Received: 28 November 2020 | Revised: 5 April 2021 | Accepted: 30 April 2021

DOI: 10.1111/mcn.13215

ORIGINAL ARTICLE

Maternal & Child Nutrition WILEY

Vitamin C levels in a Central-African mother–infant cohort: Does hypovitaminosis C increase the risk of enteric infections?

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Funding information
LabEx IBEID, Grant/Award Number: ANR-16-COV-005; Institut Pasteur Paris, Grant/Award Number: 91-17

Abstract

In the MITICA (Mother-to-Infant TransmIssion of microbiota in Central-Africa) study, 48 mothers and their 50 infants were followed from delivery to 6 months between December 2017 and June 2019 in Bangui (Central-African Republic). Blood tests and stool analyses were performed in mothers at delivery, and their offspring at birth, 11 weeks and 25 weeks. Stool cultures were performed in specific growth media for *Salmonella*, *Shigella*, *E. coli*, *Campylobacter*, *Enerobacter*, *Vibrio cholerae*, *Citrobacter* and *Klebsiella*, as well as rotavirus, yeasts and parasitological exams. The median vitamin C levels in mothers at delivery were 15.3 μmol/L (inter-quartile-range [IQR] 6.2–27.8 μmol/L). In infants, the median vitamin C levels at birth were 35.2 μmol/L (IQR 16.5–63.9 μmol/L). At 11 and 25 weeks, the median vitamin C levels were 41.5 μmol/L (IQR 18.7–71.6 μmol/L) and 18.2 μmol/L (IQR 2.3–46.6 μmol/L), respectively. Hypovitaminosis C was defined as seric vitamin C levels <28 μmol/L and vitamin C deficiency was defined as vitamin C levels <11 μmol/L according to the WHO definition. In mothers, the prevalence of hypovitaminosis-C and vitamin C deficiency

at delivery was 34/45 (75.6%) and 19/45 (42.2%), respectively. In infants, the prevalence of hypovitaminosis-C and vitamin C deficiency at 6 months was 18/33 (54.6%) and 11/33 (33.3%), respectively. Vitamin C levels in mothers and infants were correlated at birth (Spearman's rho = 0.5; *P* value = 0.002), and infants had significantly higher levels of vitamin C (median = 35.2 μmol/L; IQR 16.5–63.9 μmol/L), compared to mothers (median = 15.3 μmol/L; IQR 6.2–27.8 μmol/L; *P* value <0.001). The offspring of vitamin C-deficient mothers had significantly lower vitamin C levels at delivery (median = 18.7 μmol/L; IQR 13.3–30.7 μmol/L), compared to the offspring of non-deficient mothers (median = 62.2 μmol/L; IQR 34.6–89.2 μmol/L; *P* value <0.001). Infants with hypovitaminosis-C were at significantly higher risk of having a positive stool culture during the first 6 months of life (adjusted OR = 5.3, 95% CI 1.1; 26.1; *P* value = 0.038).

KEYWORDS
bacterial carriage, Central-Africa, infant malnutrition, pregnant women, vitamin C deficiency

1 | INTRODUCTION

On 4 October 1808 the Swedish fleet entered the harbour of Karlskrona. Sailors were suffering from scurvy of the 'most inveterate kind'(Arnold, 1809). Although the ills were increasing in number, the Swedish king's physician did not believe dysentery to be contagious, because 'the disease severity depended upon scurvy; and in proof of this, it did not spread among the town's people of Karlskrona'(Arnold, 1809). Scurvy is the clinical condition caused by vitamin C deficiency, with vitamin C seric levels <0.2 mg/dl or the equivalent <11 μmol/L(Vitamin C Deficiency (Scurvy) - StatPearls - NCBI Bookshelf, n.d). In healthy non-smoker adults, the mean levels of vitamin C range from 49 μmol/L (Schleicher et al., 2009) to 53 μmol/L (Langlois et al., 2016). Moderate forms of scurvy include symptoms such as irritability, anorexia, asthenia, fever, petechiae, gingival swelling or bleeding. More severe forms entail limb swelling, arthralgia, hyperkeratosis and haematological dysfunctions, personality changes, infections and systemic haemorrhages(Vitamin C (Ascorbic Acid) - PubMed, n.d). Indeed, vitamin C, also known as Ascorbate, is an essential water-soluble micronutrient with an important role in immunity and significant antioxidant properties (Gombart et al., 2020). Albeit its essential physiological functions, humans are unable to synthesise vitamin C and, therefore, dietary intake between 75 and 90 mg per day is recommended by the NIH in adults(Vitamin C - Health Professional Fact Sheet, n.d.). It is found abundantly in many vegetables, such as guava, blackcurrants, citrus fruits, strawberries, capsicum, tomatoes, potatoes and broccoli (Truswell, 1990).

Since the 19th century, ecological reports have suggested that hypovitaminosis C might be associated with a higher risk of dysentery (… & 2003, n.d.; Arnold, 1809; Bartholomew, 2002; Bollet, 1992). However, the effect of moderate vitamin C deficiency on the symptoms and the severity of dysentery remains largely unexplored.

Indeed, during the 20th century, economic growth, hygiene and medical interventions have reduced the prevalence of nutritional deficiencies and infectious diseases in Europe and North America, establishing new public health priorities on the Western World. In this sense, a 2020 review illustrates the shortage of epidemiological studies of vitamin C status (Rowe & Carr, 2020). At present, vitamin C deficiency is frequent in low- and middle-income countries and not

Key messages

- Vitamin C deficiency was highly prevalent in mothers at delivery (42.2%) and infants at 6 months (33.3%) in the MITICA cohort of Central-African mother–infant couples.
- At birth, vitamin C levels in mothers and infants were correlated, and infants had significantly higher levels of vitamin C, compared to mothers.
- At birth, the offspring of mothers with vitamin C deficiency had significantly lower levels of vitamin C, compared to the offspring of mothers without vitamin C deficiency.
- Infants with hypovitaminosis C were at significantly higher risk of having a positive stool culture for *Salmonella*, *Shigella*, *E. coli*, *Campylobacter*, *Enterobacter*, *Vibrio cholerae*, *Citrobacter*, or *Klebsiella* during the first 6 months of life.

uncommon in high-income countries (Rowe & Carr, 2020). Different surveys have found a significant prevalence of vitamin C deficiency (levels <11 μmol/L) worldwide: 14% of men and 10% of women in the USA, 19% of men and 13% of women in India, 40% of elderly people living in institutions in the UK and 23% of children and 39% of women in Mexico (Hemilä, 2017), for instance. Importantly, in Africa, nutritional deficiencies and infectious diseases are still the major contributors to the global burden of disease nowadays. Indeed, they are of particular concern in the Central-African Republic (CAR), where the national prevalence of stunting in children under 5 years was 39.6% in 2019(Unicef WHO The World Bank, 2019). Despite the epidemiological significance of nutritional deficiencies and its repercussions in Africa, no current evidence on vitamin C levels in African mother–infant cohorts exists. This prevents accurately assessing the extent of vitamin C deficiency and thereby understanding its associations with a range of diseases, including enteric infections, highly prevalent in Africa. Some evidence from preclinical animal models suggests that vitamin C might stand as an underestimated risk factor for infant susceptibility to enteric infections (André et al., 2020), which are highly prevalent in the CAR. For all these reasons, we aimed at assessing the vitamin C seric levels of 48 mothers and their offspring until 6 months in the Central-African MITICA cohort and analysing the association of vitamin C levels with a positive stool culture from delivery until 6 months of age.

