Journal of Tuberculosis Research, 2022, 10, 111-123
https://www.scirp.org/journal/jtr
ISSN Online: 2329-8448
ISSN Print: 2329-843X

SLCO1B1, *NAT2* Polymorphisms and Pharmacokinetic Variability of Rifampicin and Isoniazid in Tuberculosis Patients from Sub-Saharan Africa

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How to cite this paper: Sanni, S., Wachinou, A.P., Merle, C.S.C., Baba-Moussa, L. and Affolabi, D. (2022) *SLCO1B1*, *NAT2* Polymorphisms and Pharmacokinetic Variability of Rifampicin and Isoniazid in Tuberculosis Patients from Sub-Saharan Africa. *Journal of Tuberculosis Research*, **10**, 111-123.
https://doi.org/10.4236/jtr.2022.103009

Received: July 18, 2022
Accepted: August 26, 2022
Published: August 29, 2022

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Abstract

SLCO1B1 and *NAT2* polymorphisms have been associated with the variability of Rifampicin and Isoniazid pharmacokinetic (PK). The objective of this study was to identify in African patients with tuberculosis (TB) or TB/HIV co-infection, the *SLCO1B1* and *NAT2* polymorphisms, associated with the variability of Rifampicin and Isoniazid pharmacokinetic. TB or TB/HIV co-infected patients from Benin, Guinea, Senegal, and South Africa were included in this study. The blood samples collected were stored at −80˚C until DNA extractions. The DNA extracts were then frozen at −80˚C after quality control. Double stranded DNA of the samples were quantified using a fluorimetric method to select suitable samples for the preparation of 96-well microplates, containing 100 µl of DNA extract per well at the concentration of 20 ng/µl. Illumina HumanOmniExpress-24 v1.2 microarray genotyping was performed by an external vendor. The genotyping data were analyzed and the polymorphisms with a call rate < 95% or presenting a departure from the Hardy-Weinberg Equilibrium (HWE) were excluded. The correlation between significant polymorphisms, the clearance, and the AUC were tested by a multiple linear regression model using the PLINK2 software. Out of 385 samples, five (05) were excluded after quality controls. After the frequency test, 384,586 SNPs failed the Hardy-Weinberg Equilibrium. Finally, 378 samples and 318,751 SNPs were included in the genetic analyses. The *SLCO1B1* and *NAT2* polymorphisms were associated with the variability of Rifampicin and

Isoniazid PK parameters. There are *SLCO1B1* and *NAT2* polymorphisms carriers among TB and TB/HIV co-infected patients from Sub-Saharan Africa.

Keywords

Polymorphism, *SLCO1B1*, *NAT2*, Rifampicin, Isoniazid

1. Introduction

Rifampicin and Isoniazid are major antituberculosis drugs in the first-line treatment of drug-sensitive tuberculosis (TB) [1]. Due to their effectiveness, cost, and accessibility; they are widely used in various TB therapeutic strategies.

Rifampicin, the more active, was first introduced in the 1970s [2]. It dramatically reduced the duration of TB treatment from 24 to 6 months [2]. According to in vitro and in vivo models, its activity depends on the concentrations tested against *Mycobacterium tuberculosis* strains [3]. However, in some patients, there are inter-individual variations of Rifampicin concentrations mainly due to *SLCO1B1* polymorphisms [3]. This transporter, expressed on the basolateral membrane of human hepatocytes, is responsible for the transport of bilirubin but also that of Rifampicin [4].

Isoniazid, used alone for the preventive treatment of latent TB or in combination with Rifampicin, Pyrazinamide and Ethambutol for the curative treatment of active TB, is the most hepatotoxic anti-TB drug because of its reactive metabolite called hydrazine [5] [6] [7]. Isoniazid is metabolized by three different enzymes, N-Acetyltransferase 2 (NAT2), cytochrome P450 2E1 (CYP2E1) and Glutathione S-transferase (GST), whose isolated or associated polymorphisms can lead to significant variations in the pharmacokinetics or the response to treatment with Isoniazid [8]. To date, *NAT2* polymorphisms, the most studied in different ethnic groups, can classify the patients into three acetylators phenotypes: slow, intermediate, and fast acetylators [9]. A total of 38 polymorphisms have been identified in the *NAT2* coding region, including several rare polymorphisms described in different populations [9]. *NAT2* genetic variants have been associated with Isoniazid metabolism variability and its toxicity [10].

