

Full Length Research Paper

Prevalence and associated risk factors of Vitamin D deficiency in children under five years of age, at the Diamniadio Children's Hospital in Senegal

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Vitamin D deficiency (VDD) is a public health problem which affects all human beings including dark-skinned subjects. In children, it can cause disabilities associated with skeletal abnormalities such as rickets or stunted growth. VDD is also associated with a significant risk of extra-skeletal, infectious, auto-immune, neoplastic, and cardiovascular diseases. The concentration of 25 (OH) D is currently considered as the best VDD indicator. Whereas VDD has been well studied in Western countries and North America, very few studies have been conducted in sub-Saharan Africa. The aim of this study was to assess the prevalence and risk factors of VDD in children aged between 0 to 59 months. This is a cross-sectional prospective study conducted from August 5, 2019, to November 30, 2020. A total of three hundred children were included in this study, two hundred of whom were malnourished and the rest with a normal P/T ratio. The variables studied were vitamin D, serum calcium, magnesium, phosphorus and iron. Ferritin, haemoglobin, protein, albumin and prealbumin were also studied. The prevalence of VDD in the general population was 30%. No significant statistical difference in vitamin D concentration values was noticed between malnourished and nourished children with $p = 0.388$. Children over 24 months of age are 2.34 times more likely to be VDD than others. Given the prevalence of VDD in the study population, it would be necessary to integrate screening and supplementation into current medical practice.

Key words: Vitamin D deficiency, malnutrition, children under 5 years of age, risk factors.

INTRODUCTION

Vitamin D deficiency is a global public health problem affecting more than one billion children and adults

worldwide. Its prevalence varies and ranks between 30 to 60% depending on the region (Mogire et al., 2020).

Pregnant women, people of colour (Black, Hispanic and people with increased skin pigmentation), children and adults suffering from obesity or who are less exposed to the sun are particularly at risk (Holick, 2017). In children, besides rickets, vitamin D deficiency can lead to respiratory disorders and muscle weakness. In addition to the precarious nutritional status that pre-disposes children to acute respiratory infections (Diop et al., 2020), there is an inverse relationship between plasma vitamin D concentration and the risk of these infections (OMS, 2009).

Patients with severe vitamin D deficiency and hypocalcaemia develop neuromuscular sensitivity, such as numbness of the limbs and even seizures that can cause mis-diagnosis (Baudin, 2014). In addition to the classic bone manifestations, vitamin D deficiency is increasingly implicated in several other extra-skeletal conditions, including cardiovascular atheromatous diseases, cancer, dysimmune pathologies and certain neurological conditions (Jan et al., 2019).

Vitamin D deficiency is an aggravating factor in much chronic pathology (Chauveau and Aparicio, 2013). Indeed, low levels of vitamin D are associated with the susceptibility and severity of acute infections and unfavourable outcomes for some chronic infections (Jan et al. 2019). The objective of this study is to evaluate the prevalence of vitamin D deficiency and associated risk factors in children up to 59 months of age.

MATERIALS AND METHODS

Type – study framework

A prospective cross-sectional study was conducted from 5 August 2019 to 30 November 2020. Recruitment was conducted at the Diamniadio Children's Hospital (HED) and biological analyses were performed at the Department of Medical Biochemistry.

Study population

After calculating the population size, according to the formula of Lorentz, patients aged between 0 to 5 years followed as outpatients or hospitalized for acute malnutrition, as well as children received for consultation with normal nutritional status were included after parental consent. Children with chronic pathology were not included in this study.

Three hundred children aged up to 59 months were recruited. 200 patients had acute malnutrition and 100 children with normal nutritional status. The average age of the children was 16.7 ± 11.8 and 16.8 ± 12.7 months respectively, with malnourished children and controls. The sex ratio was 1.02 in malnourished children and 2.3 in nourished children. The ethics committee of Cheikh Anta Diop University approved the study: Ref CER/UCAD/AD/MSN/015/2020.

Assessment of nutritional status

Children were weighed using the "Uniscale scale", with a tare function. Height was measured using the UNICEF fleece, consisting in a lying down position for patients under two years of age and standing for patients over 2 years of age.

