

Prevalence and Sensitization and Intestinal Parasitic Infestation of Vernal Keratoconjunctivitis in School Children of Kinshasa

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Abstract

Background: There is no study that estimates the prevalence of vernal keratoconjunctivitis and the association between vernal keratoconjunctivitis and intestinal parasitic infestation in our setting. Purpose: This study aimed to estimate the vernal keratoconjunctivitis prevalence, describe the profile of sensitization and determine the association between vernal keratoconjunctivitis disease and intestinal parasitic infestation in school children of Kinshasa during the scholar year from 2022 to 2023. Methods: An observational, crosssectional study was performed from September 2022 to June 2023. The children with vernal keratoconjunctivitis were recruited by using the four-stage probability sampling technique. Children attending in the school children of Kinshasa with vernal keratoconjunctivitis were enrolled in the classroom and underwent a clinical examination and skin prick test for 11 allergens and stool examination direct with microscope in the Laboratory. Data were entered in Microsoft Sheets using SPSS version 20.0. The Chi-square test was used to compare the sex, age groups, home environment (grow trees and/or flowers around the yard), dampness in the house, keeping pets (cat and/or dog), number of people per household, number of people sharing a bedroom and intestinal parasitic infestation. The significant level was set to a value of p < 0.05. Results: A total of 28,800 students from four-stage probabilist sampling technique in school of Kinshasa were included, and 2100 students had symptoms according to the vernal keratoconjunctivitis-related symptom questionnaire. Children with vernal keratoconjunctivitis were enrolled and the mean age \pm standard was 7.2 \pm 3.7 years, with a prevalence of 7.2% and gender was three boys for one girl. All vernal keratoconjunctivitis children

recruited in urban and rural part had 33.1% positive skin prick test (SPT) and 67.9% showed polysensitization. Children an urban part was more sensitized than rural respectively with *Dermatophagoides pteronyssinus* 28.1% vs 28.9%, p = 0.00001, *Blomia tropicalis*. 15.9% vs 14.9%, p = 0.00001 and cockroach 12% vs 13%, p = 0.00001 in both parts. Vernal keratoconjunctivitis children in rural part were more affected to the intestinal parasite than urban with *Ascaris lumbricoides* 14% vs 18.3%, p = 0.0006, followed by *Ancylostoma duodenale* 9.5% vs 12.5%, p = 0.003, Anguillule 7.9% vs 10.1%, p = 0.001, Oxyure 5.7% vs 8.2%, p = 0.0001 and *Trichuris trichiura* 2.6% vs 3.3%, p = 0.0009. **Conclusion**: This study outlines that the prevalence of vernal keratoconjunctivitis in school children had a positive skin prick test to at least one allergen, in particular for *Dermatophagoides pteronyssinus, Blomia tropicalis* and cockroach. The most common intestinal parasitic infestation was *Ascaris lumbricoides*, *Ancylostoma duodenale*, Anguillule and *Trichuris trichiura*.

Keywords

Prevalence, Sensitization, Intestinal Parasitic Infestation, School Children, Kinshasa

1. Introduction

The World Health Organization (WHO) considered allergic disease as the 4th disease in the world after cancer, cardiovascular pathologies and Acquis Immunodeficiency Disease Syndrome. The WHO estimates that by 2050, half of the world's population will be allergic [1].

Allergic disorders are increasing and are well-documented in industrialized countries.

Red eyes accounted for 15% of ophthalmological consultations and allergic conjunctivitis was the most diagnosis, with 35% in Eastern Europe and the Middle East [2].

Rising frequency of allergic diseases has been reported in many African countries [3].

Vernal keratoconjunctivitis is classified as the tarsal or limbic forms and the mixed form.

The tarsal form is more common in temperate countries while the limbic form is more common in Africa [4] [5].

The life quality of vernal keratoconjunctivitis children is affected because of negative repercussions, including absenteeism, school failure, poor learning and high cost of treatment [6].

In the year 2008, the vernal keratoconjunctivitis prevalence in Western Europe varies between 0.02% and 2.7% depending on the country [7] [8]. The prevalence of vernal keratoconjunctivitis in schoolchildren in North Africa ranges

from 3.3% to 5.8% [9] [10].

