##### Transcription factor 7-like 2 (TCF7L2) rs12255372 Gene Polymorphism in non-diabetic hypertensive patients in Abidjan, Côte d’Ivoire

##### Abstract

**Background**: The association of the *Transcription Factor 7-Like 2* (*TCF7L2*) gene with type 2 diabetes mellitus (T2DM) has been demonstrated in several populations of diverse genetic origins. Studies have also shown that 13% of non-diabetic hypertensives develop diabetes.

**Objective**: The aim of this study was to identify the TCF7L2 gene polymorphism (rs12255372 G > T) in non-diabetic hypertensive patients in order to contribute to better management of their disease.

**Methodology**: One hundred and sixty (160) non-diabetic patients, 100 of whom suffered from arterial hypertension, were recruited from the Abidjan civil servants' medical service. Blood samples were taken to isolate genomic DNA from the patients, and the *TCF7L2* gene involved in predisposition to diabetes was then tested by PCR.

**Results**: The results of this study concluded that the polymorphism of the rs12255372 allele of the *TCF7L2* gene associated with predisposition to type 2 diabete was not detected in non-diabetic hypertensive patients in Abidjan, Côte d’Ivoire.

**Key words**: polymorphism, rs12255372 allele, *TCF7L2* gene, hypertension, diabete, Côte d’Ivoire.

#### INTRODUCTION

Arterial hypertension (ATH) is now considered to be a major worldwide concern in

because of its prevalence and the increased risks of cardiovascular and renal diseases associated with it.

According to the World Health Organization (WHO), hypertension affects a third of adults worldwide (**WHO, 2023**).

Defined as a blood pressure (BP) equal to or greater than 140/90 mm Hg, hypertension currently affects around 27-28% of adults in sub-Saharan Africa **(Kearney *et al*., 2005)**. In Côte d'Ivoire, the World Health Organization estimated the overall prevalence of hypertension at 21,7% in 2005 **(Sackou et *al.,* 2019)**, and according to health authorities, the prevalence of hypertension estimated by the national program for the prevention of non-communicable diseases in 2024 was 39.92% **(MSHPCMU, 2024)**. Moreover, in a prospective study of 2588 hypertensive patients without diabetes, **Boned et *al.* (2016)** showed that 13% developed new-onset diabetes. The association of the *Transcription Factor 7-Like 2* (*TCF7L2*) gene with type 2 diabete mellitus (T2DM) has been consistently demonstrated in several populations of diverse genetic origins, representing one of the most powerful genetic associations discovered in studies of complex diseases **(Tong *et al.,* 2009)**. Polymorphisms in the *TCF7L2* gene, in particular *rs7903146* and *rs12255372*, are among the most important genetic factors associated with T2DM **(Grant *et al.,* 2006).**

The *TCF7L2* gene polymorphism predisposing to diabete in non-diabetic hypertensive subjects has not been documented in Côte d'Ivoire; we therefore felt it necessary to conduct a study to investigate the existence of a *TCF7L2* gene polymorphism in order to contribute to better management of hypertensive patients.

#### MATERIALS AND METHODS

##### Site and type of study

This was a prospective cross-sectional study which took place from 16 April to 16 July 2024 (three months) at the Government Employees' Medical Service (GEMS) in Abidjan, Côte d’Ivoire for patient recruitment and sampling. The biological analyses were subsequently carried out at the Pasteur Institute of Côte d'Ivoire (IPCI).

##### Study population

The study population consisted of subjects followed at the GEMS whose bioclinical status (blood pressure and glycaemia) was known. The study involved a target population of one hundred and sixty (160) participants, including one hundred (100) non-diabetic and hypertensive patients and sixty (60) non-diabetic and non- hypertensive patients. Blood pressure was monitored using an electronic blood pressure monitor (Omron M2 HEM-7121-E) by a certified nurse.

##### Ethical considerations

The study was approved by the National Ethics Committee for Life Sciences and Health. Indeed, after being informed of the study, each participant was asked for verbal and written consent prior to any sampling procedure.

