

## Study of coinfection of *Salmonella typhi*, *Salmonella paratyphi* with *Candida spp.*, in four hospitals of Douala- Cameroon

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### Abstract

*Candida spp.*, are saprophytic yeasts capable of creating a favorable environment for bacterial infection, amplifying or inhibiting their activity. On the other hand, bacteria produce molecules that reduce the proliferation of *Candida spp* or promote their adherence to surfaces. The resurgence of typhoid and paratyphoid fevers in endemic individuals and the relative effectiveness of contemporary conventional therapies arouse curiosity to explore other factors that may influence, the re-emergence of infection in patients. We carried out a cross-sectional study of 2500 patients in four hospitals in the city of Douala, Cameroon, from January to December 2019, to determine the influence of *Candida spp.*, on the onset of these infections in patients. Widal and Felix test was used to form the sample, culture on specific media and microscopy confirmed the identity of *Salmonella typhi*, *Salmonella paratyphi* and *Candida spp*. Biochemical tests on a classic tube gallery revealed the biochemical characteristics of bacteria. The results showed that infection with *S. typhi* is predominant, 32.76 % versus 18.4 % of *S. paratyphi* infection. Infection with *Candida spp.*, would increase 4-5 times the frequency of infection with *S. typhi* and *S. paratyphi*, respectively from 3.08 % to 26.03 %, and from 7.08 % to 32.76 %. The presence of *Candida spp* increases the risk of reoccurrence of *S. typhi* and *S. paratyphi* in patients.

**Keywords:** *S. typhi*; *S. paratyphi*; *Candida spp*; Coinfection; Re-emergence

### 1. Introduction

*Candida spp.* are commensal saprophytic yeasts in humans, localized on the skin and mucous membranes. This germ becomes pathogenic following in the balance between the yeast's capacity for colonization, the expression of virulence factors and the control by the immune system's defenses. *Candida albicans* accounts for at least 50 % of all yeast infections and is the fourth leading cause of death, between 1 and 8% of systemic infections [1]. This risk is increased when they are associated with bacteria or other microorganisms in multicellular structures known as mixed biofilms, which constitute infectious reservoirs for bacteria and yeasts, making diagnosis and therapy difficult [2, 3].

Indeed, biofilms are the site of synergistic and inhibitory relationships, allowing for their stability, control of competition for nutrients and infection of new sites [4]. These mechanisms are modulated by molecular factors promoting intercellular communication such as the N-acylhomoserine lactones (AHL) derivative, observed in gram-negative bacteria, or an auto-inducing system 2 (AI-2) common to all bacteria [5, 6].

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The interaction between bacteria and yeasts, particularly *Candida albicans*, is well documented. This is the case of: «the improved adhesion of yeast to the bladder mucosa by *Escherichia coli* during certain urinary tract infections» [7]; «the fixation of *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* on yeast» [3,8]; «the inhibition of *Candida albicans* hyphae through the production of competency stimulating peptides (CSPs) by *Streptococcus mutans*» [9]; «the stimulation of *Staphylococcus aureus* in the biofilm by prostaglandin E2 (PGE2) produced by *C. albicans*» [10]; «the stimulation and amplification of *S. aureus* infection by *C. albicans*» [11]; «the increased risk of bacterial co-infection 3.2 times higher in the presence of filamentous fungal keratitis» [12].

The re-emergence of typhoid and paratyphoid fevers caused by *S. typhi* and *S. paratyphi* in patients from endemic areas raises questions about the mechanisms of infection and resistance of the pathogens involved. Endogenous factors of the infection, beyond contamination through water and foods soiled by stool (sick or asymptomatic carriers) are considered. They affect about 20.000.000 people/year and are responsible for more than 600.000 deaths per year [13]. In Africa, in particular *S. typhi* infects 10 to more than 100 cases per 100.000 inhabitants [14].