Several studies, in West Africa, reported that the vernal keratoconjunctivitis frequency varies from 0.5% to 21.4% while in East Africa, the prevalence of vernal keratoconjunctivitis in schools is 4% in Rwanda [11] [12] [13].

In Central Africa, vernal keratoconjunctivitis frequency was reported respectively in Cameroon at 23.7%, Congo Brazzaville at 30.3% and in the Democratic Republic of Congo with a frequency varies from 21% to 32.9% [14] [15] [16] [17].

Despite the wealth of data in industrialized countries on the immunology, epidemiology and allergology of children with vernal keratoconjunctivitis, data in Africa remain limited. A study was carried out in the year 2013 over a period of ten months, at the Ophthalmology Department of the University Hospital of Kinshasa reported a frequency vernal keratoconjunctivitis of 21% [16].

Therefore, we aimed to estimate the vernal keratoconjunctivitis prevalence in urban and rural part in of Kinshasa province between the 2022-2023 school year, to describe the clinical and epidemiological characteristics of children with vernal keratoconjunctivitis, to determine the associated allergenic factors of sensitization and to describe the pattern of intestinal parasite in school children.

2. Methods of Study Design

2.1. VKC Diagnosis

VKC diagnosis was based on ocular symptoms, including photophobia, brownish discoloration conjunctiva, itchy eyes, eyelids rubbing, tearing, red eyes, tarsal papillary, hypertrophy and perilimbal pigmentation on the portable slit-lamp examination. The cornea was stained with fluorescein to rule out the presence of corneal lesions.

2.2. Skin Prick Test

Skin prick test was performed with 11 allergens (Stallergenes, Belgium). The allergen extracts included *Dermatophagoides pteronyssinus* (DPT), *Blomia tropicalis*, cockroach, cat dander, dog dander, Grass pollen mix, *Aspergillus fumigatus, Alternaria alternata*, peanuts, shrimp and eggs.

Histamine dihydrochloride 10 mg and saline were used as positive and negative control respectively.

A drop of each allergen was placed on the innerside of the forearm. Next, a sterile lancet needle was used to puncture the skin and allow the allergen solution to penetrate the skin barrier. The result was evaluated 20 minutes later by taking the size of the skin reaction. The test was considered positive if the papule (raised bump) measured > 3 mm or greater in diameter or \geq half than positive control [18].

2.3. Operating Definitions

A subject was considered sensitized in the presence of a positive skin prick test to one or more allergens.

2.4. Stool Examination

The empty and labeled bottles were given to the children to bring back the morning stool the next day. The samples were brought back to the laboratory for direct examination with the microscope. The following parasites: *Ascaris lumbricoides, Ancylostoma duodenale, Anguillule, Oxyure and Trichuris trichiura.* A screening exam of stool was considered positive in the presence of *Ascaris lumbricoides, Ancylostoma duodenale, Anguillule, Oxyure and Trichuris trichiura lumbricoides, Ancylostoma duodenale, Anguillule, Oxyure and Trichuris trichiura lumbricoides, Ancylostoma duodenale, Anguillule, Oxyure and Trichuris trichiura [19].*

2.5. Study Area and Population

The study was conducted in Kinshasa. The Kinshasa area covers an area of 9965 km² with a density of 557 inhabitants/km² and a population of 12 million. The growth rate of Kinshasa is 5.1% per year. An observational, cross sectional study was performed during scholar years from September 2022 to June 2023 in the school children of Kinshasa. The urban part is characterized by many industries, promiscuity and intense circulation of automobile and the population drink a water which is purified and the rural population part drink a water from deep which is not purified and the house is distanced and have the farm.

2.6. School Children of Kinshasa

Kinshasa town has five Educational provincial division whose Lukunga, Funa, Mont-Amba, Plateau and Tshangu, We have selectionned the Educational Provincial Division of Tshangu and Plateau on the list. The Educational Provincial Division of Plateau and Tshangu are located in the East part of Kinshasa.

2.7. Participants' Selection

The inclusion criteria were the parents, guardians or children seven years and over who gave informed consent before enrollment, children were complaints of vernal keratoconjunctivitis, tarsal papillary hypertrophic and perilimbal pigmentation on the portable slit-lamp examination.

Parents were invited for an interview on the school visit day. Informed consent was obtained from parents or guardians.

Exclusion criteria included children who have cried or fearied and those who the parents or guardians did not give the informed consent or were not in the class the examination day.