The nutritional status of the children was determined based on the weigh to height ratio in relation to The WHO growth standards. Normal nutritional status is defined by a weigh to height ratio between -2 and +2 z-score. Moderate acute malnutrition (MAM) is retained in front of a weigh to height ratio between -2 and -3 z-score and it is classified severe acute malnutrition (SAM) for a weigh to height ratio < -3 z-score (OMS, 2009).

Sample taking

Blood samples were collected from patients on an empty stomach with bent elbow using a dry tube, a tube with ethylene diamine tetraacetic acid (EDTA) and another tube with sodium heparinate. The blood sample on EDTA tube was used immediately to determine the complete blood count (CBC). The blood sample on dry and heparinated tubes was centrifuged at 3000 rpm for 5 min. The protein was measured immediately on a portion of the serum. The remaining quantity was kept at -20°C for the measurement of vitamin D, ferritinemia, albumin and zinc. The samples were dosed over several days per group. The other parameters are dosed on the plasma and stored at minus 20°C.

Methods of analysis

Vitamin D and ferritin were measured using the Maglumi 600 automate reference 23020018, by the immunoluminometric method (CLIA) at the Medical Biochemistry Laboratory of the Faculty of Medicine, Pharmacy and Dentistry, Cheikh Anta Diop University.

Principle test

The 25-OH Vitamin D assay is a competitive chem-iluminescence immunoassay. The 25-OH Vitamin D assay is a two-incubation chemi-luminescence immunoassay for the quantitative determination of total 25-OH vitamin D in human serum in the first incubation, the 25-OH vitamin D is dissociated from its binding protein by the displacing reagent, and binds to the 25-OH vitamin D antibody on the magnetic microbeads forming an antibody-antigen complex. Following a second incubation, the 25-OH Vitamin D labeled ABEI (N-aminobutyl-N- ethylisoluminol) are added. The rest unbound material is removed during a wash cycle. Subsequently, the Starter 1+2 are added to initiate a flash chemi-luminescent reaction. The resulting chemi-luminescent reaction is measured as relative light units (RLUs) which is inversely proportional to the concentration of 25-OH Vitamin D present in the sample (or calibrator/control, if applicable) (MAGLUMI" 25-OH Vitamin D (CLIA) reference 130211004M).

The CBC was determined using the Sysmex XS-1000i and other biochemical parameters (calcium, phosphorus, serum iron, proteinemia, albumin and prealbumin) with the A25 Biosystem® at the medical analysis laboratory of Children's Hospital in Diamniadio. Vitamin D status was defined as 25(OH)D < 30 nmol/L, 25(OH)

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D < 50 nmol/L and 25(OH) D between 50 and 75 nmol/L (20 to 30 µg/L).

The level of 25(OH) D greater than 75 nmol/L is normal (Holick et al., 2011). To perform the biological diagnosis of anaemia in children, Beutler study standard was used (Beutler and Waalen, 2006). A value of less than 60 g/L, 30 g/L and 150 g/L was used for hypo-prothrombinaemia, hypo-albuminemia and low pre-albuminemia, respectively. Hypoferritinemia and low serum iron are retained for a value of less than 30 ng/ml and 50 µg/dl. Hypophosphoremia, hypomagnesaemia and hypocalcemia were selected for values below 25, 15 and 85 mg/L, respectively. These values were adopted after considering the pediatric reference values provided by Canadian laboratories (Adeli et al., 2017).

Data collection and statistical analysis

After collecting and entering data on Excel, the statistical analyses were performed using the Jamovi software (Version 1.6.22.0). Categorical data are described by numbers and percentages, while quantitative data are presented, based on their statistical distribution, in terms of mean and standard deviation or median and interquartile interval. Normality (Gaussian distribution) was studied by the Shapiro-Wilk test. Comparisons between groups (according to malnourished and teminus) concerning the parameters of a categorical nature were made using the Chi2 test or, if applicable, the exact Fisher test. Comparisons between groups for quantitative variables were made using the T test or the Mann Withney test. Univariate and multivariate binary logistic regression is performed for the study of risk factors. A p-value greater than 5% is considered significant.

RESULTS

Sociodemographic and clinical characteristics of patients

The average z-score of weight for height ratio is 0.09 ± 0.19 Kg/cm in malnourished patients and 0.12 ± 0.22 Kg/cm in controls. Socio-demographic characteristics are shown in Table 1. Most of the children were exclusively breastfed.

