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RESEARCH ARTICLE

Persistence of onchocerciasis and associated dermatologic and ophthalmic pathologies after 27 years of ivermectin mass drug administration in the middle belt of Ghana

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Abstract

Objectives: There is a pressing need to regularly evaluate the progress of onchocerciasis elimination programmes to timely identify and mitigate potential risks hindering the reaching of the 2030 targets proposed by the World Health Organization (WHO) in its roadmap on neglected tropical diseases (NTDs). We determined the prevalence of onchocerciasis and associated dermatological and ophthalmological manifestations in six endemic communities in the Bono Region of Ghana after 27 years of ivermectin mass treatment.

Methods: In a cross-sectional study, 564 participants aged ≥5 years were enrolled (49.1% females), with a median age of 26 (range: 5–89) years. In 54% and 47%, skin-snip microscopy and Ov16 rapid diagnostic tests were performed, respectively. Skin disease was determined using the WHO Skin NTD App. Visual function assessments included tests of visual acuity.

Results: The overall microfilarial prevalence was 12.5% (38/305) and Ov16 seroprevalence was 24.2% (64/265). Severe itching was recorded in 24.3%, acute papular onchodermatitis in 52.8%, chronic papular onchodermatitis in 12.5%, lichenified onchodermatitis in 0.7%,

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skin atrophy in 11.3%, depigmentation in 1.7% and palpable nodules in 5.3%. Of the 301 persons in which visual acuity was examined, 17% were visually impaired and 5.3% were blind and 47.3% presented with cataract. Chronic papular onchodermatitis, lichenified onchodermatitis, depigmentation and visual impairment were significantly associated with the presence of skin microfilariae and Ov16 seropositivity.

Conclusions: The persistence of *Onchocerca volvulus* infection and onchocerciasis-associated dermatological and ophthalmological pathologies after prolonged treatment is of concern. There is a need to include morbidity management in onchocerciasis elimination programmes and understand better patterns of treatment coverage, adherence and actual intake of ivermectin.

KEYWORDS

Ov16 seroprevalence, microfilariae, onchocercal skin disease, onchocerciasis, prevalence, visual acuity

INTRODUCTION

Onchocerciasis (river blindness) is considered to be the second leading cause of blindness due to an infectious disease being second only to trachoma [1]. It is caused by the filarial nematode *Onchocerca volvulus* and transmitted by *Simulium* blackflies. According to the 2019 Global Burden of Disease Study, 19 (95% uncertainty interval, 95% UI = 17–21) million people are infected, with a global burden of 1.23 (95% UI = 0.765–1.82) million disability-adjusted life-years (DALYs) [2]. Currently, more than 240 million people live in areas known to be endemic for onchocerciasis [3]. Africa bears approximately 99% of the global risk and disease burden [4]. In Ghana, the 2016–2020 NTD Master Plan estimated that the at-risk population was over 2 million in 3115 communities [5].

The disease is well known for its dermatological and ophthalmic pathologies which are generally accepted to occur as a result of dying and dead microfilariae provoking an immunological/inflammatory response, ultimately resulting in tissue damage and scarring [6]. Dermatological onchocerciasis comprises pruritus/severe itch (PRU) and common secondary bacterial infections, acute papular onchodermatitis (APOD), chronic papular onchodermatitis (CPOD), lichenified onchodermatitis (LOD), skin atrophy (ATR) and depigmentation (DPM)—usually on the anterior side of the lower legs, palpable onchocercal nodules (NOD), lymphadenopathy, hanging groin (HG) and lymphoedema (LYM) [7]. Ophthalmic onchocerciasis may involve any part of the eye from the conjunctiva and cornea to the uvea and posterior segment including the retina and optic nerve and may lead to loss of visual acuity, and ultimately blindness [8]. In fact, onchocerciasis is better known as river blindness because of the high prevalence of blindness in villages located along fast-flowing rivers, where the vectors breed [9]. Up to 500,000 cases of severe visual impairment and 270,000 of blindness have been attributed to onchocerciasis [9]. However, these figures underestimate the true magnitude of the public health problem caused by onchocerciasis [10] as other morbidities, including onchocerciasis-associated epilepsy (OAE), are not currently included in assessing its burden of disease [2].

In Ghana, the control of onchocerciasis evolved from vector control through aerial larviciding during the Onchocerciasis Control Programme in West Africa (OCP, 1974–2002) to mass drug administration (MDA) with ivermectin since 1995. Despite the early start of community-directed treatment with ivermectin (CDTI) in Ghana in the late 1990s, several operational and implementation challenges were encountered by the control programme. Inadequate financial support, coupled with management challenges, led to erratic distribution of ivermectin with poor therapeutic and geographic coverage for most of the treatment areas [11]. From 2004, drug distribution as part of the Lymphatic Filariasis Elimination Programme was combined with that of the National Onchocerciasis Control Programme (NOCP), resulting in notable improvements in geographic and therapeutic coverage [11]. However, up-to-date mapping data were not available for the country, so the NOCP relied on historical data compiled from regional and district health teams, as well as community surveys, to guide onchocerciasis treatment [11].

