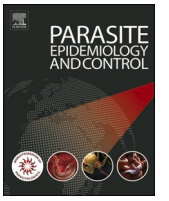
Parasite Epidemiology and Control 25 (2024) e00352

Contents lists available at ScienceDirect

Parasite Epidemiology and Control

journal homepage: www.elsevier.com/locate/parepi



Field sensitivity and specificity of the SD BIOLINE onchocerciasis IgG4 Rapid Diagnostic Test in children <10 years old from endemic areas in Burkina Faso

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ARTICLE INFO

Keywords:
Onchocerciasis
Diagnosis
Skin snip
Endemic area
Community Directed Treatment with Ivermectin
West Africa

ABSTRACT

Skin biopsies (Skin snips) have historically been the gold standard for the diagnosis of onchocerciasis. However, in low prevalence areas and in areas with successful ivermectin mass drug administration (MDA) programs, skin snips are not sensitive enough to decide when to stop MDA; thus, serological diagnostic tools have been recommended for this purpose. This study assessed the sensitivity and specificity of the Ov16 Rapid Diagnostic Test (SD BIOLINE Onchocerciasis RDT) compared to skin snip in endemic areas undergoing ivermectin mass distribution using Community Directed Treatment with Ivermectin (CDTI) strategy. A cross-sectional study was conducted between September and November 2016 in five endemic villages in the Cascades region in Burkina Faso. Children aged 2 to 9-years were examined during the impact epidemiological survey using both the skin snip and Ov16 Rapid Diagnostic Test. The Ov16 Rapid Diagnostic Test sensitivity and specificity were determined with reference to the skin biopsy. Skin snip positivity was 1.25% in this population, while seroprevalence was 6.5%. When compared to the skin snip as the gold standard, the sensitivity of the Ov16 Rapid Diagnostic Test was 60% and the specificity 94%. When the Ov16 Rapid Diagnostic Test was considered as the gold standard, the skin snip exhibited a sensitivity of 11.5% and a specificity of 99.5%. These results are similar to other studies comparing the performance of the Ov16 ELISA to skin snips, suggesting that the Ov16 RDT may be a useful tool for ivermectin STOP MDA and post transmission surveys, assuming that the prevalence of infection is low or close to zero, and the Ov16 RDT detected also pre patent infections.

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https://doi.org/10.1016/j.parepi.2024.e00352
Received 23 January 2024; Received in revised form 4 March 2024; Accepted 21 April 2024
Available online 23 April 2024
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1. Introduction

Onchocerciasis is caused by infection of the parasite *Onchocerca volvulus,* is one of the preventative chemothrerapy neglected tropical diseases (PC-NTDs) targeted for elimination by the international community by 2030 (Brattig et al., 2021). To reach the goal of elimination, Community Directed Treatment with Ivermectin (CDTI) for populations living in areas at risk is the strategy recommended by World Health Organization. Onchocerciasis is endemic in three WHO regions, the Pan American region (PAHO), the East mediteranean region (EMRO) and the African (AFRO), where 99% of at -risk communities live. In Africa, where >99% of the population at risk for onchocerciasis resides, some countries have already reported success in interrupting transmission in some foci (Richards et al., 2020; Zarroug et al., 2016). So, onchocerciasis elimination is progressing and efficient tools to decide when to stop Mass Drug Administration (MDA) and/or for post treatment surveillance are critically needed.

In Burkina Faso, two regions currently remain endemic for onchocerciasis; the South West region and the Cascades region. In the Cascades region, as a result of the recrudescence of onchocerciasis, the National Programme for the Neglected Tropical Diseases Control, introduced twice per year CDTI in the endemic health districts (Banfora, Mangodara) as recommended by the World Health Organization (Koala et al., 2017). In 2016, an impact study of CDTI in the 28 sentinel villages assessed in 2010/2011 was conducted to monitor infection decline using parasitological analysis of skin biopsies (skin snips).