73.3% lived in the suburban city. 58% of the malnourished children had an acute form of malnutrition. The average vitamin D level is 45.2 (µg/dl) and 45.1 (µg/dl) in malnourished and nourished children, respectively. As illustrated in in Table 2, a large proportion of prealbumin, iron and hemoglobin deficiency are observed regardless of the group in Table 2. On the other hand, the percentage of hypo-phosphoremia is low. Severe vitamin D deficiency is observed in malnourished people (Table 2).

No significant differences were found between concentrations of biochemical markers at the level of the two groups as evidenced in Table 3.

Factors associated with vitamin D deficiency

For malnourished, in bivariate analysis, the age of the child, severe acute malnutrition and low serum iron were

significantly associated with vitamin D deficiency (Table 4). Certainly, the probability of vitamin D deficiency in children under 12 months aged between 13 and 24 months and between 25 and 60 months is respectively 3.13, 2.38 and 3.47 times. This association was found with SAM and low iron concentration in children. For the nourished children, only a low serum iron level is associated with vitamin D deficiency. Hypocalcaemia and hypo phosphoremia are not associated with vitamin D deficiency (Table 4). In multivariate analysis, the most predictive factor for vitamin D deficiency was age, specifically between 25 to 60 months (OR=2.34; 95% CI = [1.18 to 16.0]; p=0.027) (Table 5). Age between 7 to 12 months and between 13 to 24 months was not confirmed as risk factors with p-values of 0.098 and 0.158 respectively. The same is true for low serum iron (p = 0.107).

DISCUSSION

In the study population, vitamin D deficiency is common, both in acutely malnourished children (28.3%) and in children with good nutritional status (33%). However, severe forms are found only in malnourished children (0.5%) (Table 2).

This high prevalence of vitamin D deficiency is reported in other similar studies conducted in Africa, particularly in Tanzania (Wally, 2017) with a rate of 30%. A systematic literature review conducted in Africa highlighted a prevalence of 58.54% of vitamin D insufficiency, 34.18% of vitamin D deficiency, and 17.31% of severe vitamin D deficiency (Mogire et al., 2020).

Lower prevalence of vitamin D levels below 50 nmol/L and below 30 nmol/L of 7.8 and 0.6% respectively, were found in another study conducted in Kenya, Uganda, Burkina Faso, Gambia, and South Africa (Mogire et al., 2021). In sub-Saharan Africa, although sunshine is permanent, children are not protected against vitamin D deficiency. Moreover, dark-skinned patients are also at risk of vitamin D deficiency because photosynthesis by ultraviolet rays is hindered by melanin. The role of melanin as a protective screen against the harmful effects of ultraviolet rays is not in favour with the synthesis of vitamin D (Clemens et al., 1982). Fair skinned people synthesize up to six times more vitamin D than those with dark skin. A case-control study in Nigeria found higher vitamin D levels in albino patients (95.9 (50.1 to 177) ng/ml) than in pigmented skin (78.2 (12.1 to 250) ng/ml) (Enechukwu et al., 2019). This high prevalence of vitamin D deficiency in Africa and particularly in Senegal could be explained by the lack of vitamin D supplementation in children and the consumption of unfortified or vitamin D defective food. Foods that are rich in vitamin D are fish such as salmon, horse mackerel, tuna, liver and eggs (Cediel et al, 2018).

The high prevalence of vitamin D deficiency in children

Table 1. Socio-demographic characteristics of malnourished children and controls.