In 2008, rapid epidemiological mapping of onchocerciasis [12] was undertaken in Ghana, with the support of the African Programme for Onchocerciasis Control (APOC). The goal was to re-map (based on NOD prevalence in adult males) and identify onchocerciasis-endemic communities [12]. Endemicity maps were developed for the preparation of a national plan for onchocerciasis control and for a relaunch of MDA with ivermectin in identified communities [11]. Mainly, high-risk communities were selected (those in the immediate vicinity of major potential vector breeding sites) [11, 13]. The number of communities treated was gradually scaled up from 2009 [11]. From 2009, biannual CDTI was implemented in all the identified mesoendemic and hyperendemic communities (NOD prevalence ≥20%; microfilarial prevalence ≥40%) [11]. Thereafter, implementation units were re-demarcated from villages to entire sub-districts, with the criterion that at least one village in the sub-district was endemic for onchocerciasis [11]. Thus, there was an increase in the number of communities treated, from 1509 in 1998 to 7043 in 2016 [11], updating previous estimates presented in [5].

Globally, the control of onchocerciasis is considered to have been largely successful, with the aim of elimination as a public health problem (EPHP) mainly achieved (but see above regarding OAE), and with elimination of transmission (EOT) having been reported for some foci in Nigeria,

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Ethiopia, Mali, Senegal, Uganda and Equatorial Guinea in Africa [3, 4]. With the fillip of these successes, the World Health Organization (WHO) has set, in its 2021–2030 (second) roadmap on neglected tropical diseases (NTDs), together with the global health community, the target of achieving verification of EOT in 12 (approximately a third) endemic countries by 2030 [14]. In 2022, the Kigali Declaration on NTDs reaffirmed a global commitment to put individuals, communities, and countries at the centre of the NTD response to ultimately contribute to the attainment of the third sustainable development goal (SDG3) on *Good Health and Well-being for All* [14, 15].

Although successes in EPHP and EOT of onchocerciasis provide reasons for optimism, CDTI may not lead to EOT in all foci [16]. In Ghana and Cameroon, sub-optimal responses to ivermectin have been reported phenotypically and using genome-wide analysis approaches in some communities [17, 18]. In some endemic foci in Ghana, there have been reports of persistent microfilaridermia (microfilariae in the skin) and *O. volvulus* transmission despite 15–20 years of ivermectin treatment [19, 20], and after the introduction of biannual CDTI in 2009 [21].

Otabil et al. showed that microfilarial prevalence and Ov16 seroprevalence among children aged below 10 years were still high in communities of the Tain District and Wenchi Municipality of the Bono region of Ghana (around 10% for the former and 12% for the latter) after 27 years of ivermectin MDA [22]. Although this study also reported on the prevalence of epilepsy in the study communities, it concluded that OAE was unlikely to have represented a problem in the region. However, other onchocercal morbidities were not reported. Therefore, the aim of this study was to determine the prevalence of onchocerciasis-associated dermatological and ophthalmic pathologies in these communities to better understand the status of clinical manifestations after 27 years of ivermectin treatment in the Bono region of Ghana.

MATERIALS AND METHODS

Description and history of onchocerciasis control in the study area

The study was conducted in six rural onchocerciasis-endemic communities in the Tain District and Wenchi Municipality of the Bono Region of Ghana. The Tain District has a total area of 1829.9 km^2 and a population size of 88,104 inhabitants, with 50.6% females and 49.4% males [23]. The Wenchi municipality has a total area of 1296.6 km^2 and a population of 89,739 (50.9% females and 49.1% males) [24]. The study communities were Abekwai 2, Abekwai 3, Attakrom and Kokomba in the Tain District, and Johnykrom and Blibor in the Wenchi Municipality (Figure 1).

The map of the study communities indicates that these make up two clusters. The first is the Wenchi cluster, consisting of four communities along the Subin River, whereas the second cluster (Tain) consists of two communities that lie west of the main Tain River. The map shows a maximum cluster diameter of 11 and 8 km, respectively. Due to the different vector control histories of these clusters, it is important to differentiate between them. The Subin River was part

