

# Contribution to the Study of the Incidence of Post-Streptococcal Complications in Republic Central African Republic from 2015 to 2018

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## Abstract

**Introduction:** Acute rheumatic fever (AAR) is a non-suppurative complication of late infection by group A. Infections due to *streptococci* remain a public health problem in the Central African Republic. The present study aims to determine the incidence rate of AAR cases and its complications. **Methodology:** This was a retrospective and analytical study over a period of 4 years (from January 2015 to December 2018) at the National Laboratory of Clinical Biology and Public Health (LNBCSP) in Bangui. It focused on samples concerning the diagnosis of AAR and patient files seen in consultation in the capital's reference health establishments. Laboratory registers and patient consultation files were used to collect data. They were entered into Excel 2010 to be analyzed with Epi Info 7. A univariate analysis by logistic regression, Fisher's exact test, and chi<sup>2</sup> at the 5% threshold (p < 0.05) were used to compare the proportions to analyze the association between qualitative and quantitative variables. **Results:** We analyzed 94 cases meeting Jones's criteria. The ages of the patients ranged from 18 to 85 years (mean age 52 years and mode 45 years). The incidence rate of AAR for the female sex was higher than that

of the male sex during the study period ( $p > 0.05$ ). It went from 166.6 in 2015 to 200 in 2016 and 2018 cases of AAR per 1000 people per year. The average incidence rate was 296.18 cases of AAR per 1000 people per year. The average incidence rate was 223.5 cases of AAR per 1000 people per year for joint damage. Joint damage represented 80.85% (RR = 0.62;  $\text{Chi}^2 = 4.88$ ; 95% CI [0.39 - 0.97];  $p < 0.01$ ). Univariate analyses showed a statistically significant association ( $p < 0.05$ ) with clinical signs and markers of inflammation. Accelerated sedimentation speed (ESR) is associated with a risk of joint complication of AAR (RR = 1.17). Polyarthrosis resumes in 89.47% of cases (RR = 4.22;  $\text{Chi}^2 = 25.34$ ; 95% CI [2.14 - 8];  $p < 0.001$ ). Polyarthrosis is read 4 times and associated with the risk of occurrence of AAR complications. Other inflammation markers are compatible with protective effect (RR < 1). The average incidence rate of cardiac damage was 57.7 cases of AAR per 1000 people per year for cardiac damage. **Conclusion:** The study allowed data on the impact rate and complications of the AAR in Bangui. Special attention to data management will help produce a complete result on the problem. Joint complications predominated. Sustaining an effective surveillance system and preventing infection would help reduce the risk of AAR occurrence.

## Keywords

Incidence, Acute Joint Rheumatism, Central African Republic

## 1. Introduction

Acute rheumatic fever (AAR) is a multi-systemic inflammatory disease, which is a non-suppurative complication of an insufficiently or untreated upper airway infection by group A hemolytic *Streptococcus*  $\beta$  (SBHA). Group "A" *Streptococcus* are facultatively anaerobic aero-anaerobic Gram-positive cocci, belonging to the family *Streptococcaceae* of the genus *Streptococcus*. They are capable of causing a range of infections with very variable manifestations ranging from mild infections to very severe infections [1] [2] [3] [4]. The complication of the disease due to SBHA occurs a few weeks after angina. These complications can affect the joints, the skin (in 5% of cases), the central nervous system, and the heart [5]. *Streptococcus* infection was reduced in developed countries in earlier years, but from the 1980 to date, it has re-emerged due to unsanitary conditions and inadequate patient care by antibiotics [6]. Joint damage represents 75% of primary damage [6], unilateral or bilateral damage to the knees and ankles is found in most children as well as adults. Post-streptococcal rheumatism in adults generally occurs between the ages of 40 and 60 and is characterized by joint manifestations [7]. Sydenham's chorea, or St. Vitus' dance, is a rare symptom that appears in 10% to 15% of cases. It occurs late after a period of up to six months [8] [9] [10]. Female subjects are more affected than male subjects [11] [12] [13]. Subcutaneous nodules occur in subjects with carditis and disappear within 1 to 2 weeks without leaving any trace [14]. It can affect the pericardium,