Variable	Malnourished (%)	Controls (%)	Total (%)
	n=200	n=100	N=300
Sex			
Male	101 (50.5)	70 (70)	171 (57)
Female	99 (49.5)	30 (30)	129 (43)
Age (months)			
Less than 6	23 (11.5)	19 (19)	42 (23)
7-12	70 (35)	27 (27)	97 (32)
13-24	71 (35.5)	32 (32)	103 (34)
25-60	36 (18)	22 (22)	58 (19)
Breastfeeding			
Exclusive	20 (87)	17 (89.5)	37 (12.3)
Mixed	2 (8.7)	2 (10.5)	4 (1.33)
Artificial	1 (4.3)	0	1 (0.2)
Ethnic group			
Wolof	88 (44)	48(48)	136 (45.3)
Serer	26 (13)	15 (15)	41 (13.6)
Diola	9 (4.5)	7 (7)	16 (5.3)
Peulh	56 (28)	20 (20)	76 (25)
Other	21 (10.5)	10 (10)	31 (10.3)
Address			
Urban	3 (1.5)	0	3 (1)
Suburban	132 (66)	88 (88)	220 (73.3)
Rural	65 (32.5)	12 (12)	77 (25.6)
Nutritional status			
Severe acute malnutrition	116 (58)	0	116 (38)
Moderate acute malnutrition	84 (42)	0	84 (28)
Normal	0	100 (100)	100 (33)
Malnutrition			
Oedematous	8 (4)	0	8 (2.7)
No oedematous	92 (96)	0	92 (97.3)

Source: Authors

was also reported in a study conducted in China with (Zhang et al., 2020) a prevalence of 48.1% of vitamin D deficiency (< 50 nmol/L) in pre-school children (3 to 6 years), 21.2% in infants aged between 1 to 3 years of age and 17.9% in infants under 1 year of age.

In a study conducted in Bahrain (Isa et al., 2020), all children (93.4%) had low levels of vitamin D, 78.3% were deficient and 15.1% had vitamin D deficiency. A significantly higher proportion of girls were deficient in vitamin D compared to boys ($p < 0.001$). More primary school children and adolescents were deficient in vitamin D in comparison to pre-schoolers ($p < 0.001$). However,

its prevalence is much higher than the one in the control group. In our study, vitamin deficiency is mostly found in children with good nutritional status (33%) than in malnourished (28.3%). However, it is more severe in malnourished (24.5µg/L) than in children with a good nutritional status (26.3 µg/L). In a study conducted in Tanzania, children with marasmus were more at risk of vitamin D deficiency than children with kwashiorkor or marasmic kwashiorkor (Walli et al., 2017). In the Netherlands, a study of a multi-ethnic cohort of children aged under six years showed that malnourished are more at risk of vitamin D deficiency (<50 nmol/L) than well-

Table 2. Frequency of decrease in biological parents of malnourished children and controls.

Variable	Malnourished children (n/total and %)	Controls (n/total and %)	Total (n/total and %)
Normal vitamin D levels	136/190 (71.5)	65/98 (66.3)	201/288 (69.7)
Vitamin D deficiency	42 (22.1)	29 (29)	71/288 (24.6)
Moderate vitamin D deficiency	11 (5.7)	4 (4)	15/288 (5.2)
Severe vitamin D deficiency	1 (0.5)	0 (0)	1/288 (0.34)
Hypocalcaemia	54/195 (27.6)	18/80 (22.5)	72/275 (26)
Hypophosphatemia	9/189 (4.7)	2/79 (2.5)	11/268 (4.1)
Hypomagnesemia	63/190 (33)	33/80 (41.2)	96/270 (35.5)
Hypoprotidemia	79/196 (40.3)	28/84 (33.3)	107/280 (38.2)
Low prealbumin	129/192 (67)	62/81 (76.5)	191/273 (69.9)
Hypoalbuminemia	45/193 (23)	16/81 (19.7)	61/274 (22.2)
Anemia	174/200 (87)	84/100 (84)	258/300 (86)
Low serum iron	132/188 (70.2)	58/79 (73.4)	190/267 (71)
Low ferritinemia	71/177 (41)	27/93 (29)	98/270 (36.3)

Source: Authors

Table 3. Variation in biological parameters by nutritional status.

Variable	Malnourished		Controls		p-value
	N (%)	Median (QT)	N (%)	Median (QT)	
Protein (g/L)	196 (98%)	62.6 (54-70)	84 (84%)	63 (58-68)	0.668
Albumin (g/L)	193 (96.5%)	40 (35-46)	81(81%)	39 (36-42)	0.314
Prealbumin (mg/L)	192 (96%)	200 (140- 275)	81(81%)	202 (164-243)	0.083
Vitamin D (ng/ml)	190 (95%)	38.6 (28.4-55.3)	98 (98%)	34.3 (17.8-50.5)	0.388
Calcium (mg/L)	195 (97.5%)	94.1 (84-103)	80 (80%)	91.0 (85-97)	0.460
Phosphorus (mg/L)	189 (94.5%)	54 (43-61.8)	79 (79%)	51 (41.5-58.9)	0.495
Hb (g/dl)	198 (99%)	10.1(9.10-11.1)	97 (97%)	10.5 (9.50-11.3)	0.119
Serum iron (µg/dl)	188 (94%)	47.9 (20.2-60.4)	79 (79%)	43.3 (18.8-51.7)	0.550
Ferritin (ng/ml)	177 (88.5%)	42.8 (12.6-103)	93 (93%)	53.2 (23-130)	0.073