2 | METHODS

2.1 | MITICA cohort description

A prospective cohort of 48 mothers and their infants was followed from delivery to 6 months of age in the context of the MITICA study (Mother–Infant TransmIssion of microbiota in Central-Africa), whose main objective was to describe the mechanisms of acquisition of a dysbiotic gut microbiota in Central-Africa. The MITICA study was approved by the Ethics Committee of the Faculty of Sciences of Bangui and the Institutional Review Board of the Institut Pasteur. It was conducted in the Henri Izamo maternity in Bangui and the Institut Pasteur de Bangui. Enrolment took place from 8 December 2017 to 29 June 2019. Mothers were pre-included either at the maternity during ante-natal visits or in the neighbourhoods surrounding the Henri Izamo maternity. The population of these neighbourhoods corresponds to middle-class Central-African families, mainly state workers and students. The study was explained to the mothers in sango (the local language) and their voluntary consent was obtained before enrollment.

Pregnant women were tested for HIV, HBV and HCV and excluded if they had one positive result. The protocol of the MITICA study included anthropometric measures, an extensive clinical examination, oral, faecal, vaginal and breastmilk microbiome analyses, stool cultures at birth and five follow-up visits until 6 months. In this article, we focus solely on the results relevant for the vitamin C–stool positive association at birth, 11 weeks and 25 weeks. Blood samples were collected at birth from venous blood in mothers and umbilical cord in infants. A complete blood count, in addition to C-reactive protein (CRP), albumin and vitamin C were assessed at birth and at 11 and 25 weeks. To monitor the delivery and infant growth, an extensive clinical examination was also performed in mothers and infants at each visit. A container was given to the mother at each visit to collect the infant's stools. The containers were collected the following day by the study nurse within the first hour after emission.

In case of disease, infants were asked to consult at the 'Centre Pédiatrique de Bangui', the national paediatric hospital, to be treated if necessary, according to Central-African guidelines. All drugs prescribed during the follow-up were free of charge.

Malnutrition indicators were defined as follows: undernourishment in mothers was defined by albumin levels<35 g/L (Gounden et al., 2020); stunting in infants was defined as length-for-age < −2 standard deviations according to WHO growth databases (WHO|Stunting in a nutshell, 2015); and low birth weight was defined as birth weight <2500 g (What's at stake Low Birth Weight Policy Brief, n.d.).

2.2 | Vitamin C quantification

Blood was drawn into a lithium-heparin tube and was immediately centrifuged for 15 min at 3000 rpm and 4°C. Two hundred microlitres of plasma was soluted into 200 μl of a deproteinization solution of 2 g of meta-phosphoric acid and 15 mL 0.1% EDTA. This mix was vortexed for 1 min, incubated for 10 min at 4°C, centrifuged for 4 min at 10,000 rpm and 4°C. Then it was stored at −80°C until its transfer to the Cochin Hospital in Paris (France), where vitamin C levels were determined using HPLC Ultimate 3000 (Thermo Scientific) through an HPLC inverse phase and UV detection technique at the Biochemistry service of the Cochin Hospital in Paris. Hypovitaminosis C was defined as seric vitamin C levels <28 μmol/L and vitamin C deficiency was defined as vitamin C levels <11 μmol/L according to the WHO definition (FAO & World Health Organization, 1998). Women and infants were not fasting. However, seric vitamin C levels are relatively stable. Complete cessation of ingestion translates into a 3% decrease of reserves per day (Baker et al., 1969). Therefore, fasting for some hours does not significantly alter seric vitamin C levels. Vitamin A deficiency was defined as vitamin C levels <1 μmol/L and vitamin E deficiency was defined by vitamin E levels <11.6 μmol/L. Vitamin A and vitamin E were levels were determined using HPLC Ultimate 3000 (Thermo Scientific) through an HPLC inverse phase and UV detection technique at the Biochemistry service of the Cochin hospital. Quality control at the Cochin Hospital is guaranteed as follows: at the beginning and ant the end of every determination series, Chromsystems quality controls are performed (CV repro niv 1: 5%, and CV repro niv 2: 3.9%). To assure external quality controls, the Biochemistry service of the Cochin Hospital is enrolled in Aqualab Vitamins (External Quality Assurance) Program.

2.3 | Microbiological examination

The coloration technique was used to detect *Cryptosporidium* (Ziehl-modified technique). Stool culture was performed to diagnose *Salmonella*, *Shigella*, *E. coli*, *Campylobacter*, *Vibrio cholerae*, *Citrobacter*, *Enterobacter* and *Klebsiella* infections using specific growth media for these pathogens (BCP, Müller-Hinton, Hektoen, Kauffman, TCBS and Kamali). Furthermore, tests on *rotavirus*, *adenovirus* and yeasts were also performed. Therefore, BIOSYNEX Adenovirus/Rotavirus BSS tests were used. Yeasts were detected using Sabouraud and Chloramphenicol growth media. A positive stool sample was defined as a positive result for any of the micro-organisms listed above. These exams were performed at the Institut Pasteur de Bangui.

2.4 | Data collection and statistical analysis

Data were collected and managed using REDCap (Harris et al., 2009, 2019) electronic data capture tools hosted at Institut Pasteur. Spearman test was used to analyse the association between vitamin C levels in mothers and infants at delivery and the association of vitamin C with vitamin A levels. Mann–Whitney tests were used to assess the effect of maternal vitamin C status at delivery (hypovitaminosis and/or deficiency) on infant vitamin C levels at later visits. Fisher test was used to estimate the association of maternal vitamin C status at delivery and positive stool culture in mothers at delivery. To analyse the effect of hypovitaminosis C and vitamin C deficiency on the risk of a positive stool culture in infants, mixed-effect logistic regression models were used to consider repeated measures per infant. Mixed-effect logistic regression models were also used to analyse the association of vitamin C levels with other nutritional indicators during follow-up (stunting, albumin, vitamin A and vitamin E). Statistical significance was set to $P < 0.05$ (two-sided tests). All statistical analyses were performed using Stata MP Software (Stata Corp, College Station, TX, USA).