Sample size

The sample size was calculated by using the Schwartz formula:

$$n = Z\alpha^2 * p * q/d^2$$

 $Z\alpha$ = Standard normal deviate of 1.96, p = probability = 0.32, q = 1 - p = 1 - 0.32 = 0.68, d = level precision.

 $Za^2 = 1.96^*1.96 = 3.84.$ $a^2 = 0.02^*0.02 = 0.0004.$

n = 3.84*0.32*0.68/0.0004 = 2088, we have rounded to 2100.

2.8. Sampling Techniques

We have used the four-stage probability sampling technique, in particular we drew up the list of Educational Provincial divisions in which we made a simple random draw and we select two Educational Provincial Divisions. We have selected 320 public primary schools of two Educational Provincial Division from the list. On the register from the selected schools, class sets the 6 classes to be used for the study. Random sampling was used to select 15 children per class, leading to the recruitment of 90 students for per school. We examined 28,800 students out of 2100 children with vernal keratoconjunctivitis were recruited.

2.9. Data Collection

All chidren with vernal keratoconjunctivitis in school children underwent a routine ocular examination, including assessment, inspection of the eyelids, portable slit-lamp examination of the anterior segment and direct fundoscopy examination. The cornea was stained with fluorescein to rule out the presence of corneal lesions.

The skin prick test with a panel of 11 allergens was used to determine sensitization and the stool screening was used using the microscope to determine the profile of intestinal parasitic in the Laboratory.

2.10. Statistically Analysis

The qualitative variables included sex, age groups, keeping pets (cat and/or dog), number of people per household, number of people sharing a bedroom, home environment (grow trees and/or Flowers) around the yard, Complaints of vernal keratoconjunctivitis, Forms, Complications, frequency of allergens and the profile of intestinal in urban and rural parts of Kinshasa. Comparisons of proportions were done with a Chi-squared test and Fishers' test was used in the chi-square conditions were not fulfilled.

The confidence Interval (95%) was used and a significance level was set to a value of p < 0.05.

2.11. Ethical Approval

The study received approval from the section of Health Public School Head Committee n° ESP/CE/077/2022.

3. Results

Sociodemographic, clinical, biological and co-proparasitology data have been systematically recorded in this study.

Two thousand and one hundred children were included. Their age ranged from 2 to 16 years with a mean age 7.2 \pm 3.7 years, three were times as many boys for girls. Of all children, 69.5% were from in urban part and 30.4% in the rural part of Kinshasa, 86.9% vs 84.5%, p = 0.00001, shared the same bedroom with at least two people in the urban and rural part, 77.5% vs 83.2%, p = 0.0001

lived in the house with 6 other people in urban and rural environmental, 35.9% vs 50.3%, p = 0.00001, having a cat and/or dog in the urban and rural part. The home environment was 27.2% vs 23.9%, p = 0.00001 in both parts. Sensitization to one or more allergens was reported in 690 children (33.1%). Other characteristics according to skin prick test results are shown in **Table 1**.

In decreasing order, the main symptoms were respectively itchy eyes 31.4% vs 39.7%, p = 0.0001, eyelids rubbing 17.7% vs 22.2%, p = 0.0002, discoloration brownish conjunctiva 12.6% vs 17.8%, p = 0.00001, photophobia 11.4% vs 12.5%, p = 0.00002, red eyes 9.1% vs 10%, p = 0.0001 and tearing 6.7% vs 8.3%, p = 0.0002 in the urban and rural parts (**Table 2**).

Table 1. Characteristics of vernal keratoconjunctivitis children according to prick test results in urban and rural.

