COMMENTARY

Open Access

CrossMark

Trends in US President's Malaria Initiative-funded indoor residual spray coverage and insecticide choice in sub-Saharan Africa (2008–2015): urgent need for affordable, long-lasting insecticides

Richard M. Oxborough[*]

Abstract

This article reports the changing pattern of US President's Malaria Initiative-funded IRS in sub-Saharan Africa between 2008 and 2015. IRS coverage in sub-Saharan Africa increased from <2 % of the at-risk population in 2005, to 11 % or 78 million people in 2010, mainly as a result of increased funding from PMI. The scaling up of IRS coverage in sub-Saharan Africa has been successful in several epidemiological settings and contributed to reduced malaria transmission rates. However, the spread and intensification of pyrethroid resistance in malaria vectors led many control programmes to spray alternative insecticides. Between 2009 and 2013, pyrethroid spraying decreased from 87 % (13/15) of PMI-funded countries conducting IRS to 44 % (7/16), while bendiocarb use increased from 7 % (1/15) to 56 % (9/16). Long-lasting pirimiphos-methyl CS received WHOPES recommendation in 2013 and was scheduled to be sprayed in 85 % (11/13) of PMI-funded countries conducting IRS in 2015. The gradual replacement of relatively inexpensive pyrethroids, firstly with bendiocarb (carbamate) and subsequently with pirimiphos methyl CS (organophosphate), has contributed to the downscaling of most PMI-funded IRS programmes. Overall, there was a 53 % decrease in the number of structures sprayed between years of peak coverage and 2015, down from 9.04 million to 4.26 million structures. Sizeable reductions in the number of structures sprayed were reported in Madagascar (56 %, 576,320–254,986), Senegal (64 %, 306,916–111,201), Tanzania (68 %, 1,224,095–389,714) and Zambia (63 %, 1,300,000–482,077), while in Angola, Liberia and Malawi PMI-funded spraying was suspended. The most commonly cited reason was increased cost of pesticides, as vector resistance necessitated switching from pyrethroids to organophosphates. There are worrying preliminary reports of malaria resurgence following IRS withdrawal in parts of Benin, Tanzania and Uganda. The increase in malaria cases following the end of the Global Malaria Eradication Programme in 1969 highlights the fragility of such gains when control efforts are weakened. At present there are several countries reliant on organophosphates and carbamates for IRS, and increasing incipient resistance is a serious threat that could result in IRS no longer being viable. A portfolio of new cost-effective insecticides with different modes of action is urgently needed.

Background

Indoor residual spraying (IRS) of insecticides has produced profound changes in malaria burden in a range of settings, including the elimination of malaria through indoor spraying of DDT (in combination with environmental management, improved housing and treatment) during the Global Malaria Eradication Programme (GMEP, 1955–1969) in the USA, Europe, parts of the Soviet Union, Israel, Lebanon, Syria, Japan, and Taiwan [1]. While IRS in Africa was largely overlooked during the GMEP, sustained IRS programmes have been

*Correspondence: oxandbull@hotmail.com
Richard Oxborough Consultancy, London, UK

successfully staged in South Africa, Zambia, Namibia, Swaziland, Zimbabwe and Botswana for several decades since the 1940s and have achieved sizeable reductions in vector populations and malaria incidence [2, 3]. IRS is applicable in many epidemiological settings, including hyperendemic areas of sub-Saharan Africa, provided that policy and programming decisions take into account the operational and resource feasibility [4]. In 2006, the World Health Organization (WHO) reaffirmed the importance of IRS as a primary intervention for reducing or interrupting malaria transmission [5]. The US President's Malaria Initiative (PMI) was launched in 2005, initially as a 5 year, $1.2 billion programme to rapidly scale up malaria prevention and treatment interventions and reduce malaria-related mortality by 50 % in 15 high-burden countries in sub-Saharan Africa [6]. Priority was given to the scale up of four proven interventions; namely long-lasting insecticidal nets (LLINs), IRS, intermittent preventive treatment in pregnancy (IPTp), and prompt diagnosis with rapid diagnostic tests (RDTs) and treatment with artemisinin-based combination therapy (ACT) [6]. IRS coverage in sub-Saharan Africa increased substantially from <2 % of the at-risk population protected in 2005, to 11 % or 78 million people in 2010 [7]. Increased IRS coverage was successful in a range of diverse epidemiological settings, with substantial reductions for all cause child mortality, malaria parasite prevalence and entomological indicators recorded in several countries including parts of Equatorial Guinea

(not a PMI-supported country) [8], Benin [9], Kenya [10], Malawi [11], and Tanzania [12].

The duration of residual efficacy and cost-effectiveness of IRS insecticides are of key importance to the sustainability of IRS programmes. A major challenge facing IRS programmes is to sustain such gains in the face of technical problems, such as vector resistance to insecticides, lack of affordable alternative insecticides and limited resources for annual renewal of each intervention. In this article the changing pattern of PMI-supported IRS in sub-Saharan Africa between 2008 and 2015 is documented and the technical challenges being faced are examined. A limitation is that data was not included for IRS conducted through other funding sources such as UK Department for International Development (DFID), The Global Fund to Fight AIDS, Tuberculosis and Malaria, private companies and national Governments.