##### Blood sampling and confetti preparation

###### Blood sampling

After obtaining their consent to take part in the study, approximately 5 ml of blood was taken from each participant in three tubes: Blood samples were taken by venipuncture from the elbow of subjects who had been fasting for at least 12 hours. Blood was collected in three different tubes, one containing the anticoagulant EDTA (Ethylene diamine tetra-acetic acid), one containing sodium fluoride and calcium oxalate and the last tube without anticoagulant (dry tube). Whole blood collected in tubes containing EDTA was used to measure glycated haemoglobin and make confetti for molecular biology. The serum obtained after centrifugation of the blood contained in the dry tube were used to measure blood lipids. Glycemia was measured with blood plasma obtained after centrifugation of the tube containing sodium fluoride and calcium oxalate as anticoagulant.

###### Preparation of confetti

Blood collected in tubes containing EDTA was used to make confetti. Approximately 50 μL of whole blood was deposited on Whatman 3 MM filter paper (chromatography Paper cat N°3030-861 grade 3MM 20x20 100 Sheets) using a micropipette with filter cones. The paper containing the blood spots was dried for approximately 60 to 120 minutes at room temperature in a dust-free environment. Unused blood from the EDTA tube was stored in cryotubes at -20°C for possible future use.

* 1. **Measuremen of biochemical parameters**

Glycaemia and lipids were measured on Erba Mannheim XL-600 automated analyzer using respectively blood plasma (obtained after centrifugation of the tube containing sodium fluoride and calcium oxalate as anticoagulant) and serum (obtained from dry tubes) obtained after centrifugation for 10 minutes at 4000 rpm.

Glycated haemoglobin was determined with whole blood of tubes containing EDTA anticoagulant using the HLC-723GX automated HbA1c analyzer.

* 1. **DNA extraction and PCR**

Genomic DNA was extracted using the resin column extraction method using a commercial kit: Spin-x viral DNA/RNA extraction kit (SD Biosensor) in accordance with the manufacturer's protocol. Briefly, this method uses silica membrane technology (Spin column) for the isolation and purification of genomic DNA. Blood cells (red blood cells) were lysed by adding 400 μl of lysis buffer (AVL) to 20 μl of proteinase K (Protease K) followed by incubation at 70°C for 10 minutes. The genomic DNA was then purified in a column by adding 500 μl of absolute ethanol to the lysate, which was briefly vortexed before centrifuging the tubes briefly (one minute) at 10,000 rpm. This operation was repeated in order to recover all the solution in a new collection tube. After washing the membrane (with buffers AW1 and AW2), the genomic DNA was eluted using AVE buffer (60μl added). The eluate (constituting the DNA extract) was collected in the Eppendorf tube.

##### II.7. Genotyping of the TCF7L2 gene

The rs12255372 (G/T) polymorphism of the *TCF7L2* gene was genotyped by allele-specific PCR **(Moran et *al.*, 2015)**. Indeed, two PCRs were performed for each sample using one common sense primer (CFW) and one of two antisense primers (Rev G or Rev T) specific to the Poly T and Poly G alleles of the rs12255372 polymorphism **(Table I)**.

**Table I**: Primers used for gene amplification

|  |  |
| --- | --- |
| Polymorphism | primers Nucleotide sequences |
|  | CFw:  5’CTGGAAACTAAGGCGTGAGGGA 3’ |
| rs12255372 G/T | Rev\_G:  5’CAGAGGCCTGAGTAATTATCAGAATATGATC 3’ |
|  | Rev\_T: 5’CAGAGGCCTGAGTAATTATCAGAATATGCTA 3’ |

The reaction mixes and programming for amplification were carried out according to the procedure

for the commercial Firepol Master Mix kit from Solis Biodyne Master Mix kit from Solis Biodyne.

To detect the T (Poly T) and G (poly G) polymorphisms we prepared reaction mixes containing the

primer pairs CFW and Rev T and CFW and Rev G as shown in Table II **(Table II)**. The same

amplification program was used to perform the amplifications using an applied biosystems thermal

cycler **(Table III).**

## Table II: Preparation of reaction mixtures.

|  |  |  |  |
| --- | --- | --- | --- |
| **Mix for T polymorphism detection** | | **Mix for G polymorphism detection** | |
| Reagents | Volume (µL) | Reagents | Volume (µL) |
| H2O Bio- mol | 15 | H2O Bio- mol | 15 |
| 5X Firepol Master Mix | 4 | 5X Firepol Master Mix | 4 |
| CFW | 0,5 | CFW | 0,5 |
| Rev T | 0,5 | Rev G | 0,5 |
| Volume Mix (µL) | 20 | Volume Mix (µL) | 20 |
| DNA | 5 | DNA | 5 |
| Reaction volume (µL) | 25 | Reaction volume (µL) | 25 |

