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ORIGINAL RESEARCH ARTICLE

RECRUDESCENCE OF ONCHOCERCIASIS IN THE COMOÉ VALLEY IN SOUTHWEST BURKINA FASO

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ABSTRACT

Onchocerciasis control by vector control was instigated in southwest Burkina Faso in January 1969 by ORSTOM/OCCGE, and continued until operations were taken over by the WHO Onchocerciasis Control Programme (OCP) in February 1975, which itself ceased operations in the area in 1989 when onchocerciasis was judged to have been reduced to insignificant levels. Initially (1969-1975) vector immigration maintained unacceptably high levels of transmission, but OCP was much larger than the preceding campaign and in 1975 the Annual Transmission Potential (ATP) dropped below 100 at all sites in the Comoé river valley except Folonzo, which continued to be subject to reinvasion, along with the whole of the Léraba river valley. However, after the southern extension of the OCP in 1979, ATPs dropped below 100 everywhere in the Comoé basin (including the Léraba valley), and further dropped to insignificant levels after the western extension of the OCP in 1985. Thus transmission dropped more quickly in the Comoé river valley than the Léraba river valley (which had been subject to vector reinvasion), and this was also reflected in prevalence of microfilaraemia in the human population. After 1986 prevalence was less than 5% in all villages in the Comoé river valley (except for two, which subsequently dropped to 0% and 3.7% by 1999). However, in 2001 (12 years after the cessation of vector control) the prevalence in one village in the Comoé river valley had increased to 39.6%, and two more had increased above 5% by 2007. New epidemiological surveys in 2011 and 2012 showed that in 13 out of 30 villages in the Comoé river valley prevalence of microfilaraemia was above 5%, although this was not observed in the Léraba river valley where prevalence remained low. This is the first documented case of recrudescence of onchocerciasis in the old OCP area, and the reasons are not clear. It is possible that there has been immigration of parasites with humans or vectors from areas where there has been a shorter period of control, or that control has been less effective. It is possible that in spite of very low levels of transmission the local parasite population was never reduced to a level below the transmission breakpoint, or that there has been a local recrudescence due to stochastic population effects. In any case it is clear that the distribution of ivermectin against lymphatic filariasis in the area since 2004 has failed to prevent the recrudescence of onchocerciasis, and the Burkina Faso *Programme National de Lutte contre l'Onchocercose* (PNLO - Ministere de la Santé) has instigated a programme of Community Directed Treatment with Ivermectin specifically aimed at onchocerciasis in accordance with the strategy developed by APOC and recommended to governments by OCP when it was dissolved in 2002.

Keywords: onchocerciasis, river blindness, *Onchocerca volvulus*, *Simulium damnosum*, Onchocerciasis Control Programme, Burkina Faso.

1. Historical introduction

In 1974 the World Health Organisation Onchocerciasis Control Programme (OCP) began operations with the objective “to eliminate onchocerciasis as a disease of public health importance and socio-economic importance” in the Volta river basin of West Africa (Boatin et al., 1997). The OCP was located in this area because there was already a significant body of knowledge concerning the clinical aspects of the disease, its entomology, parasitology, epidemiology and socio-economics (PNUD, 1972; Philippon and Le Berre, 1974), and because of the high rates of the disease in the West African savannah belt, especially the Volta river basin and surrounding areas. For example, at that time Burkina Faso (as Haute-Volta) had a population of 4.5 million people, of whom 400,000 were infected and 10% of these had serious ocular manifestations (WHO, 1994). In the worst affected areas blindness might afflict 10% of the adult population (including 50% of males over 40 years of age) (WHO, 2002). Elimination of the disease was to be achieved by weekly aerial application of insecticide (temephos) to the riverine breeding sites of the vector *Simulium damnosum* s.l. The original OCP area included all of Burkina Faso (except the extreme north where there were no vector breeding sites) and parts of Mali, Côte d’Ivoire, Ghana, Togo, Benin and Niger (Figure 1). Parts of southwest Burkina Faso had already been subject to ground larviciding with DDT. In 1962-1963 the Comoé river was treated every ten days for 13 months by an ORSTOM-OCCGE team led by Drs René Le Berre and Max Ovazza, and in January 1969 larviciding recommenced to cover 60,000 km^2 including the Comoé basin (consisting of the Comoé river with its main tributaries, the most important being the Léraba river), and known as the FED campaign (because it was supported by the Fonds Européen de Développement) and continued until OCP commenced operations (Walsh, 1990). This local control led to a significant drop in annual biting rate (ABR). For example, at Folonzo (6 km from the Comoé river) ABR dropped from 65,000 to 25,000, but with the commencement of the OCP, covering a much wider area, ABR immediately dropped to less than 200 in most years (Philippon et al., 1990). The important events in the control history of the Comoé basin are summarised in Table 1.

The vector populations breeding in the Comoé river in both Burkina Faso and northern Côte d'Ivoire, along with its major tributary, the Léraba river, have been identified as predominantly savannah cytospecies (*S. damnosum* s.str. and *S. sirbanum*) along with *S. soubrense* in the Léraba and a few *S. squamosum* near the source of the Comoé (Quillévéré, 1975; Vajime and Quillévéré, 1978; Boakye et al., 1998). This area came under control by OCP in February 1975 and weekly treatments with larvicide (temephos) continued until late 1989 when onchocerciasis had been reduced to levels that were considered insignificant such that it was no longer of public health importance in the area. However, at the beginning (after 1975) ABRs had remained high at some localities in the Comoé basin, especially along the Léraba river and the Comoé river valley near Folonzo. As a consequence, the Annual Transmission Potential (ATP) had quickly dropped below 100 (considered to be the epidemiological threshold, below which onchocerciasis would not represent public health significance – WHO, 1994; Diawara et al., 2009) at all sites, except those along the Léraba river and the Comoé near Folonzo (Garms et al., 1981). The biting flies were not breeding locally. They were found to be old (parous) savannah flies which were migrating into the area with the prevailing monsoon winds in the first part of the rainy season from uncontrolled rivers to the southwest outside of the OCP area

(Bellec et al., 1984), and they were often carrying infective *Onchocerca* larvae. To solve this problem OCP operations were extended southwards in Côte d'Ivoire, and after the rivers which were the sources of the immigrants came under continuous control in March 1979 ABRs and ATPs were reduced to acceptable levels throughout the Comoé basin (which includes both the Comoé and Léraba river valleys) in Burkina Faso and northern Côte d'Ivoire (Philippon et al., 1990). For example, at Léraba Bridge (on the Léraba river between Côte d'Ivoire and Burkina Faso) in the first part of the rainy season (April-August) the monthly biting rate (MBR) and monthly transmission potential (MTP) dropped from 4697 and 511 to 428 and 34 respectively, and at Kafolo (by the Comoé river in northern Côte d'Ivoire) they dropped from 2006 and 51 to 119 and 0 respectively (Walsh et al., 1981). Extension of larviciding operations westwards in 1984 further reduced the reinvasion of the Léraba river in 1985 when the Upper Sassandra river basin in SE Guinea was brought under control, and average MBRs and MTPs were reduced to 75 and 1 (respectively) over the three-month reinvasion season April-June 1985-1989 (Baker et al., 1990).