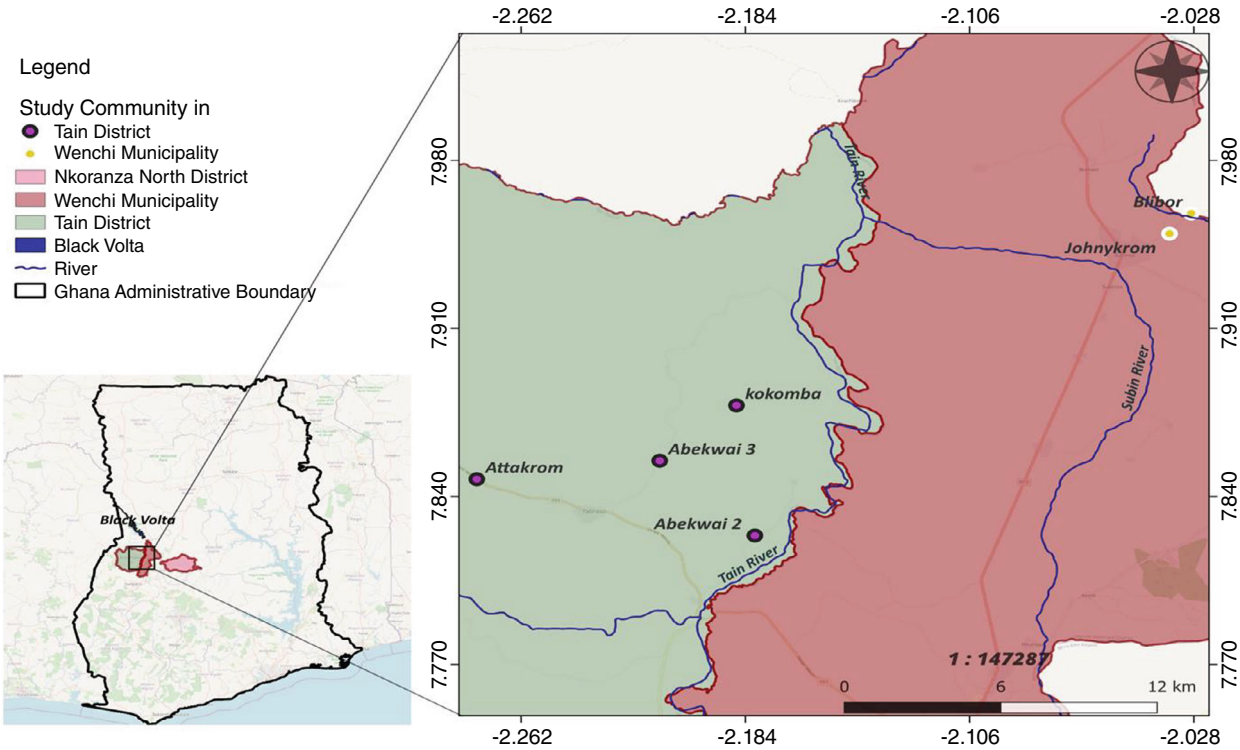

FIGURE 1 Map of Ghana showing the location of the study communities in the Tain District and the Wenchi Municipality, Bono Region, Ghana.

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of the South-Eastern Extension of the OCP that became operational in 1988. The section of the main Tain River from the village of Tainso to the junction with the Black Volta started vector control in 1976 as part of Phase II of the OCP. The Subin River was under vector control from 1992 onwards, but vector control may have started a few years earlier. Vector control ended in both the Tain and Subin rivers in 1996. The OCP undertook detailed entomological evaluations along both rivers with fly-catching points at the village of Tainso along the Tain River from 1974 to 1985, and at the village of Subinso along the Subin River from 1979 to 1996. The results of these entomological evaluations are consistent with the vector control history. At Tainso, the Annual Biting Rate (ABR, no. bites/person/year) fell from 3500 in 1974 to less than 200 bites/person/year in 1980, and from then on, the Annual Transmission Potential (ATP, no. L3 larvae/person/year) was close to 0. At Subinso, the ABR and ATP did not show a declining trend before 1989 but fluctuated around an ABR of 3000 and an ATP of 150 (close to the threshold of 100 when onchocerciasis is considered to be no longer a public health problem). After 1990, the ABR declined to less than 1000, whereas the ATP was 0 in all but 1 year.

The baseline *O. volvulus* (crude) microfilarial prevalence for Kwanware (in the Wenchi cluster) in 1989 was 48.1% (95% confidence interval [CI] = 41.5%–54.8%) and the community microfilarial load was 7.26 microfilariae per skin snip (mf/ss), indicating mesoendemicity according to OCP data. In a survey conducted by the OCP in the year 2000, these values had decreased to 15.6% (95% CI = 10.0%–23.6%) and 0.33 mf/ss, respectively, and in another survey conducted in 2012 (supported by APOC Trust Fund), the microfilarial prevalence was 5.6% (95% CI = 2.2%–13.6%). In 2017, the Ghana Health Service (GHS) performed an onchocerciasis impact assessment reporting a prevalence in Kwanware of 29.3% (95% CI = 16.1%–46.6%) in adults aged ≥ 20 years [22]. All the other study communities in the Wenchi cluster lie within 8 km of Kwanware and are located within the Subin River basin. For the Tain cluster, there are no data on pre-control microfilarial prevalence for our specific study villages. However, there is one nearby OCP community, Tainso, for which pre-control (crude) microfilarial prevalence is available for 1980 (40.7% [95% CI = 35.4%–46.2%]) and which is situated within 4–10 km from each study village in the Tain cluster, also indicating baseline mesoendemicity.

The villages in both clusters have received MDA by mobile teams since 1994–1995, and CDTI since 1998. They have, therefore, received ivermectin MDA for the past 27 years. Since 2009–2010, the treatment strategy in the study area switched from annual to biannual CDTI in Tain and subsequently in Wenchi [11]. Data on MDA coverage in the study communities were obtained from coverage registers and data sheets provided by the Tain District and Wenchi Municipality health directorates. The coverage reported in this study represents the therapeutic coverage, that is, the proportion of the population receiving treatment out of the total population during the first round of MDA in 2021 (see below).

Ethical considerations

The study obtained ethical clearance from the Committee for Human Research and Ethics of the University of Energy and Natural Resources in Sunyani, Ghana, West Africa (approval number: CHRE/AP/012/021). The objective of the study was explained to the participants in the local dialect (*Twi*). For children below 18 years, written informed consent was given by their parents or legal guardians, whereas the children assented (if between 10 and 17 years) to affirm their willingness to participate in the study. Participants were informed that they had the option to withdraw at any stage of the investigations, without giving any reasons.

Study design and recruitment of study participants

The study adopted a cross-sectional design. Data were collected between October 2020 and August 2021 to determine the prevalence of *O. volvulus* microfilariae, the seroprevalence of IgG4 antibodies to the Ov16 antigen, and the prevalence of dermatological and ophthalmic pathologies frequently associated with onchocerciasis. During 2020, MDA was not conducted in Ghana due to the COVID-19 pandemic; the last treatment round was delivered in October 2019. Therefore, in October 2020, 12 months had elapsed before treatment and the commencement of our study. In March 2021, the first of the two biannual rounds of MDA was delivered, with the second round in August 2021 (immediately after completion of the study). One to 2 weeks before the recruitment of study participants, announcements were made in the study communities via the community information centres or with the aid of a 'gong-gong' beater (a local means of giving information to the community residents where the 'beater' moves around sounding a metallic instrument 'the gong-gong', whereas intermittently shouting out the information). Community residents were informed to gather at chosen social centres in the community. Once they were gathered, the study was explained in English and the local '*Twi*' language during the meeting with the village elders and community members at the designated points in the community. All individuals aged at least 5 years were invited to participate in the study and recruited once they agreed and consented. A written informed consent form, either signed or thumb-printed and/or witnessed (when relevant), was obtained from all participants. The informed consent forms were in English and the content was explained in Twi to participants who could not read or write English, with a literate community resident as a witness.