Could the re-emergence of typhoid and paratyphoid fevers in subjects in endermal areas not be endogenous to the human host? The interaction between *S. typhi*, *S. paratyphi* and *candida spp.*, would contribute to the re-emergence of typhoid fever or paratyphoid fever in patients. The objective of this study is to investigate the relationship between *S. typhi*, *S. paratyphi* - *candida spp.*

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## 2. Material and methods

### 2.1. Study site, sampling and biological material

The cross-sectional and prospective study ran from January to December 2019. It was carried out on 2500 patients, selected for the study according to the accidental sampling method, during their consultation for any diarrheal disease. After having responded to criteria inclusion such as having a recurrent history of typhoid fever, residing in the Douala area for at least 3 months and being between 11-70 years old, they had to be referred to the diagnosis of typhoid fever.

The district hospitals of Deido (HDD), Bonassama (HDB), Nylon Brazzaville (HDN) and the Military Hospital of Coastal Region II (HMR2) were the place of sample collection based on a questionnaire whose focus was mainly on the recurrence of the disease in patients and the absence of an immunosuppressive pathology. These health establishments were chosen for their geographical location allowing them to accommodate a more heterogeneous population, representing the miniature city of Douala, from the point of view of the cosmopolitan character, the low level of accessibility to drinking water and questionable compliance with basic hygiene rules.

The biological material consisted of serum and stool collected from patients, assigned for diagnosis of typhoid fever after consultation by a physician. The age interval made it possible to exclude cases of re-emergence of the disease related to the moral immaturity of hygiene of the patients (< 11 years old) or the aging of the immune system (>70 years old). The Institutional Ethics Committee for Research for Human Health at the University of Douala issued the ethical clearance document registered at number 1658 CEI-Udo / 06/2018 / T. Data collection in hospitals has been authorized under to N° 2798 / AR / MISANTE / DRSP / BCASS by the Littoral Regional Health Delegation.

### 2.2. Search for anti-*Salmonella* antibodies

The detection of anti-O and anti-H agglutinins directed against *S. typhi* and *S. paratyphi* in the diluted serum of patients was done by the Widal and Felix test. The positive cases were selected according to the titles of *S. typhi*  $\leq 1/400$  and *S. paratyphi*  $\geq 1/1600$ , according to the approved standards of the World Health Organization [13].

### 2.3. Isolation and identification of *S. typhi* and *S. paratyphi*

Isolation of *S. typhi* and *S. paratyphi* was performed according to the WHO protocol [13]. A stock suspension of the inoculum was pre-enriched for 24 hours by dilution of 25 g of stool in 225 mL of buffered peptone water. Then the mixture was enriched with selenite broth for 24 hours. This step was followed by inoculation on *Salmonella-Shigella* gelose (SS Agar) and then on Hektoen medium within 24 hours. The Gram control test combined with light microscopy confirmed the Gram-negative character of the bacteria. The differentiation of the strains in the culture medium was completed by the biochemical tests in the classical gallery tube: gas detection (GAS positive), hydrogen sulfide production (H<sub>2</sub>S positive), glucose fermentation (glucose positive), absence of lactose fermentation (lactose negative) by Kligler Hajna test; absence of  $\beta$ -galactosidase (ONPG negative); detection of decarboxylase (LDC, ODC) and

dihydrolase (ADH); determination of urease and indole according to the Fergusson method (urease and indole negative).

#### 2.4. Isolation and identification of *Candida spp.*

Stool collected on an empty stomach in the morning in a sterile box was delivered directly to the bench within a maximum of 2 hours for diagnosis. 25 g of stool was added to 225 mL of Peptonneous water for the preparation of the initial suspensions according to NF EN ISO 6887-1(2017). 10 mL of the sample were introduced into the mixture potash 10% + glycerol 10 mL + 80 mL deionized water, and left to stand + 4°C. After 15 min, the yeasts and mycelial filaments were observed under an optical microscope, stained with May Grunwald Giemsa [15]. Another stool of equal mass was introduced into 9 mL of NaCl solution of weight concentration 8.5g/L, contained in a test tube, initially centrifuged at 1200 rpm for 15 min. Using a sterile loop, an extract of the medium was inoculated onto a sabouraud medium and the reading was taken 24 hours later after incubation at 37°C. A control test was carried out to determine the biochemical aspect of the yeast wall, gram-positive using the Gram test.