**Table III: Amplification programming for the detection of T and G polymorphisms.**

|  |  |  |  |
| --- | --- | --- | --- |
| Steps | Temperatures (°C) | Time | Cycles |
| Initial denaturation | 95 | 3 min | 1X |
| Final denaturation | 95 | 20 sec | 40X |
| Hybridization | 60 | 30 Sec |
| Elongation | 72 | 30 Sec |
| Final elongation | 72 | 5 min | 1X |

Amplifications were carried out in an Eppendorf vapo protect thermal cycler using the following program: initial denaturation at 95°C for 3min followed by 40 cycles comprising denaturation at 95°C for 20 sec, primer hybridization for 30 sec at 60°C, elongation at 72°C for 30 sec and final extension at 72°C for 5min.

##### 2.8. Detection and analysis of PCR products

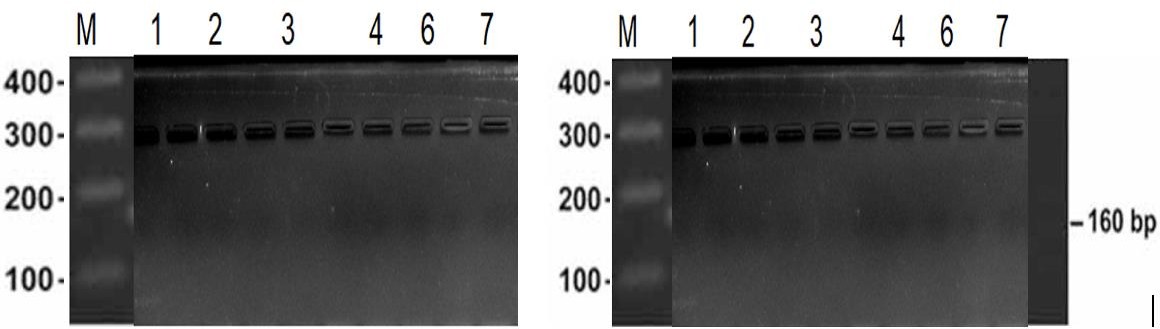
PCR products were separated by electrophoresis on a 2% (W/V) agarose gel to detect specific alleles. After migration, the gel was recovered and observed under a UV lamp using

the UV transluminator (Gel DocTM EZ Imager) to assess the presence or absence of bands

The bands obtained were compared with those of the molecular weight marker to estimate the

Size of the DNA bands on the electrophoregram. The size of the gene (Poly T, Poly G) of

interest in the amplicon is 160 bp (Figure 1).



T reaction product G reaction product

##### Figure 1: Genotyping of the TCF7L2 rs12255372 polymorphism (G/T) using a PCR test allele-specific

*For each sample, two PCR reactions were performed, each comprising a common forward primer and a reverse primer rs12255372 G (G reaction) or rs12255372 T (T reaction), depending on the allele to be amplified. A DNA fragment of 160 bp indicated the presence of the allele, while amplification failure indicated the absence of the allele in the sample. In a 3% w/v agarose gel, M indicates the molecular size marker, G and T indicate the product of the G reaction and the T reaction respectively, amplified from a selected DNA sample of each possible genotype (GG, GT and TT).*

##### II.8. Data analysis

RStudio software version 4.1.3 **(R Core Team, 2020)** was used to analyze the biological characteristics of hypertensive and non-hypertensive patients. Analyses were conducted using appropriate statistical parameters according to the nature of the data.

For comparisons of blood glucose and glycated haemoglobin, a proportion test (prop. test) was applied.

For continuous variables, such as total cholesterol, HDL cholesterol and triglycerides, a normality test (shapiro. test) was performed.

A difference was considered statistically significant when the p-value was below the threshold α = 0,05.