3 | RESULTS

3.1 | Cohort follow-up and sample characteristics

Between December 2017 and June 2019, 48 mother–infant pairs (including two couples of twins, i.e., 50 infants) were included in the cohort. Seric vitamin C concentration and stool cultures were performed in 37 women at delivery, 29 infants at birth, 22 infants at 11 weeks and 29 infants at 25 weeks. The main characteristics of mothers and infants at birth are presented in Table 1 and Table 2.

The median age of women at delivery was 23 years, ranging from 15 to 39 years, and 15/43 (34.9%) women were undernourished. Forty women out of 48 (83.3%) had secondary or higher education, 22/48 (45.8%) worked at home and 24/48 (50.0%) were students.

At birth, 11/50 (22.0%) infants were stunted, 5/50 (10.0%) infants had low birth weight and 4/40 (10.0%) infants had ongoing inflammation. Their median head circumference was 33 cm (inter-quartile range [IQR] 32–35 cm). Their albumin levels were normal (median = 40.5 g/L; IQR 38–43 g/L). The distribution of seric vitamin C levels at delivery in mothers and in infants during follow-up is shown in Figure 1, and the evolution of the main nutritional indicators in infants is presented in Table 2.

TABLE 1 Maternal characteristics

Characteristics	n / median and inter-quartile range / n and percentages
N participants	48
With a vitamin C measure	45
With a stool culture	40
With a vitamin C measure and a stool culture	37
Undernourishment[a]	15/43 (34.9%)
Age (years)	22.9 (20.7; 29.7)
Weight (kg)	64 (60; 68)
Height (m)	1.6 (1.6; 1.7)
Albumin (g/L)	36 (33; 38)
Vitamin C seric levels (μmol/L)	15.3 (6.2; 27.8)
Vitamin C hypovitaminosis (<28 μmol/L)	34/45 (75.6%)
Vitamin C deficiency (<11 μmol/L)	19/45 (42.2%)
Vitamin A seric levels (μmol/L)	0.9 (0.8; 1.2)
Vitamin A deficiency (<1 μmol/L)	23/37 (62.2%)
Vitamin E seric levels (μmol/L)	26.2 (20.6; 30.7)
Vitamin E deficiency (<11.6 μmol/L)	5/38 (13.2%)
Inflammation (CRP > 5 mg/L)	26/43 (60.5%)
Positive stool culture at delivery	24/40 (60.0%)
Positive stool culture among women with a vitamin C measure	23/37 (62.2%)
Education	
Primary	8/48 (16.7%)
Secondary and higher	40/48 (83.3%)
Occupation	
Homecare	22/48 (45.8%)
Work outside home	2/48 (4.2%)
Student	24/48 (50.0%)

Note: For continuous variables, median and inter-quartile range are provided.For binary and variables with categories, n and percentages are provided.

[a]Undernourished status was defined according to albumin levels <35 g/L.

3.2 | Vitamin C levels and prevalence of hypovitaminosis C and vitamin C deficiency

3.2.1 | At birth

The median vitamin C level in mothers, at delivery, was 15.3 μmol/L (IQR 6.2–27.8); 34/45 women (75.6%) had hypovitaminosis C, and 19/45 women had severe vitamin C deficiency (42.2%). In infants, the median vitamin C level at birth was 35.2 μmol/L (IQR 16.5–63.9);

TABLE 2 Infant characteristics during follow-up

	Birth	11 weeks	25 weeks
N participants	50	48	48
With a vitamin C measure	40	37	33
With a stool culture	36	25	33
With a vitamin C measure and a stool culture	29	22	29
Stunting[a]	11/50 (22.0%)	9/39 (23.1%)	9/35 (25.7%)
Low birth weight (<2500 g)	5/50 (10.0%)		
Female	26/50 (52.0%)	24/48 (50.0%)	24/48 (50.0%)
Weight (g)	3175 (2750; 3300)	5835 (5330; 6500)	7350 (7000; 7900)
Length (cm)	48 (47; 50)	58 (56; 49.15)	66 (63.5; 67.5)
Positive stool culture	8/36 (22.2%)	20/25 (80.0%)	27/33 (81.8%)
Positive stool culture among infants with a vitamin C measure	8/29 (27.6%)	17/22 (77.3%)	24/29 (82.8%)
Albumin (g/L)	40.5 (38; 43)	42 (40; 44)	42 (40; 44)
Inflammation (CRP > 5 mg/L)	4 (10.0%)	7/36 (19.4%)	6/33 (18.2%)
Vitamin C seric levels (μmol/L)	35.2 (16.5; 63.9)	41.5 (18.7; 71.6)	18.2 (2.3; 46.6)
Vitamin C hypovitaminosis (<28 μmol/L)	17/40 (42.5%)	13/37 (35.1%)	18/33 (54.6%)
Vitamin C deficiency (<11 μmol/L)	6/40 (15.0%)	9/37 (24.3%)	11/33 (33.3%)
Vitamin A seric levels (μmol/L)	1.3 (1.1; 1.4)	0.8 (0.9; 1.2)	0.9 (0.7; 1.0)
Vitamin A deficiency (<1 μmol/L)	6/25 (24.0%)	20/31 (64.5%)	22/30 (73.3%)
Vitamin E seric levels (μmol/L)	7.2 (4.1; 8.5)	16.4 (9.9; 22.4)	11.2 (6.8; 18.1)
Vitamin E deficiency (<11.6 μmol/L)	22/25 (88.0%)	11/32 (34.4%)	17/31 (54.8%)

Note: For continuous variables, median and inter-quartile range are provided. For binary and variables with categories, n and percentages are provided.
[a]Stunting is defined according to −2 standard deviations of length-per-age databases of the WHO.

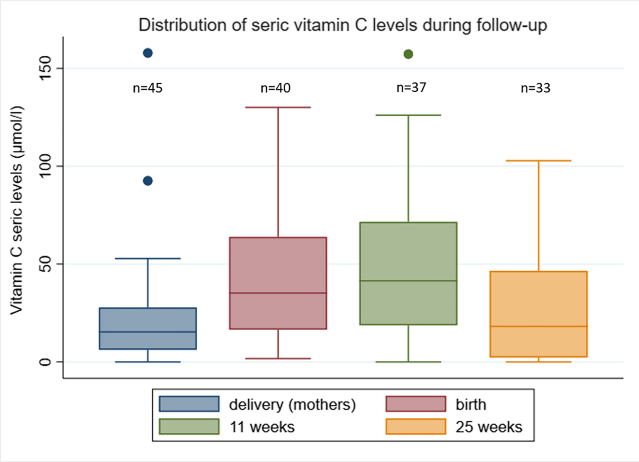

FIGURE 1 Distribution of vitamin C levels during follow-up

17/40 infants (42.5%) had hypovitaminosis C, and 6/40 infants had severe vitamin C deficiency (15.0%). The Spearman rho coefficient of correlation between the mother and the infants' vitamin C levels was 0.5 at birth (P value = 0.002, Figure 2). Infants had significantly higher levels of vitamin C at delivery (median = 35.2 μmol/L; IQR 16.5–63.9 μmol/L), compared to mothers (median = 15.3 μmol/L; IQR 6.2–27.8 μmol/L; P value <0.001). Furthermore, the offspring of mothers with vitamin C deficiency had significantly lower levels of vitamin C (median = 18.7 μmol/L; IQR 13.3–30.7 μmol/L), compared to the offspring of mothers without vitamin C deficiency (median = 62.2 μmol/L; IQR 34.6–89.2 μmol/L; P value <0.001, Figure 2).