#### 2.5. Statistical analysis

Frequencies, Chi-square and Cramer's index were analyzed using the descriptive statistics method with SPSS 23.0 software, at 0.05 significance level. The correlation of the transformed values, the discrimination measure and the attached diagram of the modality points were highlighted by the factorial analysis of the multiple components.

### 3. Results and discussion

#### 3.1. Frequency of distribution of typhoid, paratyphoid fevers and candidiasis

Table (1) shows the distribution of *S. typhi*, *S. paratyphi* and *Candida spp.*, by gender and hospital on 2.500 patients, 661 were from the Bonassama District Hospital (420 women, 241 men), 830 from the Deido District Hospital (451 women, 379 men), 442 from the Region 2 Littoral Military Hospital (226 women, 216 men), and 567 from the Nylon Brazzaville District Hospital (347 women, 220 men). 1.82% (n=12) of women and 1.39% (n=9) of men were infected with *S. typhi* at the Bonassama district hospital, 0.73 % (n=6) of women and 1.2% (n=10) of men with *S. typhi* at Deido District Hospital, 3.84% (n = 17) of women and 2.26% (n = 10) of men simultaneously by *S. typhi* and *S. paratyphi* at the Region 2 Littoral Military Hospital and 0.88% (n = 5) of women and 1.06 (n = 6) of the men of *S. typhi* at the District Hospital of Nylon Brazzaville. Regardless of the pathogen, the difference was significant at the  $P < 0.05$  ( $P = 0.000$ ; Phi: 29. 2 %) threshold.

#### 3.2. Occurrence of typhoid fever and candidiasis in hospitals

Figure (1) shows the evolution of typhoid fever, paratyphoid fever, and candidiasis in hospitals during 2019. It shows that the frequency of *Candida spp.*, infection peaked relatively early in July (13 %) and fell in December (3.4 %). The difference between candidiasis and period is significant at the threshold of  $P < 0.05$  ( $P = 0.007$ ), with a low binding strength of 10.20 %, in contrast to *S. typhi* and *S. paratyphi* infection, which is not significant ( $P = 0,112$ ). The frequencies of *S. typhi* and *S. paratyphi* increased from June to August 2019, respectively *S. typhi* (9.7 % January; 11.5 % June), *S. paratyphi* (11.5 % March, 10.2% June; 15.2 % July) and *S. typhi* and *S. paratyphi* (12.1% March, 12.7% June; 10.3% July). *S. paratyphi* was most infected in the [11-20] age group, 0.72 % (n = 18) and 0.60 % (n = 15) of men, and patients in the [21-30] age group, 0.68 % (n = 17) of women and men; *S. typhi* infected more patients in the [11-20] age group, 3.2 % (n = 80) of women and 2.24 % (n = 56) of men.

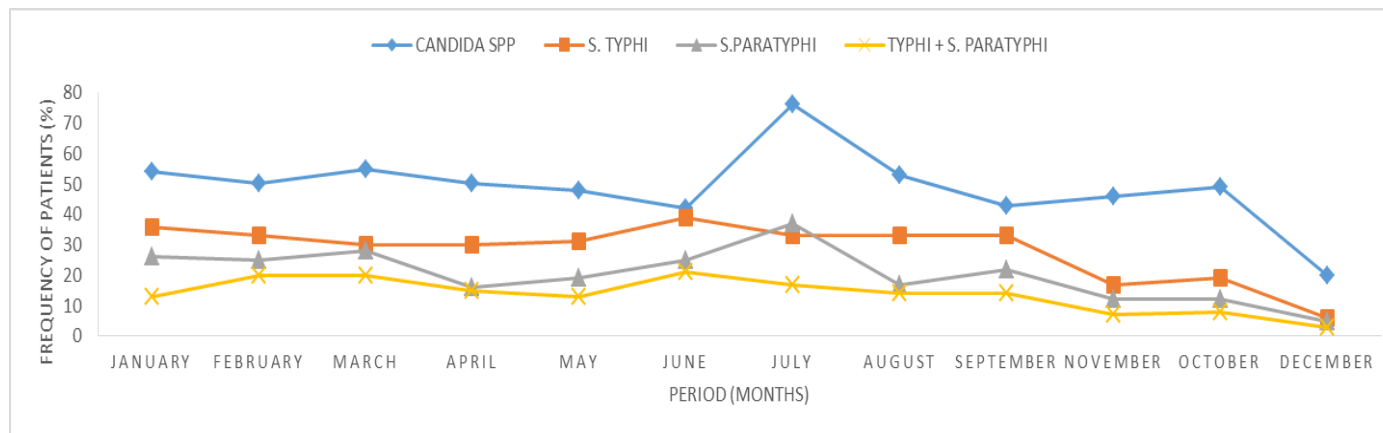
#### 3.3. Frequency of patients infected with *S. typhi*, *S. paratyphi* and *Candida spp.*, and relationship between the pathogens

