_2 were used across the different studies, and in most

studies, we do not have information relating to important equipment settings such as sampling rate and averaging time (Hill et al., 2016).[c] Secondly, the data available across the publications used different approaches for central tendency measures, with some studies reporting means while others reported medians. Similarly, in relation to dispersion, different measures were used including percentiles, standard deviation, confidence intervals and interquartile ranges. Thirdly, ethnic background is a key influence on high altitude adaptation and data presented here represent populations with different adaptive mechanisms. Fourth, only two studies measured Hb concentration levels. Importantly, SpO_2 alone is a limited indicator of oxygen delivery to the tissues, especially in the setting of polycythemia.

However, this review also has notable strengths. In total 20 studies were analyzed which included 8347 SpO_2 data; furthermore, the quality assessment of most studies was high with a low risk of bias. Importantly, diurnal-nocturnal variation highlighted from sleep data cannot be accounted for by hemoglobin concentration fluctuations, suggesting genuinely compromised adaptation to high altitude in some children that may have implications for later life chronic mountain sickness vulnerability. Finally the data synthesized in this review offer interesting insights into the concept of SpO_2 maturation at high altitude.

The need for international reference data on ranges of SpO_2 across childhood at high altitude remains pressing. Future studies should use standardized oximetry protocols (uniform devices and settings) and standardized reporting of data to confidently establish such reference data in healthy children to support clinical decision-making. In the meantime, the data synthesized in this review provides a

preliminary guide for clinicians managing children with cardio-respiratory disorders at high altitude.

CONCLUSIONS

At high altitude mean/medians SpO_2 improves in infants and children with aging; a significant gap between wake and sleep states is seen in the first months of life, which narrows, as the infant gets older; SpO_2 dispersion at high altitude is wider at younger ages; at high altitude SpO_2 shows a non-normal distribution skewed to the left, this bias becomes more evident as altitude increases, at younger ages and during sleep. SpO_2 has inter-individual differences at a same given age and altitude, being significantly lower in 1 out of 4 children. Collaborative studies using similar oximeters/protocols for measuring SpO_2 at different altitudes in healthy children across high-altitude geographical regions are urgently needed.

DISCLOSURES

The authors have no conflict of interests to declare.

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Table 1. Pulse oximetry device used and duration of SpO_2 measurement

Study/ref	Oximeter type	Duration of recording
Alducín 2005[3]	NONIN	No data during wakefulness. Overnight for nocturnal measurement (3:25 to 5:45 hours).
Beall 2000[4]	CRITICARE M 503	Six observations were recorded and their average was used as the individual's SpO_2.
Dueñas-Meza 2015[7]	MASSIMO RAD 8	All the time during wakefulness and sleep during polysomnography study up to 10 hours. Minimum time and mean time: no data.
Gamponia 1998[8]	NELLCOR N 10	At least 10 seconds.
Hill 2016[11]	NONIN, PLYMOUTH, (MN)	Sampling rate and data averaged over 4 successive pulse beats.
Hill 2016[12]	MASIMO RADICAL	At least 3 minutes for diurnal measurement. Overnight for nocturnal measurement (minimum 5 hours of artefact free data).
Huicho 2001[14]	NELLCOR	Values were recorded after machine stabilization. When values oscillated, the average of three consecutive readings was used.
Lozano 1992[20]	NELLCOR N 1O	At least 10 seconds. All readings were duplicated.
Mattos 2005[24]	NO DATA	No data
Nicholas 1993[28]	NEONATAL FLEX IT	At least 2 minutes.
Niermeyer 1993[29]	BIOX 3700BIO	Value was considered acceptable when the electrocardiographically measured heart rate was within 5 beats/min of the oximetry-determined pulse rate and the pulse waveform displayed on the oximeter was clear and full.
Niermeyer 1995[30]	BIOX 3740	1-minute intervals for a total of 10 minutes.
Ramírez-Cardich 2004[33]	NELLCOR N 20	One-minute intervals for a total of 10 minutes.
Rojas-Camayo 2018[35]	NELLCOR 560	Every 10 s for a total of six measurements and the average was the final value.
Schult[38]	DEVON MEDICAL 300C-1	More than 10 sec
Shrestha 2012[41]	CMS- 50DL	Several readings until a consistent value was displayed
Torres 1999[45]	MASIMO SET	Two registers, one minute each one and average was the final value.
Ucrós 2015[46]	NONIN M 8008J	All the time during overnight polysomnography study. Minimum time 180 min –Mean time 250 min.
Ucrós 2017[47]	NONIN M 8008J	All the time during overnight polysomnography study. Minimum time 180 min –Mean time 250 min.
Weitz 2007[49]	NONIN 8500	Between 5 and 10 minutes.

