Scientific Research Publishing

Open Journal of Preventive Medicine, 2024, 14, 211-225
https://www.scirp.org/journal/ojpm
ISSN Online: 2162-2485
ISSN Print: 2162-2477

Interruption of Yaws in Central African Republic: What Dose of Azithromycin and How Many Cycles of Mass Treatment?

Germain Piamale[1,2*], Bohy-Ngombet Romaric Ghislain Zarambaud[1], Rodrigue Herman Doyama-Woza[2], Emmanuel Fandema[2], Christian Maucler Pamatika[3], Juvénal Constantin Dombeti[4], Henri Saint Calvaire Diemer[2], Jean De Dieu Longo[2], Gérard Gresenguet[1,2]

[1]Doctoral School of Human and Veterinary Health Sciences, University of Bangui, Bangui, Central African Republic
[2]Department of Public Health, Faculty of Health Sciences, University of Bangui, Bangui, Central African Republic
[3]Integrated Disease Surveillance Service, Bangui University Hospital Center, Bangui, Central African Republic
[4]Laboratory Department, Maman Elisabeth Domitien University Hospital Center, Bangui, CAR
Email: *germain.piam@yahoo.fr

How to cite this paper: Piamale, G., Zarambaud, B.-N.R.G., Doyama-Woza, R.H., Fandema, E., Pamatika, C.M., Dombeti, J.C., Diemer, H.S.C., Longo, J.D.D. and Gresenguet, G. (2024) Interruption of Yaws in Central African Republic: What Dose of Azithromycin and How Many Cycles of Mass Treatment? *Open Journal of Preventive Medicine*, **14**, 211-225.
https://doi.org/10.4236/ojpm.2024.1412016

Received: October 25, 2024
Accepted: December 8, 2024
Published: December 11, 2024

Abstract

Introduction: The WHO recommends mass administration of azithromycin 30 mg/kg to eradicate yaws and 20 mg/kg to eliminate trachoma. We evaluated the effectiveness of azithromycin at 20 and 30 mg/Kg, and the number of cycles of mass administration on the treatment and interruption of yaws transmission in the Mbaïki health district in the Central African Republic. **Methods:** Following a yaws prevalence survey, azithromycin was administered as a mass treatment in four yaws endemic communities in the Mbaïki health district. Azithromycin 30 mg/kg was administered in one cycle in Kenengué and three cycles spaced three months apart in Bambou. In Kapou and Bangui-Bouchia, azithromycin was administered at a dose of 20 mg/kg in one cycle and three cycles, respectively, spaced three months apart. Before the mass treatment round, confirmed yaw cases were selected and followed for seven months. The primary endpoint was serological cure seven months after the first treatment cycle. Secondary endpoints were clinical cure at four weeks after the first treatment cycle and serological cure at four months after the first treatment cycle. A non-inferiority margin (Δ) of 10% was used. **Results:** A total of 92 participants aged 1 to 90 years, including 52 men, were included in the study. The frequently encountered skin lesions were ulcers (65.22%) and were localized to the lower limbs (59.78%). Clinical cure was not obtained in Bangui-Bouchia and Kapou (Δ = 17.1% and 30.8%). Serological cure at four and seven months was not obtained in Kapou (Δ equal to 17.9% and 13.8%

respectively). **Conclusion:** This study confirms the effectiveness of azithromycin 30 mg/kg in a single dose for the treatment of yaws. However, the study suggests that for yaws eradication programs, two to three cycles of mass administration of azithromycin at 20 or 30 mg/kg spaced three months apart, with therapeutic coverage greater than 90% are essential.

Keywords

Eradication, Yaws, Mass Administration, Azithromycin, Central African Republic

1. Introduction

Yaws is a neglected tropical disease caused by *Treponema pallidum ssp pertenue*. It occurs in isolated communities in 14 countries in Africa, Asia and the Western Pacific [1] [2]. It is transmitted by direct skin contact between a healthy person and a person with an early infectious yaws skin lesion. It mainly affects children under 15 years old.

These early lesions (primary and secondary) manifest mainly as skin ulcers and papillomas. The serological diagnosis of yaws requires the detection of treponemal and non-treponemal antibodies [3]. Recently, point-of-care serological testing and PCR assays have become available to aid diagnosis [3]-[6].

If left untreated, yaws can progress to destructive damage to bone and soft tissue. Long-acting injectable penicillin was the mainstay of yaw treatment during campaigns led by the World Health Organization (WHO) and the United Nations Children's Fund in the 1950s [7] [8].

In 2012, a randomized controlled trial (RCT) in Papua New Guinea showed that a single dose of 30 mg/kg azithromycin (maximum 2 g) was not inferior to benzathine benzylpenicillin for the treatment of yaws [9]. Following this discovery, the WHO developed a new yaws eradication strategy based on mass treatment of the community with azithromycin [10]. Mass treatment with azithromycin in the community is also essential for the WHO SAFE strategy to eliminate trachoma as a public health problem [11]. The dose of 20 mg/kg (maximum 1 g) of azithromycin used in trachoma elimination programs is lower than the recommended dose for the treatment of yaws [12]. In areas where trachoma and yaws are endemic, if the dose of azithromycin used in mass treatment campaigns for trachoma elimination is effective against yaws, these campaigns can contribute to yaws eradication efforts, and this would have implications in the fight against both diseases. On the contrary, if the dose of 20 mg/Kg of azithromycin is not effective in the treatment of yaws, it could have negative consequences in the fight against yaws with the possibility of selection of resistant strains of *Treponema pallidum ssp pertenue* to macrolides [13]-[15].