The distribution of patients infected with *S. typhi*, *S. paratyphi* and *Candida spp.*, according to age group and sex showed that 2.12 % (n = 53) of women and 1.36 % of men (n = 34) were infected with *S. paratyphi*, 3.96 % (n = 99) of women and 3.12 % of men (n = 78) with *S. typhi*, 3.88 % (n = 97) of women and 2.80 % of men (n = 70) of *S. typhi* and *S. paratyphi*, 13.6 % (n = 340) of women and 9.84 % of men (n = 246) of *Candida spp.*, (Table 2).

**Table 1** Frequency of distribution of typhoid fever, paratyphoid fever and candidiasis fevers by gender and location.

<i>Salmonella</i>	Gender	<i>Candida spp</i>							
		HDB		HDD		HMR2		HDN	
		Négative	Positive	Négative	Positive	Négative	Positive	Négative	Positive
TH+PTH(-) (%)	W	305(46,14)	42(6,35)	338(40,73)	50(60,24)	90(20,36)	58(13,12)	187(32,98)	125(22,05)
TH+PTH(-)(%)	M	183(27,68)	18(2,72)	276(33,25)	56(67,47)	102(23,07)	45(10,18)	120(21,16)	74(13,05)
PTH(+)(%)	W	20(3,02)	4(0,61)	7(0,84)	3(0,36)	12(2,72)	3(0,68)	2(3,52)	2(3,52)
PTH(+)(%)	M	5(0,75)	0(0,00)	11(1,33)	1(0,12)	12(2,72)	3(0,68)	2(3,52)	0(0,00)
TH(+)(%)	W	21(3,17)	12(1,82)	34(4,9)	6(0,73)	5(1,13)	3(0,68)	13(2,3)	5(0,88)
TH(+)(%)	M	14(2,11)	9(1,36)	13(1,57)	10(1,2)	12(2,72)	7(1,58)	7(1,23)	6(1,06)
TH+PTH(+)(%)	W	15(2,26)	1(0,15)	9(1,08)	4(0,48)	38(8,59)	17(3,84)	8(1,41)	5(0,88)
TH+PTH(+)(%)	M	11(1,67)	1(0,15)	9(1,08)	3(0,36)	25(5,66)	10(2,26)	8(1,41)	3(0,53)
Total(%)	M + W	574(86,84)	87(13,16)	697(83,98)	133(16,02)	296(66,97)	146(33,03)	347(61,20)	220(38,80)

TH + PTH (-): *S. typhi* and *S. paratyphi* negative; PTH (+): *S. paratyphi* positive; TH (+): *S. typhi* positive; TH + PTH (+): *S. typhi* and *S. paratyphi* positive; W: Women; M: Man