	Urb	an	Rural				
-	Children w	vith SPT+	Children with SPT+				
	N = 1460 (U)	N = 490 (U1)	N = 640 (R)	N = 207 (R1)	p-value	p-value	
-	n (%)	n (%)	n (%)	n (%)	U vs R	U1 vs R	
Sex							
М	1075 (73.6)	415 (84.6)	473 (73.9)	143 (69)	0.01	0.0001	
F	385 (26.3)	75 (15.3)	167 (26)	64 (30.9)	0.00001	0.007	
Age/years							
2 - 6	815 (55.8)	208 (42.4)	336 (52.5)	98 (47.3)	0.00001	0.00001	
7 - 11	432 (29.5)	174 (35.5)	209 (32.6)	67 (32.3)	0.00001	0.06	
12 - 16	213 (14.5)	108 (22)	95 (14.8)	42 (20.2)	0.00001	0.03	
umber of people per household							
1 - 5	328 (22.4)	134 (27.3)	107 (16.7)	21 (10.1)	0.00001	0.00001	
≥6	1132 (77.5)	356 (72.6)	533 (83.2)	186 (89.8)	0.0001	0.00001	
Number of people Sharing a bedroom							
1 - 2	1269 (86.9)	367 (74.8)	541 (84.5)	149 (71.9)	0.00001	0.01	
≥3	191 (13)	123 (25.1)	99 (15.4)	58 (28)	0.00001	0.003	
Having a pets							
Cat and/or Dog	525 (35.9)	256 (52.2)	322 (50.3)	84 (40.5)	0.00001	0.0003	
Home environmental and/or flowers around the yard	398 (27.2)	189 (38.5)	153 (23.9)	75 (36.2)	0.00001	0.04	
Self declared dampness in the house	167 (11.4)	66 (13.4)	77 (12)	34 (16.4)	0.00001	0.01	

N = Number, % = percentage, p = probability, U = Urban, R = Rural.

Table 3 showed that the limbic was predominant with 76% vs 74%, p = 0.0001, followed by a mixed form with 13% vs 15%, p = 0.0001, and tarsal form with 11% vs 10.9% in the urban and rural part.

The main complications were, in decreasing order, superficial punctate keratitis 36.5% vs 45.8 %, p = 0.0001, corneal erosion 6.9%vs 11.1%, p = 0.0001, shield ulcer 3.6%vs 5.3%, p = 0.00001, corneal plaque 2.8% vs 3.3%, p = 0.00001 in the urban and rural parts (**Table 4**).

The most prevalent allergens were *Dermatophagoides pteronyssinus*, *Blomia tropicalis*, cockroach followed to a lesser extent by pollens in urban and rural part. Children with vernal keratoconjunctivitis in the urban part were more sensitized than children in the rural part for all allergens (**Table 5**).

Table 6 showed that children with vernal keratoconjunctivitis in rural part were more affected than children in rural part. The most prevalent intestinal parasite was *Ascaris lumbricoides* 14% vs 18.3%, p = 0.0006, *Ancylostoma duode-nale* 9.5% vs 12.5%, p = 0.003, Anguillule 7.9% vs 10.1%, p = 0.001, Oxyure 5. 7% vs 8.2%, p = 0.0001, followed to a lesser extent by *Trichuris trichiura* 2.6% vs 3.3%, p = 0.0009 in the urban and rural part.

Table 2. Complaints of vernal keratoconjunctivitis in urban and rural.

	1	Urban		1	1	
	All children	Sensitized children	All children	Sensitized children	p-value U vs R	p-value U1 vs R1
Complaints	n = 1460 (U)	n = 490 (U1)	n = 640 (R)	n = 207 (R1)		
	n (%)	n (%)	n (%)	n (%)		
Itchy eyes	750 (51.3)	195 (39.7)	335 (52.3)	65 (31.4)	0.0001	0.0001
Eyelids rubbing	225 (15.4)	87 (17.7)	118 (18.4)	46 (22.2)	0.0001	0.0002
Discoloration brownish conjunctiva	200 (13.6)	62 (12.6)	89 (13.9)	37 (17.8)	0.0001	0.00001
Photophobia	162 (11)	56 (11.4)	40 (6.2)	26 (12.5)	0.0002	0.00002
Red eyes	68 (4.6)	49 (10)	37 (5.7)	19 (9.1)	0.08	0.00001
Tearing	55 (3.7)	41 (8.3)	21 (3.2)	14 (6.7)	0.01	0.00002

N = Number, % = percentage, p = probability, U = Urban, R = Rural.

Table 3. Forms of vernal keratoconjunctivitis children in urban and rural.