Studies in Ghana, Papua New Guinea and the Solomon Islands show that mass

administration campaigns of azithromycin lead to a reduction in the prevalence of yaws [16] [17]. Conversely, other studies have reported the reappearance of yaws after a single cycle of mass treatment with azithromycin [18].

In the Central African Republic (CAR), yaws and trachoma are endemic [19]-[22]. If mass administration of 20 mg/kg azithromycin in one or more cycles proves effective in reducing yaw transmission, this would contribute to effective control of both diseases.

The objective of this study was to evaluate the effectiveness of azithromycin at 20 mg/Kg and 30 mg/Kg, in one, two or three cycles of massive administration on the treatment and reduction of yaws transmission in the health district (DS) of Mbaïki in CAR.

2. Methods

2.1. Study Design

This is a therapeutic evaluation study of the effectiveness of azithromycin at 20 and 30 mg/Kg on the treatment and transmission of yaws in four yaws endemic communities, DSM in CAR.

2.2. Setting

The Mbaïki DS is one of the 35 DS in the CAR. It is in the southwest of the country and shares common borders with the Republic of Congo and the Democratic Republic of Congo to the south, the DS of Boda to the west, the DS of Bossembelé to the North and that of Bimbo to the East. It has respectively 219,000 and 227,000 inhabitants in 2020 and 2021 according to the latest estimates from the 2003 General Population and Housing Census. The study took place from August 22, 2020, to March 24, 2021. Four communities have been selected following a yaws prevalence survey carried out from March 31 to April 24, 2020, in the Mbaïki DS. In each of the selected communities, 20 or 30 mg/Kg of azithromycin were administered as mass treatment, either in a single cycle or in three cycles spaced three months apart.

2.3. Participants

In the four selected communities, all individuals aged over one year were identified and examined for skin lesions. Individuals with a skin lesion consistent with infectious yaws, including at least one ulcerative lesion or papilloma, as described in the WHO booklet for yaws identification [23], were invited to participate in the study. In individuals with at least one skin lesion, a 5 ml blood sample was collected. On each sample, RPR (Rapid Plasma Reagin) and TPHA (Treponema Pallidum Hemaglutination Assay) tests were performed. These two diagnostic tests detect treponemal and non-treponemal antibodies directed against Treponema pallidum. Individuals with a clinically suspicious yaws lesion and both positive serological tests (RPR and TPHA) met the inclusion criteria and were invited to participate in the study. Participants with a known allergy to azithromycin or

macrolides and those who received an antibiotic against Treponema pallidum or had another contraindication to azithromycin were excluded.

Eligible participants were randomly distributed by simple drawing into four communities (Kenengué, Bambou, Bangui-Bouchia and Kapou), corresponding to one of the four protocols used in the study. In Kenengué (reference group) and Kapou, people eligible for treatment received respectively 30 mg/kg (maximum 2 g) and 20 mg/kg (maximum 1 g) of azithromycin in a single massive administration cycle. In Bambou and Bangui-Bouchia, eligible persons received respectively 30 mg/Kg (maximum 2 g) and 20 mg/Kg (maximum 1 g) of azithromycin in three mass administration cycles, each spaced three months apart.

The team of investigators directly supervised the administration of azithromycin and observed the treated individuals for one hour after taking the drug to monitor the occurrence of immediate adverse effects. If vomiting occurred within this time, the person received a new dose of medication. All side effects were monitored and managed by the study team. Otherwise, these cases were transferred to the district hospital for further treatment. Immediate adverse reactions have been documented at the time of drug administration. Secondary adverse events reported by participants were documented at follow-up visits four weeks after each mass treatment cycle.

Participants who were included underwent an initial standard skin examination, during which information on the number, type, and location of lesions was collected. Initially, all participants benefited from the administration of azithromycin according to the protocol chosen for each of their communities.

The implementation of each mass processing cycle took two days. The first day was devoted to the census of residents and people eligible for treatment who were invited to go to the treatment site the next day. The second day corresponded to the treatment day. The census and tally sheets of the treated population were used to evaluate therapeutic coverage.

Before the start of the study, team members underwent standardized training on the clinical diagnosis of yaws, collection of blood samples, management of adverse events, and completion of documentation according to the guidelines of good clinical practices [24] [25].

All study participants, their parents or guardians when they were children, gave oral informed consent for screening and treatment. Individuals suspected of having yaw skin lesions provided written informed consent for biological sample collection. The study was authorized by the Central African Ministry of Population and Health. The study protocol was approved by the Scientific Committee for the Validation of Study Protocols and Health Research Results of the University of Bangui (N˚16/UB/FACSS/CSCVPER/19). The study was carried out in accordance with the Declaration of Helsinki [26].

Data were collected during different phases of mass azithromycin administration and one month after each mass treatment cycle in the four communities. Participants were followed for seven months. At the first visit, four weeks after the

first cycle of mass azithromycin treatment, an assessment of clinical lesions was performed. If there was no healing of the lesion (scarring), the participant was offered benzathine benzylpenicillin as an alternative treatment. At the four- and seven-month visits, a 5 ml blood serum sample was collected from each participant for serological assessment based on changes in RPR titers.