Serological diagnostic tools have been under development for more than a decade to be used as an alternative to skin snips to survey onchocerciasis in low prevalence areas (Lipner et al., 2006). Serological tools are also needed to support decisions of when to stop MDA, and also to serve as suveillance tools to detect potential recrudesence during the post-treatment phase (Golden et al., 2016; Lipner et al., 2006; Richards et al., 2018a; Weil et al., 2000). Indeed, when CDTI is effective, prevalence of microfilaroderma becomes low, and skin snip becomes less sensitive for the diagnosis of onchocerciasis (Boatin et al., 2002). To decide when to stop mass treatment, and for the post treatment surveillance phase, WHO has recommended using serodiagnostic tools based on the detection of antibodies specific to a 16 kDa species specific antigen of *O. volvulus* (Ov16), utilizing either rapid diagnostic test or Enzyme-Linked Immunosorbant Assay (ELISA) platforms (World Health Organization, 2016a). The Antigen Ov16 serves an early marker of onchocerciasis infection, so seroconversion to Ov16 may be used to diagnose pre-patent infection, which is not possible with the skin snip (Lobos et al., 1991). Community Directed Treatment with ivermectin aims to reduce the community microfilarial load to near zero. Thus, effective CDTI should prevent children born after the interruption of transmission from exposure to the parasite, and thus they should be seronegative to Ov16. Seronegativity in this cohort is therefore a good indicator that transmission has indeed been suppressed and this can be used as one metric in making stop MDA decisions (Guevara et al., 2020; Unnasch et al., 2018; World Health Organization, 2016b).

During an impact survey in the Cascades region carried out in 2016, we used the Ov16 Rapid Diagnostic Test in parallel with the skin snip. As the sensitivity of the skin snip is known to decrease with the reduction of prevalence following repeated several successful rounds of CDTI, we hypothesised that the Ov16 RDT would exhibit an enhanced ability to detect ongoing transmission when compared to skin snips in children.

In this study, we present the comparative results of Ov16 RDT and skin snip in children aged <10 years old from five endemic villages undergoing ivermectin treatment since 2011 and discuss the implications for the use of Ov16 RDT as a tool to decide when CDTI may be safely stopped.

2. Methods

2.1. Study sites and design

This study was part of a cross-sectional survey of the impact of CDTI conducted in 28 onchocerciasis endemic villages located along the Comoé River between September and November 2016 in the Cascades region. Details of the study site may be found in our previous publication (Nikièma et al., 2021). Five villages were selected: Badara Karaboro, Badara Nofesso, Bolibana, Congala 2 and Kossoumani. These villages were those that had a crude prevalence of onchocerciasis exceding 25% and a community microfilarial load of >0.5 microfilariae per biposy (mf/b) in 2010/2011 (Table 1) and which applied the strategy of twice-yearly CDTI under community guidelines since 2011.

2.2. Selection of participants

The participants were drawn from the census records of the inhabitants of each village during the 2016 epidemiological assessment

Table 1
: Crude prevalence in the study sites during epidemiological assessement survey in 2010/2011.

Village	Crude prevalence (%)	CMFL (mf/b)
Badara Karaboro	70.97	5.17
Badara Nofesso	57.29	3.57
Bolibana	46.25	2.21
Congala 2	25.50	1.07
Kossoumani	33.87	0.62

survey using WHO/OCP/APOC protocol (World Health Organization, 1995). This was a household-by-household census of all the inhabitants of the village. The participants were children aged between 2 and 9 years old present on the day of the survey. They were examined simultaneously by skin snip and the Ov16 Rapid Diagnostic Test (SD BIOLINE Oncherciasis IgG4 Rapid test, Abott Standard Diagnostics, Inc. Yongin, Republic of Korea).

2.3. Parasitological diagnosis by skin snip

Skin snips were collected and analyzed following the method described by Prost and Prod'hon (1978). This consisted of taking skin biopsies from each participant using a 2 mm Holth forceps from the left and right iliac crests. Each piece of skin was then incubated in distilled water for 30 min and the solution was microscopically examined for the presence of microfilaria, and if found, the number of microfilariae was recorded. Negative biopsies were incubated in physiological water for 24 h and then re-examined.

2.4. Serological diagnosis by the Ov16 RDT

The Ov16 Rapid Diagnostic Test (SD BIOLINE Oncherciasis IgG4 Rapid test, Abbott Standard Diagnostics, Inc. Yongin, Republic of Korea) was used to test for IgG4 antibodies. The manufacturer's protocol was followed. The Ov16 Rapid Diagnostic Test were performed on whole blood spotted directly on to the test strip. On the field, 10 µl of capillary blood were collected using a micro-capillary pipette and dispensed into the sample well on the test device. Four drops of the assay diluent were added to the assay diluent well. A chronometer set for 20 min was started after adding the 4 drops of diluent to the well. At the end of the 20 min, the test result was read. The technician registered the start and ending time of each RDT performed in the data collection form.

2.5. Data analysis

Logicel StataCorpTM Stata Statistical Software for Windows (Version 14.0, College Station, Texas, United States of America) was used for data analysis. The crude prevalence of microfilaria was determined as the number of participants with microfilaria out of the total examined. Seroprevalence was calculated as the number of Ov16 RDT positive participants out of the total examined. The sensitivity and specificity of the Ov16 Rapid Diagnostic Test were calculated.