	ı	Urban		Rural			
	All children Sensitized children		All children Sensitized children		p-value	p-value	
Forms $n = 1460 (U)$ $n = 490 (U1)$ n		n = 640 (R)	n = 207 (R1)	U vs R	U1 vs R1		
1	n (%)	n (%)	n (%)	n (%)	U VS R	UI VS KI	
Tarsal Form	162 (11)	97 (19.7)	70 (10.9)	51 (24.6)	0.0001	0.002	
Limbic Form	1107 (76)	250 (51)	474 (74)	91 (43.9)	0.002 0	0.00001	
Mixed Form	Mixed Form 191 (13) 143 (29.1)		96 (15)	65 (31.4)	0.0001	0.009	

N = Number, % = percentage, p = probability, U = Urban, R = Rural.

	Urban			1		
Complications	All children	Sensitized children	All children	Sensitized Children	p-value	p-value
	n = 1460 (U)	n = 490 (U1)	n = 640 (R)	n = 207 (R1)	.	U1 vs R1
	n (%)	n (%)	n (%)	n (%)	U vs R	
Superficial punctate keratitis	387 (26.5)	179 (36.5)	116 (18.1)	95 (45.8)	0.00001	0.001
Corneal erosion	50 (3.4)	34 (6.9)	15 (2.3)	23 (11.1)	0.00001	0.0001
Shield ulcer	34 (2.3)	18 (3.6)	13 (2)	11 (5.3)	0.0002	0.00001
Corneal plaque	30 (2)	14 (2.8)	12 (1.8)	7 (3.3)	0.0001	0.00001
No complications	959 (65.6)	245 (50)	484 (75.6)	71 (34.2)	0.01	0.0001

Table 4. Complications of vernal keratoconjunctivitis children in urban and rural.

N = Number, % = percentage, p = probability, U = Urban, R = Rural.

Table 5. Profile of allergens in urban and rural.

	Ur	ban	Rural	n	
	All children		p-value		
	n = 2100 (U)	n = 490 (U1)	n = 207 (R1)	111 D1	
Allergens	n (%)	n (%)	n (%)	— U1 vs R1	
Dermatophagoides pteronyssinus	198 (9.4)	138 (28.1)	60 (28.9)	0.00001	
Blomia tropicalis	109 (5.1)	78 (15.9)	31 (14.9)	0.00001	
Cockroach	87 (4.1)	59 (12)	28 (13.5)	0.00001	
Cat dander	29 (1,3)	18 (3.6)	11 (5.3)	0.04	
Dog dander	24 (1.1)	15 (3)	9 (4.3)	0.001	
Grass pollen mix	45 (2.1)	33 (6.7)	12 (5.7)	0.003	
Aspergillus fumigatus	21 (1)	16 (3.2)	5 (2.4) 0	0.0004	
Alternaria alternata	15 (0.8)	12 (2.4)	3 (1.4)	0.01	
Peanuts	72 (3.5)	53 (10.8)	19 (9.1)	0.00001	
Eggs	65 (3.1)	44 (8.9)	21 (10.1)	0.00001	
Shrimp	32 (1.6)	24 (4.8)	8 (3.8)	0.01	

N = Number, % = percentage, p = probability, U = Urban, R = Rural.

Table 6. Pattern of Parasite intestinal and	sensitization of children wit	th vernal keratoconjunctivitis in urban and	rural.

	Urban			Rural	,	
	All children	Sensitized children	All children	Sensitized children	p-value	p-value
	n = 1460 (U)	n = 490 (U1)	n = 640 (R)	n = 207 (R1)		UI DI
	n (%)	n (%)	n (%)	n (%)		U1 vs R1
Ascaris lumbricoides	87 (5.9)	69 (14)	188 (29.3)	38 (18.3)	0.00001	0.0006

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Continued						
Ancylostoma duodenale	63 (4.3)	47 (9.5)	105 (16.4)	26 (12.5)	0.00001	0.003
Anguillule	53 (3.6)	39 (7.9)	74 (11.5)	21 (10.1)	0.00001	0.001
Oxyure	35 (2.3)	28 (5.7)	49 (7.6)	17 (8.2)	0.001	0.0001
Trichuris trichiura	18 (1.2)	13 (2.6)	25 (3.9)	7 (3.3)	0.001	0.0009

N = Number, % = percentage, p = probability, U = Urban, R = Rural.

4. Discussion

The purpose of the study was to estimate the vernal keratoconjunctivitis prevalence, to describe the profile of sensitization and to determine the association between sensitization and intestinal parasitic infestation in school children of Kinshasa.