Figure 1 describes the therapeutic trial diagram.

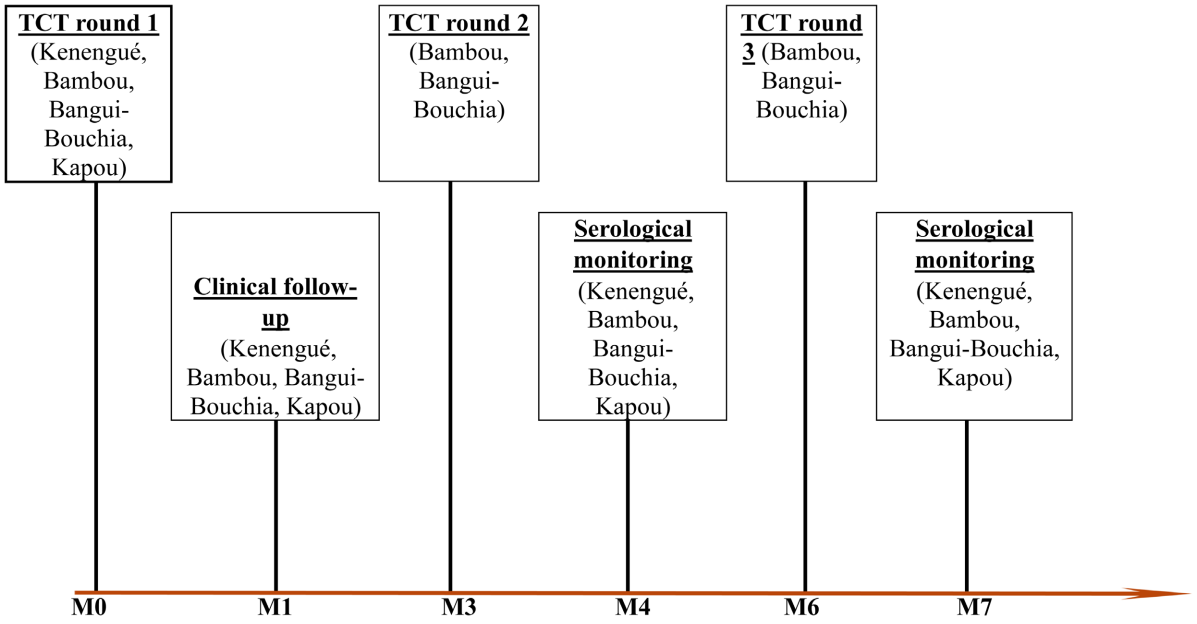


Figure 1. Therapeutic trial diagram.

2.4. Variables

Age, sex, type of skin lesion and its location, treponemal serology results as well as the state of clinical cure or therapeutic failure four weeks after the first treatment cycle, serological cure or serological failure at fourth and seventh months of follow-up after the first cycle of mass treatment, were the variables studied.

2.5. Data Sources and Measurements

Data were collected during initial screening, different phases of total community treatment, and follow-up visits. These different data made it possible to measure and evaluate in each of the four communities, the clinical and serological prevalence of yaws, the therapeutic coverage, the clinical cure rate, the therapeutic failure rate, the serological cure rate at four and seven months, the serological failure rate at four and seven months. Finally, the difference in proportions (*i.e.* the proportion of participants from Kenengué, reference group) who managed to cure minus the proportion of participants from the other groups who were cured) was calculated in order to determine the margin of non-inferiority. The primary endpoint was recovery seven months after initial treatment. The cure was a composite outcome of both clinical cure and serological cure. Serological cure at four months and clinical cure at four weeks were analyzed separately as secondary outcomes.

- Clinical prevalence: is the ratio of the number of people examined presenting a skin lesion compatible with yaws, to the total number of people examined multiplied by 100.
- Serological prevalence: corresponds to the number of people with a skin lesion compatible with yaws and whose treponemal serology was positive compared to the number of people with a skin lesion multiplied by 100.
- Therapeutic coverage: measures the number of the target population treated in the community. It is calculated from care score sheets and corresponds to the number of people treated in each treatment cycle (numerator) divided by the number of people eligible for treatment (denominator) multiplied by 100.
- Clinical healing: is defined as complete or partial resolution of the skin lesion(s), four weeks after the initial treatment.
- Therapeutic failure: is defined as the absence of clinical healing of skin lesions during the follow-up visit four weeks after the initial treatment.
- Serological cure: is defined as a negativation or a reduction of more than four times in the RPR titer (seroconversion) between the initial examination and seven months after the initial treatment.
- Serological failure: is defined as an RPR test whose titer remained exchanged or increased by at least two, between the start of the study and seven months after initial treatment.

2.6. Bias

Given that participants had the opportunity to move from one community to another and that yaw is a contagious disease, a participant could easily become reinfected through contact with members of another community and constitute bias in the interpretation of our data. To reduce sources of bias, participants and investigators performing statistical analyses or laboratory analyses of samples were blinded to the different massive azithromycin administration protocols.

2.7. Sample Size

We opted for exhaustive sampling. In the four selected communities, anyone with serologically confirmed yaws, according to our case definition, was enrolled in the study.

2.8. Quantitative Variables

The age of the participants was the quantitative variable measured. Extreme ages, median age, mean and standard deviation were calculated.