Contrary to the high number of studies that have investigated the influence of *NAT2* polymorphisms on the pharmacokinetics of Isoniazid, only a limited number have explored the influence of *SLCO1B1* polymorphisms on the pharmacokinetics of Rifampicin [11].

Understanding the interactions between the genetic polymorphisms and the pharmacokinetics of Isoniazid and Rifampicin would contribute to optimize the outcomes of various therapeutic strategies [1]. In particular, this would contribute to a better understanding of why Rifampicin plasma concentrations are lower in African patients with TB [12]. Indeed, the genetic polymorphisms of

the Rifampicin transporter *SLCO1B1*, and the reduction of its absorption, are responsible for this reduction in plasma concentrations [12]. Heterozygous and homozygous patients show 18% to 28% reductions respectively in the bioavailability and therefore in the area under the curve (AUC) of Rifampicin [12].

Differences in Rifampicin and Isoniazid plasma concentrations in populations are partly due to *SLCO1B1* and *NAT2* polymorphisms [12]. The frequencies of these two polymorphisms and their simultaneous presence in certain African TB patients would increase the risks of the resistance occurrence to Rifampicin and liver toxicity linked to Isoniazid.

We report here, the preliminary results of antituberculosis drugs pharmacogenetic study, conducted in Benin Republic, Guinea, Senegal, and South Africa. Our objective was to identify in patients under antituberculosis treatment containing Rifampicin and Isoniazid, the genetic polymorphisms associated with the pharmacokinetic variability of these drugs.

2. Material and Method

2.1. Study Setting

Patients were recruited at the Medical Research Council (Durban, South Africa), CNHU-PPC (Cotonou, Benin), CNHU Akron (Porto-Novo, Benin), hospital Ignace Deen (Conakry, Guinea), and Ambulatory Treatment Center (Dakar, Senegal) from March 2014 to September 2016. These are national reference centers for the management of TB and TB/HIV co-infected patients. The expertise and infrastructure required for conducting Pharmacokinetic studies in these centers were available and accessible.

2.2. Study Population

TB or TB/HIV co-infected patients who participated in the Pharmacokinetic studies annexed to the OFLOTUB and RAFA clinical trials were included after their informed consent. The inclusion, non-inclusion, and exclusion criteria of both clinical trials are summarized in **Table 1**.

2.3. Study Samples and DNA Extractions

Whole blood samples were collected from fasting patients in 10 ml EDTA tubes and stored at −80˚C until the genomic DNAs extractions. South Africa patients' samples were sent to the Mycobacteria Reference Laboratory (MRL) in Cotonou where genomic DNAs were extracted using QIAGEN® kits QIAamp® DNA Blood Maxi according to manufacturer's instructions. On the other hand, the genomic DNAs of samples from Guinea, and Senegal were extracted respectively at the Mycobacteria Reference Laboratory (Hospital Ignace Deen, Conakry, in Guinea), and at the Medical Biology Laboratory (Ouakam Military Hospital, Dakar, in Senegal). All the extracted genomic DNAs were then sent to the MRL in Cotonou for the quality control procedures.

Table 1. Inclusion, non-inclusion, and exclusion criteria for the OFLOTUB and RAFA trials.

Criteria	OFLOTUB trial [13]	RAFA trial [14]
Inclusion criteria	Patients with pulmonary tuberculosis 18 - 65 years old TB treatment naïve Informed consent	TB/HIV co-infected patients (pulmonary and extra-pulmonary tuberculosis) > 18 years old ARV naïve 50 ≤ LT CD4 ≤ 350 Cells/mm^3 Informed consent
Non-inclusion criteria	None	Patients co-infected with HIV2, alcohol consumption or concomitant treatment incompatible with the RAFA trial, breastfeeding women or women who don't want to use a contraception method during the study period
Exclusion criteria	Patients with a history of TB treatment within the last 3 years, with diabetes mellitus or non-insulin dependent diabetes mellitus requiring treatment, Concomitant infections requiring anti-infective treatment especially with ARVs, some HIV patients at Stage 3, and all patients at Stage 4 of the WHO classification	MDR-TB patients
PK study countries	Benin, Guinea, Kenya and Senegal Quantification of anti-TB drugs plasma concentrations of the patients randomized in the two study arms: ▪ **Gatifloxacin arm** (Rifampicin, Isoniazid, Pyrazinamide, and Gatifloxacin) ▪ **Control arm** (Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol)	Benin and Guinea Quantification of anti-TB drugs (Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide) plasma concentrations of the patients randomized in the three study arms: ▪ **arm A** (First-line anti-TB + ARVs after two weeks) ▪ **arm B** (First-line anti-TB + ARVs after two months) ▪ **arm C** (First-line anti-TB with high-dose of Rifampicin + ARVs after two months)