Skin snipping and microscopy

A piece of cotton wool soaked in methylated spirit was used to clean both sides of the iliac crest of each person. Bloodless skin snips (approx. 2 mg) were obtained from the two iliac crests of each individual participant with a sterilised 2-mm Holth corneoscleral punch to determine the prevalence

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of onchocerciasis in each community as previously described [22]. The skin biopsies were incubated in physiological saline for 24 h and microscopic examinations (using a 10× objective lens) were performed to detect *O. volvulus* microfilariae (mf). The crude prevalence was determined as the number of mf-positive persons out of the total examined, expressed in per cent. We report the results of the skin-snip survey conducted in November 2020 (and in August 2021 for comparison), as in reference [22].

Ov16 rapid diagnostic test

IgG4-based rapid diagnostic tests (RDTs) were performed to determine the exposure of participants (all ages) to the Ov16 *O. volvulus* antigen using the SD Bioline Onchocerciasis IgG4 kit (Abbott Diagnostics Korea Inc, catalogue #61FK10). Tests were conducted following the manufacturer's instructions and quality assurance procedures. The test cassette was labelled with the identification number of the participant. A finger of the participant was selected, cleaned with an alcohol swab, and pricked with the lancet provided with the kit. Blood was collected using a capillary tube and placed in the specimen well of the cassette. Four drops of assay diluent were placed in the well. Test results were read in the field after 20 min [25]. The method used in the determination of Ov16 seroprevalence was the same as that used by the GHS in the 2017 onchocerciasis impact assessment. However, the population sampled in the 2017 assessment included only children under 10 years, whereas in the present study, Ov16 antibody testing was done among all age groups. We report the results of the serological survey, conducted in June 2021 (as in reference [22]).

Nodule palpation

Individuals were palpated to check for the presence of nodules (onchocercomas) harbouring adult *O. volvulus* worms as previously described [26]. Nodules were 'suspected' onchocercomas (not confirmed by dissection or biopsy) and defined as being firm, often flattened or bean-shaped, usually movable, non-tender and up to several centimetres in diameter. Palpation was done on bony prominences of the ribs, iliac crests, sacrum and upper leg of the participants by a medical team composed of a medical doctor (Joseph Ameyaw), a physician assistant (Joseph G. Bamfo) and two nurses (Blessing Ankrah and Theophilus Nti Babae).

Physical examination for dermatological manifestations associated with onchocerciasis

Participants were examined for signs of dermatological pathologies associated with onchocerciasis by the medical team. The team had been trained to utilise the WHO Skin NTD App, which provides pictorial guides and potential diagnosis for skin NTDs through automated algorithms, and is simplified for use by both healthcare workers and the public [27]. The App is designed for frontline workers who encounter skin NTDs during routine examinations. Dermatologic pathologies were classified as severe itch, acute (pruritic) and chronic (non-pruritic) papular dermatitis, lichenified onchodermatitis, atrophy and depigmentation according to case definitions proposed by Murdoch et al. [7]

Examination for ophthalmological manifestations associated with onchocerciasis

Participants were also examined by the medical team for possible vision loss suspected to be associated with past or ongoing infection with *O. volvulus* using a Snellen chart to determine whether the participants had 20/20 vision or showed signs of visual impairment [28]. Visual impairment was defined as visual acuity worse than 6/12 (mild), 6/18 (moderate) or 6/60 (severe), whereas blindness was defined as presenting with visual acuity worse than 3/60. The above classification of visual impairment is based on the WHO's International Statistical Classification of Diseases and Related Health Problems [29]. Other eye conditions such as cataracts (opacity of the lens), conjunctivitis (redness of the conjunctiva), and pterygium (a raised, wedge-shaped growth of the conjunctiva that extends onto the cornea) were diagnosed by examining the front of the eye using a torch [30]. All examinations were done with the participants not wearing corrective glasses. One of the study nurses (Blessing Ankrah), who performed the front eye examinations, had undergone training at the Ophthalmic Unit of the St. Theresa's Hospital, Nkoranza, Ghana.

Statistical analysis

Data were entered in a purposely designed MS Excel spreadsheet. Analyses were conducted using Jamovi Desktop (version 2.3.19) and GraphPad Prism 8 for macOS (version 8.2.1). Crude microfilarial prevalence was expressed as a percentage (number of persons positive for *O. volvulus* mf divided by number examined × 100), as previously described [22]. Chi-square tests were used to test for statistical significance of associations between mf infection status/Ov16 seropositivity and dermatological and ophthalmic pathologies of onchocerciasis. A two-tailed p value lower than 0.05 was considered statistically significant. Ninety-five confidence intervals (95% CIs) around prevalence values were calculated using the Wilson Score Interval [31].

RESULTS

Demographic descriptive statistics of study participants

The study included a total of 564 individuals who participated in any or all parts of the study based on consent.