2.9. Statistical Methods

The study aimed to evaluate the effectiveness of azithromycin at 30 mg/Kg and 20 mg/Kg, in one, two or three cycles of administration, for the reduction of yaws transmission. A predefined non-inferiority margin of 10% was used. Non-inferiority was defined as an upper limit of the two-sided 95% confidence interval (CI),

for the difference in proportions Δ (*i.e.*, the proportion of Kenengué participants (reference group) who managed to recover minus the proportion of participants from other communities who recovered) less than or equal to 10%. This margin was chosen to reflect the maximum difference in effectiveness that would allow the 20 mg/kg dose to remain acceptable for use in yaw eradication efforts.

The first analysis involved participants whose serum samples were positive for RPR and TPHA (confirmed case of yaws) at baseline and who received regular monitoring during all follow-up phases. Next, we conducted secondary analyses planned for the four-week and four-month follow-ups. The analyses were carried out with SPSS version 22. The proportions were calculated and the x^2 tests were carried out for a significance level of $p < 0.05$.

The statistical processing did not consider the data of people who refused the blood test, or whose age was not recorded, or whose sample was defective. Participants with missing data at baseline or during follow-up were removed from analyses.

3. Results

3.1. Participants

From August 22 to 31, 2020, 1008 people were examined in four known yaws-endemic communities in the Mbaïki health district, of whom 130 (12.89%) had skin lesions consistent with yaws. Of the 130 people, 92 (70.77%) were confirmed positive in RPR and TPHA tests simultaneously, and are included for follow-up and distributed across four communities. We had respectively 8, 17, 41 and 26 participants in Kenengué, Bambou, Bangui-Bouchia and Kapou.

3.2. Descriptive Data

The ages of the 92 participants ranged from 1 to 90 years. The mean age was 16.9 years, and the median age was 11 years with a standard deviation of 18.275. Men represented 56.52% of our sample with a sex ratio of 1.3. Seven-year-old children were more frequently found in our sample. The age group of 15 years and over were more represented (32.61%), followed by that of children aged 1 to 5 (23.91%). Ulcer-type skin lesions (65.22%), followed by macules (26.08%) were more frequent and were more often found on the lower limbs (59.78%), upper limbs (16.30%) and face/head (14.14%). Table 1 below presents the demographic and clinical characteristics of participants by community.

3.3. Results Data

Of the 1008 people examined, 130 had skin lesions suggestive of yaws. Of the 130 samples, serological tests confirmed 92 cases of yaws. The clinical prevalence was higher in Bangui-Bouchia (19.14%), compared to other communities where it varied between 8.08% and 9.52%. Serological prevalence was higher in Kenengué (100%) and Kapou (92.86%). Table 2 below presents the clinical and serological prevalence in each community.

Table 1. Sociodemographic and clinical characteristics of participants by community.

Variables	Community				Total %	P
	Kenengué n (%)	Bambou n (%)	Bangui-Bouchia n (%)	Kapou n (%)		
Sex						
Male	6 (75.00)	10 (58.80)	21 (51.20)	15 (57.70)	52 (56.52)	0.652
Female	2 (25.00)	7 (41.20)	20 (48.80)	11 (42.30)	40 (43.48)	
Rang age						
1 - 5 years	2 (25.00)	10 (58.80)	6 (14.60)	4 (15.40)	22 (23.91)	0.016
6 - 9 years	1 (12.50)	3 (17.60)	9 (22.00)	6 (23.10)	19 (20.65)	
10 - 14 years	1 (12.50)	1 (5.90)	9 (22.00)	10 (38.50)	21 (22.83)	
≥15 years	4 (50.00)	3 (17.60)	17 (41.40)	6 (23.00)	30 (32.61)	
Type of lesion						
Papilloma	1 (12.50)	0 (0.00)	4 (9.80)	3 (11.50)	8 (8.70)	0.213
Ulcer	5 (62.50)	16 (94.10)	23 (56.10)	16 (61.50)	60 (65.22)	
Macule	2 (25.00)	1 (5.90)	14 (34.10)	7 (27.00)	24 (26.08)	
Location of lesions						
Head/Face	1 (12.50)	3 (17.60)	6 (14.60)	3 (11.50)	13 (14.14)	0.669
Upper limbs	0 (0.00)	3 (17.60)	5 (12.20)	7 (27.00)	15 (16.30)	
Lower limbs	6 (75.00)	11 (64.80)	25 (61.00)	13 (50.00)	55 (59.78)	
Thorax/abdomen	1 (12.50)	0 (0.00)	5 (12.20)	3 (11.50)	9 (9.78)	

Table 2. Clinical and serological prevalence of yaws by community.

Communities	People examined (n = 1008)	Suspected yaws case (n = 130)	Clinical prevalence (%)	Confirmed yaws cases (n = 92)	Serologic prevalence (%)
Kenengué	99	8	8.08	8	100.00
Bambou	244	23	9.43	17	73.91
Bangui-Bouchia	371	71	19.14	41	57.75
Kapou	294	28	9.52	26	92.86

Therapeutic coverage measured the number of target populations treated in the community. These coverages ranged from 91% during the first phase (A) of total community treatment (TCT), to 67% during the third and final phase (C). Table 3 below presents the evolution of therapeutic coverage by phase and by community treated.