TB: tuberculosis; PK: pharmacokinetic; ARVs: antiretrovirals; MDR-TB: multidrug resistant tuberculosis.

2.4. DNA Quality Control Procedures

The quality control was performed on all the samples and their DNA concentrations quantified with the NanoDrop 8000 spectrophotometer. All the extracts were then stored at −80˚C until their shipment to the University of Liverpool (United Kingdom) for genotyping analyses.

2.5. Quantification and Normalization of DNA Extracts

The double-stranded DNA concentrations of the extracts were quantifid by a fluorimetric method using Quant-iT™ PicoGreen™ dsDNA kits following the manufacturer's instructions. The extracts were then diluted to prepare 96-well microplates, each containing 100 µl of DNA extract at 20 ng/µl.

2.6. Microarray-Based Genotyping

Genotyping of DNA extracts was performed by an outsourced service based in Oxford using illumina HumanOmniExpress-24 v1.2 chips (illumina, San Diego,

CA, USA).

2.7. Genotyping Data Analyzes

Quality control of genotyping data. It was done according to the method of Coleman *et al.* for multiple purposes: to search missing data and duplicates, to check gender concordance and heterozygosity in the patients, to check the minor alleles frequency and the adherence to Hardy-Weinberg equilibrium [15]. Genetic polymorphisms with <95% call rate or presenting a deviation from Hardy-Weinberg equilibrium (HWE) were removed [16].

2.8. Identification of Genetic Polymorphisms

The genotyping data were visualized on the Manhattan plot (**Figure 1**) to identify the significant genetic polymorphisms at the threshold of $p < 5 \times 10^{-8}$ [17].

2.9. Correlation between Genotyping Data and PK Parameters

The correlation between the genotyping data, plasma clearance, and the AUC was tested by a multiple linear regression model using PLINK2 software [18] [19].

3. Results

3.1. Recruitment of Study Participants

A total of 408 participants from four countries were included in this study (**Table 2**). In all the countries, they were mostly men (sex ratio: 1.582). The sex ratio by country varies from 1.093 in Guinea to 5.250 in Senegal, where the number of participants was the lowest. The distributions of participants by country are not related to the national TB prevalences.

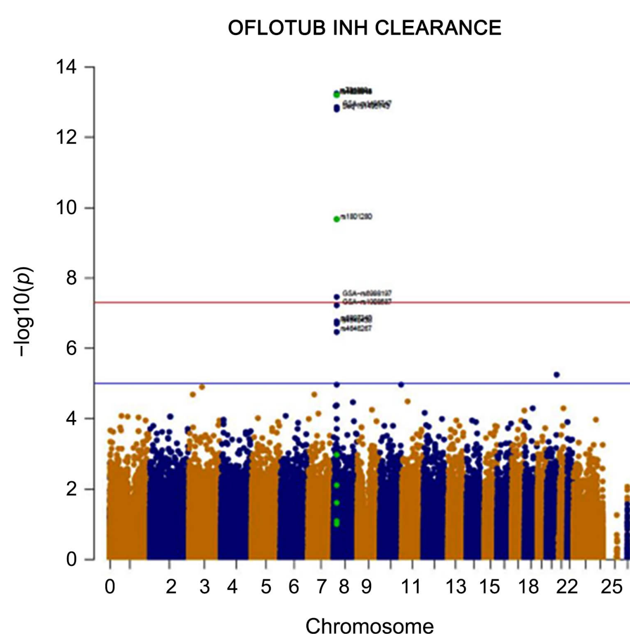

Figure 1. Manhattan diagram.

Table 2. Summary of study participants.