During the course of the OCP there have been a number of interruptions to the normal pattern of weekly aerial applications of larvicide in the Comoé basin. Insecticide treatments were suspended at the Gréchan rapids on the river Léraba between the 13 January and 10 February 1976 (Elsen et al., 1981) and between the 13 January and 16 March 1977 (Davies et al., 1981) to carry out observations on the rate of vector recolonisation, the build-up of the biting fly population, the fly dispersal from the breeding site and its decline following the reintroduction of control. This was considered to have had minimal effect on transmission because the Gréchan rapids are situated in the uninhabited Comoé Game Park, and whilst the daily biting rate (DBR) reached a maximum of 150 (on 18 March) on the banks of the rapids, at inhabited localities outside the game park (including Folonzo near the Comoé river) there was no detectable effect (Davies et al., 1981). Larvicide treatments were also suspended along a 120 km stretch of the Comoé river near Folonzo from the beginning of October 1977 until 12 February 1978 to investigate the effectiveness of adulticides. By the end of December 1977 a moderate local population of *S. damnosum* s.l. had become established giving DBRs of 30-50 at Folonzo ford (Davies et al., 1982), and experimental doses of adulticides were then applied to the riverside vegetation between 27 January and 01 February. Daily biting rates averaged approximately 104, 180, 24 and 30 (depending upon catching site) in the three days before adulticiding, and approximately 100, 180, 1 and 10 after adulticiding until 12 February when larviciding recommenced. It is difficult to estimate the excess transmission that these experiments might have yielded, but it is likely to have been minimal in the southern part of the project area where the river runs through an uninhabited forest reserve. Further north in the project area, DBRs between 30 and 180 would be expected to yield a transmission potential of around 300-1800 over three months (assuming approximately 100 third stage *Onchocerca* larvae/1000 biting *S. sirbanum*/*damnosum* s.str. – Quillévéré et al., 1978), which is much higher than the target ATP of 100 (see above). However, the period of this research was before the southern extension of the OCP, and so this part of the Comoé valley was still subject to moderate reinvasion during the rainy season. It was only after the southern extension of OCP operations in 1979 that the area was subject to satisfactory levels of control.

In 1980 resistance to temephos appeared in *S. sanctipauli* on the lower Bandama river in southern Côte d'Ivoire. Resistant populations quickly spread and occupied the previous range of *S. sanctipauli* and *S. soubrense* in Côte d'Ivoire, including the Léraba river but not the Comoé river in Burkina Faso (Kurtak, 1990). Chlorphoxim was introduced as a replacement larvicide for weekly treatment of resistant populations, but in 1981 *S. sanctipauli* became resistant to Chlorphoxim, and *Bacillus thuringiensis* (*B.t.* H14) was introduced. Temephos resistance appeared in savannah flies (*S. sirbanum/damnosum* s.str.) in the 1981/82 dry season on the lower Bandama river, but the resistant population was eradicated using alternative larvicides. Resistant savannah cytospecies vector populations eventually reappeared in the rainy season of 1985 and spread widely including the Comoé basin in Burkina Faso (Kurtak, 1990). However, by that time OCP had developed an effective management strategy, and by the rotation of seven larvicides good control was maintained throughout the OCP area (Hougard et al., 1993).

Larviciding in the Comoé basin in Burkina Faso (Comoé and Léraba rivers) and northern Côte d'Ivoire was terminated at the end of the rainy season in 1989 after 15 years of more or less continuous treatment. Entomological surveillance was continued for a further two years and ATPs in the Comoé basin in Burkina Faso were reported to be zero or close to zero (Boatin et al., 1997), confirming permanent cessation of larviciding. This was not the case, however, in the adjacent river basins of the upper Black Volta near Dienkoa and the Bougouriba, north and northeast (respectively) of the Comoé basin (Boatin et al., 1997). In these two areas ATPs were above 100 and prevalence of microfilaraemia was 15-30% in some villages. Dienkoa has a complex history of treatment and monitoring. Larviciding turned out to be very difficult, and had been carried out irregularly and local breeding had maintained a focus of transmission. Post-1989 control measures included ivermectin distribution (already started in 1988) and ground larviciding (Borsboom et al., 2003). At Bougouriba it seemed that transmission had been successfully controlled for more than 14 years by regular larviciding (Hougard et al., 1997). After the cessation of control, biting fly populations increased immediately (as expected) but there was also an unexpected steady rise in infectivity rate in the fly population (which reached almost 6% by 1998) and a corresponding rise in mf prevalence in the human population (around 20% in some villages in 1996). Ivermectin distribution was instigated in 1996 and by 2001 mf prevalence had dropped below 10%. The reasons for the recrudescence are not properly understood, but in retrospect larviciding may have been stopped prematurely (Hougard et al., 1997). There had been many difficulties in accessing the rivers and on some tributaries larviciding had already stopped in 1987. Furthermore, there had been government-sponsored immigration and it had not been appreciated that the settlers had modified the environment and thereby created new artificial breeding sites (Borsboom et al., 2003).

Regular larviciding within the boundaries of the original OCP area was only terminated after a minimum of 14 years of vector control and when epidemiological indicators (principally prevalence of microfilaraemia, CMFL and ATP) were judged to be below the threshold for a 1% risk of recrudescence (Agoua et al., 1995). OCP strategy was to continue entomological surveillance for two years, to confirm that there was no immediate recrudescence of transmission, and eventually to devolve responsibility for periodic surveillance (and possible control) to the member countries with support from NGDOs as necessary. There is no doubt that by the end of 1989

OCP had succeeded in its objective and that onchocerciasis was no longer a disease of public health importance throughout the original OCP area (with a few exceptions such as Dienkoa and Bougouriba – see above) (Hougard et al., 1997), and extensive post-control entomological studies up to 1994 confirmed the continued absence of significant transmission (Agoua et al., 1995). Intensive studies over a longer time frame in the Centre-Sud and Centre-Est administrative regions of Burkina Faso also confirmed this in a hyperendemic area which had not been subject to vector reinvasion and the local vectors were savannah cytospecies (Hougard et al., 2001). In this area 14 years of vector control (1976 to the end of 1989) had reduced average ABRs to between 233 and 1465 (depending upon locality), and this was accompanied by a steady reduction in ATP, which was below 100 in the period 1982-1989, and for the two years of continued monitoring after control had ceased. In 2000 only one infective fly was found amongst 27,100 flies dissected (Hougard et al., 2001). Prevalence of infection in humans dropped from pre-control average of 71.9% to 0.6-7.7% (depending upon locality) when control ceased, and was negligible (or nil) in 2000 (with only three likely autochthonous cases).