2.6. Ethical considerations

The study was approved by the ethics committee of Burkina Faso's Ministry of Health. In the study sites, the day of the survey, informed consent was obtained from the children parents or guardians.

3. Results

3.1. Prevalence and seroprevalence of onchocerciasis

In total, 400 children aged between 2 and 9 years were included in this study. The mean age was 5.79 years (sd = 2.04) with a median age of 6 years old. Males were slightly over-represented (52.50% (210/400) of the participants enrolled). Children distribution by site and age group is shown in Table 2. Bolibana village had a greater number of children enrolled than the other villages. Stratification of children into two age groups showed that age group of 5–9 years was more represented (275 participants) than 2–4 years group (Table 2).

The overall prevalence of microfilaroderma was 1.25% (5/400) ranging from 0% to 6.67%. Badara Karaboro has recorded the higest prevalence. Of the total of 5 children who were microfilariae positive, one child was age betewen 2–4 years and was from

Table 2
Distribution of participants by site, gender and age group.

Variable	Enrolled	Skin snip result			Ov16 Rapid Diagnostic Test result		
By village		Positive	Negative	Mf prevalence	Positive	Negative	Ov-16 Prevalence
Bolibana	140	2	138	1.43%	15	125	10.71%
Badara Nofesso	61	0	61	0%	6	55	9.84%
Badara Karaboro	45	3	42	6.67%	4	41	8.89%
Congala 2	129	0	129	0%	1	128	0.78%
Kossoumani	25	0	25	0%	0	25	0%
By gender							
Male	210	3	207	1.43%	15	195	7.14%
Female	190	2	188	1.05%	11	179	5.79%
By age group							
2–4 year	125	1	124	0.8%	3	122	2.4%
5–9 year	275	4	271	1.45%	23	252	8.36%
Total	400	5	395	1.25%	26	374	6.5%

Bolibana village.

The overall seroprevalence of antibody IgG4 against Ov-16 was 6.5% (26/400) ranging from 0 to 10.71% according to the village. In contratst to the skin snip prevalence, Bolibana has recorded the highest seroprevalence. Of the total 26 children who tested IgG4 positive, 3 children were under 5 years. The distribution of participants examined by site, gender and age group is shown in Table 2.

3.2. Comparison of both diagnostic methods

With the skin snip considered to be the gold standard, the Ov16 Rapid Diagnostic Test had a sensitivity of 60% and a specificity of 94.18%. Of the 400 total participants examined by both methods, two participants had microfilariae in their skin snip but were Ov16 Rapid Diagnostic Test negative, whereas twenty-three participants developed antibodies against Ov16 without microfilariae in skin snip (Table 3). The two children who were skin snip positive and Ov16 negative were from Bolibana and Badara Karaboro village.

4. Discussion

The use of effective tools to stop mass treatment and to monitor areas where mass treatment has been stopped is a challenge. In fact, the decision support tool must be effective because any error in judgement may lead to a resurgence of infection in the area. The skin snip, which is considered to be a gold standard for diagnostic and surveillance, cannot be used as a decision-making tool for stopping safely CDTI because its sensitivity is decreased in the face of ivermectin CDTI, which is a very effective microfilaricide. To this end, the WHO recommends the use of the Ov16 based serological tests as a decision-making tool for stopping safely CDTI in humans, together with and entomological data (Unnasch et al., 2018).

In this study, we evaluated the performance of the Ov16 RDT under field conditions in comparison with the skin snip in children under 10 years. To our knowledge, this is the first time that a study included children aged between 2 and 9 years, and which compared the skin snip to Ov16 RDT in the field conditions in the elimination context in West Africa. When compared to the skin snip, the Ov16 RDT exhibited a sensitivity of 60%. This finding is similar to the performance of the Ov16 RDT reported in studies of adults, which reported a sensitivity from 60 to 80% when compared to the skin snip (Hotterbeekx et al., 2020; Shintouo et al., 2021). One difference in the method used to perform Ov16 RDT in this study was the use of whole blood directly applied to the RDT strip, rather than using serum. For insistance, Hotterbeekx (2020) (Hotterbeekx et al., 2020) used serum collected from adults. It is possible that the difference in methods of sample preparation may result in variations in the sensitivity or specificity of the assay i.e. whether it serum or whole blood are used (https://maxanim.com/content/abbott/sd-bioline/sd-bioline-onchocerciasis-igg4.pdf).

The relatively low sensitivity relative to the skin snip gold standard observed here is similar to other studies comparing the skin snip to both the Ov16 RDT and the Ov16 ELISA assay (Dieye et al., 2017; Hotterbeekx et al., 2020; Richards et al., 2018a). The reasons for this low level of sensitivity are not unclear. However it has long been observed that infection with *O. volvulus* can result in both general and parasite specific immunosuppression and previous studies have shown that up to 20% of *O. volvulus* infected individuals may not produce antibodies against the parasite (Lobos et al., 1991). This phenomenon could partially explain account for the instances where children who tested positive with skin snip were found negative when tested with Ov16 RDT.