#### RESULTS

##### Gender distribution of participants

The study enrolled 160 participants, including 98 (61,25%) females and 62 (38,75%) males. The sex ratio was 0.63. Statistical analysis revealed a significant difference between the proportions of male and female participants (p=0.0044). Among the hypertensive patients, 66 (66%) were female and 34 (34%) were male **(Figure 2).**

**80**

**60**

**Percentage (%)**

**40**

**20**

**0**

**Men Women**

# Sex

##### Figure 2: Gender distribution of participants

* 1. **Participants profile according to age**

The analyses revealed that the average age of the hypertensive group was 60,16 ± 9,39 years and that of the non-hypertensive group 49,10 ± 14,11 years, with a statistically significant difference between the average ages of the two groups (p = 0,006**) (figure 3).**

**100**

p = 0,006

**80**

**Pourcentage (%)**

**60**

**40**

**20**

**0**

**Hypertensive**

**Non-hypertensive**

##### Figure 3: Age distribution of participants

**III.3. Glycaemic parameters**

The mean blood glucose level in participants was 0,97 g/L. The lowest blood glucose level recorded was 0,61 g/L, while the highest was 1,29 g/L. The mean blood glucose level for hypertensive patients was 1,01 ± 0,14 g/L, while that for non-hypertensive patients was 0,89 ±

0,15 g/L, with a statistically significant difference (p = 0,0011**) (Figure 4).**

Assessment of blood glucose levels revealed that 10% of non-hypertensive participants had hypoglycaemia (blood glucose < 0,70 g/L), while no cases were detected in hypertensive participants. This difference was statistically significant (p = 0,023). With regard to blood glucose levels in the normal range (0,70 to 1,26 g/L), the majority of hypertensive patients (98%) and non-hypertensive patients (86,67%) were in this zone, although there was a significant difference between the two groups (p = 0,043). With regard to hyperglycaemia (blood glucose > 1,26 g/L), the proportions were comparable between hypertensives (2%) and non-hypertensives (3,33%), with no statistically significant difference (p = 0,712) (**Table IV**). With regard to haemoglobin, the average glycated haemoglobin (HbA1c) in the participants was 5,57%. The lowest value recorded was 3,10%. In people with hypertension, the average

HbA1c was 5,56± 0,53%, while in those without hypertension it was 5,59± 0,70%. There was no statistically significant difference between the two groups (p = 0.5400) **(Table IV).**

None of the hypertensive participants had a glycated haemoglobin level of less than 4%, while 3,33% of the non-hypertensive participants had a glycated haemoglobin level of less than 4%, although this difference was not statistically significant (p = 0,193). The majority of hypertensives (84%) and non-hypertensives (73,33%) had glycated haemoglobin levels between 4% and 6%, with no significant difference between the two groups (p = 0,248). In addition, 16% of hypertensive patients and 23,33% of non-hypertensive patients had levels above 6%, although this difference was also not statistically significant (p = 0,416) **(Table IV) (Figure 4)**.

**8**

**6**

**Mean values**

**4**

**2**

**0**

**Glycemia Glycated hemoglobin**

## Glycemic parameters

##### Figure 4: Blood glucose levels and HbA1C in participants

**III.4. Lipid parameters measurement**

The lipid profile of the participants revealed the following results **(Figure 5).** The mean concentration of total cholesterol of participants was 2,10 g/L (SD = 0,52 g/L) and the minimum observed was 1,23 g/L, while the maximum concentration reached 3,40 g/L.

Total cholesterol levels were similar between hypertensives (2,12 ± 0,56 g/L) and non- hypertensives (2,07 ± 0,45 g/L), with a range of 1,28 to 3,40 g/L for hypertensives and 1,23 to

3,09 g/L for non-hypertensives. The difference between the two groups was not statistically significant (p = 0,804**) (Table IV).**

HDL cholesterol had a mean concentration of 0,65 g/L (SD = 0,11 g/L) with a minimum and maximum concentration of 0,36 g/L and 0,80 g/L respectively.

HDL cholesterol was also similar between hypertensives (0,65 ± 0,11 g/L) and non- hypertensives (0,64 ± 0,12 g/L), with close ranges of values (0,36 – 0,80 g/L for hypertensives and 0,37 – 0,80 g/L for non-hypertensives). No statistically significant differences were observed (p = 0,537**) (Table IV).** The mean concentration of triglycerides was 1,04 g/L (SD = 0,37 g/L) with a minimum concentration observed of 0,35 g/L, and a maximum concentration reaching 2,16 g/L.