Insecticide resistance and scaling down of IRS

There are four classes of insecticide recommended for IRS for malaria control and prevention, each with various attributes (Table 1). Global use of vector control insecticides was dominated by pyrethroids in terms of surface area covered (81 % of total) between 2000 and 2009, with the upsurge in use of pyrethroid IRS partly as a result of PMI-funded spraying in Africa [13]. The scaling up of pyrethroid IRS in sub-Saharan Africa between 2006 and 2010 was attainable as pyrethroid insecticides were inexpensive and had a relatively long residual action

Table 1 Attributes of insecticide formulations commonly used for IRS for malaria control and prevention

Class of insecticide	Insecticide formulation	Susceptible vectors[a]	Residual duration	Cost	Packaging[b]	Other
Organochlorine	DDT WP	🔴	🟢	🟢	🔴	Should be phased out globally according to UNEP POP statement. Public, commercial, environmental and political resistance.
Pyrethroid	Lambdacyhalothrin CS Deltamethrin SC-PE	🔴	🟢	🟢	🟢	WHO does not recommend pyrethroid IRS in areas of moderate/high LLIN coverage.
Organophosphate	Pirimiphos-methyl EC	🟢	🔴	🔴	🔴	Strong odor shortly after spraying.
Organophosphate	Pirimiphos-methyl CS	🟢	🟢	🔴	🔴	Microcapsules and synthetic odorant added to improve odor compared to EC.
Carbamate	Bendiocarb WP	🟢	🔴	🟢	🟢	None.

Most positive 🟢, moderate 🟢, least positive 🔴

[a] Frequency of vector resistance recorded in sub-Saharan Africa [56]

[b] Related to the volume of formulation required, packaging, ease of shipping and disposal or recycling requirements

[14, 15]. However, increased coverage of pyrethroid IRS, often in parallel with pyrethroid LLIN distribution and agricultural use, has led to the spread and intensification of pyrethroid resistance across most of malaria endemic sub-Saharan Africa [16, 17]. WHO has since recommended that pyrethroid IRS should not be used for IRS in areas of moderate to high LLIN usage, in an attempt to preserve the effectiveness of pyrethroid LLINs [18].

Despite the Stockholm Convention on Persistent Organic Pollutants stipulating that, 'countries using DDT should eliminate the use of DDT over time and switch to alternative insecticides', the use of DDT for malaria control has been allowed to continue under exemption [19, 20]. DDT has a long residual action of more than 6 months and is relatively inexpensive, with a cost similar to pyrethroids [14, 15]. However, there is high frequency of mutations in the *knockdown resistance* gene (*kdr*) across sub-Saharan Africa, conferring cross-resistance to DDT and pyrethroid insecticides [17]; in addition there is political resistance, with several countries reluctant to register or utilize DDT due to perceived environmental or export concerns [21, 22].

The carbamate bendiocarb is highly effective, but has a short residual duration, meaning that multiple spray cycles may be required for optimal protection in areas of prolonged transmission [23, 24]. Propoxur is a carbamate insecticide that is currently used for IRS in Ethiopia, but is not utilized through the PMI as the product specifications are not listed under the Joint FAO/WHO Meeting on Pesticide Specifications (JMPS) [25].
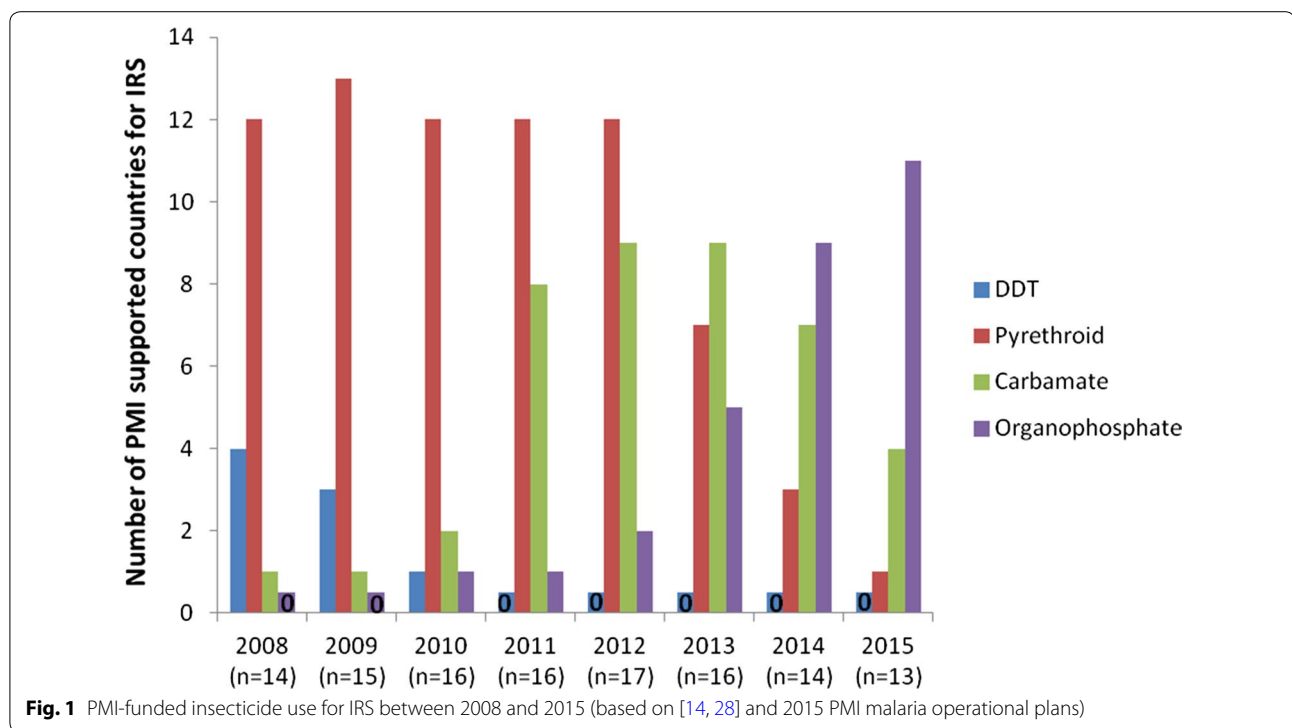
Pirimiphos-methyl (p-methyl) emulsifiable concentrate (EC), an organophosphate insecticide that was developed in the 1970s, shows high toxicity to *Anopheles* mosquitoes but has infrequently been utilized despite having WHO recommendation for IRS [15, 26]. Between 2009 and 2012, p-methyl EC was sprayed in Malawi, Benin and Zambia but was subsequently replaced due to the prohibitive expense and short residual activity [27, 28]. In 2013, a new formulation of p-methyl capsule suspension (CS) was recommended by WHO for IRS, with experimental hut trials demonstrating vastly improved residual duration of up to 12 months [29–31].