Table 2. Resting SpO2 in high altitude resident Andean children during the wake state by age group and altitude (ordered from lower to higher altitude)

Author /year	Country	Altitude (masl)	Age range	n	%SpO_2 median/mean	SpO_2 dispersion measurements
Rojas-Camayo/2018[35]	Perú	2500	1-5 yrs	87	96.0 (median)	$p5^{th}$ 93.0%, $p95^{th}$98.0%
Rojas-Camayo/2018[35]	Perú	2500	5-17 yrs	234	97.0 (median)	$p5^{th}$ 94.0%, $p95^{th}$99.0%
Hill/2016[12]	Bolivia	2500	4-10 yrs	9	94.0 (median)	IQR 1%
Torres /1999[45]	Colombia	2640	1-30 days	300	95.0 (median)	$p5^{th}$ 90.5%, $p95^{th}$98.8%
Lozano /1992[20]	Colombia	2640	1-3 mo	35	95.3 (median)	95% CI [90.5%-98.8%]
Dueñas-Meza/2015[7]	Colombia	2640	1 ± 0.3 mo	106	92.5 (median)	$p5^{th}$ 88.0%, $p95^{th}$ 96.0%
Dueñas-Meza /2015[7]	Colombia	2640	3.6 ± 0.5 mo	89	93.0 (median)	$p5^{th}$ 88.0%, $p95^{th}$ 96.0%
Dueñas-Meza /2015[7]	Colombia	2640	6.3 ± 0.8 mo	89	93.0 (median)	$p5^{th}$ 90.0%, $p95^{th}$ 97.0%
Lozano/1992[20]	Colombia	2640	7-12 mo	23	93.4 (median)	95%CI [92.4%-94.4%]
Dueñas-Meza/2015[7]	Colombia	2640	13.2 ± 1.9 mo	25	94.0 (median)	$p5^{th}$ 91.0%, $p95^{th}$ 96.0%
Rojas-Camayo/2018[35]	Perú	2880	1-5 yrs	95	95.0 (median)	$p5^{th}$ 92.0%, $p95^{th}$ 98.0%
Rojas-Camayo/2018[35]	Perú	2880	5-17 yrs	122	96.0 (median)	$p5^{th}$ 92.0%, $p95^{th}$ 98.0%
Rojas-Camayo/2018[35]	Perú	3250	1-5 yrs	140	93.0 (median)	$p5^{th}$ 89.0%, $p95^{th}$ 95.0%
Rojas-Camayo/2018[35]	Perú	3250	6-17 yrs	181	94.0 (median)	$p5^{th}$ 91.0%, $p95^{th}$ 97.0%
Mattos/2005[21]	Bolivia	3600	1-2 wk	60	85.3 (mean)	± 1SD 10.5%
Rojas-Camayo/2018[35]	Perú	3600	1-5 yrs	30	93.0 (median)	$p5^{th}$ 87.0%, $p95^{th}$ 95.0%
Rojas-Camayo/2018[35]	Perú	3600	6-17 yrs	117	93.0 (median)	$p5^{th}$ 90%, $p95^{th}$ 95.0%
Hill/2016[12]	Bolivia	3700	6-12 mo	7	94.0 (median)	IQR 2%
Hill/2016[12]	Bolivia	3700	4-10 yrs	18	94.0 (median)	IQR 1%
Hill/2016[12]	Bolivia	3700	13-17 yrs	7	94.0 (median)	IQR 2%
Ramírez-Cardich/2004[33]	Perú	3750	2 wk	30	91.0 (mean)	No data
Ramírez-Cardich /2004[33]	Perú	3750	1 mo	33	92.0 (mean)	No data