3.4. Main Results

The thresholds for serological cure at seven months and incidentally those for clinical cure at four weeks and serological cure at four months were the indicators sought during our study. Table 4 presents the clinical and serological cure rates by community and by follow-up period. Clinically, the non-inferiority criterion was not reached in Bangui-Bouchia and Kapou (Δ equal to 17.1 and 30.8 respectively). The eight participants who were not cured after four weeks were either in Bangui-Bouchia or Kapou.

Table 3. Evolution of therapeutic coverage by TCT round by community.

Communities	Total population (n = 1536)	Target population (n = 1490)	People treated with azithromycin Round A (n = 1297)	Coverage (%)	People treated with azithromycin Round B (n = 654)	Coverage (%)	People treated with azithromycin Round C (n = 554)	Coverage (%)
Kenengué	286	277	249	90	ND	-	ND	-
Bambou	398	386	330	85	280	73	260	67
Bangui-Bouchia	439	426	386	91	374	88	294	69
Kapou	413	401	332	83	ND	-	ND	-

Table 4. Clinical and serological cure rate by community and follow-up period.

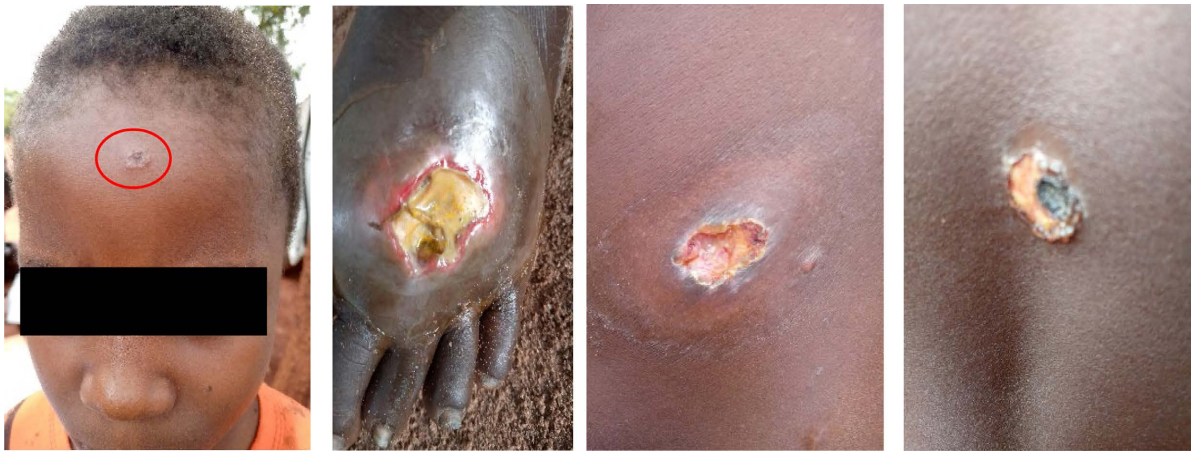
Community	Follow-up week four n = 85			Follow-up month four n = 81			Follow-up month seven n = 77		
	Cured (%)	Δ	p	Cured (%)	Δ	p	Cured (%)	Δ	p
Kenengué*	8/8 (100.0)			6/8 (75.0)			7/8 (87.5)		
Bambou**	17/17 (100.0)	0	nd	15/16 (93.8)	−18.8	0.19	14/15 (93.3)	−5.8	0.636
Bangui-Bouchia***	34/38 (82.9)	17.1	0.451	28/36 (77.8)	−2.8	0.865	31/35 (88.6)	−1.1	0.932
Kapou****	18/22 (69.2)	30.8	0.2	12/21 (57.1)	17.9	0.376	14/19 (73.7)	13.8	0.43

*Azithromycin 30 mg/Kg×1, **Azithromycin 30 mg/Kg×3, ***Azithromycin 20 mg/Kg×3, ****Azithromycin 20 mg/Kg×1.

Serological failures at four months were observed in Kenengué (25%) and Kapou (42.85%) where participants had only received one cycle of azithromycin administration. These rates were 6.25% in Bambou and 22.22% in Bangui-Bouchia. The non-inferiority criterion at four months was not reached in Kapou (Δ = 17.9).

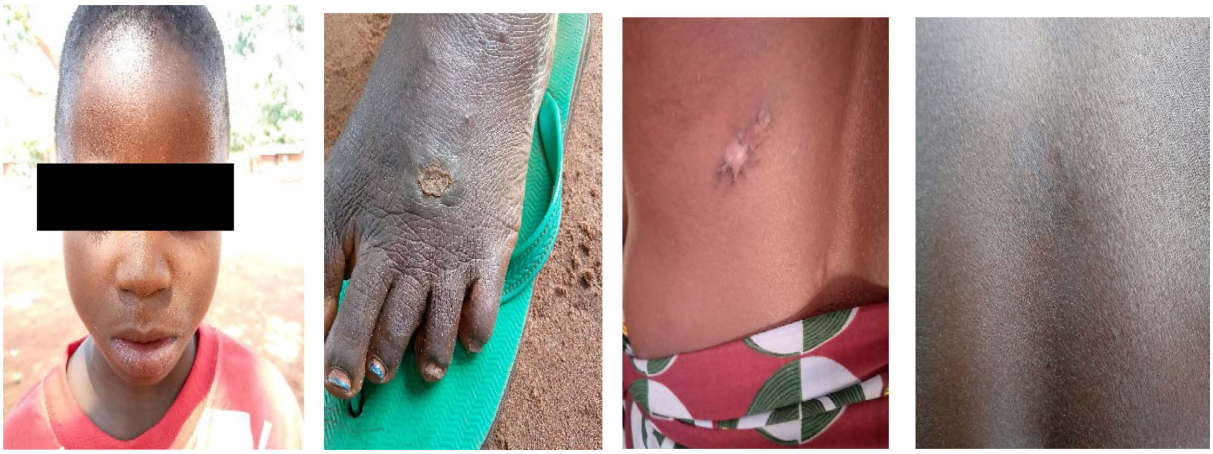
Among the eleven participants who did not obtain serological cure at seven months (one in Kenengué and Bambou, four in Bangui-Bouchia and five in Kapou), three met the definition of definitive serological failure (one in Kenengué and two in Kapou), five had an insignificant change in RPR title at seven months, four (two in Bangui-Bouchia and two in Kapou) had no change in RPR title. The RPR title doubled for a participant in Kapou. The non-inferiority criterion at seven months was not reached in Kapou (Δ = 13.8).