The present study reported a prevalence of 7.2% in school children of Kinshasa. The vernal keratoconjunctivitis prevalence is different to the prevalence of VKC reported respectively in Egypt 3.3% and Ethiopia 5.8% by the authors Hatem et al. and Dereje et al. [9] [10].

The difference between our study and the authors such as Hatem et al. and Dereje et al., could be explained by the study design, particularly the sample size and the setting [9] [10].

The sex ratio reported in the current study, male is more affected three times than for one girls.

This finding is similar to the results reported by others authors such as Hall et al., Shafiq et al., and Bonini et al. [20] [21] [22].

The most prevalent complaints in our work were respectively itchy eyes, eyelids rubbing, discoloration brownish conjunctiva, photophobia, red eyes and tearing.

The difference with other authors such as Hatem et al., and Makita et al., could be explained by the study design, particularly the sample size and the setting [9] [15].

In our series, the most prevalent forms were respectively limbic, mixed and tarsal.

The difference between our study and a lot of studies in Africa, may be explained by sample studied and some geographic variation [9] [13].

The current study reported the most common complications were superficial punctate keratitis, corneal erosion, shield ulcer and corneal plaque. This profile complications and the allergen profile reported in the current study which is predominated by house dust mite followed by cockroach and pollen. This finding is in agreement with Muamba's study [23].

Our study reported three foods predominantly peanuts followed by eggs and shrimp.

In their study, Al-Hammadi et al., reported that eggs, fruits and fish were predominant [24].

The frequency of allergens differs between studies because food habits and

cooking procedure are different [25].

In the current study, children with vernal keratoconjunctivitis in urban part were more sensitized than children in the rural. Throughout the world many studies reported that children lived in urban were more affected than rural children, this finding is in aggreement of those studies. Thus, it could be explained because the lifestyle is different in the two parts. In the urban environment, polluted pollens have a higher allergenic potential. The polluted pollens have a synergistic effect of increasing the oxidative stress of the mucous membranes and can induce respiratory allergies and conjunctivitis in sensitized subjects. Ozone, mobile particles and sulfur dioxide have inflammatory effects by increasing the penetration of allergens in the mucous membranes and increased interactions with immune cells and diesel particles promote the synthesis of IgE in atopic subjects [26] [27].

The intestinal parasitic infestation profile reported in the current study is predominated by *Ascaris lumbricoides*, *Ancylostoma duodenale*, Anguillule, Oxyure and *Trichuris trichiura* in the urban and rural parts.

Vernal keratoconjunctivitis children in the rural environnemental were more affected by intestinal parasitic infestation than children in the urban. The predominant profile of intestinal parasitic infestation in rural than urban could be explained because the style of life is different in the two parts. The Regideso serves only 40% of the population of Kinshasa city, thus, this population who live in the rural areas drink a water from drilling which is not purified and the rural population is exposed to lot of diarhoeal disease particularly intestinal parasitose. These factors may explained the high level of intestinal parasitic infestation among rural children [28].

There are some weaknesses and constraints associated with the present study.

A selection bias may be present as we did not use a representative sample of students of all Provincial Division Educational of Kinshasa. However, this bias was minimized by using a four-stage probability sampling technique. A second limitation is related to cross-sectional study, which is weak to establish relationship between intestinal parasitic infestation and allergens. Nevertheless, it is the first study providing new insight among children with vernal keratoconjunctivitis in Kinshasa about the skin prick test and intestinal parasitic infestation.

5. Conclusion

This study outlines that prevalence of vernal keratoconjunctivitis was 7.2% and 33.1% of children attending for vernal keratoconjunctivitis in school children had a positive skin prick test in particular to at least one allergen, in particular for Dermatophagoides, *Blomia tropicalis* and cockroach. The most common intestinal parasitic was *Ascaris lumbricoides*, *Ancylostoma duodenale*, Anguillule and *Trichuris trichiura*.

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Impact Statement

In daily practice, the Ophthalmologist should change the habits in the management and prescribe worming drugs to vernal keratoconjunctivitis children having intestinal parasitic infestation.

Authors' Contributions

Design: Léon Muamba Nkashama, David Kayembe Lubeji.
Data collection: Léon Muamba Nkashama, David Kayembe Lubeji.
Analysis data: Léon Muamba Nkashama.
Redaction: Léon Muamba Nkashama, Mireille Solange Nganga Nkanga.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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