The spread and intensification of pyrethroid resistance in malaria vectors has led to policy changes regarding insecticide choice for IRS programmes. There is limited epidemiological evidence of pyrethroid IRS or LLIN failure, possibly due to a shortage of suitable data collection or alternatively pyrethroid insecticides may successfully kill older, less resistant infective mosquitoes and also provide some protection through repellency and the physical barrier effect of LLINs [32]. WHO cylinder bioassays have demonstrated an increased frequency of resistant malaria vectors and this has led many control programmes to stop spraying pyrethroids in favour of alternative insecticides [28, 33].

In 2009, 87 % (13/15) of PMI-funded countries with IRS programmes sprayed pyrethroid IRS (Fig. 1). This proportion decreased annually, with only 44 % (7/16) of countries having sprayed pyrethroids in 2013, while carbamate use increased during the same period from 7 % (1/15) in 2009 to 56 % (9/16) in 2013 (Fig. 1). Bendiocarb was sprayed despite being relatively expensive and having a limited residual duration, as there were few viable alternatives (namely DDT and organophosphates). P-methyl EC was rarely utilized and was sprayed in <10 % of countries between 2009 and 2012. Following the development of a long-lasting formulation of p-methyl CS came a dramatic shift in usage, with 85 % (11/13) of PMI-supported countries spraying p-methyl CS in 2015 (Fig. 1), compared with 31 % (5/16) in the first year of production in 2013. The gradual replacement of relatively inexpensive pyrethroids firstly with bendiocarb (carbamate) and subsequently with p-methyl CS (organophosphate) has also led to substantial changes in IRS spray coverage. The cost of a pyrethroid (Icon™ lambdacyhalothrin capsule suspension (CS) 10 % ai, Syngenta) sachet is estimated to be \$5, compared with \$12 for bendiocarb (Ficam™ WP 80 % ai, Bayer CropScience), \$20 for a container of p-methyl EC (Actellic™ EC, 50 % ai, Syngenta) and \$23.50 for p-methyl CS (Actellic™ CS, 30 % ai, Syngenta), all with equivalent quantity of active ingredient to spray 250 m^2 at WHO recommended target dosages [34]. It should be noted that there are additional insecticide cost drivers such as shipping, disposal of insecticide packaging, and environmental precautions, which vary according to formulation. For example, DDT WP may be the cheapest formulation at \$2 but the additional environmental precautions and testing needed can increase overall costs considerably [35]. The type of insecticide formulation purchased is one of the most important cost drivers for spray programmes. In 2014, insecticides were the second largest cost category across PMI IRS programmes (per 100 m^2) and accounted for 28 % of the total unit cost (across all countries regardless of insecticide formulation sprayed) [36]. For the few countries where pyrethroids were sprayed, insecticide accounted for only 6 % of all costs compared with 37 % where organophosphates were used [36]. However, it should be noted that there was considerable variation between countries in spray operations costs.