3.2.2 | During follow-up

At 11 and 25 weeks, the median vitamin C seric levels in infants were 41.5 μmol/L (IQR 18.7–71.6) and 18.2 μmol/L (IQR 2.3–46.6), respectively. The proportion of infants with hypovitaminosis C decreased from 17/40 (42.5%) at birth to 13/37 (35.1%) at 11 weeks and then increased to 18/33 (54.6%) at 25 weeks. Finally, the number of infants with vitamin C deficiency increased from 6/40 (15%) at birth to 9/37 (24.3%) at 11 weeks and then to 11/33 (33.3%) at 25 weeks (Table 2).

3.3 | Vitamin C levels and risk of a positive stool culture

At birth, 23/37 (62.2%) of the mothers and 8/29 (27.6%) of the infants with a vitamin C measure had a positive stool culture (Tables 1 and 2). *Escherichia coli* and *K. pneumoniae* were the most prevalent species. *Escherichia coli* was present in 22/37 (59.5%) of the mothers

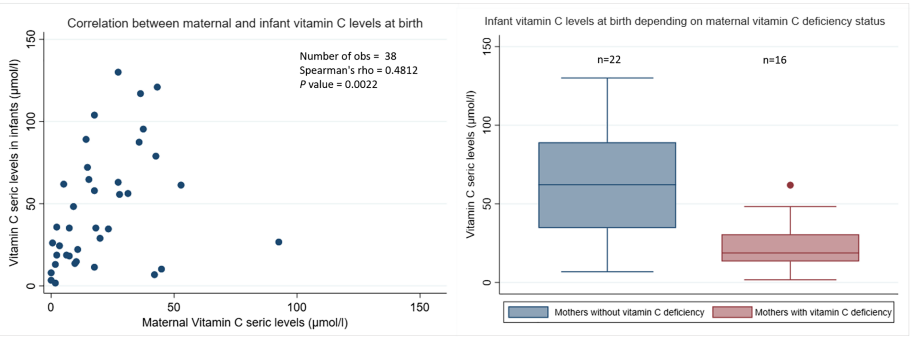

FIGURE 2 Correlation between maternal and infant vitamin C levels at birth

TABLE 3 Aetiology of the different stool exams during follow-up among individuals with a vitamin C measure

Species	Mothers	Infants at birth	Infants at 11 weeks	Infants at 25 weeks
Stool cultures	23/37 (62.2%)	8/29 (27.6%)	17/22 (77.3%)	24/29 (82.8%)
Eschericchia coli	22/37 (59.5%)	6/29 (20.7%)	14/22 (63.6%)	19/29 (65.5%)
Klebsiella pneumoniae	1/37 (2.7%)	1/29 (3.5%)	4/22 (18.2%)	4/29 (13.8%)
Klebsiella oxytoca	0	0	2/22 (9.1%)	1/29 (3.5%)
Other gram positive bacili	0	1/29(3.5%)	1/22 (4.6%)	0
Klebsiella ornithinolytica	0	0	1/22 (4.6%)	0
Citrobacter	0	1/29(3.5%)	0	0
Parasitological exam	14/37 (37.8%)	0	0	0
Entamoeba coli	12/37 (32.4%)	0	0	0
Chilomastix mesnili	2/37 (5.4%)	0	0	0
Giardia intestinalis	1/37 (2.7%)	0	0	0
Entamoeba histolytica	1/37 (2.7%)	0	0	0
Other laboratory tests	0	0	3/29 (10.3%)	3/29 (10.3%)
Rotavirus	0	0	3/22 (13.6%)	3/29 (10.3%)
Yeasts	0	0	0	0

with a vitamin C measure, and *K. pneumoniae* grew in 1/37 (2.7%) of their stool samples. Among infants with a vitamin C measure, *E. coli* was present in 39/80 (48.8%) of the samples and *K. pneumoniae* grew in 9/80 (11.3%) of the stool cultures. In infants with a vitamin C measure, there were 3/22 (13.6%) and 3/29 (10.3%) positive tests for *rotavirus* at 11 and 25 weeks, respectively. None of the mothers or infants' stool was colonised by *rotavirus* at delivery. There were no positive tests for yeasts during the entire follow-up in mothers or infants with a vitamin C measure. The concrete prevalence of each micro-organism at each follow-up visit is presented in Table 3.

In mothers, at delivery, hypovitaminosis C and vitamin C deficiency were not associated with a positive stool culture (P value = 0.71 and P value = 0.99, respectively). In infants with a vitamin C measure, the risk of having a positive stool culture increased during follow-up from 8/29 (27.6%) at birth, to 17/22 (77.3%) at 11 weeks and 24/29 (82.8%) at 25 weeks (Table 4A). Therefore, the statistical model evaluating the association of vitamin C status with a stool positive result was adjusted on the age of the infant.

Overall, vitamin C levels were lower in infants with a stool positive culture, compared to stool-negative infants (Table 4A). In a multivariate mixed model gathering evidence on 80 stool cultures of 41 infants, hypovitaminosis C was significantly associated with a higher risk of a positive stool culture during the first 6 months of life, adjusted on the age of the infant (aOR = 5.3; 95% CI 1.1; 26.1; P value = 0.038, Table 4B). In contrast, Vitamin C deficiency was not found to be associated with increased risk of positive stool culture (P value = 0.19). Potential co-variates, such as maternal positive stool test at delivery, stunting, and ongoing inflammation were removed from the final model as they were not statistically significant in univariate analysis. Vitamin C levels were not significantly associated with other nutritional indicators, such as albumin (P value = 0.07), stunting (P value = 0.07), or vitamin E (P value = 0.14). However, vitamin C levels were associated with vitamin A levels (Spearman's rho coefficient = 0.31, P value = 0.004). Furthermore, infants with vitamin A deficiency were at significantly higher risk of vitamin C deficiency (OR = 5.7; 95% CI 1.35; 24.1, P value = 0.018).