Country	Sex		Total
	Men (%)	Women (%)	
South Africa	71 (28.40)	48 (30.38)	**119**
Benin	111 (44.4)	63 (39.87)	**174**
Guinea	47 (18.80)	43 (27.22)	**90**
Senegal	21 (8.40)	4 (2.53)	**25**
Total	**250**	**158**	**408**

3.2. Characteristics of OFLOTUB and RAFA Trials Participants

OFLOTUB trial participants were approximately twice as numerous as those in RAFA trial (Table 3). They were about 6 years younger than the RAFA trial participants. The RAFA trial conducted in Benin, Guinea, and Senegal did not concern South Africa. Body mass indices (BMI) of the participants randomized in the different arms of both clinical trials were identical.

3.3. Quality Control of Genotyping Data

Three (03) samples with more than 5% missing genotypes, two (02) duplicated samples; 384,586 genetic polymorphisms having failed to the frequency test and to the Hardy-Weinberg equilibrium were excluded. In summary, a total of 378 samples (209 OFLOTUB + 169 RAFA) and 318,751 genetic polymorphisms were included in the genetic analyses.

3.4. Association between Polymorphisms and Pharmacokinetics of Rifampicin

There was no significant association between the genetic polymorphisms and the pharmacokinetic parameters of Rifampicin. The *SLCO1B1* polymorphisms (rs-11045819 and rs4149032) were not significantly associated with variations in Rifampicin pharmacokinetic parameters. However, the rs11792875 polymorphism appears to be associated (p = 2.44e-07) with Rifampicin clearance but not with its AUC.

3.5. Association between Polymorphisms and Pharmacokinetics of Isoniazid

Two *NAT2* polymorphisms (rs1801280 and 1495741) were associated with the variation of Isoniazid clearance in OFLOTUB trial patients (Figure 1).

The horizontal red line represents the significance threshold $p < 5 \times 10^{-8}$ at the genome scale (−log10). The *NAT2* polymorphisms associated with isoniazid clearance are in green and located on chromosome 8.

4. Discussion

We conducted this pharmacogenetic study in TB and TB/HIV co-infected patients, to identify the polymorphisms of *SLCO1B1* (Rifampicin transporter), and

Table 3. Characteristics of patients in the OFLOTUB and RAFA trials.

Features	OFLOTUB Trial (N = 1692)		RAFA trial (N = 780)		
	Gatifloxacin arm (n = 848)	Control arm (n = 844)	Arm A (n = 263)	Arm B (n = 258)	Arm C (n = 259)
Country, n (%)					
South Africa	191 (22.5)	181 (21.4)	N/A	N/A	N/A
Benin	158 (18.6)	158 (18.7)	71 (27.0)	71 (27.5)	70 (27.0)
Guinea	221 (26.1)	225 (26.7)	158 (60.1)	157 (60.9)	155 (59.8)
Kenya	100 (11.8)	100 (11.8)	N/A	N/A	N/A
Senegal	178 (21.0)	180 (21.3)	34 (12.9)	30 (11.6)	34 (13.1)
Age (Years)					
Mean ± SD	30.9 ± 9.1	30.6 ± 9.0	36.4±9.2	36.5±10.1	35.9 ± 9.7
Female sex	229	233	129	112	118
BMI (kg/m^2)					
Mean ± SD	17.4 ± 4.9	17.5 ± 5.0	18.2 ± 3.1	17.7 ± 2.9	18.4 ± 2.6

*NA: Not applicable.

NAT2 (most important metabolizing enzyme of Isoniazid) genes associated with the variability of both drugs' clearance and/or AUC.

Rifampicin and Isoniazid are first-line antituberculosis drugs, used as monotherapy, in the treatment of latent TB or in combination with Ethambutol and Pyrazinamide for the treatment of active TB [20].

Our study patients, all from black origin, were initially involved in the pharmacokinetic studies annexed to OFLOTUB and RAFA trials. Their ethnicities had not been recorded during the recruitment in both trials. In fact, the protocols of the trials had not planned the subsequent use of their genetic material in pharmacogenetic studies that could help for a better understanding of the genetic mechanisms associated with the therapeutic outcome (failure, cure, or death), the occurrence of a treatment relapse, or adverse effects. Furthermore, the National Ethics Committees in some countries had not given their approval or had issued restrictive conditions for the record and use of the study participants' ethnicities. Nevertheless, the majority ethnic groups in all the four countries are known and available in published studies. For example, the majority ethnic groups are Wolofs in Senegal, Sothos and Zulu in South Africa [21].