After vector control had ceased throughout most of the original OCP area (including the Comoé basin) in 1989, it was continued in the southern and western extensions, where it was combined with ivermectin distribution (Boatin et al., 1997). The aim was to reduce onchocerciasis to a state where it was no longer of public health significance in these areas, but control operations would also have the effect of suppressing the emigration of infective flies into the original OCP area until the source areas no longer posed a threat. The OCP programme formally ceased its operations in December 2002, after responsibility for onchocerciasis surveillance and any necessary control operations in each member country had been devolved to the respective Ministry of Health. The strategy for surveillance and control (in the event of a recrudescence) recommended by OCP to Ministries of Health consisted of epidemiological surveillance of sentinel villages (Prost and Prod'hon, 1978; WHO, 1994), entomological surveillance of sentinel sites (WHO, 1988; Toé et al, 1997; Yaméogo et al, 1999), CDTI in any health districts affected by recrudescence (WHO, 1994; Amazigo and Crump, 1998), and information, education and communication to the affected communities.

Unfortunately civil unrest in Côte d'Ivoire has interfered with the full implementation of CDTI since 2002, and the national and regional impact of this interruption is unknown (Thylefors and Alleman, 2006). The Comoé basin in Burkina Faso was never subject to ivermectin treatment against onchocerciasis, but mass drug administration against lymphatic filariasis was instigated by the Ministry of Health in 2004, with annual doses of ivermectin (at 150 mg per kg – which is similar to the normal therapeutic dose for onchocerciasis) and albendazole.

Routine evaluation of onchocerciasis prevalence and CMFL (Community MicroFilarial Load) were carried out in the Comoé basin under the auspices of the OCP after the cessation of larviciding in 1989 until the programme closed in 2002 after which responsibility for surveillance was devolved to the Burkinabé Ministry of Health. The results of the epidemiological surveillance in 2001 showed higher than expected prevalence, and this was also the case in 2007 and 2008. We report here the results of epidemiological surveys carried out by the Burkinabé Programme National de Lutte contre l'Onchocercose (PNLO – part of the Ministry of Health) in 2010 and

2011 which confirm this recrudescence, along with the historical data starting in 1973, and the instigation of control by Community Directed Treatment with Ivermectin (CDTI).

Table 1

Summary history of the main events in the control of onchocerciasis in the Comoé and Léraba river valleys in SW Burkina Faso.

Year	Event	Valleys affected*	
		Comoé	Léraba
1962/63	Larviciding with DDT introduced by OCCGE for 13 months	✓	-
1969	OCCGE-FED Campaign commences larviciding with DDT	✓	✓
1975	OCP follows on from OCCGE larviciding with temephos	✓	✓
1976	Suspension of larviciding at Gréchan rapids for 1 month (Jan-Feb)	-	✓
1977	Suspension of larviciding at Gréchan rapids for 2 month (Jan-Mar)	-	✓
1977/78	Suspension of larviciding at Folonzo for 4.5 month (Oct-Feb)	✓	-
1979	Southern extension of OCP	✓	✓
1980	Temephos resistance in *S. sanctipauli*	-	✓
1984/85	Western extension of OCP	(✓)	✓
1985	Temephos resistance in savannah cytospecies	(✓)	(✓)
1987/89	OCP introduces CDTI to western extension	(✓)	✓
1989	OCP stops larviciding in core area	✓	✓
1992	OCP introduces CDTI to southern extension	✓	✓
1998	OCP stops larviciding in southern extension	✓	✓
2001	First indication of recrudescence in Comoé valley at Sakora village	✓	-
2002	OCP stops larviciding in western extension	(✓)	✓
2004	MDA with ivermectin initiated against lymphatic filariasis	✓	✓
2010/11	Recrudescence in Comoé valley confirmed	✓	-
2011	CDTI introduced against onchocerciasis	✓	-

*✓, event relevant to valley indicated; (✓), event may have had minor affect; -, event not relevant.

2. Materials and Methods

2.1 Description the study area

The Comoé basin in SW Burkina Faso includes both the Comoé and Léraba river valleys, and is situated in the southern sudan savannah vegetation zone (= sudano-guinea savannah) with annual rainfall mostly between 900 and 1100 mm (but reaching 1300 mm near the border with Côte d'Ivoire). There are two seasons, a wet season from April to October in which the SW monsoon wind predominates and a dry season in which the NE dry harmattan wind predominates. The temperature usually lies between 39^{o}C and 17^{o}C, which are the extremes of the monthly maxima and minima respectively. The vegetation is open savannah woodland, but with gallery forests fringing the permanent watercourses to a width of more or less 50 m (Molyneux et al., 1978; Jeune Afrique, 2005). The major rivers are the Comoé river which arises near Peni and its various tributaries, of which the most important is the Léraba river (which arises in Burkina Faso but runs along the border with Côte d'Ivoire before it joins the Comoé), all of which are situated in the Burkinabé administrative and health region of Les Cascades (Figure 1).

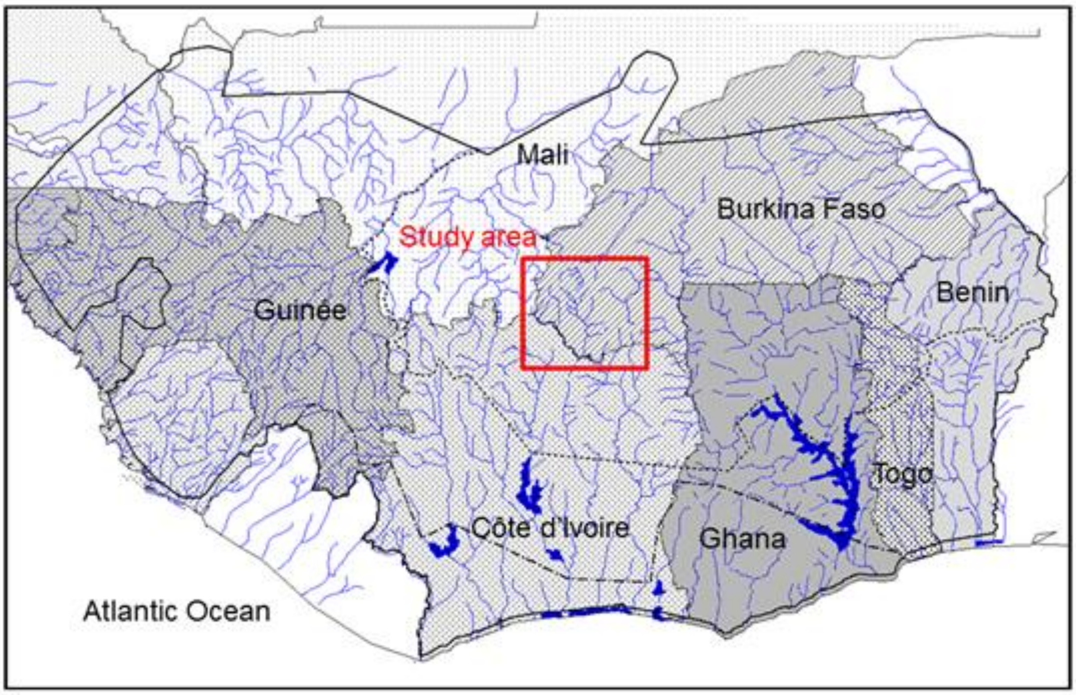

Fig. 1. Map of the Onchocerciasis Control Programme in West Africa showing the study area. Rivers and lakes are shown in blue. International borders are shown with solid grey lines and the different countries have different shading. The maximum extent of the Onchocerciasis Control Programme (OCP) is outlined in solid black line, whereas the original core area is shown by a black dotted line, and the southern extensions are indicated by a black dash-dot line.