TABLE 4 Infant vitamin C levels and risk of a positive stool culture

A. Infant vitamin C levels and prevalence of a positive stool culture during follow-up

	Birth		11 weeks		25 weeks	
	Stool positive	Stool negative	Stool positive	Stool negative	Stool positive	Stool negative
N participants with a vitamin C measure	8/29 (27.6%)	21/29 (72.4%)	17/22 (77.3%)	5/22 (22.7%)	24/29 (82.8%)	5/29 (17.2%)
Vitamin C seric levels (μmol/L)	36.3 (17.6; 76.9)	56.2 (26.1; 72.1)	41.5 (26.1; 67.6)	60.2 (40.9; 76.1)	12.5 (2.0; 53.9)	40.3 (36.9; 41.5)
Vitamin C hypovitaminosis (<28 μmol/L)	4/8 (50.0%)	7/21 (33.3%)	5/17 (29.4%)	0	17/24 (70.8%)	1/5 (20.0%)
Vitamin C deficiency (<11 μmol/L)	1/8 (12.5%)	1/21 (4.8%)	2/17 (11.8%)	0	10/24 (41.7%)	1/5 (20.0%)

B. Association between vitamin C status and risk of a positive stool culture during follow-up

	N (observations)	N with positive stool cultures (%)	N (infants)	Crude OR(95% CI)	*P*	Adj. OR(95% CI)	*P*
Maternal positive stool at delivery			39	1.1 (0.5; 2.7)	0.8		
No	40	23 (57.5%)					
Yes	43	26 (60.5%)					
Stunting[a]			44	0.6 (0.2; 1.8)	0.4		
No	69	42 (60.9%)					
Yes	20	10 (50.0%)					
Inflammation (CRP > 5 mg/L)			42	2.5 (0.6; 10.1)	0.2		
No	70	38 (54.3%)					
Yes	12	9 (75.0%)					
Vitamin C hypovitaminosis (<28 μmol/L)			41	3.0 (1.2; 7.1)	**0.025**	5.3 (1.1; 26.1)	**0.038**
No	44	22 (50.0%)					
Yes	36	27 (75.0%)					
Age of the infant[b]			45				
Birth	36	8 (22.2%)					
11 weeks	25	20 (80.0%)		21.8 (2.8; 167.9)	**0.003**	24.7 (2.5; 245.5)	**0.006**
25 weeks	33	27 (81.8%)		24.6 (3.4; 179.5)	**0.002**	23.7 (2.3; 239.5)	**0.007**

95% CI: 95% confidence interval; Adj. OR: Adjusted-odds ratio

[a]Stunting is defined according to −2 standard deviations of length-per-age databases of the WHO.
[b]Birth is the baseline to which age categories at each visit are compared.

4 | DISCUSSION

Vitamin C deficiency was highly prevalent in mothers at delivery (42.2%) and infants at 6 months (33.3%) in the MITICA cohort of Central-African mother–infant couples. Maternal micronutrient status is determinant for foetal growth and survival (Ramakrishnan et al., 1999). This is particularly relevant in Central-Africa, as the prenatal dietary intake of micronutrients is considered to be insufficient to meet the increased nutritional needs during pregnancy (Allen, 2005). More precisely, vitamin C requirements increase to 85 mg per day during pregnancy(Vitamin C - Health Professional Fact Sheet, n.d.). Vitamin C is actively transported across the placenta to ensure healthy vitamin C levels to the infant. Furthermore, physiologic pregnancy-associated haemodilution contributes to diminish proportionally vitamin C levels in mothers at delivery. Indeed, vitamin C levels at delivery are significantly higher in infants, compared to the mothers. Due to this active placental transport, maternal plasma vitamin C levels fall (Streeter & Rosso, 1981). The 75.6% prevalence of maternal vitamin C hypovitaminosis at delivery suggests that vitamin C storage in these women is not sufficient to fulfil both the infant and maternal needs during pregnancy. Indeed, the offspring of mothers with vitamin C deficiency had significantly lower vitamin C levels at birth, compared to offspring born to non-deficient mothers. Considering the role in epigenetics of vitamin C (Camarena & Wang, 2016; Young et al., 2015), low vitamin levels at this age might have considerable repercussions for growth and development (Camarena & Wang, 2016).

At 2–3 months of life, cassava boiled dough called 'bouillie de manioc' becomes an important part of the Central-African diet. As cassava is boiled for at least 20 min there is no active form of vitamin C left. Furthermore, lactation requires up to 120 mg/day ingestion of vitamin C (Vitamin C - Health Professional Fact Sheet, n.d.), which is rare among Central-African women and certainly not the case of the 75.6% of the mothers who had hypovitaminosis C in our cohort. In conclusion, infants do not get sufficient vitamin C from diet nor breastmilk and, therefore, vitamin C levels decrease over time. Indeed, vitamin C deficiency doubled during the first 6 months of life from 15.0% at birth to 33.3% at 6 months. Moreover, the high prevalence of vitamin C deficiency at 6 months suggests that the vitamin C storage resulting from the active placental transportation is already exhausted, a very early stage of development.

Similar results have been found in pregnant women in other African settings. In North-West Nigeria there was an 80% prevalence of hypovitaminosis C in 400 pregnant women in a study conducted in 2009(Ugwa et al., 2016). In this study, the mean vitamin C levels was 20 μmol/L, very similar to our data. In another study from 2009 to 2011 conducted in Uganda, mean vitamin C levels was 11 μmol/L, and vitamin C deficiency prevalence was 70% of 400 pregnant women from Kampala (Kiondo et al., 2012), a higher prevalence than in our study. Finally, a vitamin C mean value of 33.4 μmol/L was found in 117 women at delivery in Southeast Brazil, including a 4.3% prevalence of vitamin C deficiency (Madruga de Oliveira et al., 2008). Unfortunately, there was no follow-up of the infants' seric vitamin C levels in these studies. The only study on vitamin C in African children found mean plasma vitamin C levels of 40.3 μmol/L in 50 children aged 8–12 years in the Niger Delta Region in 1986(Ofuya et al., 1986). In 2003, a Mexican study found mean vitamin C levels of 28 μmol/L and a 23% rate of vitamin C deficiency in 1815 children aged 0–11 years. Moreover, 30% of children <2 years of age were vitamin C-deficient (Villalpando et al., 2003). In 2005, the median vitamin C seric levels of 511 children 2–13 years from Puerto Rico ranged from 18.2 to 83 μmol/L, with a median value of 50.6 μmol/L (Preston et al., 2006). Consequently, the seric vitamin C levels found in the infants of our study are among the lowest, compared to previous data of paediatric population.