Source: Authors

nourished children (Pham et al., 2019). In Ecuador, the average vitamin D level was about the same in malnourished as in nourished children. However, vitamin D deficiency was more common in malnourished than in those with good nutritional status (22.0 vs. 12.3%).

Infants aged 6 to 12 months had higher average rates than older infants (>12 months) and malnourished were twice as likely to have vitamin D deficiency as normal children (unadjusted OR = 2.0; 95% CI 1.2 to 3.4) (Mokhtar et al., 2018).

To identify factors associated with vitamin D deficiency, sociodemographic, biological, and clinical parameters were studied (Table 4 and 5).

Thus, univariate binary logistic regression analysis showed a significant association for age groups greater than six months, acute malnutrition, and low serum iron levels. On the other hand, in multivariate binary analysis, only the age group greater than 24 months is a factor

significantly associated with the occurrence of vitamin D deficiency (Table 4).

The probability of vitamin D deficiency in children over 24 months of age is 3.47 times (95% CI: 1.45 to 8.30) (Table 4).

Therefore, age above 24 months is considered as a risk factor associated with vitamin D deficiency. This result highlights the importance of food intake, because beyond this age, children are no longer breastfed as they start dietary diversification. Breastfeeding could be a protective factor knowing that before the age of six months, most children are on exclusive breastfeeding.

The results of a study conducted in Turkey (Cihan and Korğalı, 2018) showed the association of vitamin D deficiency with the decrease in serum iron. Indeed, in vitro, there is a bi-directional relationship between the metabolism of vitamin D and that of iron. 25(OH)₂ D can influence the level of iron by reducing the level of

Table 4. Prediction of vitamin D deficiency by univariate analysis in malnourished and controls.

Variable	Univariate analysis (Malnourished/controls)		
	OR	CI95%	p-value
Gender (female)			
Male	1.38 / 0.6	8.26 - 2.32 / 0.25 - 1.74	0.219 / 0.410
Female	Reference	-	-
Age (month) (Reference Less than 6)			
7-12	3.13 / 1.70	1.47 - 6.92 / 0.50 - 5.79	0.003 / 0.389
13-24	2.38 / 2.22	1.12 - 5.03 / 0.7 - 7.06	0.023 / 0.176
25-60	3.47 / 2.58	1.45 - 8.30 / 0.72 - 9.12	0.005 / 0.143
Breastfeeding (Reference exclusive)			
Mixed	6.74e-8 / 6.08e ⁺⁷	0.000- inf / 0.000 - inf	0.995 / 0.995
Artificial	2.11 / -	0.17 - 25.35 / -	0.556 / -
Ethnicity (Reference Wolof)			
Serer	0.93 / 2.62	0.42 - 2.08 / 0.65 - 10.5	0.875 / 0.175
Diola	0.47 / 0.86	0.16 - 1.37 / 0.17 - 4.35	0.168 / 0.809
Peulh	0.93 / 1.70	0.37 - 1.29 / 0.52 - 4.56	0.246 / 0.337
Other	0.90 / 1.52	0.37 - 2.14 / 0.35 - 6.66	0.813 / 0.572
Address (Reference urban)			
Suburban	1.04 / 1.36	0.092 - 11.6 / 0.35 - 5.18	0.977 / 0.656
Rural	1.65 / -	0.14 - 19.03 / -	0.691 / -
Nutritional status (Reference undernutrition)			
SAM	3.36 / -	1.28 - 8.80 / -	0.013 / -
MAM	2.4 / -	0.91 - 6.46 / -	0.075 / -
Normal	1.97 / -	0.77 - 5.02 / -	0.155 / -
Malnutrition			
Oedematous	0.83 / -	0.16 - 4.26 / -	0.826 / -
Not oedematous	Ref	-	-
Biology (Reference normal)			
Hypocalcemia	1.20 / 0.42	0.65 - 2.20 / 0.14 - 1.24	0.553 / 0.116
Hypophosphatemia	2.49 / 7.37e ⁺⁶	0.60 - 10.24 / 0 - inf	0.205 / 0.993
Hypomagnesemia	1.33 / 0.96	0.62 - 2.82 / 0.36 - 2.56	0.466 / 0.939
Hypoprotidemia	1.20 / 0.9	0.70 - 2.05 / 0.345 - 2.35	0.497 / 0.829
Low prealbumin	0.75 / 2.25	0.42 - 1.35 / 0.75 - 6.70	0.341 / 0.145
Hypoalbuminemia	1.08 / 0.95	0.56 - 2.05 / 0.29 - 3.11	0.821 / 0.932
Anemia	0.60 / 1.10	0.23 - 1.57 / 0.45 - 2.66	0.299 / 0.834
Low serum iron	0.54 / 3.07	0.30 - 0.96 / 1.06 - 8.90	0.039 / 0.02
Low ferritinemia	0.78 / 0.739	0.45 - 1.37 / 0.288 - 1.89	0.40 / 0.52