myocardium, and endocardium. This manifestation can also be earlier or later [15]. The rate of AAR and heart disease remains high in Africa due to the socio-economic conditions of the population [16]. The biological signs show during the RAA, a sedimentation rate (ESR) greater than 60 mm in the first hour [17] [18]. The concentration of C-reactive protein (CRP) is generally above 7.0 mg/dL. In current practice, antistreptolysins O (ASL) are the most requested to make the diagnosis of RAA. The titer of ASL is high one week after infection, and then decreases from the 8th week [19]. Taking antibiotics and corticosteroids can reduce ASL antibody levels [20]. Young age, ethnicity, socio-economic situation, and lack of quality care are risk factors that contribute to the occurrence of AAR [21] [22]. The risk of developing rheumatic heart disease is twice as high in women as in men. The epidemiology of AAR and its complications varies depending on region, time, and individual [23] [24]. Its incidence is much higher in the age group of children 5 to 15 years [25]; Beyond the age of 35, it is reduced and is very low in subjects under 4 years of age. Worldwide, the number of new cases per year is estimated at 471,000, including 336,000 cases in children aged 5 to 14; In low-income countries, more than 250,000 deaths among young and adult subjects are estimated. Surveys carried out in Mozambique, then in Uganda and Senegal, demonstrated that ultrasound detects more cases of sub-clinical rheumatic heart disease (RC), estimated between 7.5 and 51.6 per 1000 children [26]. The Jones criteria facilitate the diagnosis of AAR [27] [28]. In Africa and particularly in the Central African Republic, conditions due to AAR do not seem to interest practitioners because they do not affect the mass but the individual and only involve the functional prognosis. Despite the existence of a disease control department, little data is available on the AAR. It is in this context that this was carried out, the main objective of which is to evaluate the incidence rate of post-streptococcal complications, particularly AAR, in Bangui in the Central African Republic.

## 2. Methodology

This was a retrospective and analytical study over a period of 4 years (January 2015 to December 2018) at the National Laboratory of Clinical Biology and Public Health (LNBCSP) in Bangui. It focused on samples concerning the diagnosis of AAR and patient files seen in consultation in the capital's reference health establishments. These files were consulted in the neurology and cardiology departments of the Central African Friendship University Hospital Center of Bangui. These samples were taken from the blood of patients referred by the various health facilities in Bangui (National University Hospital Center of Bangui (CNHUB), Sino Central African Friendship University Hospital Center, Mama Elisabeth Domitien Hospital Center, the community hospital addressed) at the LNBCSP for the ASL test, blood count, determination of the sedimentation rate (ESR), C-Reactive Protein (CRP) dosage. A standardized form made it possible to collect data at the laboratory level and the specialty department level. Patient files seen in consultation outside the study period and not meeting the case definition according

to the Jones criteria, as well as the examinations carried out were excluded. The Jones criteria are a set of clinical and biological arguments after confirmation of a *streptococcal* infection. They are based on two (02) or one (01) major criteria and two (02) minor criteria. The major criteria are carditis, polyarthritits, Chorea, Erythema marginatum, and subcutaneous nodules. Minor criteria are fever, arthralgia, recent history of angina, accelerated sedimentation rate, leukocytosis, increased CRP, prolonged PR space, increased ASL, and isolation of streptococci in throat swab.

## 2.1. Biological Diagnosis

The ASL Latex test from Cypress Diagnostics (Hulshout, Belgium) by slide agglutination, intended for the qualitative and semi-quantitative determination of Anti-Streptolysin O in human serum, had been carried out. The qualitative method allows you to have either a negative reaction indicated by a uniform milky suspension without agglutination as observed with the negative control; either a positive reaction indicated by the presence of visible agglutination, resulting in a heterogeneous solution, different from that of the negative control. The presence of agglutination indicates an ASL concentration greater than or equal to 200 IU/ml. In the semi-quantitative method, the titer is the reciprocal of the highest dilution with a positive result. The CRP-Latex (C-reactive protein) assay provided by Cypress Diagnostics (Hulshout, Belgium) was carried out using a slide agglutination test for the qualitative and semi-qualitative determination of CRP in human serum. The performance of the test and the interpretation are comparable to those of the ASLO Latex test. The hemogram was carried out on Mindray BC-20S (Mindray, Shenzhen, China) and CYAN HEMATO machines from Cypress Diagnostics (Hulshout, Belgium), and the sedimentation rate was carried out by filling a VS tube by capillary action until zero line and placed in a vertical position on its rack. The plasma height is read after exactly one hour of sedimentation and then at 2 hours.