The proportion of PMI-supported countries spraying bendiocarb increased greatly between 2011 and 2013 (Fig. 1), yet the number of structures sprayed remained high in most countries despite the increased

Fig. 1 PMI-funded insecticide use for IRS between 2008 and 2015 (based on [14, 28] and 2015 PMI malaria operational plans)
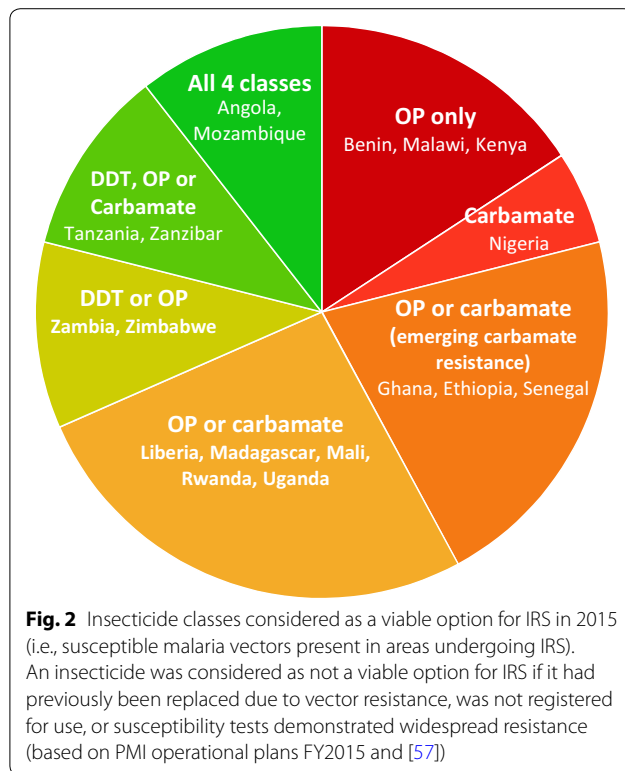
cost compared to pyrethroids (12 countries reached peak numbers of structures sprayed between 2011 and 2013 (Table 2). This increase in cost was exacerbated by subsequent replacement with more expensive p-methyl CS, which, by 2015, had become the insecticide of choice for the majority of PMI-funded spray programmes (Fig. 1). Despite the increased cost, p-methyl CS was preferred to bendiocarb WP due to the extended duration of action (offsetting some of the added cost) and also in response to increasing reports of bendiocarb resistance in countries including Malawi, Benin, Ghana, Ethiopia and Senegal (Fig. 2) [4, 37, 38].

The substantial increase in insecticide cost, firstly caused by increased use of carbamates (2011–2014), followed by replacement with organophosphates (2014–2015), has led to the scaling-down of most PMI-funded IRS programmes. Overall, there was a decrease of 53 % in the total number of structures sprayed between years of peak coverage to 2015 estimates (Table 2). In Malawi, PMI supported the spraying of 97,329 structures in 2010, but the spread of pyrethroid and carbamate resistance resulted in the withdrawal of IRS support in 2012, due to the 'high cost and short residual action of p-methyl EC' [27] (Table 2). While the majority of IRS programmes have continued, there is a clear downward trend in coverage from the heights achieved when pyrethroids were the insecticide of choice (Table 2). In Tanzania (mainland), a total of 1,224,095 structures were sprayed in 2012, compared with 389,714 in 2015, with the reduction

Table 2 Decrease in number of house structures sprayed with insecticide for malaria prevention between year of peak coverage and 2015 (data taken from PMI national malaria operational plans 2010–2016) [21, 22, 28, 37–45, 74–80]

Country	Year of peak coverage	Structures sprayed in year of peak coverage	Structures sprayed in 2015	% Reduction in structures sprayed
Angola	2011	145,264	0	100
Benin	2014	254,072	252,706	1
Ethiopia	2011	858,657	670,303	22
Ghana	2012	371,362	231,345	38
Kenya	2008	764,050	0	100
Liberia	2012	96,901	0	100
Madagascar	2010	576,320	254,986	56
Malawi	2010	97,329	0	100
Mali	2013	228,985	131,894	42
Mozambique	2011	660,064	440,579	33
Nigeria	2013	62,592	0	100
Rwanda	2011	358,804	213,271	41
Senegal	2012	306,916	111,201	64
Tanzania	2012	1,224,095	389,714	68
Uganda	2011	908,627	850,000	6
Zambia	2010	1,300,000	482,077	63
Zanzibar	2008	200,731	66,497	67
Zimbabwe	2013	622,300	163,922	74
Total	*NA*	*9,037,069*	*4,258,495*	*53*

Fig. 2 Insecticide classes considered as a viable option for IRS in 2015 (i.e., susceptible malaria vectors present in areas undergoing IRS). An insecticide was considered as not a viable option for IRS if it had previously been replaced due to vector resistance, was not registered for use, or susceptibility tests demonstrated widespread resistance (based on PMI operational plans FY2015 and [57])

attributed to 'the high cost of p-methyl CS' [39]. Similar sizeable reductions in the number of structures sprayed were reported in Ghana (38 %), Madagascar (56 %), Mali (42 %), and Zambia (63 %). The most commonly cited reasons for the reduced spray coverage were the limited availability of alternative insecticides and increased cost of insecticides, as vector resistance necessitated switching from pyrethroids to organophosphates [40, 41]. PMI-funded IRS was also withdrawn from Angola, Liberia and temporarily in Kenya, although in Kenya political and insecticide registration issues were the main drivers, rather than increased cost of insecticides [21, 42, 43]. In Nigeria, the PMI-funded IRS programme was only intended as a pilot to demonstrate IRS feasibility [44]. It is also important to note that in some countries IRS has been partially funded through other sources, for example in Ethiopia where the Government has taken over spray operations in graduated districts where PMI has developed sufficient capacity [45].