Ramírez-Cardich/2004[33]	Perú	3750	2 mo	32	92.0 (mean)	No data
Ramírez-Cardich/2004[33]	Perú	3750	3 mo	33	92.0 (mean)	No data
Ramírez-Cardich /2004[33]	Perú	3750	4 mo	30	92.0 (mean)	No data
Alducín/2005[3]	Argentina	3775	7-31 wk	12	86.0 (mean)	± 1SD 2.6%
Ramírez-Cardich/2004[33]	Perú	3750	2 wk	30	91.0 (mean)	No data
Ramírez-Cardich /2004[33]	Perú	3750	1 mo	33	92.0 (mean)	No data
Ramírez-Cardich/2004[33]	Perú	3750	2 mo	32	92.0 (mean)	No data
Ramírez-Cardich/2004[33]	Perú	3750	3 mo	33	92.0 (mean)	No data
Ramírez-Cardich /2004[33]	Perú	3750	4 mo	30	92.0 (mean)	No data
Gamponia/1998[8]	Bolivia	4018	1-60 mo	128	88.3(median)	95% CI [87.8% -88.1%]
Rojas-Camayo/2018[35]	Perú	4338	1-5 yrs	47	86.0 (median)	$p5^{th}$ 82.0%, $p95^{th}$ 90.0%
Rojas-Camayo/2018[35]	Perú	4338	6-17 yrs	126	88.0 (median)	$p5^{th}$ 82.0%, $p95^{th}$ 92.0%
Schult/2011[38]	Perú	4340	5-6 yrs	78	83.8 (mean)	± 2SD 10%
Schult/2011[38]	Perú	4340	7-8 yrs	43	83.7 (mean)	± 2SD 8.4%
Schult/2011[38]	Perú	4340	9-10 yrs	108	84.7 (mean)	± 2SD 5.4%
Schult/2011[38]	Perú	4340	11-12 yrs	40	86.5 (mean)	± 2SD 8.6%
Schult/2011[38]	Perú	4340	13-14 yrs	54	88.1 (mean)	± 2SD 7.0%
Schult/2011[38]	Perú	4340	15-16 yrs	63	88.4 (mean)	± 2SD 6.6%
Rojas-Camayo/2018[35]	Perú	4500	1-5 yrs	36	85.0 (median)	$p5^{th}$ 78.0%, $p95^{th}$ 90.0%
Rojas-Camayo/2018[35]	Perú	4500	6-17 yrs	121	85.0 (median)	$p5^{th}$ 79.0%, $p95^{th}$ 90.0%
Rojas-Camayo/2018[35]	Perú	4715	1-5 yrs	28	83.0 (median)	$p5^{th}$ 78.0%, $p95^{th}$ 89.0%
Rojas-Camayo/2018[35]	Perú	4715	6-17 yrs	133	86.0 (median)	$p5^{th}$ 79.0%, $p95^{th}$ 92.0%
Rojas-Camayo/2018[35]	Perú	5100	1-5 yrs	74	80.0 (median)	$p5^{th}$ 73.0%, $p95^{th}$ 85.0%
Rojas-Camayo/2018[35]	Perú	5100	6-17 yrs	168	81.0 (median)	$p5^{th}$ 75.0%, $p95^{th}$ 86.0%

masl=meters above sea level, yrs=years, mo=months, wk=weeks, CI=confidence intervals, SD=standard deviation, IQR=interquartile range.

Table 3. Resting SpO_2 in high altitude resident Himalayan children during the wake state by age group and altitude

Author /year	Country	Altitude (masl)	Age range	N	%SpO_2 mean	SpO_2dispersion measurements
Shresta/2012[41]	Nepal	2700	2-14 yrs	56	95.0	± 1SD 1.3%
Shresta/2012[41]	Nepal	2800	2-14 yrs	22	95.0	± 1SD 1.2%
Weitz/2007[49]	China	3200	5-9 yrs	157	90.8	± 1SD 3.9%
Wetiz/2007[49]	China	3200	10-14 yrs	172	90.	± 1SD 3.2%
Wetiz/2007[49]	China	3200	15-19 yrs	148	91.3	± 1SD 3.0%
Shresta/2012[41]	Nepal	3550	2-14 yrs	19	91.0	± 1SD 1.7%
Niermeyer/1995[30]	China/Han	3658	1-16 wk	15	87.0	± 1SD 6.0%
Niermeyer/1995[30]	China/Tibetan	3658	1-16 wk	15	89.0	± 1SD 3.0%
Beall/2000[4]	China	3800	0-9 yrs	735	89.3	No data
Beall/2000[4]	China	3800	10-19 yrs	735	90.9	No data
Shresta/2012[41]	Nepal	3800	2-14 yrs	9	91.0	± 1SD 1.2%
Wetiz/2007[49]	China/Tibetan	3800	5-9 yrs	93	86.5	± 1SD 3.9%
Wetiz/2007[49]	China/ Han	3800	5-9 yrs	103	85.5	± 1SD 4.1%
Wetiz/2007[49]	China	3800	10-14 yrs	217	86.6	± 1SD 3.8%
Wetiz/2007[49]	China	3800	15-19 yrs	172	87.6	± 1SD 2.8%
Beall/2000[4]	China	4200	0-9 yrs	294	85.5	No data
Beall/2000[4]	China	4200	10-19 yrs	294	88.7	No data
Weitz/2007[49]	China	4300	5-9 yrs	49	84.0	± 1SD 4.3%
Weitz/2007[49]	China	4300	10-14 yrs	62	85.0	± 1SD 3.0%
Weitz/2007[49]	China	4300	15-19 yrs	47	85.8	± 1SD 3.7%

masl=meters above sea level, yrs=years, wk=weeks, SD=standard deviation.

Table 4. Resting SpO_2 in high altitude resident children during the wake state by age group and altitude in Colorado - USA

Author /year	Country	Altitude (masl)	Age range	N	%SpO_2 mean	SpO_2 dispersion measurements
Nicholas/1993[28]	USA	2774-2818	2 days-22 mo	72	91.7	SD 2.0%
Niermeyer/1993[29]	USA	3100	1 wk	14	87.8	SD 4.8%
Niermeyer/1993[29]	USA	3100	2 mo	13	89.9	SD 2.4%
Niermeyer/1993[29]	USA	3100	4 mo	14	91.1	SD 1.7%

masl= meters above sea level, mo=months, wk= weeks, SD= standard deviation.