2.2 Epidemiological methods

The epidemiological evaluation was carried out by Ministry of Health officials from the Direction de la Lutte contre la Maladie (DLM) and the Région Sanitaire des Cascades in collaboration with the health districts and their respective Centres de Santé et de la Promotion Sociale (CSPS) according to the standard methods used by OCP (Prost and Prod'hon, 1978; WHO, 1994). Twenty eight villages were evaluated between January and April 2010 and a further eight between January and February 2011. In 2010, whenever possible, villages were chosen which had been sentinel villages from the old OCP, otherwise they were chosen because they were closest to the river and would give an even distribution of villages from Moussodougou dam to the border with Côte d'Ivoire. In 2011 they were chosen mostly from the Léraba valley (six villages) but with two villages along the Comoé river which were close to the Léraba. The geographic distribution of the villages surveyed in the Comoé basin is shown in Figure 4.

Since 2004 the villages in the study area had been undergoing Mass Drug Administration (MDA) with ivermectin against lymphatic filariasis. MDA was carried out in April and our village surveys were carried out 9-12 months later. In each village to be evaluated a census was made of the whole population. A bloodless skin snip was taken from both iliac crests using a Holth corneo-scleral punch from all inhabitants over the age of three years. The skin snips were incubated in distilled water for 30 minutes at ambient temperatures in a microtitre plate, and examined under a dissecting microscope, and the numbers of emergent microfilariae were recorded on the evaluation form. The distilled water was removed and replaced with normal saline and the skin snips were re-examined after 24 hours to count any more microfilariae which had emerged. Inhabitants found to be positive were interrogated to determine their migration history to investigate the possibility that the parasites might have been picked up elsewhere. The geographical co-ordinates of the village were recorded from a GPS. Any microfilariae which were found were preserved dry between slide and cover slide and labelled according to patient for any possible future reference that might be required. Finally, any microfilariae-positive inhabitants were treated with ivermectin (as an individual therapy before the recrudescence became evident and a CDTI campaign could be organised – see section 4 below) and the preliminary results communicated to the village, with thanks.

The National Onchocerciasis Control Programme (NOCP) was established in 1992 by the Ministry of Health to eliminate onchocerciasis as a public health issue. As such all its standardised activities (including CDTI, entomological surveillance and epidemiological evaluation) were given blanket ethical approval, and the Ministry of Health determined that this would not need to be reconsidered for individual projects within the programme.

2.3 Sources of historical data

Historical data covering the period up to 2010 were originally collected by either the WHO Onchocerciasis Control Programme (including all entomological data) or the Ministry of Health of Burkina Faso (with the support from the WHO African Programme for Onchocerciasis Control - APOC). Surveys were carried out according to standardised methods (WHO, 1987; Davies and Crosskey, 1991) which were similar to those described above (including the protocol for examination of skin snips), and data are the property of the Ministry of Health of Burkina Faso.

3. Results and discussion

3.1 Identifying the recrudescence

Historical and new results for the prevalence and CMFL in all villages surveyed epidemiologically in the Comoé basin from 1973 to 2011 are shown in Supplementary Material Table 1, and as separate time-series for the villages along the Léraba and Comoé valleys in Figures 2 and 3, and the geographic distribution of prevalence of onchocerciasis in the villages surveyed in 2010/2011 is shown in Figure 4. Current WHO elimination guidelines (WHO, 2016) make no recommendations on the issue of post-elimination recrudescence (although they do say that 'surveillance can be centred on entomological assessments'). However, at the time when this recrudescence was being documented WHO-APOC guidelines (APOC, 2010) stipulated that recrudescence was counter-indicated if prevalence was less than 1% in all villages. On that basis recrudescence is not judged to be occurring in the Léraba valley where 100% of villages (n=6) surveyed in 2010-2011 had prevalence <1%, in contrast to the Comoé valley where 70% of villages were >1% (n=30) (see Supplementary Material Table 1), and this difference is statistically significant (Fisher exact test P=0.0026). The results clearly confirm the recrudescence of onchocerciasis in the Comoé river valley, and illustrate the absence of recrudescence in the Léraba river valley.

In retrospect, the first indication of a recrudescence occurred in 2001when the village of Sakora in the Comoé valley was found to have a prevalence rate of 39.6%, compared with a mean of 3.7% over the preceding ten years (four surveys 1990-1999).

There are a number of possible reasons for this recrudescence. It could have been the result of parasites being carried back into the area by vector and/or human immigration. It could be that the local population of parasites had never been reduced to a level where it was not self-sustaining (i.e. below the epidemiological transmission breakpoint), and this could have been due to unsatisfactory historical vector control operations or a highly efficient local vector population. It is also possible that ivermectin resistance played a role in the recrudescence in combination with some of these other factors.