After the quality control procedures, the samples selected were genotyped using the illumina HumanOmniExpress-24 v1.2 chips (illumina, San Diego, CA, USA).

The pharmacokinetic parameters of Rifampicin and Isoniazid used in this study were obtained from the OFLOTUB and RAFA trials databases. These parameters were calculated from the plasma concentrations of both antituberculosis drugs quantified by high performance liquid chromatography [22] [23].

4.1. *SLCO1B1* Polymorphisms and Rifampin Pharmacokinetic

SLCO1B1 polymorphisms frequencies are variable in TB or TB/HIV co-infected patients and from one ethnic group to another. Thus, *SLCO1B1* rs11045819 polymorphism frequency is 19% in African TB patients, and 25% in healthy American controls [24]. In previous studies, *SLCO1B1* rs11045819 polymorphism was associated with decrease in Rifampicin plasma concentrations [24]. Similarly, *SLCO1B1* rs4149032 polymorphism was associated with lower Rifampicin exposures in African populations, suggesting the need for increased therapeutic doses of Rifampicin. This very common polymorphism is present in 70% of South Africans [24]. In children with TB, the *SLCO1B1* rs2306283 polymorphism has been associated with lower Rifampicin concentrations [11].

Unlike Allegra *et al.*, who found an association between *SLCO1B1* rs4149056 polymorphism and higher plasma concentrations of Rifampicin, our results showed that there was no association [25]. In addition, our results failed to confirm the effects of *SLCO1B1* rs2306283, rs4149032, and rs11045819 polymorphisms identified in previous conflicting studies. On the contrary, *SLCO1B1* rs11792875 polymorphism we identified could be a new genetic marker of great interest for further investigations in later studies. Kim *et al.*, in their study on Korean patients with TB, concluded that *SLCO1B1* polymorphisms did not influence Rifampicin plasma concentrations and clearances [24]. Therefore, *SLCO1B1* polymorphisms are not the only genetic factors responsible for the variability of Rifampicin plasma concentrations in TB and TB/HIV patients. In addition, *SLCO1B1* polymorphisms would have no effect on the time to conversion of Acid-Fast Bacilli smears and cultures, as well as on the occurrence of Rifampicin adverse effects [24].

4.2. *NAT2* Polymorphisms and Isoniazid Pharmacokinetic

Polymorphisms of drug metabolizing enzymes can be single nucleotide polymorphisms (SNPs) or haplotypes. In the case of our study, the SNPs associated with the variability of Isoniazid clearance were *NAT2* rs1801280 (p = 2.14e-10), rs3008589 (p = 3.346e-08), and rs12641762 (p = 2.565e-08). The SNP rs1495741 was associated with the variability of the AUC (p = 1.14e-09) and clearance (p = 6.18e-14) of Isoniazid. Some previous studies in other populations have also found the existence of a good correlation between *NAT2* polymorphisms and Isoniazid pharmacokinetics [1] [26] [27]. This correlation suggests that *NAT2* genotyping could allow the optimization of Isoniazid doses in order to increase its efficacy while reducing its toxicity [28].

*NAT2*12A* polymorphisms are most frequent in black populations in Sub-Saharan Africa. Unlike the more common *SLCO1B1* polymorphisms in South African patients, the frequencies of *NAT2* polymorphisms could be similar in all patients from the countries involved in this study. Thus, according to Mthiyane *et al.*, the genotypic frequencies of slow, intermediate, and fast acetylators were 52.5; 35.8, and 11.7% respectively in South African, black and TB/HIV co-in-

fected patients [28]. *NAT2*4*, *NAT2*5B* polymorphisms, less frequent in the black ethnicity, were not identified in the patients of this study. Similarly, *NAT2*6A* and *NAT2*7B* polymorphisms, common in Caucasian and Asian populations, were not observed in this study.

The microarray-based genotyping used in this study made it possible to identify new genetic polymorphisms that can modify the pharmacokinetic of Rifampicin and Isoniazid. The microarray-based genotyping method would identify a greater number of polymorphisms than other genotyping method. Unlike this genotyping method, some authors carry out a literature review to select the most significant genetic polymorphisms. Participants from Guinea and Senegal were the least numerous because few patients from these two countries had participated in the pharmacokinetic studies.