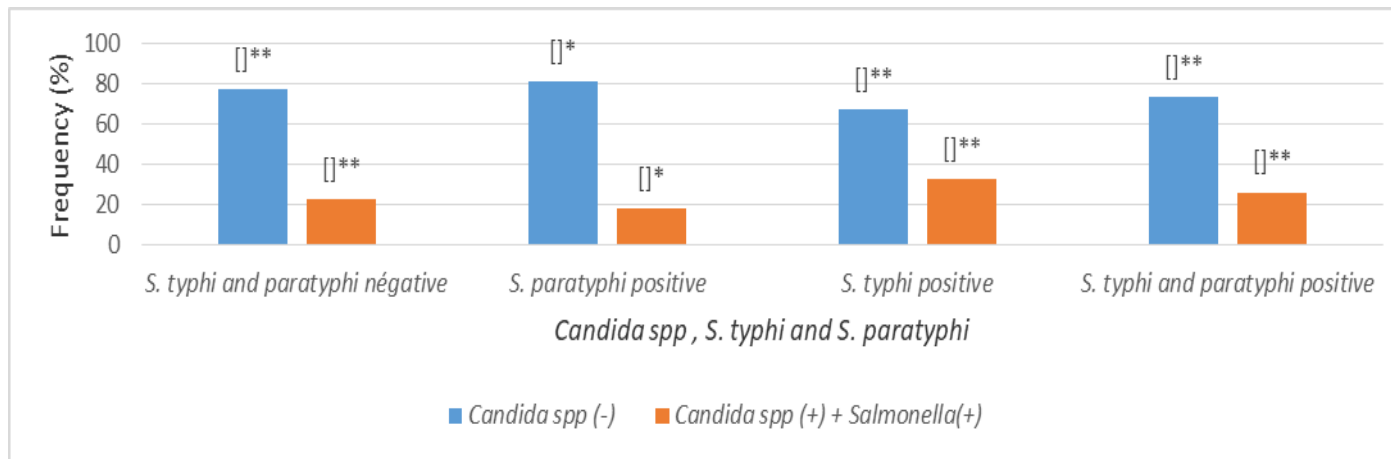


**Figure 1** Occurrence of typhoid fever, paratyphoid and candidiasis in hospitals.

**Table 2** Frequency of patients infected with *S. typhi*, *S. paratyphi* and *Candida spp.*, based on age group and sex.

AGE	TH and PTH negative (%)		PTH positive (%)		TH positive (%)		TH and PTH positive (%)		<i>Candida spp</i> (%) positive	
	Woman	Man	Woman	Man	Woman	Man	Woman	Man	Woman	Man
11-20	65(2.6)	52(2.08)	18(0.72)	15(0.6)	80(3.2)	56(2.24)	34(1,36)	18(0.72)	35(1.4)	36(1.44)
21-30	398(15.92)	272(10.88)	17(0.68)	17(0.68)	8(0.32)	21(0.084)	37(1,48)	40(1.6)	120(4.8)	97(3.88)
31-40	274(10.96)	216(8.64)	12(0.48)	1(0.04)	6(0.24)	1(0.04)	17(0,68)	9(0.36)	61(2.44)	46(1.84)
41-50	188(7.52)	151(6.4)	3(0.12)	0(0.00)	2(0.08)	0(0.00)	2(0,08)	1(0.04)	52(2.08)	31(1.24)
51-60	232(9.28)	154(6.16)	3(0.12)	1(0.04)	2(0.08)	0(0.00)	5(0,2)	2(0.08)	60(2.4)	32(1.29)
61-70	38(1.52)	29(1.16)	0(0.00)	0(0.00)	1(0.04)	0(0.00)	2(0,08)	0(0.00)	12(0.48)	4(0.16)
Frequency (%)	1195(47.8)	874(34.96)	53(2.12)	34(1.36)	99(3.96)	78(3.12)	97(3,88)	70(2.8)	340(13.6)	246(9.84)

TH + PTH: *S. typhi* and *S. paratyphi*; PTH: *S. paratyphi*; TH: *S. typhi*;



**Figure 2** Relationship between *S. typhi*, *S. paratyphi* and *Candida spp* as a function of age group and sex; (\*\*): Significant difference at the threshold of  $p < 0,05$ ; (\*): none significant difference at the threshold of  $P < 0,05$ .