Despite the low sensitivity when compared to the skin snip, the Ov16 RDT resulted in a prevelence of seropositive individuals which was roughly four fold greater than what was found using the skin snip. This is similar to other studies using the Ov16 ELISA, which also observed a much higher prevalence of Ov16 seropositivity than skin snip positivity (Hotterbeekx et al., 2020). There are several explanations for this finding. Firstly, this may indicate a lack of specificity in the Ov16 RDT. However, this is unlikely, as studies employing the Ov16 ELISA on populations where *O. volvulus* transmission had been eliminated have reported a specificity in excess of 99.9% (Richards et al., 2018b). A second possibility is that the difference seen in the prevalences estimated by the Ov16 RDT and the skin snip reflects the fact that the two assays measure different things. The Ov16 serological assays measures exposure to the parasite, whereas the skin snip measures patent infection. Finally, as mentioned above, CDTI will dramatically reduce microfiladermia in patently infected individuals, and all individuals 5 years of age and older are provided ivermectin during CDTI. Thus, a low prevalence of microfilaroderma in individuals taking ivermectin is to be expected.

The Ov16 RDT was easy to use in the field, did not required substantial logistics and was also well accepted by the endemic

Table 3
Comparison of the two diagnostic methods.

		Ov16 Rapid Diagnostic Test		
		Positive	Negative	Total
Skin snip	Positive	3	2	5
	Negative	23	372	395
	Total	26	374	400

Skin snip gold as standard:
Sensitivity: 3/5 = 60%.
Specificity: 372/395 = 94%.
Ov16 Rapid Diagnostic Test as gold standard:
Sensitivity 3/26 = 11.5%.
Specificity: 372/374 = 99.5%.

communities (Dieye et al., 2017; Ekanya et al., 2023). Although serological tests, like Ov16 RDT cannot distinguish exposure from current infection, the presence of anti-Ov16 antibodies in young children provides evidence for ongoing transmission in interruption context (Vlaminck et al., 2015). The challenge will be to improve the performance of existing diagnostic tools to aid in the ambitous goal of eliminating onchocerciasis transmission in at least 12 countries by 2030. To reach this goal, OTS currently recommends using Ov16 RDT on eluted Dried Blood Spots (DBS). The Ov16 RDT needs to be ≥60% sensitive and ≥ 99.8% specific for mapping, whereas for supporting stopping decisions it requires to be ≥89% sensitive and ≥ 99.8% specific (World Health Organization, 2021).

Our study had some limitations. First, we did not quantify the antiOv16 IgG4 levels by ELISA and thus could not determine the level of antibodies necessary to obtain a positive RDT test. Secondly, transmission of onchocerciasis is related to factors like the intensity of infection in the community and the level of human/vector contact. Therefore, it would be of interest to conduct a study comparing Community Microfilarial Load (CMFL) to RDT prevalence and the actual levels of Ov16-IgG4 seen in a community.

5. Conclusions

Our findings showed that while the Ov16 RDT had a low sensitivity in our study area, the seroprevalence was higher than skin snip. These findings suggest that the Ov16 RDT may be a useful tool for STOP MDA and post transmission surveys, assuming that the prevalence of infection is low or close to zero.

Funding

The research was funded by national budget of Burkina Faso and also received support from the Sightsavers Bureau Sénégal Burkina Côte d'Ivoire. The funders have no role in the study design, data collection and anlysis, preparation of the manuscrit and decision to publish.

Authors contribution

Conceptualization: ASN, ST, RKD. Data curation: ASN, JD, JC, ST. Formal anlaysis: ASN, JD, JC, ST. Funding acquisition: CB, RCB, ST. Investigation: ASN, LK, JC, CMK, MWO, DB, CB. Methodology: ASN, JD, DK, ST. Project administration: ST. Supervision: TRU, BF, ST, RKD. Validation: ASN, ST, DB, RKD. Visualization: ASN, TRU, ST, BF, RKD. Writing-original draft: ASN, TRU, ST. Review & editing: ASN, LK, TRU, JD, JC, MWO, CMK, DB, CB, BF, ST, RKD.

Declaration of competing interest

The authors declare that they have no competing interest.

Data availability

The data analyzed during the investigation can be access for rational request adress to corresponding author.

Acknowledgements

The authors are grateful to regional health of Cascades authorities and the population of endemic sites especially the participants and the health profesionnal of study villages, the community leaders and the community distributors.

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