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Gender data were available for 536 participants, 51% females and 49% males. The median age of the study participants was 26.0 (interquartile range = 13–43) years, with an age range between 5 and 89 years. Table 1 presents descriptive statistics of the study participant characteristics per community, and provides therapeutic coverage data (of total population) for the last MDA round in 2019 and the first round of 2021 (as in [22]). Figure S1 presents the pyramid of the age and sex distribution of the study population.

Gender data were not available for a total of 28 participants due to logistical reasons; therefore, the recruited population shown corresponds to the individuals for whom gender was available. The total recruited population was 564. The total population for each village corresponds to the census population according to the coverage data presented in reference [22]. Coverage data for the Wenchi Municipality were adjusted according to the proportion of non-eligible population [22].

Microfilaridermia and Ov16 seroprevalence

Only 305 (54.1%) of the 564 study participants were tested for the presence of skin mf in November 2020, and 265 (47.0%) for the presence of Ov16 antibodies (Table 2). The overall microfilarial prevalence in all study communities (November 2020) was 12.5% (38/305, 95% CI = 9.2%–16.6%), with Johnykrom presenting the highest microfilarial prevalence, of 18.6% (22/118, 95% CI = 12.7%–26.6%). The overall Ov16 seroprevalence (June 2021) was 24.2% (64/265, 95% CI = 19.4%–29.7%), with Kokomba recording the highest Ov16 seroprevalence, of 42.5% (17/40, 95% CI = 28.5%–

TABLE 1 Characteristics of the study participants in the six study communities and mass drug administration (MDA) coverage.

Community	Recruited/ population: *n*/*N* (%)	Gender: *n* (%)		Median age (years), (range)	Reported therapeutic MDA coverage 2019 2nd round (October)	Reported therapeutic MDA coverage 2021 1st round (March)
		Females	Males			
Tain District						
Abekwai 2	73/476 (15.3%)	38 (52.1%)	35 (48.0%)	20.0 (5–89)	83.0% (395/476)	81.9% (390/476)
Abekwai 3	119/971 (12.3%)	53 (44.5%)	66 (55.5%)	25.0 (5–83)	82.7% (803/971)	82.6% (802/971)
Attakrom	79/515 (15.3%)	42 (53.2%)	37 (46.8%)	39.5 (5–80)	81.0% (417/515)	80.0% (416/520)
Kokomba	45/495 (9.1%)	24 (53.3%)	21 (46.7%)	24.0 (7–60)	81.6% (404/495)	80.6% (399/495)
Wenchi Municipality						
Johnykrom	143/170 (84.1%)	79 (55.2%)	64 (44.8%)	24.0 (6–78)	NA	NA
Blibor	77/240 (32.1%)	36 (46.8%)	41 (53.2%)	25.0 (5–80)	77.9% (187/240)	80.3% (244/304)
Total	536/2867 (18.7%)	272 (50.8%)	264 (49.3%)	26.0 (5–89)	81.8% (2206/2697)	81.4% (2251/2766)

Note: NA: Coverage data for Johnykrom were not available.

TABLE 2 Prevalence of microfilaridermia and Ov16 IgG4 antibodies in the six study communities.

Community	Prevalence of mf, % (*n*+ve/*N* examined) [95% CI] (November 2020)	Prevalence of mf, % (*n*+ve/*N* examined) [95% CI] (August 2021, for comparison)	Prevalence of Ov16 antibodies, % (*n*+ve/*N* examined) [95% CI] (June 2021)
Tain District			
Abekwai 2[a]	4.6% (3/66) [1.6%–12.5%]	11.9% (5/42) [5.2%–25.0%]	16.7% (5/30) [7.3%–33.6%]
Abekwai 3[a]	11.0% (8/73) [5.7%–20.2%]	4.0% (4/100) [1.6%–9.8%%]	32.2% (19/59) [21.7%–44.9%]
Attakrom	10.4% (5/48) [4.5%–22.2%]	20.7% (6/29) [9.9%–38.4%]	22.0% (9/41) [12.0%–36.7%]
Kokomba	NA	10.0% (4/40) [4.0%–23.1%]	42.5% (17/40) [28.5%–57.8%]
Total Tain	8.6% (16/187) [5.3%–13.5%]	9.0% (19/211) [5.8%–13.6%]	29.4% (50/170) [23.1%–36.7%]
Wenchi Municipality			
Johnnykrom	18.6% (22/118) [12.7%–26.6%]	7.1% (1/14) [1.3%–31.5%]	18.8% (9/48) [10.2%–31.9%]
Blibor	NA	19.5% (8/41) [10.2%–34.0%]	10.6% (5/47) [4.6%–22.6%]
Total Wenchi	18.6% (22/118) [12.7%–26.6%]	16.4% (9/55) [8.9%–28.3%]	14.7% (14/95) [9.0%–23.2%]
Total	12.5% (38/305) [9.2%–16.6%]	10.5% (28/266) [7.4%–14.8%]	24.2% (64/265) [19.4%–29.7%]

Note: NB: The number of participants examined for mf (305) and Ov16 (265) was lower than the total number of recruited participants (564) for logistical reasons and refusal to participate.

[a]Only two of the study communities (Abekwai 2 and Abekwai 3, captured as a single community, and spelt as Abekwae) were included in the 2017 onchocerciasis impact assessments conducted by the Ghana Health Service. The prevalence [% (*n*+ve/*N* examined) [95% CI]] of mf and Ov16 seropositivity were, respectively, 13.9% (9/65, 95% CI: 7.5%–24.3%) and 9.3% (7/75, 95% CI: 4.6%–18.0%). NA: Not available.