## 2.2. Data Analysis

To determine the incidence rate of AAR, the data were collected, codified, and entered into Microsoft Excel software (Redmond, Washington, USA) then exported and analyzed using Epi Info 7.2 software (WHO, Geneva, Switzerland and CDC, Atlanta USA), the texts were entered using World 2010 software (Redmond, Washington, USA). The quality of the data was assessed by searching for duplicates, aberrant, and missing data to be excluded, corrected, or completed. The study variables were age, sex, place of residence, year, ASLO, CRP, Hemogram, ESR, Leukocytes, Polynuclear cells, fever, cardiac, joint, and skin damage. Descriptive tests were used to calculate measures of central tendency (mean, mode, standard deviation, and confidence interval) with  $p < 0.05$ . The Fischer Exact and Yates tests made it possible to compare the proportions. The relative risks (RR) were calculated to measure the degree of association. The in-

cidence rate of the AAR was expressed in person-years and was determined by the ratio of the number of new cases occurring in the year per person-time.

### 3. Results

From January 2015 to December 2018; 304 blood samples were taken from patients for AAR research. The age of the patients ranged from 18 to 85 years with a mean of 54 years (standard deviation: 16 years) and the mode 60 years. The female gender predominated with 56 cases or 59.57% (56/94) the male gender 38 cases or 40.42% (38/94) and the sex ratio (M/F) was 0.67 at the expense of the female sex.

**Table 1** presents the evolution of the AAR incidence rate during the study period. The average incidence rate was 314.24 cases of AAR per 1000 people per year. As the incidence rate is unstable from one year to the next, the cumulative incidence rate over five years has not been determined.

**Table 2** presents the distribution of the incidence rate of AAR cases according to age groups.

The incidence of AAR cases for the age group between 45 and 59 years old was 125.5 cases per 1000 people per year ( $p > 0.05$ ). She resumes 36.17% (34/94) of cases.

**Table 1.** Evolution of the incidence rate of AAR cases according to the years.

Year	Population at risk	Incidents cases	I* AAR/year	I/100 AAR	I/1000 AAR
2015	120	35	0.29	29.16	291.66
2016	40	13	0.32	32.50	325.00
2017	69	24	0.34	34.78	347.82
2018	75	22	0.29	29.33	293.33
<b>Total</b>	<b>304</b>	<b>94</b>	<b>0.31**</b>	<b>31**</b>	<b>314.24**</b>

\* = Incidence rate; \*\* = Average incidence rate.

**Table 2.** Distribution of the incidence rate of AAR cases according to age groups.

Population at risk	120	40	69	75	<b>304</b>
Incidents cases	35	13	24	22	<b>94</b>
<b>Frequency</b>	<b>case (I*)</b>	<b>case (I*)</b>	<b>case (I*)</b>	<b>case (I*)</b>	<b>case (I**)</b>
<b>Age range</b>					
[15 - 29]	4 (3.33)	0 (0)	4 (5.79)	2 (2.66)	<b>10 (2.94)</b>
[30 - 44]	7 (5.83)	1 (2.5)	4 (5.79)	6 (8)	<b>18 (3.44)</b>
[45 - 59]	11 (9.16)	8 (20)	9 (13.04)	6 (8)	<b>34 (12.55)</b>
≥60	13 (10.83)	4 (10)	7 (10.14)	8 (10.67)	<b>32 (10.41)</b>
<b>Total</b>	<b>35 (29.15)</b>	<b>13 (32.5)</b>	<b>24 (34.76)</b>	<b>22 (29.33)</b>	<b>94 (29.24)</b>

\* = Incidence rate; \*\* = Average incidence rate.

**Figure 1** presents the evolution of the incidence rate of AAR by sex from 2015 to 2018.

The incidence rate of AAR for the female sex was higher than that of the male sex during the study period. It went from 166.6 in 2015 to 200 in 2016 and 2018 cases of AAR per 1000 people per year.

**Table 3** presents the incidence rate of AAR complication cases according to the conditions. Joint damage represented 80.85% (RR = 0.62;  $\text{Chi}^2 = 4.88$ ; 95% CI [0.39 - 0.97];  $p < 0.01$ ).

Joint damage was more frequent with an average incidence rate of 246.6 cases per 1000 people per year.

They represent 80.85% (76/94) as heart attainments resume 19.15% (18/94). The complication rate increased from 74.28% (26/35) in 2015 to 77.27% (17/22) in 2018. There is compatibility with protective effect.