Diarrhoea is the second leading cause of mortality in children under five years of age in the CAR, although it is both preventable and treatable(Global Burden of Disease (GBD) | Institute for Health Metrics and Evaluation, n.d). It was responsible for 8310 years of life lost (YLL) in 2017(Global Burden of Disease (GBD)|Institute for Health Metrics and Evaluation, n.d). Malnutrition is the disease that drives the highest number of deaths and disabilities combined in the CAR(Global Burden of Disease (GBD)|Institute for Health Metrics and Evaluation, n.d). Therefore, it is highly interesting to note that infants with hypovitaminosis C had a higher prevalence of a positive stool culture during the first 6 months of life in a prospective cohort. Indeed, the low number of infants with vitamin C deficiency at the beginning of the follow-up (only two infants among those with a stool culture result at birth and 11 weeks) might explain the lack of statistical significance of the model on vitamin C deficiency. Further investigations are required to address this specific question. Altogether, these results suggest that moderate levels of vitamin C might be an additional risk factor for microbial intestinal carriage. So far, epidemiological studies have shown that during an infection (like the common cold) seric levels of vitamin C decrease to half their original concentration (Hume & Weyers, 1973), reaching suboptimal levels with a risk of vitamin C levels ≤50 μmol/L (Carr et al., 2015; Panel & Nda, 2013). Regrettably, no study has investigated the association between vitamin C status and enteric infections in children beyond the 19th-century ecologic correlations and the recent work in animal models of *Shigella* infection (André et al., 2020). Nevertheless, physio-pathological observations might shed some light on why malnourished children - including vitamin C-deficient children - have impaired immunity and reduced physiological resources to respond to infections (Gombart et al., 2020). Vitamin C deficiency might impair the integrity of innate barriers (Carr & Maggini, 2017; Maggini et al., 2008), and immune cell proliferation, differentiation and functioning (including antibody production) (Carr & Maggini, 2017; Gombart et al., 2020; Maggini et al., 2008, 2018; Tina Suksmasari, 2015; Wishart, 2017; Wu et al., 2019). Vitamin C has essential antimicrobial properties: it increases serum levels of complement proteins (Micronutrient information center, Linus Pauling Institute,, & Oregon State University, n.d.) and is involved in IFNγ production (Carr & Maggini, 2017; Tina Suksmasari, 2015), which might be defective in vitamin C-deficient infants. Besides, vitamin C has a relevant role in inflammation and oxidative burst (Carr & Maggini, 2017; Gombart et al., 2020; Wintergerst et al., 2006).

Regarding vitamin C-bacteria interactions, *E. coli*, *Shigella* and *Salmonella* are the Gram-negative bacteria mostly responsible for enteric infections worldwide(Diarrhoeal disease, n.d.). Gram-negative bacteria have a lipopolysaccharide (LPS) complex associated with the outer membrane known as endotoxin. There are many studies in mice, which demonstrate the beneficial effect of vitamin C loading in LPS injury, either preventing the endothelial dysfunction caused by LPS of *E. coli* without altering the responsiveness of the vascular smooth muscle (Pleiner et al., 2002) or inhibiting bacterial replication and restoring physiology in septic rats (Armour et al., 2001). Moreover, in humans, oral Vitamin C pretreatment (as little as 1 g) has been demonstrated to completely block the increase in circulating endotoxin, and it might also prevent endotoxin translocation from the gut (Ashton et al., 2003; Gutierrez et al., 1995). Finally, a very recent study on guinea pigs demonstrated that hypovitaminosis C increased the susceptibility of guinea pigs to *Shigella* infection, associated with more severe and prolonged diarrheal episodes (André et al., 2020).

In conclusion, additional data are needed to accurately assess the association between vitamin C levels and enteric infections in infants. The small sample size of the cohort is the main limitation of this study. During the first 3 months of life, the stool is liquid and not easy to collect from a newborn in sterile conditions. Therefore, the rate of stool cultures collected during this period might seem relatively low. In any case, MITICA is the first mother–infant cohort to determine vitamin C in Africa, to our knowledge. Indeed, this cohort was not originally conceived to analyse the association between vitamin C and enteric infections. Therefore, results should be interpreted carefully. A positive stool culture does not mean that infants were sick. It means that there was a significant bacterial carriage of a certain strain, enough to grow in a laboratory culture. Unfortunately, molecular tests on pathogenicity genes were not available. Consequently, *E. coli* strains could be pathogenic or not. In any case, more *Enterobacteriaceae* were found in children with hypovitaminosis C. This suggests there may be a possible overcolonisation by *Enterobacteriaceae* falling into the category of pathobionts in these infants. Also, hypovitaminosis C may not necessarily be associated with an increased risk of a positive stool culture in pregnant women. The immunity in infants is still developing, and vitamin C might play a more important role than in adults when immunity is fully functional. Furthermore, due to active transportation in the placenta, vitamin C is temporarily decreased in pregnant women and recovers after delivery. It is also possible that, in this context, hypovitaminosis has not been present long enough to have a significant impact on an immune-competent adult. In any case, nutritional deficiencies are generally more worrisome in children compared to adults.

5 | CONCLUSION

Vitamin C deficiency was highly prevalent in mothers and infants in the MITICA prospective longitudinal cohort of Central-African pregnant women and infants. At birth, maternal vitamin C levels were significantly correlated with their offspring's. Maternal vitamin C deficiency was associated with lower levels of vitamin C in the offspring at birth. Our results suggest that infants might not receive sufficient vitamin C during the first 6 months of life from breastmilk nor diet. Besides, the protective vitamin C storage resulting from the active placenta transportation during pregnancy is importantly reduced after 6 months. Finally, hypovitaminosis C was associated with a higher risk of a positive stool culture during the first 6 months of life. Additional epidemiological studies are necessary to evaluate the effect of vitamin C levels on the occurrence and severity of enteric infections and thereby pave the way to finally elucidate, 212 years later, why the citizens of Karlskrona did not get sick.

ACKNOWLEDGMENTS

We thank all participating women and infants, the MITICA Consortium, the Henri Izamo Maternity staff in Bangui and the Institut Pasteur de Bangui staff for their continuous support in the MITICA study; Jean-François Damaras, Patrick Sanchez and Jean-Pierre Lombart for their logistic and moral support, essential for the project; Ionéla Gouandjika and Emmanuel Nakouné for the scientific and technical advice; Pascale Vonaesch for her essential contribution to the conception of the MITICA study; Pascale Vonaesch, Sean Kennedy and Tamara Giles-Vernick for their scientific guidance in the MITICA study; Lavoisier Dieu-Merci Welekoï Yapondo for the preparation of the bio-banking; the field workers Carole Senga Mamadou, Déborah Bendima, Maryse Dongoya, Alex Bebangui, Sidonie Koumangou, Prisca Kondolas Singa, Isidore Ndilbe and Stevie Gbembongo for countless hours spent in the field; the Centre de Recherche Translationelle and the Direction Internationale of the Institut Pasteur and especially Sylvie Gratepanche, Cécile Artaud, Mohand Ait-Ahmed, Nathalie Jolly and Pierre-Marie Girard for precious help in setting up and steering the MITICA study; Bérengère Menu for the legal help and support; and all local authorities (chefs de quartier) that welcomed us to work in the Bangui neighbourhoods. This project was mainly funded by a PTR (Programmes transversaux de Recherche) grant N°91-17 from the Institut Pasteur Paris. We also thank the LabEx IBEID as this study was also partly funded by a postdoctoral fellowship from the LabEx IBEID (ANR-16-COV-005). Also, VMA was supported by this postdoctoral fellowship from the LabEx IBEID.