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TABLE 3 Cross tabulation of mf and Ov16 data for the study participants.

mf, *n* (%)	Ov16, *n* (%)					
	Negative	Positive	NA	Total	X^2 value,[a] *df*	*p* Value
Negative	70 (26.3%)	18 (6.7%)	179 (67.0%)	267 (47.3%)	57.761, 4	<0.001
Positive	9 (23.7%)	2 (5.3%)	27 (71.0%)	38 (6.7%)		
NA	122 (47.1%)	44 (17.0%)	93 (35.9%)	259 (46.0%)		
Total	201 (35.6%)	64 (11.3%)	299 (53.1%)	564 (100.0%)		

Note: NA: Those for whom data were missing due to logistical challenges; *n* = number of individuals.
[a]Pearson's Chi-squared test.

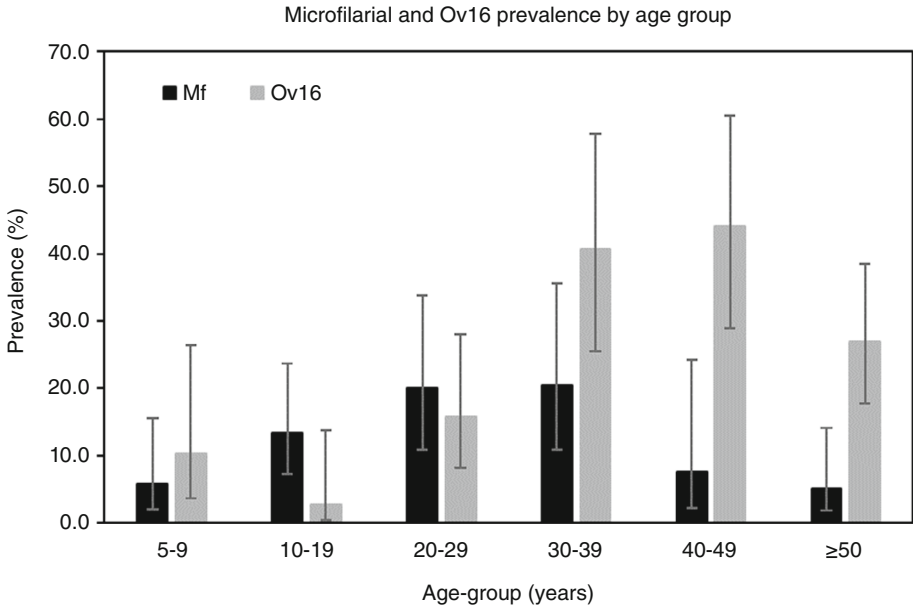

FIGURE 2 Age-stratified prevalence of *Onchocerca volvulus* mf and IgG4 antibodies against Ov16 in the study area. The black bars represent the prevalence of skin microfilariae and the grey bars the Ov16 seroprevalence for all ages. The error bars are the (Wilson score) 95% CI values.

57.8%). For comparison, in August 2021 (just before the second round of ivermectin MDA of that year), the overall microfilarial prevalence was 10.5% (28/266, 7.4%–14.8%; Table 2) [22].

A crosstabulation of mf and Ov16 data, including information on the number of people for which mf, Ov16 or both indicators are missing, is also presented in Table 3.

Microfilarial prevalence and Ov16 seropositivity by age group

Figure 2 presents the prevalence of mf and of IgG4 antibodies against Ov16 by age group. Both microfilarial and Ov16 prevalence tended to increase with age, with microfilarial prevalence reaching the greatest value for those aged 20–29 and 30–39 years (about 20%), and Ov16 seroprevalence reaching the greatest value for those aged 30–39 and 40–49 (41% and 44%, respectively). Microfilarial and Ov16 prevalence decreased (non-significantly) in those aged ≥40 and ≥50 years, respectively. There was a reasonably good agreement between microfilarial prevalence and Ov16 seroprevalence for the 5–9 to 30–39 years, but microfilarial prevalence was significantly lower than Ov16 seroprevalence in those aged ≥40 years. The Ov16 seroprevalence in children under 10 years was 10.3% (3/29, 95% CI = 3.6%–26.4%).

Prevalence of dermatological and ophthalmological manifestations associated with onchocerciasis

The most prevalent dermatological pathology was APOD (52.8% [262/496], 95% CI: 48.4%–57.2%), followed by severe itch (24.3% [109/449], 95% CI: 20.5–28.5; Table 4). The least prevalent was LOD (0.7% [4/549], 95% CI: 0.3–1.9). The most prevalent ophthalmological pathology was cataract (47.3% [52/110], 95% CI: 38.2%–56.5%). In 16.9% (51/301, 95% CI: 13.1–21.6) of study participants, some form of visual impairment was observed and 5.3% (16/301, 95% CI: 3.3%–8.5%) were blind (in one or both eyes). Other ophthalmic pathologies (not associated with

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TABLE 4 Prevalence of dermatological and ophthalmological manifestations associated with onchocerciasis in the study communities.