Source: Authors

hepcidin, while low iron levels can indirectly influence vitamin D status by decreasing its activation enzymes (Mogire et al., 2021).

In malnourished, the acute form is considered a risk

factor associated with vitamin deficiency with OR = 3.36, 95% CI (1.28 to 8.80). However, further studies are needed for confirmation. The decrease in other biochemical parameters is not associated with vitamin D

Table 5. Prediction of the occurrence of vitamin D deficiency by multivariate analysis in malnourished.

Variable	Multivariate analysis			
	N (%)	OR	CI95%	p-value
Age in months (Reference less than 6)				
7 -12	70 (35)	2.88	0.82 - 10.1	0.098
13 - 24	71(35.5)	2.43	0.70 - 8.36	0.158
25 - 60	36 (18)	2.34	1.18 - 16.0	0.027
Malnutrition (Reference undernutrition)				
SAM	116 (58)	1.06	0.22 - 5.10	0.933
MAM	84 (42)	0.88	0.18 - 4.32	0.882
Normal	0	0.88	0.22 - 3.5	0.864
Seric Iron (Reference normal)				
Low serum iron	132 (70.2)	1.653	0.89 - 3.05	0.107

OR= Odd ratio, CI= Confidence interval.
Source: Authors

deficiency (Table 4), especially since no significant difference is noted in concentration between the groups (Table 3). There is no great difference between the percentages of people with a decrease in the parameters studied in the two groups. For the rest of the biological markers studied, there is no association with vitamin D deficiency. Similarly, criteria such as ethnicity, the origin of children in urban, sub-urban or rural areas and the presence of oedema in malnourished people are not associated with vitamin D deficiency.

Normal concentrations of protein, albuminemia, prealbumin, calcium, and phosphorus were found in the groups by nutritional status and whether vitamin D deficiency was present (Table 3). In malnourished, their median values are 62.6 (54 to 70) g/L for proteins, 40 (35 to 46) g/L for albumin, 200 (140 to 275) mg/L for prealbumin, 94.1 (84 to 103) mg/L for calcium and 40 (43 to 61.8) mg/L for phosphorus.

In Nebata's study 52.1% of malnourished children had normal calcium levels compared to 31.7% of well-nourished children. 2.4% of these children had normal phosphorus levels compared to 43.6% of malnourished (Nabeta et al., 2015).

These results are also found in adults, except for calcium, albumin and phosphorus showed no significant difference between vitamin D deficient and non-vitamin D deficient (Merker et al., 2019). Our results demonstrate that the prevalence of vitamin D deficiency in children increases with age, which is in line with the data in the literature (Ahmed et al., 2017; Andiran et al, 2012).

Conclusion

Vitamin D deficiency is common in both malnourished and well-nourished children but is more severe in

malnourished infants. The prevalence of deficiency in children aged between 0 to 59 month's increases with age, justifying the need for vitamin D supplementation but also the fortification of food.

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CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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