The MITICA was approved by the Ethics Committee of the University of Bangui and the Institutional Review Board of the Institut Pasteur.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

CONTRIBUTIONS

VMA, PJS, SN, GU and NN designed the research analyses. VMA, JCJK, LMK, JRM, HS, SD, YTN, DMB, JBK, SN, GU and NN performed the research. VMA, JRM, HS, SN, GU, NN, YM, BM and MV analysed the data. VMA, YM, PJS, MV and BM wrote the paper. All authors have read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

… A. B.-O. A.-H. M. S. A. O., & 2003, undefined. (n.d.). Malnutrition in Civil War armies. *Europepmc.Org*. Retrieved from https://europepmc.org/article/med/14725189

Allen, L. H. (2005). Multiple micronutrients in pregnancy and lactation: An overview. *American Journal of Clinical Nutrition*, *81*(5), 1206–1212. https://doi.org/10.1093/ajcn/81.5.1206

André, A. C., Mulet, C., Anderson, M. C., Injarabian, L., Buch, A., Prade, V. M., … Sansonetti, P. (2020). The ascorbate-deficient guinea pig model of shigellosis allows the study of the entire Shigella life cycle. *Biorxiv*, 1–25.

Armour, J., Tyml, K., Lidington, D., & Wilson, J. X. (2001). Ascorbate prevents microvascular dysfunction in the skeletal muscle of the septic rat. *Journal of Applied Physiology*, *90*(3), 795–803. https://doi.org/10.1152/jappl.2001.90.3.795

Arnold, J. (1809). Dr. Arnold, on typhus, dysentery, and scurvy. *The Medical and Physical Journal*, *21*(119), 17–23.

Ashton, T., Young, I. S., Davison, G. W., Rowlands, C. C., McEneny, J., Van Blerk, C., … Jackson, S. K. (2003). Exercise-induced endotoxemia: The effect of ascorbic acid supplementation. *Free Radical Biology and Medicine*, *35*(3), 284–291. https://doi.org/10.1016/S0891-5849(03)00309-5

Baker, E. M., Hodges, R. E., Hood, J., Sauberlich, H. E., & March, S. C. (1969). Metabolism of ascorbic-i in experimental—'4C acid scurvy' 2. *The American Journal of Clinical Nutrition*, *22*, 549–558. https://doi.org/10.1093/ajcn/22.5.549

Bartholomew, M. (2002). James Lind's treastis of the scurvy (1753). *Postgraduate Medical Journal*, *1753*, 695–697.

Bollet, A. J. (1992). Scurvy and chronic diarrhea in civil war troops: Were they both nutritional deficiency syndromes? *Journal of the History of Medicine and Allied Sciences*, *47*(1), 49–67. https://doi.org/10.1093/jhmas/47.1.49

Camarena, V., & Wang, G. (2016). The epigenetic role of vitamin C in health and disease. *Cellular and Molecular Life Sciences*, *73*(8), 1645–1658. https://doi.org/10.1016/j.physbeh.2017.03.040

Carr, A. C., & Maggini, S. (2017). Vitamin C and immune function. *Nutrients*, *9*(11), 1–25. https://doi.org/10.3390/nu9111211

Carr, A. C., Shaw, G. M., Fowler, A. A., & Natarajan, R. (2015). Ascorbate-dependent vasopressor synthesis: A rationale for vitamin C administration in severe sepsis and septic shock? *Critical Care*, *19*(1), 1–8. https://doi.org/10.1186/s13054-015-1131-2

Diarrhoeal disease. (n.d.). Retrieved August 19, 2020, from https://www.who.int/en/news-room/fact-sheets/detail/diarrhoeal-disease

FAO, & World Health Organization. (1998). *Vitamin and mineral requirements in human nutrition second edition* (pp. 1–20). World Health Organization.

Global Burden of Disease (GBD)|Institute for Health Metrics and Evaluation. (n.d.). Retrieved January 15, 2020, Retrieved from http://www.healthdata.org/gbd

Gombart, A. F., Pierre, A., & Maggini, S. (2020). A review of micronutrients and the immune system–working in harmony to reduce the risk of infection. *Nutrients*, *12*(1). https://doi.org/10.3390/nu12010236

Gounden, V., Vashisht, R., & Jialal, I. (2020). *Hypoalbuminemia*. StatPearls. StatPearls Publishing. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30252336

Gutierrez, G., Hurtado, F. J., & Fernandez, E. (1995). Inhibitory effect of *Escherichia coli* endotoxin on skeletal muscle contractility. *Critical Care Medicine*, *23*(2), 308–315. https://doi.org/10.1097/00003246-199502000-00017

Harris, P. A., Taylor, R., Minor, B. L., Elliott, V., Fernandez, M., O'Neal, L., McLeod, L., Delacqua, G., Delacqua, F., Kirby, J., Duda, S. N., & Redc, C. (2019). The REDCap consortium: Building an international community of software partners. *Journal of Biomedical Informatics*, *95*, 103208. https://doi.org/10.1016/j.jbi.2019.103208

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. (2009). Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, *42*(2), 377–381.

Hemilä, H. (2017). Vitamin C and infections. *Nutrients*, *9*(4). https://doi.org/10.3390/nu9040339

Hume, R., & Weyers, E. (1973). Changes in leucocyte ascorbic acid during the common cold. *Scottish Medical Journal*, *18*(1), 3–7. https://doi.org/10.1177/003693307301800102

Kiondo, P., Tumwesigye, N. M., Wandabwa, J., Wamuyu-Maina, G., Bimenya, G. S., & Okong, P. (2012). Plasma vitamin C assay in women of reproductive age in Kampala, Uganda, using a colorimetric method. *Tropical Medicine and International Health*, *17*(2), 191–196. https://doi.org/10.1111/j.1365-3156.2011.02907.x

Langlois, K., Cooper, M., & Colapinto, C. K. (2016). Vitamin C status of canadian adults: Findings from the 2012/2013 Canadian health measures survey. *Health Reports*, *27*(5), 3–10.