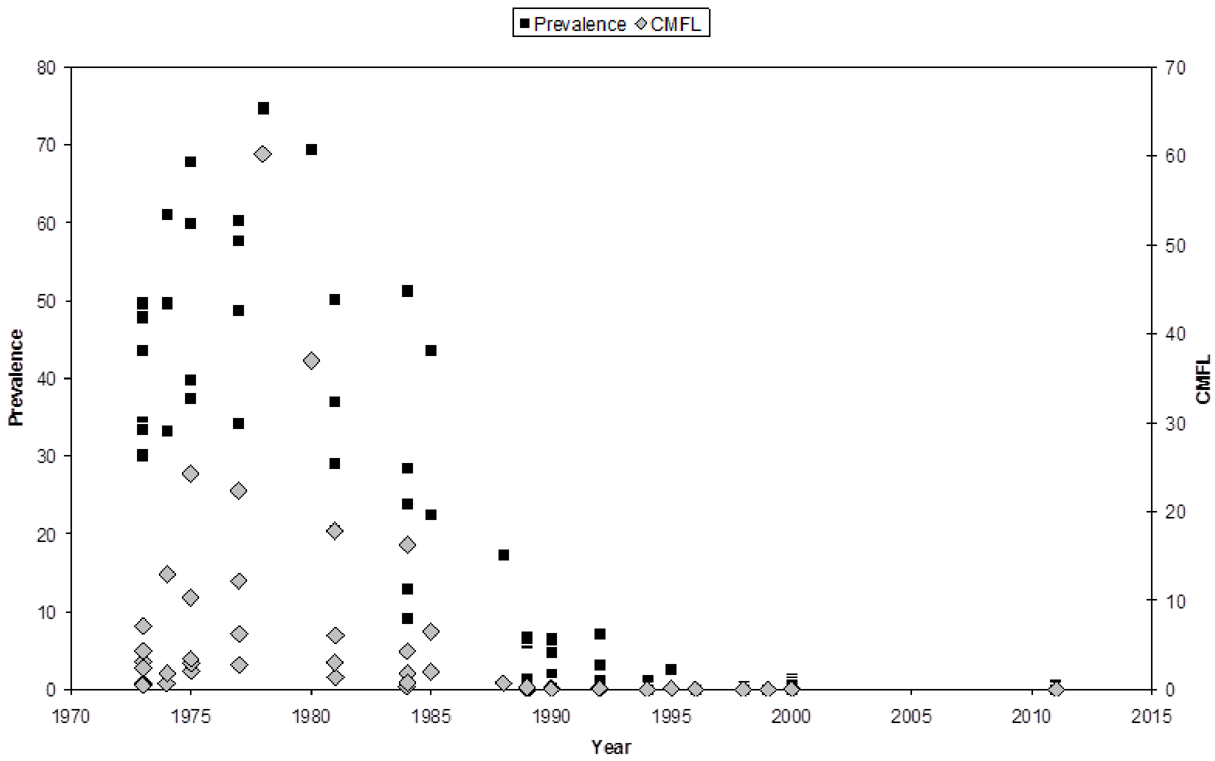

Fig. 2. Trends in the prevalence and community microfilarial load (CMFL) of onchocerciasis in villages along the Léraba river valley 1973-2011.

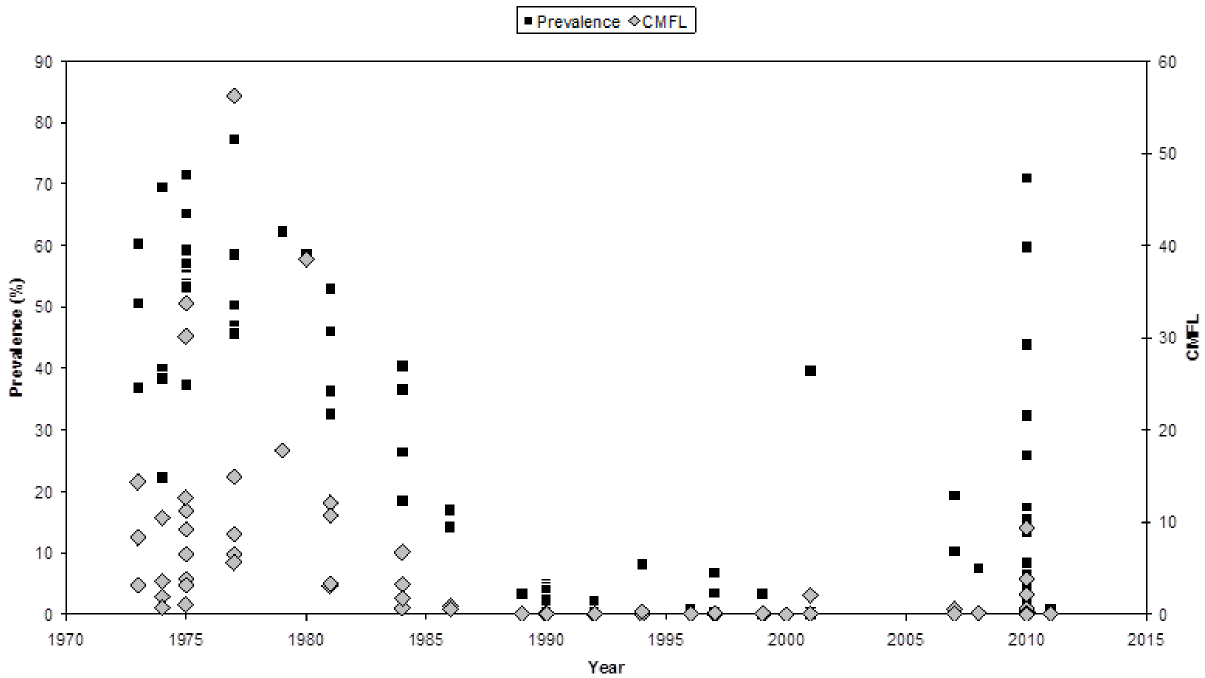

Fig. 3. Trends in the prevalence and community microfilarial load (CMFL) of onchocerciasis in villages along the Comoé river valley 1973-2011.

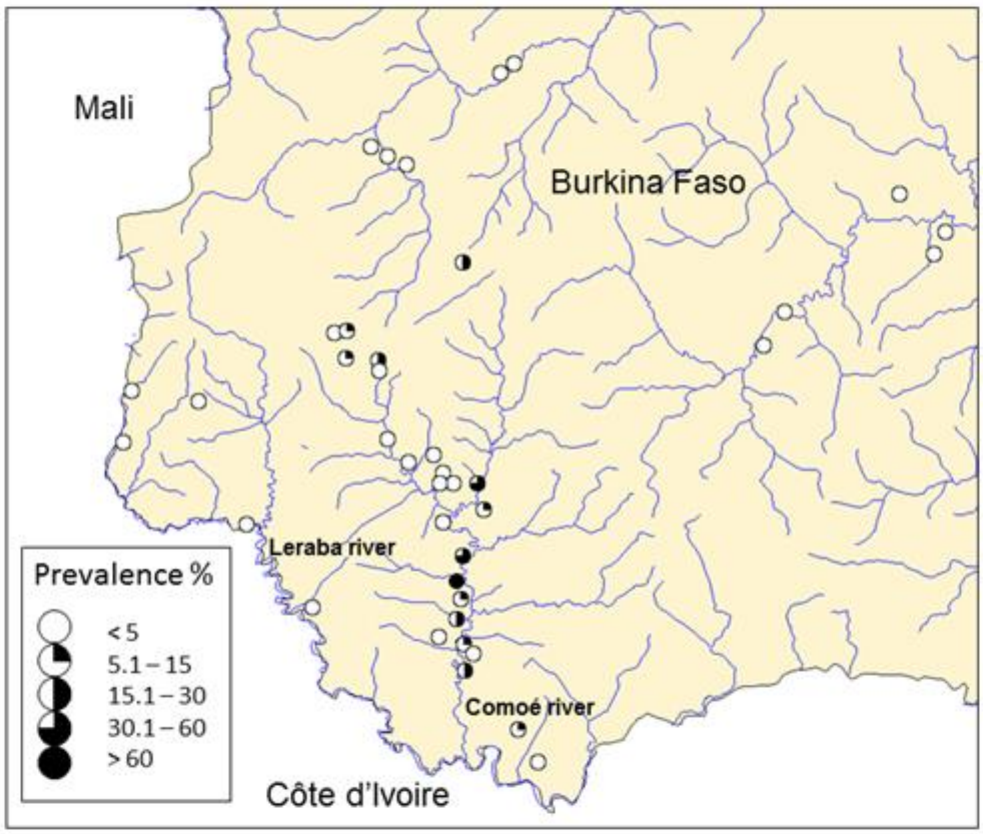

Fig. 4. The geographic distribution of prevalence of onchocerciasis in the villages surveyed in the Comoé basin (consisting of the Léraba and Comoé river valleys) and surrounding basins in SW Burkina Faso in 2010 and 2011.