Table 5. SpO_2 in sleeping children at different ages resident at high altitudes across the world

Author/Year	Country	Altitude (masl)	Age range	N	%SpO_2 median/mean	SpO_2 dispersion measurement
Hill/2016[12]	Bolivia	2500	4-10 yrs	9	93.7 (median)	IQR 2.4%
Ucrós/2015[46]	Ecuador	2560	1-4 mo	36	92.0 (median)	$p5^{th}$ 86.0%, $p95^{th}$ 94.0%
Torres/1999[45]	Colombia	2640	1-30 days	300	95.0 (median)	$p5^{th}$ 87.5%, $p95^{th}$ 96.0%
Dueñas-Mesa/2015[7]	Colombia	2640	1±0.3 mo	106	92.5 (median)	$p5^{th}$ 87.5%, $p95^{th}$ 96.0%
Dueñas-Mesa[9]/2015[7]	Colombia	2640	3.6±0.5 mo	89	93.0 (median)	$p5^{th}$ 86.0%, $p95^{th}$ 94.0%
Dueñas-Mesa[9]/2015[7]	Colombia	2640	6.3±0.8 mo	89	93.0 (median)	$p5^{th}$ 90.0%, $p95^{th}$ 96.0%
Dueñas-Mesa[9]/2015[7]	Colombia	2640	13±1.9 mo	25	94.0 (median)	$p5^{th}$ 91.0%, $p95^{th}$ 96.0%
Niermeyer/1993[29]	USA/active sleep	3100	1 wk	14	83.0 (mean)	± 1SD 5.6%
Niermeyer/1993[29]	USA/quiet sleep	3100	1 wk	14	80.6 (mean)	± 1SD 5.3%
Niermeyer/1993[29]	USA	3100	2 mo	13	86.6 (mean)	± 1SD 4.7%
Niermeyer/1993[29]	USA/quiet sleep	3100	4 mo	14	86.6 (mean)	± 1SD 4.4%
Ucrós/2017[47]	Ecuador	3200	1-4 mo	18	92.0 (median)	$p5^{th}$ 66.0%, p 5^{th} 91.0%
Niermeyer/1995[30]	China/Han	3658	1-16 wk	15	84.0 (mean)	± 1SD 9%
Niermeyer/1995[30]	China/Tibetan	3658	1-16 wk	15	87.0 (mean)	± 1SD 5%
Hill/2016[11]	Bolivia	3650	7-10 yrs 13-16 yrs	26	89.0 (median)	IQR 3%
Hill/2016[12]	Bolivia	3700	6-12 mo	7	87.5 (median)	IQR 7.7%
Hill/2016[12]	Bolivia	3700	4-10 yrs	18	90.3 (median)	IQR 6.1%
Hill/2016[12]	Bolivia	3700	13-17 yrs	7	91.2 (median)	IQR 3.1%
Ramírez-Cardich/2004[33]	Peru	3750	2 wk	14	86.2	No data
Ramírez-Cardich/2004[33]	Peru	3750	1 mo	15	86.0	No data
Ramírez-Cardich/2004[33]	Peru	3750	2 mo	20	87.5	No data
Ramírez-Cardich/2004[33]	Peru	3750	3 mo	17	88.0	No data

masl=meters above sea level, mo=months, wk=weeks, SD=standard deviation, IQR=interquartile range, CI=confidence interval

Ramírez-Cardich/2004[33]	Peru	3750	4 mo	12	89.2	No data
Gamponia/1998[8]	Bolivia	4018	0–5 mo	12	84.6 (median)	CI 95% [81.3%-87.9%]

Table 6. SpO_2 in feeding infants at different ages and high altitudes across the world

Author/Year	**Country**	**Altitude (masl)**	**Age range**	**n**	**% SpO_2 mean**	**Difference in SpO_2% with the wake state**
Torres/1999[45]	Colombia	2640	1-30 days	294	93.5	Minus 1.5
Niermeyer/1993[29]	USA	3100	1 wk	14	85.8	Minus 3.0
Niermeyer/1993[29]	USA	3100	2 mo	13	89.5	Minus 0.4
Niermeyer/1993[29]	USA	3100	4 mo	14	90.9	Minus 0.2
Niermeyer/1995[30]	China/Han	3658	1 wk	15	85	Minus 2
Niermeyer/1995[30]	China/Han	3658	1 mo	15	81	Minus 4
Niermeyer/1995[30]	China/Han	3658	2 mo	11	80	Minus 2
Niermeyer/1995[30]	China/Han	3658	4 mo	9	79	Minus 6
Niermeyer/1995[30]	China/Tibetan	3658	1 wk	15	87	Minus 3
Niermeyer/1995[30]	China/Tibetan	3658	1 mo	15	86	Minus 3
Niermeyer/1995[30]	China/Tibetan	3658	2 mo	13	86.5	Minus 2
Niermeyer/1995[30]	China/Tibetan	3658	4 mo	13	86	Minus 0.5
Ramírez-Cardich /2004[33]	Peru	3750	2 wk	13	88	Minus 3.0
Ramírez-Cardich /2004[33]	Peru	3750	1 mo	16	89.5	Minus 2.5
Ramírez-Cardich /2004[33]	Peru	3750	2 mo	21	90.5	Minus 1.5
Ramírez Cardich /2004[33]	Peru	3750	3 mo	13	91	Minus 1.0
Ramírez-Cardich /2004[33]	Peru	3750	4 mo	20	91.5	Minus 0.5
Gamponia/1998[8]	Bolivia	4018	0-5 mo	4	83.5	Minus 3.5

masl= meters above sea level, mo=moths, wk= weeks, yrs=years.