*S. paratyphi* was highly infection in the age group [11-20], such as 0.72 % (n = 18) and 0.60 % (n = 15) of men, and patients aged [21- 30] with 0.68 % (n = 17) of women and men; *S. typhi*, infected more patients within [11-20] age group of which 3.2 % (n = 80) of women and 2.24 % (n = 56) of men; both pathogens affect simultaneously 1.36% (n = 34) of women and 0.72% (n = 18) of the age group [11-20], 1.48 % (n = 37) of women and 1.6 % (n = 40) of men in the age group [21-30]; *Candida spp.* affect mainly 4.8 % (n = 120) of women and 3.88 % (n = 97) of men. Overall, *S. typhi*, *S. paratyphi* and *Candida spp.* infect more patients aged between [11-20], followed by those aged between [21-30]. However, the difference is significant at the threshold of  $P < 0.05$  ( $P = 0.000$ ;  $\Phi = 50.5\%$ ), between *S. typhi*, *S. paratyphi*, age group and sex. Nevertheless, it is significant at the  $P < 0.05$  ( $P = 0.000$ ) threshold, between *S. typhi* and age, *S. paratyphi* and age with a weak binding strength of 59.1 % and 25.5 % respectively. The infection of *S. typhi* is dependent on *S. paratyphi* and vice versa, with a binding strength of 59.10 %. The infection with *S. typhi* and *S. paratyphi* according to age is significant at  $P < 0.05$  ( $P = 0.000$ ,  $\Phi = 59.10\%$ ). The study of *Candida spp.* by age and sex shows a non-significant difference at the  $P < 0.05$  ( $P = 0.079$ ;  $\Phi = 6.3\%$ ) threshold. However, the significance is positive between *Candida spp.*, age and period ( $P = 0.007$ ), influenced by the age group [31-40] ( $P = 0.005$ ) with a low bond of 22.4 %, (Table 2).

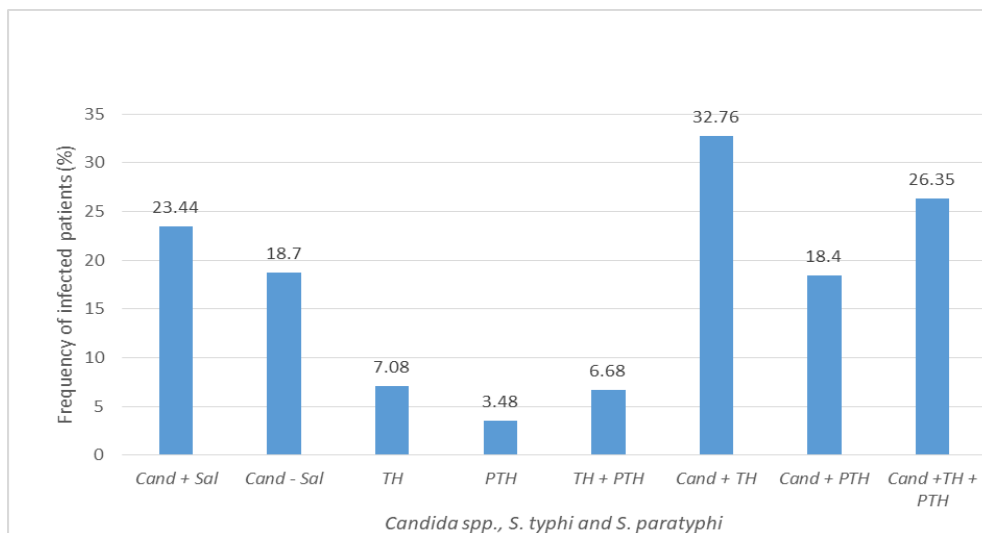
### 3.4. Influence of *Candida spp.* on *S. typhi* and *S. paratyphi*

The infection with *Candida spp.*, increases the percentage of infection of *S. typhi* from 7.08 % (n = 177) to 32.76 %, (n = 58), that of *S. paratyphi* from 3.48 % (n = 87) to 18.4 % (n = 16) and, that of *S. typhi* associated with *S. paratyphi* from 6.68 % (n = 167) to 26.35 % (n = 44), figure (3).