3.2 Possible parasite reinvasion carried by immigrant vectors or humans

The Léraba valley had been subject to vector reinvasion during the period of the OCP, and this is reflected in Figure 5, which shows continuing high levels of biting and transmission after the commencement of OCP control operations in February 1975, but after the instigation of the southern extension in March 1979 these parameters showed a marked improvement, although they were still high at some collecting points, and only after the instigation of the western extension in February 1985 did ABR and ATP become insignificant everywhere (ABR range = 0 - 3418, mean = 832; ATP range = 0 - 21, mean = 5 at four collecting points, although not all four were operational every year). In 1990, after control was terminated, the biting rate immediately increased (as expected), but transmission remained insignificant up to 1996 (the last year of entomological surveillance) (ATP range = 0 – 26, mean = 6.5 at five collecting points, although not all five were operational every year). The entomological results of vector control are also reflected in the levels of human infection illustrated in Figure 2. After the commencement of the OCP prevalence of onchocerciasis dropped steadily and was less than 5% in 10 out of 11 villages surveyed in 1990 in the Léraba valley (after the cessation of vector control) and no village has been above 3% since 1992, and only one out of six villages above zero (0.45%) in 2011. These excellent results have been obtained in the face of the history of reinvasion in the Léraba valley and the various disturbances to the weekly programme of larviciding (see above).

The Comoé valley in Burkina Faso was only subject to vector reinvasion along its lower length near Folonzo, and this is reflected in the entomological parameters (Figure 6). After commencement of the OCP control operations only two sites had ABRs above 10,000 in 1975 (Folonzo and Koflande) and this had dropped below 5,000 at all points in 1976 and remained low until the cessation of control (except for one high ABR at Folonzo in 1989). ATP remained at high levels at a few sites until 1978, when it dropped below 100 at all sites and thereafter never exceeded 15, and after the cessation of control at the end of 1989 ATP ranged from zero to two with a mean of 0.4. Thus transmission dropped more rapidly and was lower in the Comoé valley than in the Léraba valley, and this also seems to be reflected in the levels of human infection (Figure 3). Prevalence dropped rapidly after 1979 and after 1986 it was less than 5% in all villages surveyed up to 2000 except Fabedougou and Sakora. Fabedougou had a prevalence of 8.2% in 1994, although in subsequent surveys in 1997 and 2001 it dropped to 3.5% and zero respectively. Sakora had a prevalence of 2.4% in 1990, which rose to 6.7% in 1997, but dropped again to 3.7% in 1999. These results were generally better than those in the Léraba valley (see above) and gave no cause for concern, but in 2001 (one year before the termination of the OCP) the prevalence at Sakora had jumped to 39.6%. After the termination of OCP epidemiological surveys carried out by the Burkinabé Ministry of Health in 2007 and 2008 also revealed higher levels of prevalence in three villages (all above 5%, including Sakora). The Ministry of Health instigated epidemiological surveys throughout the Comoé basin in 2010 and 2011 to investigate the extent of the problem, and 13 out of 30 villages in the Comoé valley showed prevalence levels above 5% (range 0 - 71%; mean 11.7% - Supplementary Material Table 1).

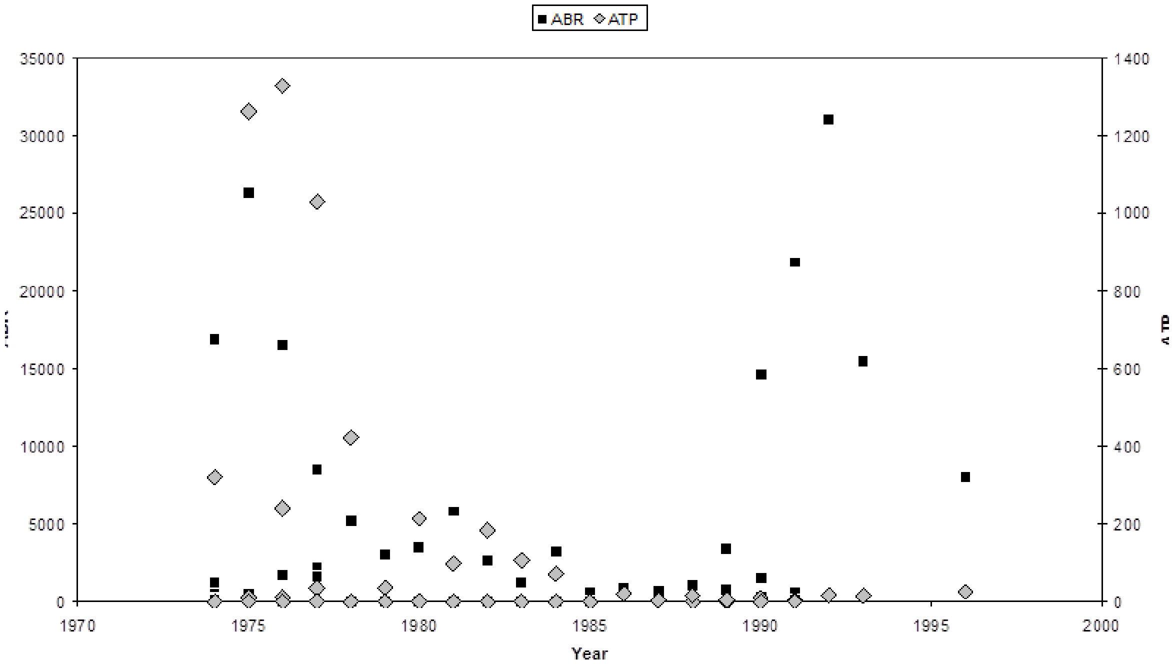

Fig. 5. Trends in annual biting rate (ABR) and annual transmission potential (ATP) at 11 sites in the Léraba river valley 1974-1996. Not all sites were monitored every year. Each point represents the ABR or ATP for one site for one year.