Age (years)	Altitude (masl)	SpO_2 median Quartile 1 (n)	SpO_2 median Quartiles 2-4 (n)	SpO_2 difference	p-value
1-5	2500	94% (21)	96% (66)	2%	<0.001
6-17	2500	95% (58)	97% (176)	2%	<0.001
1-5	3600	88% (8)	93% (30)	5%	<0.001
6-17	3600	91% (29)	93% (88)	2%	<0.001
1-5	5100	75% (19)	81% (168)	6%	<0.001
6-17	5100	77% (41)	82% (131)	5%	<0.001

Table 7. Differences in SpO2 between Quartiles 1 and Quartiles 2 to 4 at several altitudes and groups of age

Table built with data from Rojas-Camayo J, (2018). Ref 35.

Figure 1. Process of study selection

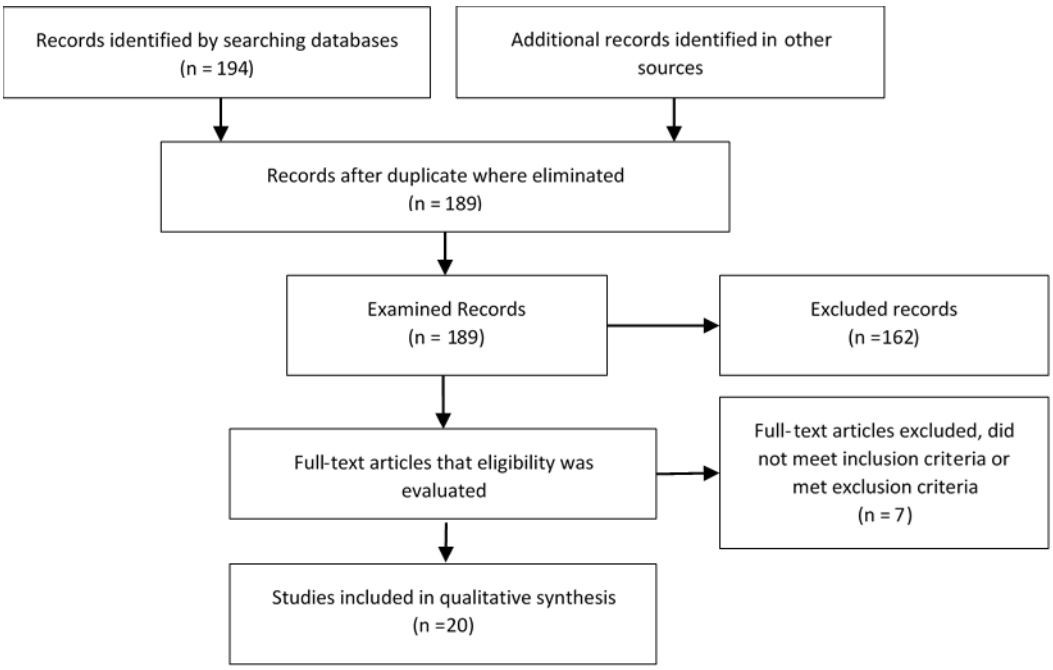
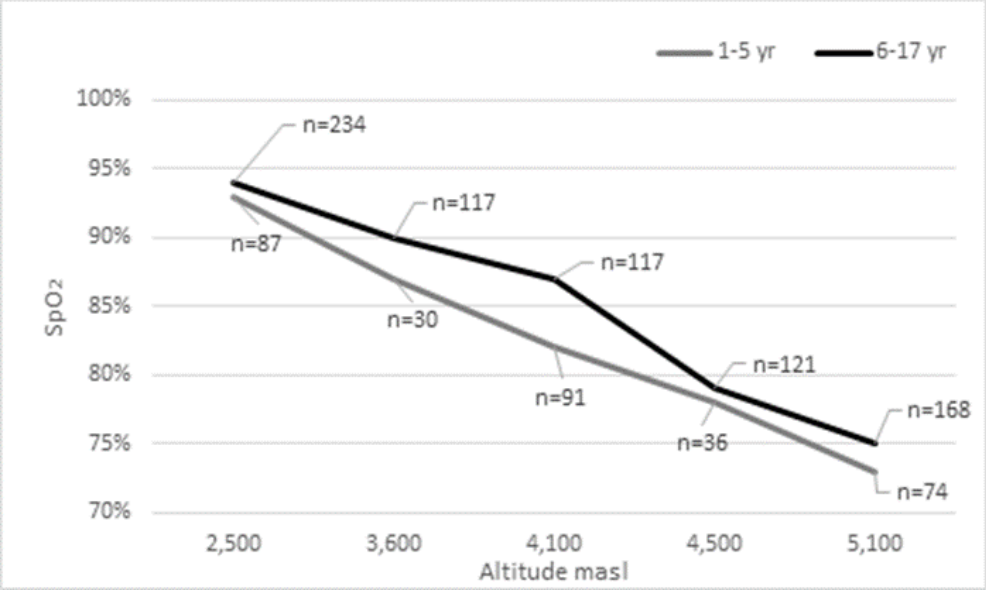
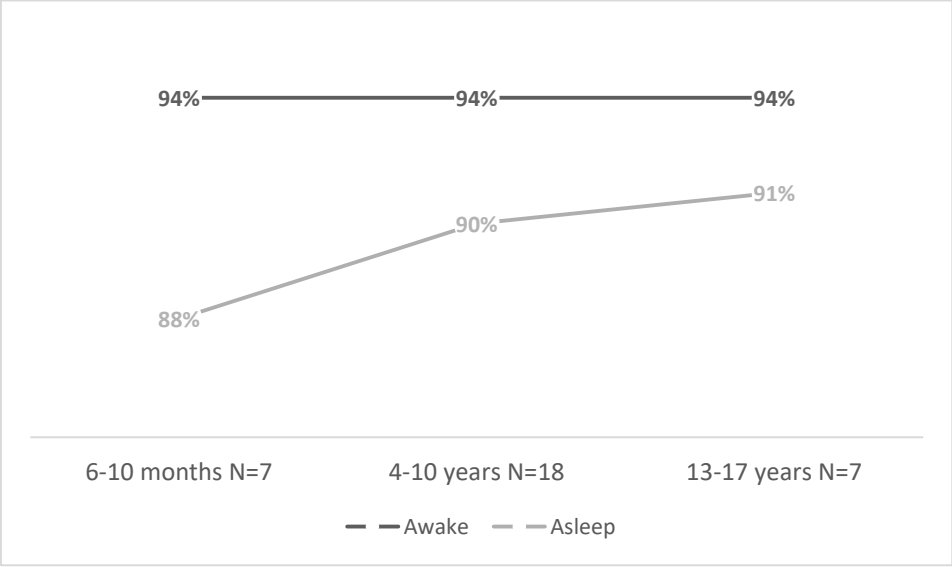