Evidence for malaria resurgence following withdrawal of IRS

A change in policy from blanket spraying towards focal targeted coverage is a valid, cost-effective strategy in areas of low transmission or at the pre-elimination phase [46, 47]. In the archipelago of Zanzibar, a combination of vector control and improved access to diagnosis and

treatment has resulted in a new target of malaria elimination by 2020 [47]. In such a setting the decrease in structures sprayed from a peak of 200,731 in 2008 down to 66,497 in 2015, while maintaining universal LLIN coverage, is perfectly justifiable (Table 2). However, failure to maintain adequate vector control coverage (LLIN and IRS) is likely to result in malaria resurgence to pre-intervention levels. A notorious example of resurgence following withdrawal of IRS is the eradication programme of Zanzibar (1957–1968) which consisted of annual spraying with dieldrin or DDT and had reduced malaria prevalence from 50–60 % to 0–3 % by 1968. In 1979, 11 years after cessation of spraying, malaria had rebounded to close to pre-intervention levels [48].

PMI has ensured that universal coverage with LLINs has been achieved in areas where IRS has been scaled back or withdrawn. Despite this, reducing the number of structures sprayed with IRS is likely to result in an increase in malaria transmission unless complementary control measures in addition to LLINs are implemented. In addition, behavior change communication (BCC) is likely to be important in areas where IRS was previously used and mosquito net use is not yet ingrained [49]. There are already worrying preliminary reports of rapid resurgence following IRS withdrawal.

Examples
Tanzania
IRS commenced in 2007 in two districts of Kagera Region, in northwest Tanzania, and was subsequently extended to cover 18 districts. Annual rounds of IRS with the pyrethroid lambdacyhalothrin were conducted between 2007 and 2011 in Muleba District and LLIN distribution was conducted in 2011 targeting universal coverage [39]. National Malaria Indicator Surveys indicated that prevalence of malaria in Kagera decreased substantially from 41 % in 2007–2008 [50] to 8 % in 2011–2012 [51]. A cluster-randomized trial (CRT) was conducted in 2012 to determine whether continued bendiocarb IRS in addition to moderate coverage with LLIN provided any additional benefit. The mean prevalence of *Plasmodium falciparum* in children aged 0.5–14 years, conducted over three time points, was 26.1 % in the arm with LLIN only compared with 13.3 % for bendiocarb IRS + LLIN [12]. IRS spraying was not conducted in Kagera between 2014 and 2016 despite the high malaria prevalence demonstrated in the arm of the CRT where IRS was withdrawn [39].

Benin
Ouémé department was chosen for IRS due to high prevalence, entomological inoculation rate, and infant mortality [52]. Four rounds of IRS with bendiocarb were conducted in Ouémé, between 2008 and 2011, after

which IRS was re-located to the northern department of Atacora [38]. Upon withdrawal of IRS an LLIN distribution campaign for all households in Ouémé took place. The technical rationale for the IRS location change involved the shorter transmission season in the north which can be covered by one round of bendiocarb IRS. Despite 81.8 % of people sleeping under LLIN after the net distribution campaign, entomological indicators of malaria transmission, including higher biting rates, increased significantly in Ouémé after IRS withdrawal [53].

Uganda

PMI supported IRS in ten northern districts between 2009 and 2014; spraying bendiocarb from 2010 due to an increased frequency of pyrethroid resistance [22]. PMI sentinel sites and Government facilities documented a sustained reduction in malaria cases during this period. Given the success of the IRS campaign in the north, PMI relocated IRS to the eastern region in 2015 (based on National Malaria Control Programme recommendations) where transmission rates were consistently high. In northern districts, where IRS was withdrawn, enhanced case surveillance, robust case management, LLIN distribution targeting universal coverage and BCC to promote net use was intended to sustain the reduced rate of malaria transmission [22]. Despite these measures, in 2015 Uganda reported a sixfold increase in confirmed malaria cases (compared to 2012–2014 average) in northern districts where IRS was withdrawn [54]. This was in contrast to sentinel monitoring in Tororo district, eastern Uganda where a substantial decrease in malaria morbidity was recorded following two rounds of IRS in 2015 [55].

Conclusions

IRS is a proven strategy for malaria control in a range of endemicity settings and is highly effective for malaria control in sub-Saharan Africa [56]. As a consequence of increased resistance in vector populations to pyrethroids, DDT and carbamates there is critical shortage of insecticides available for IRS use in sub-Saharan Africa (Fig. 2). Resistance to pyrethroids and DDT is particularly widespread, with twelve PMI-funded countries only having carbamate and/or organophosphate insecticides as viable options for IRS (as indicated by WHO cylinder tests) (Fig. 2) [57]. While in Kenya, Malawi, and Benin the situation is even more precarious, with only the organophosphate class of insecticides remaining a viable option for IRS (Fig. 2).