The proportion of participants achieving clinical cure (75.3%) did not differ significantly (p = 0.20) between communities. Figure 2 shows four initial clinical lesions in four participants in each of the four communities. The evolution of initial skin lesions four weeks after azithromycin treatment is presented in Figure 3. Likewise, the proportions of participants who achieved serological cure at four months (90.6%) and at seven months did not present any statistically significant difference (p = 0.08 and 0.36).



Source: Field survey.

Figure 2. Initial yaws-like skin lesions in each of the four study villages.



Source: Field survey.

Figure 3. Evolution of yaws-like skin lesions four weeks after treatment Evolution of yaws-like skin lesions four weeks after treatment.

4. Discussion

4.1. Key Results

In this study evaluating the effectiveness of the number of cycles of massive administration of azithromycin at 20 mg/Kg and 30 mg/Kg on the reduction of yaws transmission, azithromycin at 20 mg/Kg in one cycle of mass administration did not meet the prior non-inferiority margin requirements specified for azithromycin

30 mg/Kg. However, the non-inferiority margin was reached after two or three cycles of azithromycin administration at a dose of 20 mg/Kg. Despite this, azithromycin at 20 mg/Kg achieved a clinical cure rate of 69.20% in Kapou, but did not differ significantly from azithromycin 30 mg/Kg in Kenengué ($p = 0.20$).

In contrast, all our preplanned analyses suggest the non-inferiority of azithromycin at 20 mg/Kg administered in two or three mass treatment cycles compared to azithromycin at 30 mg/Kg. These results suggest that azithromycin 20 mg/Kg in two or three cycles of administration and administration of a single dose of azithromycin at 30 mg/Kg are likely to be equally effective in reducing yaw transmission. However, we could not demonstrate this unequivocally in the present study.

The overall proportion of participants who achieved serological cure after seven months (85.70%) was lower than the 90% expected to achieve the necessary margin to reduce the transmission of yaws. This result could be explained by the low therapeutic coverage (67% to 91%) achieved during the different cycles of mass treatment in the communities targeted by our study. The serological cure rates at four months (93.80%) and seven months (93.30%) obtained in Bambou, higher than the 75% and 87.50% obtained in Kenengué (reference group), give an indication of the need to organize at least two cycles of mass treatments to hope to reduce the transmission of yaws and, ultimately, to interrupt the transmission of the disease.

4.2. Limits

A major limitation of this study is the lower-than-expected proportion of individuals enrolled in the study who have serologically confirmed yaws. The other limitation is the fact that for this study, the serological confirmation of yaws used the RPR and TPHA tests which do not provide certainty as to the nature of the yaw's pathogen, *Treponema pallidum pertenue*. Indeed, several studies have shown that skin lesions that are serologically positive in the usual serological tests do not make it possible to detect *Treponema pallidum pertenue* with specific tests such as PCR. From this point of view, serological diagnosis methods for skin lesions constitute an additional challenge in the fight against yaws.

Although a significant number of participants (eleven) did not reach the definition of serological cure after seven months of follow-up, several factors related to the interpretation of treponemal serologies must be considered. First, among the eleven participants who had not achieved a serological cure at seven months, three participants had an RPR titer multiplied by four, which corresponded to definitive serological failure, while one participant had an RPR titer multiplied by two to follow-up. We cannot exclude the possibility of reinfection during the follow-up period, which could explain the increased RPR titer in these patients. Two of the participants who did not achieve the expected serological cure during the intervention achieved clinical cure but showed no change in RPR titer. In five participants with serological failure, the RPR titer did not change significantly. It may

take at least twelve to twenty-four months for the full extent of the reduction in RPR titer to be expressed after successful treatment, particularly in the case of latent yaws. Extending the follow-up period to twelve months or more could have increased the proportion of patients receiving serologic treatment, particularly among participants with presumed latent yaws.

Second, it is possible that some participants classified as having confirmed yaws at baseline (positive RPR and TPHA serology) are stereotyped with low non-treponemal antibody titers and for whom no significant change in RPR titers at seven months is possible even after a successful treatment. Unfortunately, there is no test to distinguish seroconversion status from latent infection. It is, therefore, not possible to precisely determine the effect of this phenomenon on the proportion of our participants who obtained a serological cure.