Figure 2. SpO_2 5th percentile at different altitudes in two age groups in Peru



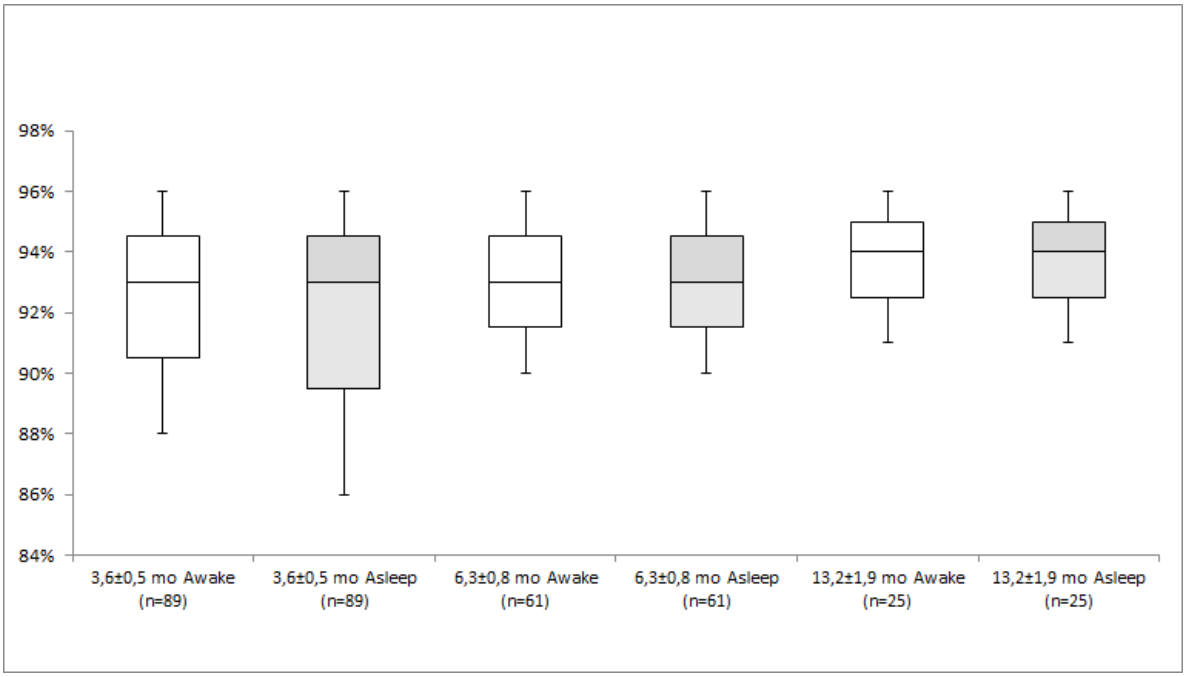
Graphic built with data from Rojas-Camayo J, (Ref 35). 5th centile data provided to offer potential thresholds below which children require further clinical evaluation.