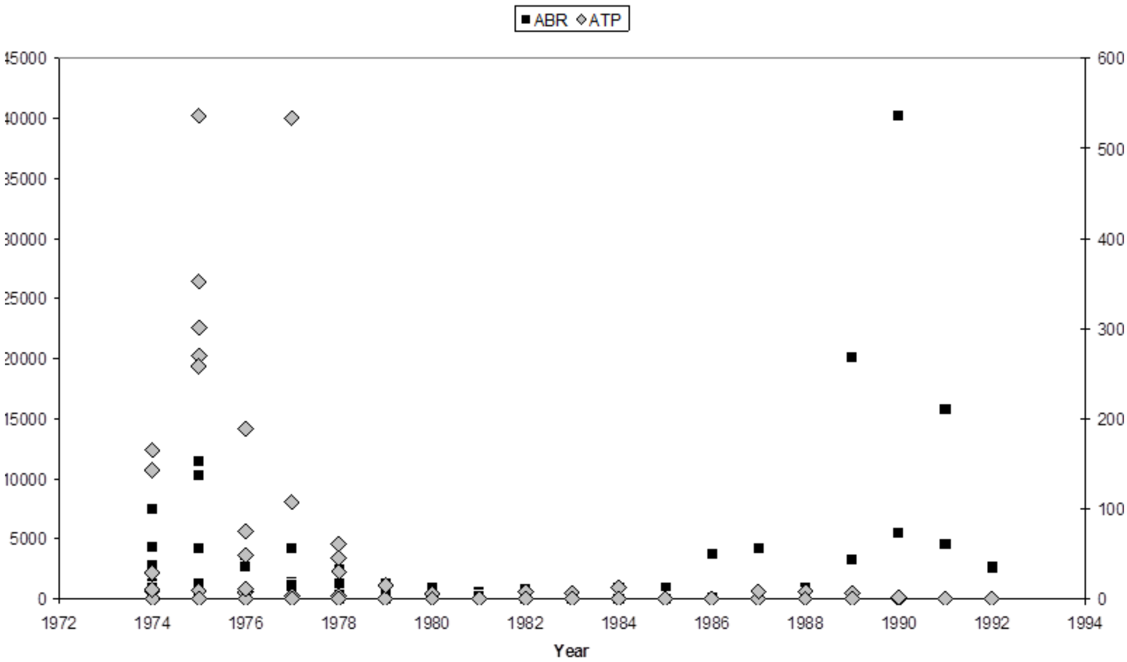

Fig. 6. Trends in annual biting rate (ABR) and annual transmission potential (ATP) at 15 sites in the Comoé river valley 1974-1992. Not all sites were monitored every year. Each point represents the ABR or ATP for one site for one year.

The Comoé basin was only sparsely inhabited at the time of the old OCP and at that time the first line villages (nearest to the river) were typically more than 15 km away from the river, but now the area has been subject to significant human immigration and the first line villages are often less than 1 km from the river. Therefore, the explanation might be to do with immigration of humans or vectors carrying infection from outside sources. Civil unrest in Côte d'Ivoire interfered with the full implementation of CDTI in the south of the country since 2002, and immigrants settled primarily along the Comoé valley. Dienkoa (over the northern watershed of the Comoé valley) has had a difficult history of control, but this was recognised and corrected in 1988. The Bougouriba basin lies over the watershed northeast of the Comoé valley, and whilst OCP operations seemed to produce satisfactory results at the time, from 1992 to 1996 there were increasing levels of infection, reaching 20% in some villages, when ivermectin distribution was introduced, along with some ground larviciding in 1997 and 1998. Ivermectin was distributed 4-monthly and there was good therapeutic coverage (70-80%), but less good geographic coverage (Borsboom et al., 2003). In 2011 seven villages in the Bougouriba basin were recorded with 5.8%, 3.4%, 1.0%, 0.5%, 0.4% and zero (two villages) prevalence respectively (PNLO, 2011), and so onchocerciasis has still not been reduced to satisfactory levels in all villages. It is unclear whether population movement of vectors or humans from Bougouriba to the Comoé valley could have reintroduced the parasite in sufficient numbers to instigate recrudescence. Migration of vectors in a northeasterly direction with the monsoon rains is well recorded (Garms et al., 1979; Baker et al., 1990), and migration in a southeasterly direction with the harmattan is presumed to occur on an unknown scale (Boakye et al., 1987; Garms et al., 1990; Boakye et al., 1998), and could bring infective flies from Bougouriba to the Comoé valley.

In summary, the pattern of vector immigration from poorly treated areas south of the study area does not support the idea that this was the cause of the recrudescence. However, refugees from civil disturbances in Côte d'Ivoire settled mainly along the Comoé valley. Reinvasion from Bougouriba might also have affected the Comoé valley disproportionately, but there is no evidence to assess this possibility.

3.3 Persistence of a viable parasite population

The Comoé valley seems to have had a better history of control than the Léraba valley, where there has been no recrudescence. For example, the Léraba valley had been subject to extensive reinvasion and as a result the entomological parameters and the levels of human infection had dropped more quickly in the Comoé valley, which had not been subject to significant vector reinvasion (except near Folonzo). Both valleys had experienced short periods of experimental suspension of larviciding in the early years, but only the Léraba valley had (short-lived) problems with insecticide resistance in the early 1980s. In summary, in comparison with the Léraba valley there is no evidence that recrudescence in the Comoé valley has been the result of an unsatisfactory history of control.

Parasitological examination of skin snips is not recommended by WHO (2016) for the assessment of onchocerciasis elimination (because it is not considered to be sufficiently sensitive to detect new infections), but it is considered to be a “useful tool for monitoring progress as an elimination programme … moves towards that goal during treatment”. APOC (2010) considered that the epidemiological transmission threshold had been reached when human prevalence of infection was below 5% in all villages and below 1% in 90% of villages. During the period 1989 to 1998 (which immediately followed the cessation of larviciding in the study area) the mean prevalence of infection was slightly higher in the Comoé river valley (2.65%, n=19) compared with the Léraba river valley (1.72%, n=26), but neither valley satisfied the APOC criteria (in the Comoé valley 11% and 58% of villages had prevalences above 5% and 1% respectively, compared to 12% and 42% in the Léraba valley).

With respect to entomological indices, onchocerciasis is considered to have dropped below the epidemiological transmission threshold (and effectively eliminated) when the upper 95% confidence interval of vector infectivity drops below one infective fly per 1000 parous flies, or the upper 95% confidence interval of the Annual Transmission Potential (ATP) drops below 20 (APOC, 2010; WHO, 2016). There was no distribution of ivermectin in the study area before 2004 (when MDA was instigated against lymphatic filariasis), and we can examine the ATPs in the two valleys in 2009 and 2010 immediately after the cessation of vector control in 2008 (see Figures 5 and 6). The mean ATP in the Léraba river valley was 6.5 (n=11, 95% CI = 1.22-11.87) and in the Comoé river valley was 0.4 (n=5, 95% CI = 0.38-1.18), and so it appears that both valleys satisfied the criteria for having dropped below the transmission breakpoint.