Triglyceride concentrations were similar in hypertensives (1,05± 0,35 g/L) and non- hypertensives (1,02± 0,40 g/L). The observed values ranged from 0,35 to 2,16 g/L in hypertensive patients, and from 0,40 to 2,03 g/L in non-hypertensive patients. There was no statistically significant difference between the two groups (p = 0,720) **(Table IV).**

For continuous variables, such as total cholesterol, HDL cholesterol and triglycerides, a normality test (shapiro. test) was performed and the results showed that the data did not follow a normal distribution, which led to the use of the non-parametric Wilcoxon test; which is the alternative test to the t-student test (parametric test).

**4**

**3**

**Average level**

**2**

**1**

**0**

**cholesterol HDL Cholesterol Triglycerides**

### Lipids

##### Figure 5: Levels of lipid parameters in participants

**Table IV:** Biological characteristics and statistical comparison between hypertensive and non- hypertensive patients

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Caracteristics** | | **Hypertensive patients**  **N=100** | **Non-hypertensive patients**  **N=60** | **p-value** |
| n (%) | n (%) |
| Blood glucose (g/L) |  |  |  |  |
|  | Hypoglycaemia ( 70) | 0 (0) | 3 (10) | 0,023 |
|  | Normal (0,70 – 1,26) | 98 (98) | 52 (86,67) | 0,043 |
|  | Hyperglycaemia ( 1,26) | 2 (2,0) | 6 (3,33) | 0,712 |
|  | Mean ( ET) | 1,01 0,14 | 0,89 0,15 |  |
|  | Min-Max | 0,73 - 1,27 | 0,61 - 1,29 | 0,0011 |
| Glycated haemoglobin (%) |  |  |  |  |
|  | 4% | 0 (0%) | 2 (3,33) | 0,193 |
|  | 4-6% | 84 (84) | 44 (73,33) | 0,2482 |
|  | * 6% | 16 (16) | 14 (23,33) | 0,416 |
|  | Average ( ET) | 5,56 0,53 | 5,59 0,70 |  |
|  | Min-Max | 4,40 - 6,4 | 3,1 - 6,4 | 0,54 |
| Total cholesterol (g/L) |  |  |  |  |
|  | Mean ( SD) | 2,12 0,56 | 2,07 0,45 | 0,804 |
|  | Min-Max | 1,28 - 3,40 | 1,23 - 1,09 |  |
| HDL cholesterol (g/L) |  |  |  |  |
|  | Mean ( SD) | 0,65 0,11 | 0,64 0,12 | 0,537 |
|  | Min-Max | 0,36 - 0,80 | 0,37 - 0,8 |  |
| LDL cholesterol (gLl) |  |  |  |  |
|  | Mean ( SD) | 1,05 0,35 | 1,02 0,40 | 0,720 |
|  | Min-Max | 0,35 - 2,16 | 0,40 - 2,03 |  |

**III.5. Detection of the** TCF7L2 **gene** by PCR

After PCR, no DNA fragment of 160 bp was revealed by electrophoresis: the polymorphism of the rs12255372 allele of the *TCF7L2* gene associated with predisposition to type 2 diabete was not detected.

#### DISCUSSION

Several studies have demonstrated the involvement of the *TCF7L2* gene in the predisposition to type 2 diabete throughout the world **(Grant *et al.,* 2006**; **Alami *et al.,* 2012)**. Indeed, **Tong et *al* (2009)** have shown that the rs7903146 and rs12255372 polymorphisms of the *TCF7L2* gene are references for exploring the susceptibility of type 2 diabete **(Tong et *al..*, 2009).**

As arterial hypertension (AH) and diabete frequently coexist in the general population **(Krzesinski and Weekers, 2005**), we felt it necessary to conduct this study to look for a polymorphism (rs12255372) in the *TCF7L2* gene predisposing to diabete in a population of hypertensive patients in the Government Employees' Medical Service (GEMS) in Abidjan, Côte d’Ivoire. The results indicate that the majority of participants were female (61,25%). This result is similar to those of **Merle *et al* (2009)** who found in a study conducted in Martinique that 59% of participants were female. In addition, 66% of hypertensive participants were female, which is consistent with the results of **Tougouma et *al.* (2018)** in Bobo Dioulasso (Burkina Fasso) where 62,50% of participants with hypertension were female.