Dermatological manifestations	
Condition	**Prevalence in % (*n*+ve/*N* examined) [95% CI]**
PRU (severe itch)	24.3% (109/449) [20.5–28.5]
APOD (acute papular onchodermatitis)	52.8% (262/496) [48.4–57.2]
CPOD (chronic papular onchodermatitis)	12.5% (62/496) [9.9–15.7]
LOD (lichenified onchodermatitis)	0.7% (4/549) [0.3–1.9]
ATR (skin atrophy)	11.3% (61/540) [8.9–14.2]
DPM (depigmentation)	1.7% (9/543) [0.9–3.1]
NOD (palpable nodules)	5.3% (29/546) [3.7–7.5]

Ophthalmological manifestations			
Condition	**Prevalence in % (*n*+ve/*N* examined) [95% CI]**	**Unilateral prevalence, in % (*n*+ve/*N* examined) [95% CI]**	**Bilateral prevalence, in % (*n*+ve/*N* examined) [95% CI]**
Mild visual impairment (6/12)	13.0% (39/301) [9.6%–17.2%]	8.3% (25/301) [5.7%–12.0%]	4.7% (14/301) [2.8%–7.7%]
Moderate visual impairment (6/18)	4.0% (12/301) [2.3%–6.8%]	2.3% (7/301) [1.1%–4.7%]	1.7% (5/301) [0.7%–3.8%]
Severe visual impairment (6/60)	0% (0/301) [0.0%–1.3%]	0% (0/301) [0.0%–1.3%]	0% (0/301) [0.0%–1.3%]
Blindness (<3/60)	5.3% (16/301) [3.3%–8.5%]	3.7% (11/301) [2.1%–6.4%]	1.7% (5/301) [0.7%–3.8%]
Conjunctivitis[a]	46.9% (143/305) [41.4%–52.5%]	3.0% (9/305) [1.6%–5.5%]	43.9% (134/305) [38.5%–49.6%]
Cataracts	47.3% (52/110) [38.2%–56.5%]	31.8% (35/110) [23.9%–41.0%]	15.5% (17/110) [9.9%–23.4%]
Pterygium[a]	11.4% (13/114) [6.8%–18.5%]	6.1% (7/114) [3.0%–12.1%]	5.3% (6/114) [2.4%–11.0%]

Note: *n*+ve = number positive; N examined = total number examined. The number of participants examined for dermatological and ophthalmological manifestations was lower than that of recruited participants (564) due to logistical reasons and refusal to participate.
[a]These pathologies are not known to be associated with onchocerciasis but were included in the eye examinations as they are known to be common eye conditions in Ghana.

onchocerciasis) were conjunctivitis and pterygium, with a prevalence of 46.9% (143/305, 95% CI: 41.4%–52.5%) and 11.4% (13/114, 95% CI: 6.8%–18.5%), respectively (Table 4).

Association between microfilarial infection, Ov16 seropositivity status and dermatological and ophthalmological manifestations

CPOD, LOD, DPM and NOD were significantly associated with microfilarial infection and Ov16 seropositivity status. PRU was significantly associated with the former but not with the latter, and the reverse applied to APOD. Mild, moderate and severe visual impairment, as well as blindness, were associated with microfilarial infection and Ov16 seropositivity. Cataract was associated with the former but not the latter (Table S1). The overlap of the key dermatological and ophthalmological manifestations typically associated with onchocerciasis is presented in Figure S2.

DISCUSSION

This study investigated the prevalence of onchocerciasis and its associated clinical manifestations in an onchocerciasis endemic area in Ghana after 27 years of ivermectin MDA. Our study showed that the communities in the study area had microfilarial prevalence ranging between 4.6% and 18.6% (November 2020), and Ov16 seroprevalence between 10.6% and 42.5% (June 2021). For comparison with the skin-snip survey conducted in August 2021 (just before the second round of biannual MDA), microfilarial prevalence ranged between 4% and 21% [22]. The results of Ov16 RDT showed a low sensitivity when compared with mf results though specificity could not be assessed due to past ivermectin use. Also, as MDA progresses, the sensitivity of skin-snip microscopy declines [32], and therefore, mf status ceases to be a reliable gold standard against which to compare the diagnostic performance of other tests. The case of Jonnykrom (microfilarial prevalence of 18.6% and Ov16 seroprevalence of 18.8%) is especially interesting because it is only about 4 km from Kwanware, an OCP community which was part of the OCP, where it was classified as mesoendemic at baseline, with a (crude) microfilarial prevalence of 48.1%, in 1989 [22]. In the 2017 onchocerciasis impact assessment by the GHS, nearly three decades later, microfilarial prevalence was recorded as 29.3% (a reduction of 39%). This trajectory of transmission is likely to be shared by Johnykrom and other communities in the Wenchi cluster. Considering that 15–17 years of ivermectin MDA has been reported to lead to interruption of transmission in other mesoendemic settings in Africa (e.g., Falémé in Mali with baseline prevalence of 20%–57% [33]; Kaduna in Nigeria, with baseline median prevalence of 52%) [34, 35], progress towards onchocerciasis elimination in our study communities seems very protracted.

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Possible explanations for the persistence of onchocerciasis in the study communities include the 1-year COVID-19 interruption of ivermectin MDA [36]; arguably high levels of systematic non-adherence to ivermectin treatment [37]—although this was not apparent from reported coverage records [22]; variable levels of therapeutic coverage over the years which do not reach and sustain for prolonged periods the required levels for EOT [22]; sub-optimal responses to ivermectin MDA [18, 21]; challenges with CDTI implementation arising from inadequate funding, scarce technical guidance, lack of human resources and tools [11], and competition for resources from other health programmes, with the buy-in of the government for onchocerciasis control activities being somewhat limited [11].