Madruga de Oliveira, A., Rondó, P. H. C., Mastroeni, S. S., & Oliveira, J. M. (2008). Plasma concentrations of ascorbic acid in parturients from a hospital in Southeast Brazil. *Clinical Nutrition*, *27*(2), 228–232. https://doi.org/10.1016/j.clnu.2007.11.006

Maggini, S., Beveridge, S., Sorbara, P. J. P., & Senatore, G. (2008, December). *Feeding the immune system: The role of micronutrients in restoring resistance to infections* (Vol. 3). CAB Reviews: Perspectives in Agriculture, Veterinary Science, Nutrition and Natural Resources. https://doi.org/10.1079/PAVSNNR20083098

Maggini, S., Pierre, A., & Calder, P. C. (2018). Immune function and micronutrient requirements change over the life course. *Nutrients*, *10*(10), 1531. https://doi.org/10.3390/nu10101531

Micronutrient information center, Linus Pauling Institute, & Oregon State University. (n.d.). Immunity in depth. Retrieved August 17, 2020, from https://lpi.oregonstate.edu/mic/health-disease/immunity

Ofuya, Z. M., Ibu, J. O., & Jack, T. (1986). Plasma ascorbic acid levels in nigerian children of Niger delta region of nigeria. *Scandinavian Journal of Gastroenterology*, *21*(S124), 153–155. https://doi.org/10.3109/00365528609093798

Panel, E., & Nda, A. (2013). Scientific opinion on dietary reference values for vitamin C. *EFSA Journal*, *11*(11), 1–68. https://doi.org/10.2903/j.efsa.2013.3418

Pleiner, J., Mittermayer, F., Schaller, G., MacAllister, R. J., & Wolzt, M. (2002). High doses of vitamin C reverse *Escherichia coli* endotoxin-induced hyporeactivity to acetylcholine in the human forearm. *Circulation*, *106*(12), 1460–1464. https://doi.org/10.1161/01.CIR.0000030184.70207.FF

Preston, A. M., Ph, D., Rodríguez, C., & Rivera, C. E. (2006). Plasma ascorbate in a population of children: Influence of age, gender, citamin C intake, BMI, and smoke exposure. *PRHSJ*, *25*(2), 137–142.

Ramakrishnan, U., Manjrekar, R., Rivera, J., Gonzáles-Cossío, T., & Martorell, R. (1999). Micronutrients and pregnancy outcome: A review of the literature. *Nutrition Research*, *19*(l), 103–159. https://doi.org/10.1016/S0271-5317(98)00178-X

Rowe, S., & Carr, A. C. (2020). Global vitamin C status and prevalence of deficiency: A cause for concern? *Nutrients*, *12*(7), 1–20. https://doi.org/10.3390/nu12072008

Schleicher, R. L., Carroll, M. D., Ford, E. S., & Lacher, D. (2009). Serum vitamin C and the prevalence of vitamin C deficiency in the United States: 2003–2004 National Health and Nutrition Examination Survey (NHANES). *American Journal of Clinical Nutrition*, *90*(2), 1252–1263. https://doi.org/10.3945/ajcn.2008.27016.1

Streeter, M. L., & Rosso, P. (1981). Transport mechanisms for ascorbic acid in the human placenta. *American Journal of Clinical Nutrition*, *34*(9), 1706–1711. https://doi.org/10.1093/ajcn/34.9.1706

Tina Suksmasari, B. H. (2015). Multivitamin supplementation supports immune function and ameliorates conditions triggered by reduced air quality. *Vitamins & Minerals*, *04*(02). https://doi.org/10.4172/2376-1318.1000128

Truswell, A. S. (1990). In A. S. Truswell, I. E. Dreosti, R. M. English, I. H. E. Rutishauswer, & N. Palmer (Eds.), *Recommended nutrient intakes: Australian papers*. Mosman, NSW: Australian Professional Publications.

Ugwa, E. A., Iwasam, E. A., & Nwali, M. I. (2016). Low serum vitamin C status among pregnant women attending antenatal care at general hospital Dawakin Kudu, Northwest Nigeria. *International Journal of Preventive Medicine*, *7*, 40. https://doi.org/10.4103/2008-7802.176166

Unicef WHO The World Bank. (2019). Country overview malnutrition burden stunting in the Central-African Republic. *Global Nutrition Report*, 1–14. https://doi.org/10.1038/s41586-019-1878-8.Notes

Villalpando, S., Montalvo-Velarde, I., Zambrano, N., García-Guerra, A., Ivonne Ramírez-Silva, C., Shamah-Levy, T., & Rivera, J. A. (2003). Vitamins A, and C and folate status in Mexican children under 12 years and women 12–49 years: A probabilistic national survey. *Salud Publica de Mexico. Instituto Nacional de Salud Publica.*, *45*, 508–519. https://doi.org/10.1590/s0036-36342003001000007

Vitamin C - Health Professional Fact Sheet. (n.d.). Retrieved August 12, 2020, from https://ods.od.nih.gov/factsheets/VitaminC-HealthProfessional/#h5

Vitamin C (Ascorbic Acid) - PubMed. (n.d.). Retrieved August 12, 2020, Retrieved from https://pubmed.ncbi.nlm.nih.gov/29763052/

Vitamin C Deficiency (Scurvy) - StatPearls - NCBI Bookshelf. (n.d.). Retrieved from August 12, 2020, from https://www.ncbi.nlm.nih.gov/books/NBK493187/

What's at stake Low Birth Weight Policy Brief. (n.d.).

WHO|Stunting in a nutshell. (2015). WHO. Retrieved from http://www.who.int/nutrition/healthygrowthproj_stunted_videos/en/

Wintergerst, E. S., Maggini, S., & Hornig, D. H. (2006). Immune-enhancing role of vitamin C and zinc and effect on clinical conditions. *Annals of Nutrition and Metabolism*, *50*(2), 85–94. https://doi.org/10.1159/000090495

Wishart, K. (2017). Increased micronutrient requirements during physiologically demanding situations: Review of the current evidence. *Vitamins & Minerals*, *06*(03). https://doi.org/10.4172/2376-1318.1000166

Wu, D., Lewis, E. D., Pae, M., & Meydani, S. N. (2019). Nutritional modulation of immune function: Analysis of evidence, mechanisms, and clinical relevance. *Frontiers in Immunology*, *10*(JAN), 1–19. https://doi.org/10.3389/fimmu.2018.03160

Young, J. I., Züchner, S., & Wang, G. (2015). Regulation of the epigenome by Vitamin C. *Annual Review of Nutrition*, *35*(1), 545–564. https://doi.org/10.1146/annurev-nutr-071714-034228

How to cite this article: Moya-Alvarez, V., Koyembi, J.-C.J., Kayé, L. M., Mbecko, J.-R., Sanke-Waîgana, H., Djorie, S. G., Nyasenu, Y. T., Mad-Bondo, D., Kongoma, J.-B., Nakib, S., Madec, Y., Ulmann, G., Neveux, N., Sansonetti, P. J., Vray, M., & Marteyn, B. (2021). Vitamin C levels in a Central-African mother–infant cohort: Does hypovitaminosis C increase the risk of enteric infections? *Maternal & Child Nutrition*, *17*(4), e13215. https://doi.org/10.1111/mcn.13215