### 3.5. Components factors of infections of *Candida spp.*, *S. typhi* and *S. paratyphi*

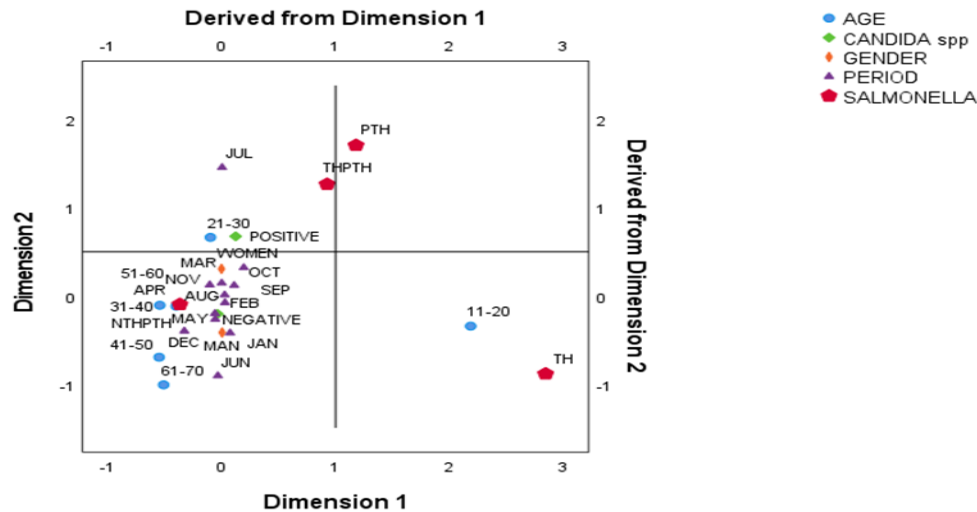
The analysis of the relationship between *S. typhi*, *S. paratyphi* and *Candida spp.* shows that 18.72 % (n = 468) of patients are infected with *Candida spp.* 0.64 % (n = 16) with *S. paratyphi* and *Candida spp.*, 2.32 % (n = 58) with *S. typhi* and *Candida spp.*, and 1.76 % (n = 44) by *S. typhi* and *S. paratyphi* and *Candida spp.* The difference at the threshold of  $P < 0.05$  is significant between *Candida spp.*, *S. typhi* and *S. paratyphi* ( $P = 0.003$ ), with a correlation of 5.9 %. This difference is non-significant at the threshold of  $P < 0.05$  ( $P = 0.849$ ), between *Candida spp.* and *S. paratyphi*, (Table 2).

The correlation of the transformed values mainly shows that *S. typhi*, *S. paratyphi* and *Candida spp.* are correlated at 5.6 %, and *Salmonella* at age, 57.9 %. The measure of discrimination includes for dimension 1 the variables period, *Candida spp.* and sex, and for dimension 2, *Salmonella* and age. The frequencies of *S. typhi* and *S. paratyphi* increase from June to August respectively *S. typhi* (9.7 % January; 11.5 % June) mainly in patients in the age group [11-20], *S. paratyphi* (11.5 % March, 10.2 % June; 15.2 % July) and *S. typhi* and *S. paratyphi* (12.1 % March, 12.7 % June; 10.3 % July, and 5.1 % October in women aged between [21-30]) (figure 4).



**Figure 3** Influence of *Candida spp.* on *S. typhi* and *S. paratyphi*

Cand: *Candida spp.*; PTH: *Salmonella paratyphi*; TH: *Salmonella typhi*



**Figure 4** Principal components factors of infections of *candida spp*, *S. typhi* and *S. paratyphi* based on sex, hospital age and period.

TH: *S. typhi* positive; PTH: *S. paratyphi* positive; THPTH: *S. typhi* and *S. paratyphi* positive; NTHPTH: *S. typhi* and *S. paratyphi* negative; JAN: January; FEB: February; MAR: March; APR: April; MAY: May; JUN: June; JUL: July; AUG: August; SEP: September; OCT: October; NOV: November; DEC: December.

March, September, August, November, January and April are more likely to be conducive to male aged group within [31-70] infection to *Candida spp*, *S. typhi* and *S. paratyphi*.

#### 4. Discussion

The aims of our study was to determine the relationship between *Salmonella typhi* and *S. paratyphi* with *Candida spp*.

The proportion of women in the study is higher than that of men (57.76 % compared to 42.24 % of men), regardless of the health center. The percentage of positive infected cases with at least one form of *Salmonella* was 14.63 % within women and 9.30 % within men. This shows that women are more exposed to *S. typhi*, *S. paratyphi* or both pathogens simultaneously (Table 1). This could be explained by their regular contact with work surfaces or utensils during routine household workplace, on which *Salmonella* could have been easily established facilitating biofilms formation; among others women, especially those living in the neighborhoods with nothing but poor hygiene standards e.g. food exposed at roadsides, sometimes processing under critical cleaning conditions (home-made juices, food roasted on embers, peeled fruit, etc.); men are not at all to be left aside, they easily consume meals in coarse fastfood. However, the infection affects both men and women without distinction of gender.