Increasing incipient resistance to bendiocarb, through the G119S mutation in the Ace-1 gene and P450-mediated detoxification, has been reported in

several countries [58, 59]. Despite impressive longevity, the high cost of p-methyl CS has resulted in downscaling of most PMI-funded IRS programmes in sub-Saharan Africa. In an attempt to achieve the Millennium Development Goals (MDG) target of 75 % reduction in the global malaria burden by 2015, integrated vector control based on simultaneous spraying of IRS and high coverage with LLIN was implemented concurrently in several countries. WHO recommend that countries investing in combined use of IRS + LLIN should conduct rigorous monitoring and evaluation to determine the degree of additional benefit [60]. While there is varied evidence for enhanced protection, significant additional benefit of IRS + LLIN has been clearly demonstrated in Tanzania and Equatorial Guinea [12, 61]. It is vitally important for more detailed cost-effectiveness analysis to be conducted at the national level in order to determine when and where IRS should be maintained, scaled up, or geographically re-targeted. There is great competition for resources for malaria control and while funding reached $2.7 billion in 2013, this represents a significant shortfall on the estimated $5.1 billion needed annually between 2014 and 2020 [4]. Funding for malaria control has stagnated in recent years with only a 3 % increase in funding between 2012 and 2013 [4]. Inevitably, this leads to competition for resources across various interventions, including new interventions such as seasonal malaria chemoprevention (SMC) in the Sahel sub-region including in Senegal and Mali [62, 63]. LLIN coverage has improved substantially in recent years but usage is still way below the levels expected of successful universal coverage campaigns [64, 65]. In addition, the spread of pyrethroid resistance may necessitate the use of more expensive combination nets with synergists, such as Olyset Plus or Permanet 3.0, which may be more effective in areas of pyrethroid resistance due to raised levels of mixed function oxidases [66, 67]. Unfortunately, with such intense competition for resources IRS is often scaled back to compensate for any shortfalls caused by increased costs of other interventions.

A potential advantage of IRS over other vector control measures, such as LLINs, is that insecticide resistance management is possible through the rotation of different chemical classes. The Global Plan for Insecticide Resistance Management (GPIRM) was developed by the WHO in 2012, but a key factor limiting the implementation of resistance management techniques is the lack of new insecticides with different modes of action [68]. Chlorfenapyr SC formulation of the pyrrole chemical class was evaluated by WHOPES in 2013 and 2014 but was found to have a short residual efficacy of between 0 and 4 weeks [31]. Chlorfenapyr has great potential to be an important IRS insecticide due to the mode of action

being different to existing IRS formulations and therefore there is low risk of cross-resistance. However, further development is required to improve the residual performance [69]. Another promising IRS formulation with a different mode of action is the neonicotinoid, clothianidin WP that is currently undergoing laboratory phase WHOPES evaluation [70]. It is critically important that new, long-lasting and affordable insecticides are developed urgently so that a portfolio of viable insecticides are made available for sustainable IRS campaigns with a goal leading towards malaria elimination. The Innovative Vector Control Consortium (IVCC) is likely to have a critical role and is currently in the process of developing new long-lasting IRS insecticides through product development partnerships with industry [71]. In order to encourage a more sustainable market for IRS products UNITAID recently committed $65 million through the IVCC over 4 years which will reduce the price of a new insecticide from $23.50 to $15 by 2020. The rationale is to build up production and batch scale as well as a larger and more competitive market to sustain affordable pricing [72]. Indeed, pyrethroid insecticides were considered expensive when first used for IRS. However, the price decreased from $20 per kg of deltamethrin WP in 1999 to just $4 by 2004 due to several factors including improved manufacture processes, larger scale production and added competition [35, 73].

There have been unprecedented reductions in malaria cases, and all-cause child mortality across much of sub-Saharan Africa in recent years largely as a result of increased spending on vector control, diagnostics and treatment. The subsequent resurgence in malaria cases following the end of GMEP in 1969 highlights the fragility of such gains when control efforts are weakened [74]. If no new cost-effective insecticides are developed there is a real danger that the downward trends for IRS coverage will continue. Malaria resurgence following downscaling of IRS, as reported in parts of Benin, Tanzania and Uganda is a major threat and there are currently no new cost-effective and widely applicable control measures than can feasibly replace IRS for use in combination with LLIN.