The predominance of female participants could be explained by the menopause, which is a risk factor for hypertension in women. Indeed, at the menopause, the disappearance of the protective effect of oestrogen, which causes vasodilatation and slows the proliferation of vascular cells, as well as the appearance of relative hyperandrogenism, contribute to an increase in hypertension **(Blacher et *al.*, 2019)** ).

With regard to the age range of the participants, the study results show that the average age of the participants was 56,01 ± 12,52 years and that of the hypertensives was 60,16 ± 9,39 years. Our results are similar to those of **Ekou et *al* (2022)**. In fact, in a study conducted in Abidjan, these authors found a mean age of 59.2 ± 12 years in a population of hypertensive patients **(Ekou et *al.,* 2022)**. This result could be explained by the fact that the prevalence of hypertension increases with age **(Blacher et *al.*, 2019)**).

With regard to the biological assessment, our results on the glycaemic profile indicate that the mean glycaemia of hypertensive participants was 1,01 ± 0,14 g/L and that of non-hypertensive participants was 0,89 ± 0,15 g/L. Our results are consistent with those of **Eak, (2016)**, in a study conducted in Algeria. Similarly, glycated haemoglobin, which averaged 5,56 ± 0,53% in hypertensive patients and 5,59 ± 0,70% in non-hypertensive patients, corroborates those of **Eak, (2016)** in Algeria. The normal glycaemic profile is explained by the choice of non-diabetic participants. The abnormal blood glucose levels observed in the participants could be either transient blood glucose levels (hyperglycaemia or hypoglycaemia) linked to activity or diet on the day before sampling, or as yet undiagnosed type 2 diabete.

With regard to the lipid profile, the results indicate that the difference in the means of the parameters was not statistically significant (p > 0,05) between the two groups. Our results contrast with those of **Youmbissi et *al* (2001)**. Indeed, these researchers found in a study conducted in Yaoundé (Cameroon) that the mean values of the lipid parameters studied were significantly higher in non-diabetic hypertensive individuals than in the control group (non- hypertensive and non-diabetic individuals) **(Youmbissi et *al*., 2001)**. This result could be explained by the fact that the participants were under treatment and properly monitored by a specialist.

As regards the molecular aspects of our work, we looked for the rs12255372 polymorphism which, along with the rs7903146 polymorphism, showed the most significant association in the Grant et al. (2016) study **(Grant et *al.*, 2006)**. The study results indicate that the TCF7L2 gene polymorphism (rs12255372) was not found in our study population. These results do not corroborate those of **Alami et *al*. (2012)**. In fact, in a study conducted in Iran, these authors found in their non-diabetic control population (hypertensive or not) 30,2% T allele and 69% G allele of the rs12255372 polymorphism **(Alami et *al.,* 2012)**. Our results are also different from those of the study carried out by **Somia et *al.* (2022**) who found 77,7% G allele and 28,3% T allele of the rs12255372 polymorphism in a non-diabetic population (hypertensive or not) during a study carried out in Egypt **(Somia et *al.*, 2022)**.

The absence of G and T polymorphisms in our study population could be explained by the fact that the frequency of rs12255372 (G/T) and rs7903146 (C/T) polymorphisms in the *TCF7L2* gene differ according to ethnic origin, due to the combined influence of environmental and genetic factors **(Pourahmadi et *al.*, 2015)**.

In carrying out this study, It would be interesting to consider a subsequent study that could be carried out over a long period, including the other Single Nucleotide Polymorphisms (SNP) of the *TCF7L2* gene that predispose to type 2 diabete and especially with hypertensive diabetic participants.

#### CONCLUSION

The aim of this study was to search for the rs12255372 polymorphism of the *TCF7L2* gene predisposing to diabete in non-diabetic hypertensive patients. Our study involved 80 participants and showed that the glycaemic profile was normal. In terms of lipid profile, the study results show that there was no statistically significant difference between the hypertensive and non-hypertensive groups. The results also showed that the rs12255372 polymorphism was not observed. We recommend that further studies be carried out to investigate the four over polymorphisms during a long period in other regions of the country in the same types of population.

#### ETHICAL CONSIDERATIONS

The study was conducted in accordance with the Declaration of Helsinki and approval was received from the National Ethics and Research Committee (CNER) of the Ministry of Health, Public Hygiene and Universal Health Coverage of Côte d'Ivoire. After appropriate information and explanations, the adult participants, parents or legal guardians of all children wishing to participate in the study gave their written consent prior to sampling.

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