4.3. Interpretations

By comparing the effect of massive administration of 20 or 30 mg/Kg of azithromycin, in one cycle on the reduction of yaws transmission, the proportion of patients serologically cured at seven months was lower (73.7%) in Kapou than among the participants registered in Kenengué (87.5%), although this difference did not reach statistical significance ($p = 0.932$). A third of our participants were registered at Kapou, which could partly explain the lower proportion (73.7%) of participants who obtained serological cure at seven months. Geographic variation in intervention studies is well recognized [27], although we do not know why serological cure rates might differ between these two communities. The results of our study show that there is a difference between the two communities, even if there is no statistically significant difference ($p = 0.43$).

As part of the yaw's eradication goal, WHO supports countries in implementing strategies to achieve this goal. It provides countries with diagnostic tests, drugs (azithromycin) and logistical support for total community treatment (TCT). In a context of scarcity of resources for neglected tropical diseases in general and yaws in particular, it would be desirable to revise the current yaws eradication strategy and propose the administration of azithromycin at a dose of 20 mg/kg in two or three cycles of TCT in yaws endemic communities.

Morges strategy recommends the administration of azithromycin at a dose of 30 mg/Kg in TCT with therapeutic coverage of approximately 90%, followed by targeted community treatment (TCT) three or six months after total community treatment. Studies evaluating the Morges strategy recommend two cycles of TCT [19]. Our results suggest, however, that to achieve the goal of yaw eradication, it is essential to organize at least two cycles of TST three to six months apart with therapeutic coverage of at least 90% at each cycle of TCT regardless of the dose of azithromycin used. From this point of view, yaws eradication programs should, on the one hand, equip themselves with community mobilization strategies, to encourage community support and participation in mass drug administration campaigns, and on the other hand, review current eradication strategies and develop

plans that consider the number of mass drug administration cycles.

5. Conclusion

In this study evaluating the effectiveness of massive administration of azithromycin at 20 or 30 mg/Kg, in one, two or three cycles on the treatment and reduction of the transmission of yaws, azithromycin at 20 mg/Kg as a single dose of a mass treatment cycle, does not meet the non-inferiority criterion for both clinical cure and serological cure at four months or seven months. The non-inferiority margin was, however, reached with azithromycin at a dose of 20 mg/Kg administered in two or three mass treatment cycles. These results, subject to being validated by other large-scale studies, suggest revising the current yaws eradication strategy and exploring the possibilities of integrating yaws and trachoma control strategies into countries where these two diseases are endemic.

Funding

This study was carried out thanks to a grant offered by the Organization for the Coordination of the Fight against Endemics in Central Africa (OCEAC), based on financial cooperation between CEMAC and the Ministry of Economic Cooperation and Development. (BMZ) of the Federal Republic of Germany through the KfW (German Development Bank).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of Interest

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

References

[1] Marks, M., Mitja, O., Solomon, A.W., Asiedu, K.B. and Mabey, D.C. (2014) Yaws. *British Medical Bulletin*, **113**, 91-100. https://doi.org/10.1093/bmb/ldu037

[2] Mitjà, O., Asiedu, K. and Mabey, D. (2013) Yaws. *The Lancet*, **381**, 763-773. https://doi.org/10.1016/s0140-6736(12)62130-8

[3] Ayove, T., Houniei, W., Wangnapi, R., Bieb, S.V., Kazadi, W., Luke, L., *et al.* (2014) Sensitivity and Specificity of a Rapid Point-of-Care Test for Active Yaws: A Comparative Study. *The Lancet Global Health*, **2**, e415-e421. https://doi.org/10.1016/s2214-109x(14)70231-1

[4] Marks, M., Fookes, M., Wagner, J., Butcher, R., Ghinai, R., Sokana, O., *et al.* (2017) Diagnostics for Yaws Eradication: Insights from Direct Next-Generation Sequencing of Cutaneous Strains of Treponema Pallidum. *Clinical Infectious Diseases*, **66**, 818-824. https://doi.org/10.1093/cid/cix892

[5] Marks, M., Goncalves, A., Vahi, V., Sokana, O., Puiahi, E., Zhang, Z., *et al.* (2014) Evaluation of a Rapid Diagnostic Test for Yaws Infection in a Community Surveillance Setting. *PLOS Neglected Tropical Diseases*, **8**, e3156. https://doi.org/10.1371/journal.pntd.0003156

[6] Marks, M., Yin, Y., Chen, X., Castro, A., Causer, L., Guy, R., *et al.* (2016) Metaanalysis of the Performance of a Combined Treponemal and Nontreponemal Rapid Diagnostic

Test for Syphilis and Yaws. *Clinical Infectious Diseases*, **63**, 627-633. https://doi.org/10.1093/cid/ciw348

[7] Asiedu, K., Fitzpatrick, C. and Jannin, J. (2014) Eradication of Yaws: Historical Efforts and Achieving Who's 2020 Target. *PLOS Neglected Tropical Diseases*, **8**, e3016. https://doi.org/10.1371/journal.pntd.0003016

[8] Marks, M. (2018) Advances in the Treatment of Yaws. *Tropical Medicine and Infectious Disease*, **3**, Article 92. https://doi.org/10.3390/tropicalmed3030092

[9] Mitjà, O., Hays, R., Ipai, A., Penias, M., Paru, R., Fagaho, D., *et al.* (2012) Single-Dose Azithromycin versus Benzathine Benzylpenicillin for Treatment of Yaws in Children in Papua New Guinea: An Open-Label, Non-Inferiority, Randomised Trial. *The Lancet*, **379**, 342-347. https://doi.org/10.1016/s0140-6736(11)61624-3

[10] WHO (2012) Eradication of Yaws—The Morges Strategy. *The Weekly Epidemiological Record*, **87**, 189-194.