References

1. Griffith ME. The World-Wide Malaria Eradication Program. Presented in the Plenary Symposium on International Programs at the meeting of the Entomological Society of America in New Orleans, November 30, 1965.
2. Mabaso ML, Sharp B, Lengeler C. Historical review of malarial control in southern African with emphasis on the use of indoor residual house-spraying. Trop Med Int Health. 2004;9:846–56.
3. Chanda E, Ameneshewa B, Angula HA, Iitula I, Uusiku P, Trune D, et al. Strengthening tactical planning and operational frameworks for vector control: the roadmap for malaria elimination in Namibia. Malar J. 2015;14:302.
4. WHO. World Malaria Report 2014. Geneva: World Health Organization. http://www.who.int/malaria/publications/world_malaria_report_2014/en/. Accessed 12 Jan 2015.
5. WHO. Indoor residual spraying; Use of indoor residual spraying for scaling up global malaria control and elimination. 2006:WHO/HTM/MAL/2006.1112.
6. USAID. President's Malaria Initiative Strategy 2015–2020. 2015. http://pmi.gov/docs/default-source/default-document-library/pmi-reports/pmi_strategy_2015-2020.pdf. Accessed 23 May 2015.
7. WHO. World Malaria Report 2011. Geneva: World Health Organization. http://www.who.int/malaria/world_malaria_report_2011/en/. Accessed Jan 17 2015.
8. Kleinschmidt I, Schwabe C, Benavente L, Torrez M, Ridl FC, Segura JL, et al. Marked increase in child survival after four years of intensive malaria control. Am J Trop Med Hyg. 2009;80:882–8.
9. Akogbeto M, Padonou GG, Bankole HS, Gazard DK, Gbedjissi GL. Dramatic decrease in malaria transmission after large-scale indoor residual spraying with bendiocarb in Benin, an area of high resistance of *Anopheles gambiae* to pyrethroids. Am J Trop Med Hyg. 2011;85:586–93.
10. Zhou G, Githeko AK, Minakawa N, Yan G. Community-wide benefits of targeted indoor residual spray for malaria control in the western Kenya highland. Malar J. 2010;9:67.
11. Skarbinski J, Mwandama D, Wolkon A, Luka M, Jafali J, Smith A, et al. Impact of indoor residual spraying with lambda-cyhalothrin on malaria parasitemia and anemia prevalence among children less than five years of age in an area of intense, year-round transmission in Malawi. Am J Trop Med Hyg. 2012;86:997–1004.
12. West PA, Protopopoff N, Wright A, Kivaju Z, Tigererwa R, Mosha FW, et al. Indoor residual spraying in combination with insecticide-treated nets compared to insecticide-treated nets alone for protection against malaria: a cluster randomised trial in Tanzania. PLoS Med. 2014;11:e1001630.
13. van den Berg H, Zaim M, Yadav R, Soares A, Ameneshewa B, Mnzava AE, et al. Global trends in the use of insecticides for vector-borne disease control. Environ Health Perspect. 2012;120:577–82.
14. RTI. An economic analysis of the costs of indoor residual spraying in 12 PMI countries, 2008–2010. 2011. http://www.pmi.gov/docs/default-source/default-document-library/implementing-partner-reports/irs_economic_analysis.pdf?sfvrsn=4. Accessed 28 March 2015.
15. WHO. WHO recommended insecticides for indoor residual spraying against malaria vectors. Geneva: World Health Organization; 2013. http://www.who.int/whopes/Insecticides_IRS_Malaria_25_Oct_2013.pdf. Accessed 17 Feb 2015.
16. Toe KH, Jones CM, N'Fale S, Ismail HM, Dabire RK, Ranson H. Increased pyrethroid resistance in malaria vectors and decreased bed net effectiveness, Burkina Faso. Emerg Infect Dis. 2014;20:1691–6.
17. Ranson H, N'Guessan R, Lines J, Moiroux N, Nkuni Z, Corbel V. Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? Trends Parasitol. 2011;27:91–8.
18. WHO. Global Plan for Insecticide Resistance Management in Malaria Vectors (GPIRM). Geneva: World Health Organization; 2012. http://www.who.int/malaria/publications/atoz/gpirm/en/. Accessed 18 Feb 2015.
19. UNEP. Ridding the World of POPs: a guide to the Stockholm convention on persistent organic pollutants. 2010. http://www.pops.int/documents/guidance/beg_guide.pdf. Accessed 26 March 2015.
20. WHO. The use of DDT in malaria vector control. Geneva: World Health Organization. 2011. http://whqlibdoc.who.int/hq/2011/WHO_HTM_GMP_2011_eng.pdf?ua=1. Accessed 26 March 2015.
21. USAID. President's Malaria Initiative Kenya malaria operational plan FY 2015. http://www.pmi.gov/docs/default-source/

default-document-library/malaria-operational-plans/fy-15/fy-2015-kenya-malaria-operational-plan.pdf?sfvrsn=3. Accessed 28 June 2015.

22. USAID. President's Malaria Initiative Uganda malaria operational plan FY 2015. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/fy-2015-uganda-malaria-operational-plan.pdf?sfvrsn=3. Accessed 28 June 2015.

23. Bradley J, Matias A, Schwabe C, Vargas D, Monti F, Nseng G, et al. Increased risks of malaria due to limited residual life of insecticide and outdoor biting versus protection by combined use of nets and indoor residual spraying on Bioko Island, Equatorial Guinea. Malar J. 2012;11:242.

24. Abt Associates; Africa Indoor Residual Spraying (AIRS) Project. Semi-annual report: April–September 2014. http://www.pmi.gov/docs/default-source/default-document-library/implementing-partner-reports/africa-indoor-residual-spraying-project-semi-annual-report-(april–september-2014).pdf?sfvrsn=5. Accessed 29 June 2015.

25. Deressa W, Loha E, Balkew M, Hailu A, Gari T, Kenea O, et al. Combining long-lasting insecticidal nets and indoor residual spraying for malaria prevention in Ethiopia: study protocol for a cluster randomized controlled trial. Trials. 2016;17:20.