Many studies have shown that people with low NAT2 activity have a higher risk of developing liver problems than those with high NAT2 activity. However, other authors have observed that rapid acetylation is a risk factor for antituberculosis drug-induced hepatitis [9].

4.3. *NAT2* Haplotype and Isoniazid Pharmacokinetic

The *NAT2* haplotype rs1041983|rs1801280|rs1799929|rs1799930|rs1208|rs1799931 identified in this study was only associated with the variability of Isoniazid clearance (p = 2.77e-09). This haplotype found in some patients included in this study is associated with Isoniazid hepatotoxicity [29] [30] [31]. Other haplotypes such as *NAT2*6A* variants have also been associated with hepatotoxicity [32]. In contrast, the wild-type *NAT2*4* haplotype is not associated with Isoniazid hepatotoxicity [29]. The lack of concordant evidence between the association of the different *NAT2* haplotype variants and the occurrence of hepatotoxicity in patients exposed to Isoniazid requires a study on a larger population. It is also possible that there is an interaction between the SNPs of the haplotype leading to the activation or inactivation of their hepatotoxic effects.

In the patients of this study, we did not detect other *NAT2* polymorphisms, probably due to their low frequencies (<1%). The haplotypes, *NAT2*4* and *NAT2*6A*, would be new predictive biomarkers of Isoniazid-induced hepatotoxicity.

4.4. Study Limitations

This study has certain limitations related to the study arms of OFLOTUB and RAFA trials, but also due to the method used for the genotyping. Indeed, unlike the patients in OFLOTUB trial, those in RAFA trial received, in addition to anti-TB drugs, antiretrovirals initiated earlier at two weeks or later at two months. It is therefore possible that drug interactions between anti-TB drugs and antiretrovirals in RAFA patients affect the pharmacokinetic parameters of Rifampicin and Isoniazid. However, since the participants in OFLOTUB trial are much more numerous, it is possible that these interactions, even if they existed, could not

bias the results of this study.

The microarray used in this study is universal, not specific to Africans requiring chips enriched with the genetic polymorphisms frequent in black populations from Sub-Saharan Africa.

5. Conclusions

The presence of *SLCO1B1* and *NAT2* polymorphisms in TB or TB/HIV co-infected patients from Sub-Saharan Africa is associated with the variability of Rifampicin and Isoniazid clearance and/or AUC. In addition, the presence of the 6-SNP *NAT2* haplotype in some of the patients could lead to an additive or null effect of the combined *NAT2* single nucleotide polymorphisms. In this study, the patients with the *SLCO1B1* and/or *NAT2* polymorphisms could have Rifampicin and/or Isoniazid low plasma concentrations, leading to the treatment failure and then increasing the risk of multidrug resistance occurrence. In TB/HIV co-infected patients with renal impairment, the defect in anti-TB drugs or their metabolites elimination could increase their plasma concentrations and therefore their adverse effects.

These preliminary findings need further investigations to know the allelic and genotypic frequencies of *SLCO1B1* and *NAT2* polymorphisms in TB or TB/HIV co-infected patients from Sub-Saharan Africa. Among the methods available for the experimental validation of these results (quantitative PCR by TaqMan Method, or mass spectrometry on Sequenom's MassARRAY® genotyping platform), the Infinium™ H3Africa Consortium Array v2, focused on African populations, could be very powerful and of great interest.

Acknowledgements

We thank the patients and staff of the recruiting centers for their participation in this study.

Financial Support

The RAFAgene project was funded by the National Institutes of Health (References: 1U01HG007046-01 REVISED).

Ethics Statement

The study protocol amendment was approved by the National Ethics Committees of South Africa (approval letter issued on March 18, 2016, RAFA gene Project: BF217/14), Benin Republic (letter N°_06/MS/DC/SGM/DFR/CNERS/SA issued on July 13, 2015), Guinea (letter N°48/CNERS/16 issued on February 25, 2016) and Senegal (letter N°00000047 MSAS/DPRS/CNERS issued on April 11, 2016).

Author Contributions

Study design (CSCM, DA), literature review (SS), data collection and analyzes (SS, APW, PA), manuscript writing (SS), critical reading of the manuscript (APW,

CSCM, DA, LBM, SP and AO). All authors have read and approved the latest version of the manuscript.

Conflicts of Interest

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

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