Worryingly, the prevalence of dermatological manifestations was substantial, with APOD and CPOD observed in 52.8% and 12.5% of the examined individuals in our MDA intervention setting, compared to 3.4% and 2.3% in a mesoendemic pre-intervention setting in Nigeria [38]. Similarly, the prevalence of PRU (24.3%) and ATR (11.3%) are greater than those (9.5%, 6.1%) reported in Nigeria, but Murdoch et al. measured ATR only in those aged <50 years to minimise confounding with age [38]. The prevalence of palpable nodules in our study communities was lower (5.3%) than the baseline NOD prevalence in the study of Murdoch et al. (21.2%) [38]. Ozoh et al. reported significant reductions in the prevalence of severe itch, APOD, CPOD, LOD, DPM and NOD in a number of settings across Africa (Cameroon, Nigeria, Sudan and Uganda after five to six MDA rounds of annual CDTI [39].

In our study, the most prevalent dermatological manifestation was APOD (strongly associated with Ov16 seropositivity status), followed by severe itch (PRU) which was strongly associated with mf infection status. Other manifestations (CPOD, LOD, DPM and NOD) were significantly associated with both mf and Ov16 positivity. These skin conditions are known to be key manifestations of onchocerciasis, with severe itch being the most frequent first sign of onchocercal skin disease (OSD) [40]. Our study findings are similar to those of a previous study in the Nkoranza North District of Ghana, where clinical manifestations of onchocerciasis persisted after more than two decades of ivermectin MDA [26].

OSD may have severe psychosocial and socio-economic consequences [40]. In some endemic communities, people with OSD were seen as 'unclean' and often stigmatised due to fear of acquiring the infection, leading to 'social ostracism' [40]. OSD has also been associated with reduced productivity, difficulties in breastfeeding, poor school attendance, and reduced marriage prospects for affected teenage girls [40]. In a study by Vlassof et al. in Africa, it was identified that one-third of residents with OSD had low self-esteem and about 1%–2% of them had contemplated suicide due to their predicament [41].

The most prevalent eye condition in this study was cataract, which was significantly associated with microfilarial infection and Ov16 positivity status. Hopkins and Boatin described that mf can penetrate the iris and cause chronic inflammation (chronic anterior uveitis) which can lead to blindness due to secondary glaucoma or secondary cataract [8]. Other ocular conditions included visual impairment, blindness, conjunctivitis and pterygium (the latter two not typically considered manifestations of onchocerciasis). In a study by Abiose et al., in a mesoendemic setting of Nigeria, 2.7% of examined individuals were bilaterally blind by acuity criteria at baseline, and 1.7% were visually impaired according to WHO criteria [42], whereas in our MDA intervention setting these values were 1.7% and 16.9%, respectively.

The high prevalence of cutaneous and ocular pathologies we report in the study communities is certainly of concern and may partly be due to methodological differences with previous studies. Although it is true that the number of prevalent cases of chronic and irreversible conditions (those less likely to respond to ivermectin treatment, such as DPM, bilateral blindness) will decrease slowly, it will be important to include them in a morbidity management and disability prevention plan [43].

LIMITATIONS

There are several limitations to this study. It was not possible to randomly select study participants. Also, the study communities were chosen based on their perceived risk of being endemic, as they were either part of the 2017 GHS onchocerciasis impact assessment or close to communities which were part of the assessment. Therefore, results obtained in these communities might not reflect the true burden of infection and disease in the entire district or municipality. Our results should be interpreted with caution as they may over- or underrepresent the extent of onchocerciasis-associated disease. For instance, to minimise overestimation and maximise the probability of *O. volvulus* infection being the underlying cause, Murdoch et al. reported ATR only in those younger than 50 years [38], and Kirkwood et al. restricted their analysis of visual acuity to those aged ≥15 years [44], whereas we report it in all age groups. In addition, only a limited number of study participants were tested for the presence of mf (57%) and Ov16 antibodies (49%). Also, as the participant recruitment took place in 2020, during the COVID-19 pandemic, several logistical challenges (e.g., refusal to participate in some examinations) hampered data collection for all participants. Furthermore, our study team did not include a dermatologist or ophthalmologist with experience in clinical onchocerciasis-associated disease sequelae, and the assessments done by the medical team were minimal. As the sensitivity and specificity of the WHO App for the diagnosis of NTD skin lesions by frontline workers are not yet well known, we may have overestimated the prevalence of onchocerciasis-associated skin conditions, as our comparison with [38] seems to indicate. Moreover, we were not able to specify the precise cause of most of the ophthalmological manifestations, likely leading to overestimation of our results, as our comparison with [42] suggests.

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CONCLUSIONS

Our study indicates the persistence of *O. volvulus* infection and associated dermal and ocular pathologies in the study communities despite decades of MDA with ivermectin. Therefore, onchocerciasis-associated morbidities need to be considered in onchocerciasis elimination planning. A morbidity management and disease prevention strategy, similar to that for lymphatic filariasis, should be developed to reach EPHP as well as EOT for onchocerciasis by 2030.

In the most recent Ghana NTD Master Plan (2021–2025) [45], the GHS emphasised that to meet EOT goals for Ghana, there is an urgent need to regularly monitor the effectiveness of ivermectin MDA, and to perform surveys and exclusion mapping in relevant communities to obtain a reliable picture of the endemic situation in Ghana, improve the quality of epidemiological data, and scrutinise evidence on the extent of previously reported sub-optimal responses to ivermectin in the country [17–21].

Another crucial avenue for further research is to understand potential discrepancies between reported and realised coverage, and in particular, any patterns and determinants of systematic non-adherence to ivermectin treatment. In order for the EOT targets to be achieved in Ghana, the role of systematic non-adherence to ivermectin intake in the persistence of *O. volvulus* transmission needs to be further investigated and this will be discussed elsewhere.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

All the data are contained in the tables and figures of the main text and the Supporting Information file. For the purpose of open access, the author has applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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