**Table 4** presents association between AAR and clinical and biological characteristics.

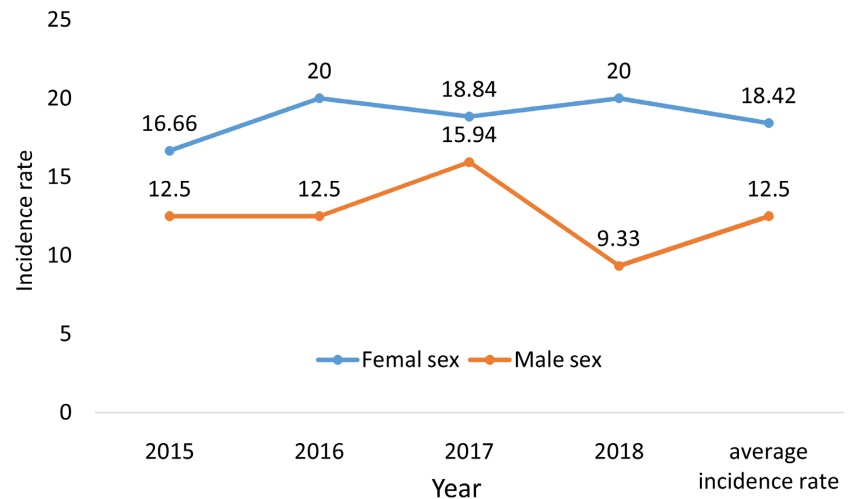
**Table 3.** Distribution of the incidence rate per year of cases of AAR complications.

Year	2015	2016	2017	2018	Total
<b>Population at risk</b>	120	40	69	75	<b>304</b>
<b>Frequency</b>	case (I*)	case (I*)	case (I*)	case (I*)	case (I**)
<b>Cardiac injuries (I*)</b>	9 (7.5)	3 (7.5)	1 (1.44)	5 (6.66)	<b>18 (5.77)</b>
<b>Joint damage (I*)</b>	26 (21.66)	10 (25)	23 (33.33)	17 (22.66)	<b>76 (24.66)</b>
<b>Total</b>	<b>35 (29.16)</b>	<b>13 (32.5)</b>	<b>24 (34.78)</b>	<b>22 (22.33)</b>	<b>94 (29.69)</b>

(I\*) = Incidence rate; (I\*\*) = Average incidence rate.

**Table 4.** Association between AAR and clinical and biological characteristics.

	RR	Chi <sup>2</sup>	95% CI	P-value
<b>Association between joint complications and clinical signs</b>				
<b>Arthritis</b>	0.75	4.2	[0.34 - 0.94]	<b>0.01</b>
<b>Polyarthritis</b>	0.82	4.1	[0.33 - 0.95]	<b>0.02</b>
<b>Association between joint complications and markers of inflammation</b>				
<b>High ASL</b>	0.73	4.5	[0.33 - 0.93]	<b>0.01</b>
<b>High CRP</b>	0.70	4.45	[0.32 - 0.93]	<b>0.01</b>
<b>Fever</b>	0.67	7.4	[0.28 - 0.79]	<b>0.003</b>
<b>High WBC</b>	0.74	5	[0.32 - 0.90]	<b>0.01</b>
<b>High ESR</b>	<b>1.17</b>	4	[0.63 - 0.84]	<b>0.02</b>
<b>Association between cardiac complications and markers of inflammation</b>				
<b>High ASL</b>	0.38	5	[0.06 - 0.89]	<b>0.001</b>
<b>High polynuclear</b>	0.57	7	[0.06 - 0.81]	<b>0.03</b>
<b>High WBC</b>	0.62	4	[0.12 - 0.98]	<b>0.03</b>



**Figure 1.** Evolution of the incidence rate of AAR cases per year according to sex.

Accelerated sedimentation speed (ESR) is associated with a risk of joint complication of AAR (RR = 1.17). Polyarthrosis resumes in 89.47% of cases (RR = 4.22;  $\text{Chi}^2 = 25.34$ ; 95% CI [2.14 - 8];  $p < 0.001$ ). Polyarthrosis is read 4 times and associated with the risk of occurrence of AAR complications.

Other inflammation markers are compatible with protective effect (RR < 1).