Figure 3. Gap between SpO_2 medians in wake and sleep states in children from 6 months to 17 years of age at 3,700 masl in Bolivia



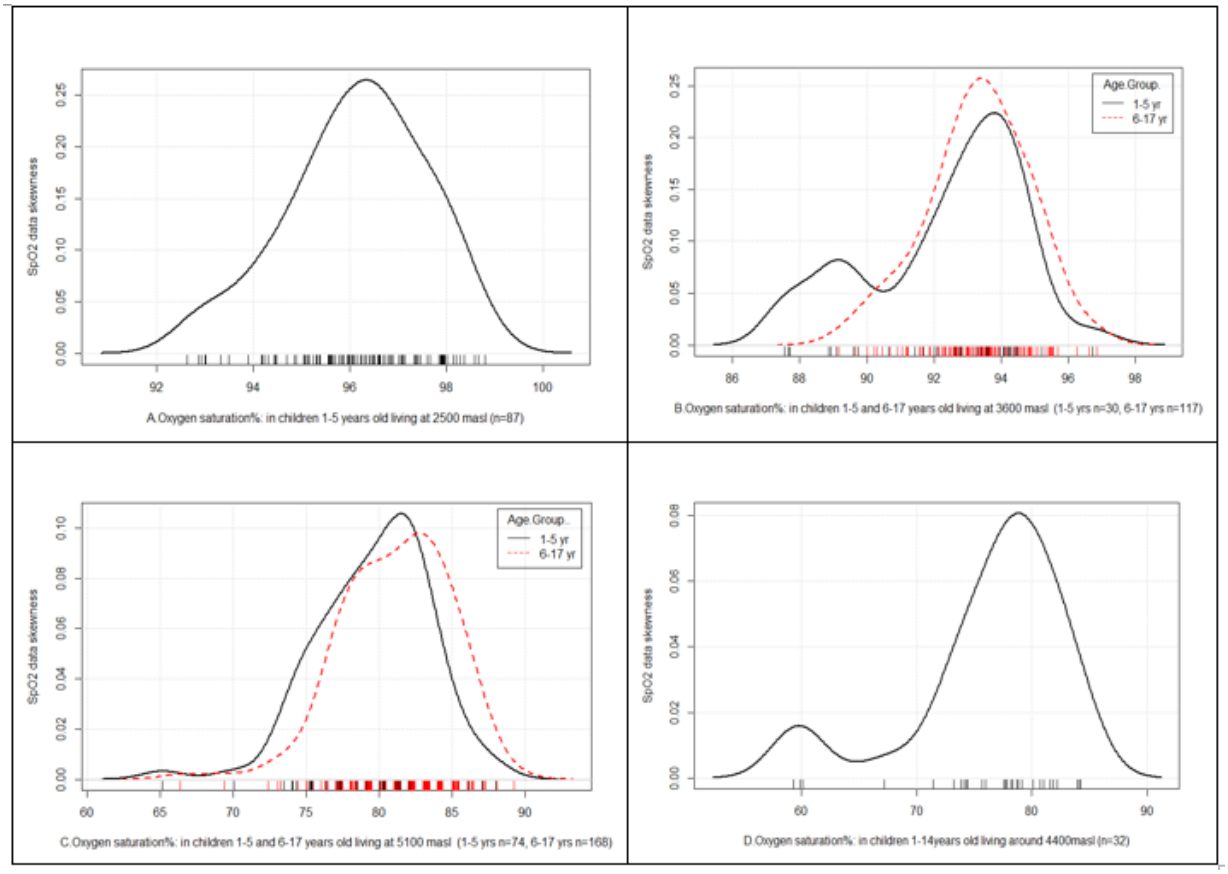
At low altitude SpO_2 developmental differences were evident between infants and children in relation with 3% dips, and were statistical significant (p=0.019). These differences were more striking at high altitude (p< 0.001). Graphic built with data from Hill CM et al. (Ref: 12).