[11] Emerson, P. (2006) The SAFE Strategy for Trachoma Control: Using Operational Research for Policy, Planning and Implementation. *Bulletin of the World Health Organization*, **84**, 613-619. https://doi.org/10.2471/blt.05.28696

[12] Yue, Y., Xiong, T., Zeng, L., Choonara, I., Qazi, S., Chen, H., *et al.* (2019) Dose and Formulation of Azithromycin in Mass Drug Administration Studies: A Systematic Review Protocol. *BMJ Paediatrics Open*, **3**, e000462. https://doi.org/10.1136/bmjpo-2019-000462

[13] Marks, M., Sokana, O., Nachamkin, E., Puiahi, E., Kilua, G., Pillay, A., *et al.* (2016) Prevalence of Active and Latent Yaws in the Solomon Islands 18 Months after Azithromycin Mass Drug Administration for Trachoma. *PLOS Neglected Tropical Diseases*, **10**, e0004927. https://doi.org/10.1371/journal.pntd.0004927

[14] Marks, M., Vahi, V., Sokana, O., Chi, K., Puiahi, E., Kilua, G., *et al.* (2015) Impact of Community Mass Treatment with Azithromycin for Trachoma Elimination on the Prevalence of Yaws. *PLOS Neglected Tropical Diseases*, **9**, e0003988. https://doi.org/10.1371/journal.pntd.0003988

[15] Solomon, A.W., Marks, M., Martin, D.L., Mikhailov, A., Flueckiger, R.M., Mitjà, O., *et al.* (2015) Trachoma and Yaws: Common Ground? *PLOS Neglected Tropical Diseases*, **9**, e0004071. https://doi.org/10.1371/journal.pntd.0004071

[16] Abdulai, A.A., Agana-Nsiire, P., Biney, F., Kwakye-Maclean, C., Kyei-Faried, S., Amponsa-Achiano, K., *et al.* (2018) Community-Based Mass Treatment with Azithromycin for the Elimination of Yaws in Ghana—Results of a Pilot Study. *PLOS Neglected Tropical Diseases*, **12**, e0006303. https://doi.org/10.1371/journal.pntd.0006303

[17] Agana-Nsiire, P., Kaitoo, E., Agongo, E.E.A., Bonsu, G., Kyei-Faried, S., Amponsa-Achiano, K., *et al.* (2014) Yaws Prevalence, Lessons from the Field and the Way Forward Towards Yaws Eradication in Ghana. *International Scholarly Research Notices*, **2014**, 1-7. https://doi.org/10.1155/2014/910937

[18] Mitjà, O., Godornes, C., Houinei, W., Kapa, A., Paru, R., Abel, H., *et al.* (2018) Re-Emergence of Yaws after Single Mass Azithromycin Treatment Followed by Targeted Treatment: A Longitudinal Study. *The Lancet*, **391**, 1599-1607. https://doi.org/10.1016/s0140-6736(18)30204-6

[19] Boock, A.U., Ntozo'o, J.P., Boua, B. and Vander, P.B. (2019) Evidence of High Endemicity of Leprosy and Yaws in the Municipality of Balé-Loko in the Central African Republic. *Médecine et Santé Tropicales*, **29**, 155-158.

[20] Manirakiza, A., Boas, S.V., Beyam, N., Zadanga, G., Konamna, F.X., Njuimo, S.P., *et*

al. (2011) Clinical Outcome of Skin Yaws Lesions after Treatment with Benzathinebenzylpenicillin in a Pygmy Population in Lobaye, Central African Republic. *BMC Research Notes*, **4**, Article No. 543. https://doi.org/10.1186/1756-0500-4-543

[21] Mitjà, O., Marks, M., Konan, D.J.P., Ayelo, G., Gonzalez-Beiras, C., Boua, B., *et al*. (2015) Global Epidemiology of Yaws: A Systematic Review. *The Lancet Global Health*, **3**, e324-e331. https://doi.org/10.1016/s2214-109x(15)00011-x

[22] Yaya, G., Kemata, B., Youfegan Baanam, M. and Bobossi-Serengbe, G. (2015) Le trachome évolutif: Résultats d'une enquête de prévalence dans huit préfectures sanitaires en RCA. *Bulletin de la Société de pathologie exotique*, **108**, 299-304. https://doi.org/10.1007/s13149-015-0446-1

[23] WHO (2012) Brochure pour la reconnaissance du pian dans les communautés.

[24] Vijayananthan, A. and Nawawi, O. (2008) The Importance of Good Clinical Practice Guidelines and Its Role in Clinical Trials. *Biomedical Imaging and Intervention Journal*, **4**, e5. https://doi.org/10.2349/biij.4.1.e5

[25] CIOMS (2002) International Ethical Guidelines for Biomedical Research Involving Human Subjects.

[26] WMA (2013) Declaration of Helsinki.

[27] Chen, X.S., Yin, Y.P., Wei, W.H., *et al*. (2013) High Prevalence of Azithromycin Resistance to *Treponema pallidum* in Geographically Different Areas in China. *Clinical Microbiology and Infection*, **19**, 975-979.