#### 4. Discussions

The study, carried out from 2015 to 2018, covered 94 confirmed cases of AAR and complications. The diagnosis of AAR was made according to the modified Jones criteria [27] [28]. The average incidence rate of AAR cases was 314.24 cases of AAR per 1000 people per year. It went from 291.66 cases of AAR per 1000 people per year in 2015 to 293.33 cases of AAR per 1000 people in 2018, with a peak of 347.82 in 2017. Cases of AAR can be confused with other diseases showing the same signs if not supported by qualified personnel [20] [21]. This drop in the incidence rate was due to the improvement in hygiene conditions, access to care, and care by qualified personnel after the crisis. Early treatment reduces cases of complications. This result was close to that of the study carried out by Sabine Halle *et al.* in 2018 in Algeria. Studies carried out by Watkins, David *et al.* in 2020 and by Baker MG *et al.* in 2019 in New Zealand showed similar results [21]. The average incidence rate for the age group bet 45 to 59 years was 125.5 cases of AAR per 1000 people ( $p > 0.05$ ). It was in decline going from 20 cases of AAR per 1000 people per year in 2016 to 8 cases of AAR per 1000 people per year in 2018. This result was higher than that of the study carried out in Australia by Jonathan R. *et al.* in 2016 with an incidence ranging between 1.5 to 3.8 cases of AAR per 1000 people per year [3]. The average incidence rate of AAR cases for females was 184.2 AAR per 1000 people per year. This result is similar to that of Lawrence JG, *et al.* in 2013 in Australia [27]. These results are similar to another study conducted by Rothenbühler M *et al.* in 2014 in Australia [28]. Our results support those of other studies carried out by Dougherty *et al.* in 2021

and Michael H Gewitz *et al.* in 2015 *et al.* [11]. Another study carried out by Webb, Rachel Helena *et al.* in 2015 in New Zealand, showed similar results [12]. The average incidence rate of AAR cases for complications was 296.9 per 1000 people per year. The average incidence rate of AAR cases for joint damage was 246.6 per 1000 people per year. These results are similar to those of Rebecca J. Burke *et al.* in 2014 and Stephan J. L. with 70% to 75% of cases of joint manifestations of AAR [17]. Joint damage was 80.85%. Multivariate analysis showed increased exposure to joint damage compared to other damage (RR = 0.62;  $\text{Chi}^2 = 4.88$ ; IC [0.39 - 0.97]  $p < 0.01$ ). The incidence rate of AAR of joint complications was decreasing. It went from 216.6 joint injuries per 1000 people per year in 2015 to 226.6 in 2018 with a peak of 33.3 in 2017. The age group most affected was those between 45 and 59 old [7]. These results are not statically significant ( $p > 0.05$ ). They are close to those of Rebecca J. Burke *et al.* [20]. These results support those of Watkins *et al.* in 2021, and Zühlke, L. *et al.* in 2017 [21] [22]. This result shows that elderly subjects are much more exposed to diseases because of their weak immunity. This observation was also made in American and European countries. The progression of AAR towards joint complications was associated with clinical signs and biological parameters. Cases of arthritis and polyarthritis were more frequent with 59.57% and 72.34% respectively [7]. The results were statistically significant with a relative risk (RR) of 2.74;  $\text{Chi}^2 = 23.66$ ; 95% CI [1.77 - 4.25];  $p < 0.001$ ; for cases of arthritis. The results for polyarthritis cases were statically significant with a relative risk of 4.22; 95% CI [2.143 - 8];  $p < 0.0006$ . There was a significant association between clinical manifestations and AAR (Table 4). Univariate analyses showed an association between general markers and the occurrence of AAR complications. The results of the biological parameters were ESR (RR = 1.17; 95% CI [0.3 - 0.9];  $p < 0.02$ ), CRP (RR = 0.67; 95% CI [0.3 - 0.9];  $p < 0.01$ ), leukocyte number (RR = 0.67; 95% CI [0.3 - 0.9];  $p < 0.01$ ). The clinical signs were hyperthermia (RR = 0.67; 95% CI [0.28 - 0.79];  $p < 0.003$ ). These results were close to those of Rebecca J. Burke *et al.*, as well as Michael H. Gewitz *et al.* [17] [18]. The average incidence rate of AAR cases of cardiac complications was 40.9 per 1000 people per year. The evolution the incidence rate of AAR cases of cardiac complications was decreasing from 66.5 in 2015 to 7.8 cardiac complications of AAR per 1000 people per year in 2019. The age group of 45 to 59 years was the most affected with 41.18%; predominated with 6.37% (RR = 1.87; 95% CI [0.06 - 0.7];  $p < 0.02$ ); compared to 4.45% of the female sex. These results were in contradiction to those of Matthew M Coates and Joseph J. Ferretti *et al.* respectively from the African Union and the University of Oklahoma Health Sciences Center in 2016 [7] [16]. This contradiction would be due to the size of the series affected by cardiac complications. Hyperthermia, asthenia, anorexia, and abdominal pain, were the frequent clinical signs, respectively 64.71%; 58.82%; 52.94%; and 29.41%. The rate of carditis was 15.47%. Those of the myocardium, endocardium, and pericardium were respectively 61.53%; 69.23%; 69.23%. These results were not statistically significant. ( $p > 0.05$ ) and could also be explained by our series and the size of the affected



population. These results are very close to those of Michael H *et al.* in 2015 from the American Heart Association, Inc. [17].