The occurrence of infections with *S. typhi*, *S. paratyphi* and *Candida spp*, shows that typhoid and paratyphoid fever is an ubiquitous disease that occurs throughout the year. Nevertheless, the number of consultations and cases of illness has increased in January, March, April, June and July (figure 1). The behaviour of the disease is said to be linked to the recurrent presence of infection foci such as swamps due to the major floods generally recorded during this period, the proximity of markets with the galloping insalubrity, and promiscuity. Also, this period corresponds to the day after the festive season with the high risk of toxemics infections (January) [16]. The increase in the frequency of infection of *candida spp*. during this period in the stools of patients suggests a certain association of *candidiasis* with the disease, (figure 2).

Infection with *S. typhi* and *S. paratyphi* is independent of age group and sex, in contrast to infection with *Candida spp*. Age groups [11-20] and [21-30] appear to be more exposed to typical and paratypical salmonellosis [17, 18]. This is thought to be related to non-compliance of basic hygiene rules and sometimes lack of health education.

This would mean that basic hygiene rules are neglected and sometimes the lack of health education. Therefore, the re-emergence of typhoid and paratyphoid fevers in patients would be influenced by the co-infection of pathogens involved

in these pathologies with *Candida spp.* However, infection *candida spp.*, would not be sufficient to bring *S. paratyphi* back to school in patients [10, 11].

*Candida spp.*, infection is thought to increase the resurgence of typhoid and paratyphoid fevers in the population 4.63 (*S. typhi*) - 5.29 (*S. paratyphi*) times, compared with the results founded by Pate, [18] about co-infection of bacterial and filamentous fungal keratitis (3.2 times). *Candida spp.*, and in particular *Candida albicans* create perforations in the intestine during infection which facilitate the penetration of *S. typhi* and *S. paratyphi* into the bloodstream, or are capable of producing chemical mediators that stimulate the growth of bacteria [11]. By metabolising certain molecules such as carbohydrates, they would provide energy for the bacteria to grow [19, 20 21]. In addition, bacteria being able to form multiple associations in mixed biofilms consolidated by yeast adhesins, would escape antibiotics to reinfect the same patients, once the therapeutic and immune system offensive has been eliminated or diminished [22]. On the other hand, the frequency of *Candida spp.* decreases with co-infection with *S. typhi* and *S. paratyphi*. The bacteria are thought to produce substances that inhibit the hyphae of *Candida spp.*, [9, 23].

Analysis of the correlation of transformed values shows that although *S. typhi* and *S. paratyphi* infection appears to be related to *Candida spp.* infection, it is weakly correlated at 5.6 %. *S. typhi* and *S. paratyphi* reinfection is also strongly correlated at 57.9 % with age. This could be explained by the co-infection of *S. typhi* with *S. paratyphi* A, for which the duration of antibiotic therapy would be insufficient due to its underestimated duration in case of co-infection and partial treatment of the infection [24]. The ability of the immune system to regulate the reduction of the *in vivo* fungal load of *Candida spp.* through the intervention of the macrophage system and the establishment of immunological barriers. This would have a positive impact on the reduction of *Salmonella* infection [24, 25, 26]. Recurrent infection with *S. typhi* and *S. paratyphi* is associated with age, and infection with *Candida spp.* with time and sex.

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## 5. Conclusion

This work aimed to determine the influence of *Candida spp.*, on the reemergence of typhoid and paratyphoid fevers in patients. In short, the reappearance of typhoid and paratyphoid fevers is independent of sex and period. Those parameters influence the infection by *Candida spp.* Also in patients, simultaneous presence of *S. typhi*, *S. paratyphi* and *Candida spp.*, would increase the percentage of reemergence of typhoid fever and paratyphoid fever in patients 4 to 5 times.

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## Compliance with ethical standards

### Acknowledgments

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### Disclosure of conflict of interest

The authors hereby certify that there is no conflicting interest of any kind in this study

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