Figure 4. SpO_2 at 2,640 masl in awake and asleep infants from 3 to 15 months of age in Colombia



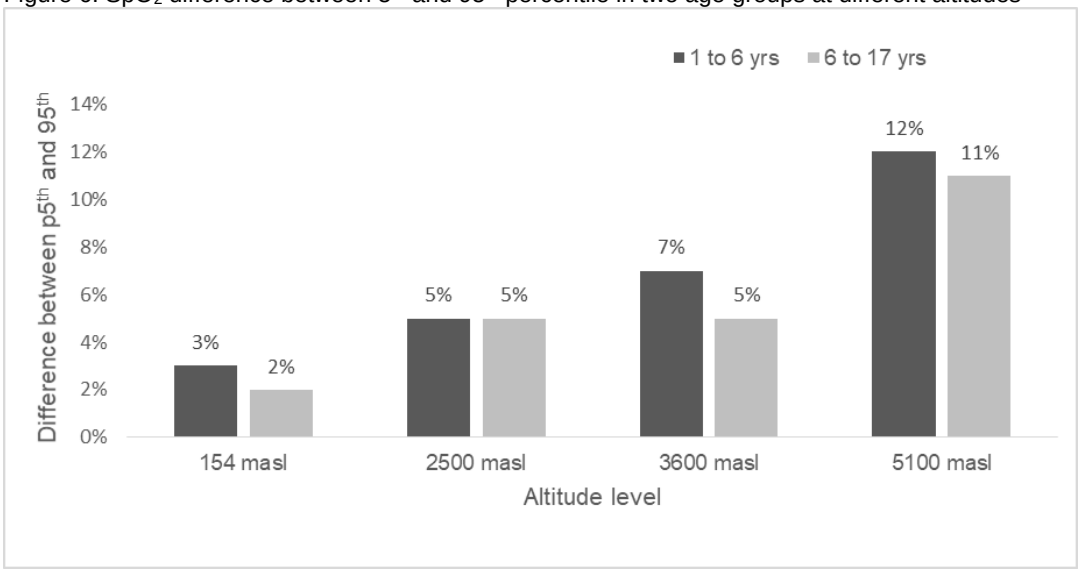
In 3,6±0,5 months subjects (awake and asleep) SpO_2 nadir, time with SpO_2 <90% and oxygen desaturation index were significantly higher in comparison in the two other groups of age (p<00.1). Graphic built with data from: Dueñas-Meza et al. (Ref 7).

Figure 5. Consistent SpO_2 left skew at different altitudes and age groups



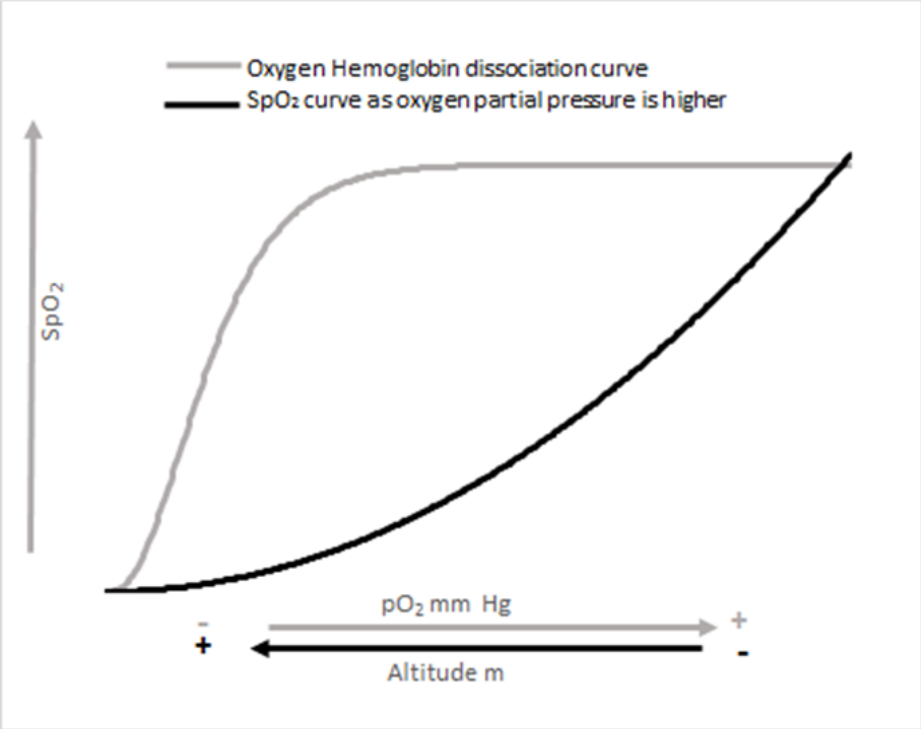
Graphics A,B and C built with data from Rojas-Camayo J et al. (Ref 35). Graphic D built with data from Sime et al. (Ref 40). The original paper from Sime shows results in means and SD. As the article delivers data of each of the children, we looked for the statistical distribution for SpO2 and built the graphic.

Figure 6. SpO_2 difference between 5th and 95th percentile in two age groups at different altitudes



Graphic built with data from Rojas-Camayo et al. (Ref 35).

Figure 7. Comparison between the oxygen-hemoglobin dissociation curve and SpO_2 curve as oxygen partial pressure increases.



Graphic built with data from Chernick V, West JB (Ref 6) and Penaloza D, Arias-Stella J (Ref 32).