#### **Ethics Statement**

Data collection and analysis were performed in accordance with the guidelines set forth by the Declaration of Helsinki. The study proposal was approved and was carried out following authorization from the Ministry of Health and Population No. 1038 MSP/DIRCAB/DR/SRH.19 of October 15, 2019.

#### **Limit of the Study**

The retrospective nature of this study did not allow us to have some information on the risk factors, the data from cases seen in pediatrics and the ECG results had not been taken into account. Skin breaches had not been exploited because of the unavailability of data.

### **5. Conclusion**

The study allowed data on the impact rate and complications of the AAR in Bangui. Special attention to data management will help produce a complete result on the problem. Joint complications predominated. Sustaining an effective surveillance system and preventing infection would help reduce the risk of AAR occurrence.

### **Conflicts of Interest**

The authors have no conflicts interest to declare for this study.

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## Annex

### Data Collection Sheet

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_; N° ID: \_\_\_\_\_;

Code: \_\_\_\_/\_\_\_\_/\_\_\_\_/\_\_\_\_

Note: yes = 1; no = 2

#### 1) Identification

Name: \_\_\_\_\_; Last Name: \_\_\_\_\_

Age (year): \_\_\_\_\_; Sex: Male / \_\_\_\_/; Female / \_\_\_\_/;

Contact: \_\_\_\_\_;

#### Place of residence:

1<sup>er</sup> borough/\_\_\_\_/; 4<sup>e</sup> borough/\_\_\_\_/; 7<sup>er</sup> borough/\_\_\_\_/;

2<sup>e</sup> borough/\_\_\_\_/; 5<sup>e</sup> borough/\_\_\_\_/; 8<sup>e</sup> borough/\_\_\_\_/;

3<sup>e</sup> borough/\_\_\_\_/; 6<sup>e</sup> borough/\_\_\_\_/;

Another has pre-curling: \_\_\_\_\_;

Nationality: Central African / \_\_\_\_/; Foreign / \_\_\_\_/

#### 2) Clinical Signs

Fever: Yes / \_\_\_\_/; No/ \_\_\_\_/;

Asthenia: Yes / \_\_\_\_/; No/ \_\_\_\_/;

Anorexia: Yes / \_\_\_\_/; No/ \_\_\_\_/;

Abdominal pain: Yes / \_\_\_\_/; No/ \_\_\_\_/;

Arthritis: Yes / \_\_\_\_/; No/ \_\_\_\_/;

Polyarthritis: Yes / \_\_\_\_/; No/ \_\_\_\_/;

Myocarditis: Yes / \_\_\_\_/; No/ \_\_\_\_/;

Pericarditis: Yes / \_\_\_\_/; No/ \_\_\_\_/;

Endocarditis: Yes / \_\_\_\_/; No/ \_\_\_\_/;

Sydenham Chorea: Yes / \_\_\_\_/; No/ \_\_\_\_/;

Meynet's skin soft nodosity: Yes / \_\_\_\_/; No/ \_\_\_\_/;

Besnier's erythema margine: Yes / \_\_\_\_/; No/ \_\_\_\_/;

Groupe A streptococcus infection: Yes / \_\_\_\_/; No/ \_\_\_\_/;

#### 3) Biological Diagnosis

ASL: >200 UI/ml Yes / \_\_\_\_/; No/ \_\_\_\_/;

CRP: >6 mg/ml Yes / \_\_\_\_/; No/ \_\_\_\_/

Neutrophil polynuclear: >70% (7 Giga/L) Yes / \_\_\_\_/; No/ \_\_\_\_/;

WBC: >10 G/L Yes / \_\_\_\_/; No/ \_\_\_\_/;

Sedimentation rate (ESR): >20 mm at the first hour Yes / \_\_\_\_/; No/ \_\_\_\_/