It seems that both river valleys had a similar history of control, and there is no reason to believe that it was less efficiently applied in the Comoé valley than the Léraba valley. The Comoé valley was less affected by vector reinvasion from the south than the Léraba, but it was more affected by human migration from Côte d'Ivoire, and it is possible that the Comoé valley was more affected by either vector and/or human immigration from Bougouriba (because it is closer), but there is no evidence for this. Vector infectivity rates never reached zero, and although they were slightly higher in the Léraba valley, they seem have been below the transmission breakpoint in both valleys. There is not much evidence concerning vector biting rates in the two valleys (which would affect the force of infection) after the cessation of vector control operations in 1989, but the little evidence which is available indicates that biting rates were not higher in the Comoé valley (mean ABR 1990-1992: Comoé = 7,107, n=4; Léraba = 7,857, n=9). Similarly, vector efficiency will affect the force of infection and this can vary between cytospecies (Cheke and Garms, 2013). There are no contemporary identifications but the historical cytospecies composition was dominated by the savannah cytospecies (*S. damnosum* s.str. and *S. sirbanum*) in both the Léraba and the Comoé river valleys. There was in addition some *S. soubrense* breeding in the Léraba river, but this cannot explain the lack of recrudescence because *S. soubrense* is a more efficient vector than the savannah cytospecies (Cheke and Garms, 2013), and so its presence should have made recrudescence more likely, not less likely.

Vector control had resulted in a huge drop in the levels of onchocerciasis throughout the study area, but prevalences of infection in the human population never dropped to zero everywhere in the ten years after the cessation of larviciding in 1989, and they were not below the level thought to represent the transmission breakpoint (APOC, 2010) in either the Comoé or Léraba river valleys. In any case, whilst epidemiological modelling indicated that prevalence below 5% had less than 1% chance of recrudescence (Diawara et al., 2009), recrudescence is still a stochastic possibility. Therefore considering the very wide area covered by OCP and the very large number of communities it is quite likely that stochastic recrudescence will occur in a few unpredictable localities even when the criteria are met.

3.4 Ivermectin resistance

Control of onchocerciasis in the Lower Black Volta and Pru river valleys in Ghana has been historically problematic. These areas are more than 200 km south east of the Comoé basin. Vector control had been initiated in 1975 and mass distribution of ivermectin was introduced to support vector control in 1987 (the same year that it was introduced into the Comoé basin in Burkina Faso). In 1997 skin snip surveys in the Lower Black Volta and Pru river valleys revealed the existence of persistent skin microfilariae in some people treated with ivermectin (Awadzi et al., 2004), and this remains a problem to this day. The explanation for this phenomenon is still uncertain, and the parasites in question are known as ‘non-responders’, but one of the possibilities is that non-responsiveness is due to the evolution of ivermectin resistance in the parasites (Osei-Atweneboana et al., 2007). The River Pru is southeast of the Lower Black Volta River and they occupy adjacent river valleys in Ghana. The middle part of the Black Volta river forms the international border between Ghana and Burkina Faso, and is east of and adjacent to the Comoé river valley in Burkina

Faso. Long-range migration of onchocerciasis vectors in West Africa is usually thought to follow a SW-NE axis in either direction, but occasional E-W dispersal between river valleys cannot be discounted. Non-responders were first recorded in Ghana in 1997 and the first sign of a recrudescence of onchocerciasis in SW Burkina Faso was seen in 2001 (and was well established by 2007). Mass distribution of ivermectin against lymphatic filariasis had begun in the study area in 2004. Large scale population movements of humans from Ghana into Burkina Faso have not occurred during this time frame (or during the preceding years). Vector control was stopped on the Lower Black Volta river in 1997 but continued along the river Pru until well after the recrudescence in SW Burkina Faso. Whilst the recrudescence event in SW Burkina Faso seems to have started before any distribution of ivermectin in the area, it is possible that immigrant vectors from the Lower Black Volta could have introduced parasites from 'non-responders'. However, because of the limited distribution of non-responders in Ghana at this time and the vector migration route would have been inconsistent with normal patterns, it is likely that such immigration would be small, although it might still have played a role in recrudescence in SW Burkina Faso after ivermectin was introduced in 2004 against lymphatic filariasis. However, the geographic and therapeutic coverage of ivermectin distribution was poor (see below) and the conditions were probably suitable for recrudescence of onchocerciasis even without ivermectin resistance. In summary, 'non-responsive' (potentially resistant) parasites might have been introduced into the study area by vector immigration, but this is likely to have been in small numbers because it would have been contrary to normally expected migration routes, and the poor coverage of ivermectin distribution against lymphatic filariasis in the Comoé river valley is probably sufficient explanation as to why the recrudescence was not prevented by ivermectin MDA. In any case future surveys are planned and should reveal the presence or absence of 'non-responders'.

4. Instigation of community directed treatment with ivermectin in the Comoé valley

Whatever the reason for the recrudescence of onchocerciasis in the Comoé valley it was clear that control measures would have to be put in place to prevent the levels of infection increasing and possibly spreading to other areas. PNLO (with assistance from its partners - APOC and SightSavers) therefore instigated a programme of Community Directed Treatment with Ivermectin (CDTI) in the two affected health districts (Banfora and Mangodara) in Région des Cascades in accordance with strategy developed by APOC and recommended by OCP when it was dissolved in 2002 and responsibility for monitoring and control was devolved to Ministries of Health. The first round of treatment was carried out 13-18 July 2011.

Ivermectin had been distributed in these two health districts since 2004 against lymphatic filariasis (see above), but during this time the prevalence of onchocerciasis had increased, and it became evident that therapeutic coverage had often fallen short. Inhabitants gave a number of reasons for non-participation, including the undesirable effects of the drugs (which had not been dealt with) and a perception that lymphatic filariasis was not a grave problem. Furthermore, the programme achieved only weak geographic coverage in these zones (with certain villages untreated).

CDTI was to be implemented against onchocerciasis under the supervision of PNLO and the two district health authorities to treat all of the villages in the area affected by the recrudescence and at least 80% of the total population in each village. The approach to CDTI was the classic APOC method to treat the entire eligible population (Amazigo and Crump, 1998), except that it was coupled with the distribution of albendazole for the elimination of lymphatic filariasis and the control of intestinal helminths.

During the first round of treatment (in July 2011) 100% geographic coverage was achieved (71 villages), with an average therapeutic coverage of 72.8% (27,543 people out of a total population of 37,846), but in 17 villages CDTI failed to reach 65% (the minimum acceptable) of the total population due to absences (range 0 - 34.5%), exclusions (range 0 - 25%) and refusals (range 0 - 5%). The high number of absences was probably due to the time of year, which corresponded to the ‘cultural season’ when there is a lot of migration to and from various festivals. In conclusion the results of the first round of CDTI are considered satisfactory, and improved communication and changing the time of year has resulted in an improvement in the levels of therapeutic coverage which is expected to lead to the successful containment and eventual elimination of the recrudescence of onchocerciasis in the Comoé valley.

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