26. Nasir SM, Ahmad N, Shah MA, Azam CM. A large-scale evaluation of pirimiphos-methyl 25% WP during 1980–1981 for malaria control in Pakistan. J Trop Med Hyg. 1982;85:239–44.

27. USAID. President's Malaria Initiative Malawi malaria operational plan FY 2010. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy10/malawi_mop-fy10.pdf?sfvrsn=6. Accessed 17 Feb 2015.

28. USAID. PMI IRS insecticide trends. 2014. http://www.pmi.gov/resource-library/training-guidance. Accessed 11 Jan 2015.

29. Rowland M, Boko P, Odjo A, Asidi A, Akogbeto M, N'Guessan R. A new long-lasting indoor residual formulation of the organophosphate insecticide pirimiphos methyl for prolonged control of pyrethroid-resistant mosquitoes: an experimental hut trial in Benin. PLoS One. 2013;8:e69516.

30. Oxborough RM, Kitau J, Jones R, Feston E, Matowo J, Mosha FW, et al. Long-lasting control of *Anopheles arabiensis* by a single spray application of micro-encapsulated pirimiphos-methyl (Actellic(R) 300 CS). Malar J. 2014;13:37.

31. WHO. Report of the Sixteenth WHOPES Working Group Meeting WHO/HQ Geneva; Review of Pirimiphos-methyl 300CS, Chlorfenapyr 240 SC, Deltamethrin 62.5 SC-PE, Duranet LN, Netprotect LN, Yahe LN, Spinosad 83.3 Monolayer DT, Spinosad 25 Extended Release GR. 2013. http://apps.who.int/iris/bitstream/10665/90976/1/9789241506304_eng.pdf. Accessed 18 Jan 2015.

32. Jones CM, Sanou A, Guelbeogo WM, Sagnon N, Johnson PC, Ranson H. Aging partially restores the efficacy of malaria vector control in insecticide-resistant populations of *Anopheles gambiae s.l.* from Burkina Faso. Malar J. 2012;11:24.

33. WHO. World Malaria Report 2012. Geneva: World Health Organization. http://www.who.int/iris/bitstream/10665/78945/1/9789241564533_eng.pdf. Accessed 28 Jan 2015.

34. Mumba P. IRS Workshop: preparing a budget for an IRS campaign. http://www.businessfightsaids.org/system/documents/category_77/530/Peter_Mumba_(Abt).pdf?1380748140. Accessed 28 July 2015.

35. Sadasivaiah S, Tozan Y, Breman JG. Dichlorodiphenyltrichloroethane (DDT) for indoor residual spraying in Africa: how can it be used for malaria control? Am J Trop Med Hyg. 2007;77:249–63.

36. Johns B, Cico A. PMI IRS Country Programs: 2014 Comparative cost analysis. Africa indoor residual spraying (AIRS) project, Abt associates inc. 2015. http://www.pmi.gov/docs/default-source/default-document-library/implementing-partner-reports/africa-indoor-residual-spraying-project-pmi-irs-country-programs-2014-comparative-cost-analysis.pdf?sfvrsn=4. Accessed 24 April 2015.

37. USAID. President's Malaria Initiative Malawi malaria operational plan FY 2015. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/fy-2015-malawi-malaria-operational-plan.pdf?sfvrsn=3. Accessed 17 May 2015.

38. USAID. President's Malaria Initiative Benin malaria operational plan FY 2015. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/fy-2015-benin-malaria-operational-plan.pdf?sfvrsn=3. Accessed 17 May2015.

39. USAID. President's Malaria Initiative Tanzania malaria operational plan FY 2015. http://www.pmi.gov/docs/default-source/

40. USAID. President's Malaria Initiative Ghana malaria operational plan FY 2015. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/fy-2015-ghana-malaria-operational-plan.pdf?sfvrsn=3. Accessed 17 May 2015.

41. USAID. President's Malaria Initiative Zambia malaria operational plan FY 2015. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/fy-2015-zambia-malaria-operational-plan.pdf?sfvrsn=3. Accessed 17 May 2015.

42. USAID. President's Malaria Initiative; Angola malaria operational plan FY 2014. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy14/angola_mop_fy14.pdf?sfvrsn=14. Accessed 17 May 2015.

43. USAID. President's Malaria Initiative Liberia malaria operational plan FY 2015. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/fy-2015-liberia-malaria-operational-plan.pdf?sfvrsn=4. Accessed 17 May 2015.

44. USAID. President's Malaria Initiative Nigeria malaria operational plan FY 2015. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/fy-2015-nigeria-malaria-operational-plan.pdf?sfvrsn=6. Accessed 17 May 2015.

45. USAID. President's Malaria Initiative Ethiopia malaria operational plan FY 2015. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/fy-2015-ethiopia-malaria-operational-plan.pdf?sfvrsn=3. Accessed 28 May 2015.

46. WHO. Malaria elimination. A field manual for low and moderate endemic countries. Geneva: World Health Organization; 2007. http://whqlibdoc.who.int/publications/2007/9789241596084_eng.pdf?ua=1. Accessed 12 May 2015.

47. ZMCP. Malaria elimination in Zanzibar; a feasbility assessment. 2009. http://www.soperstrategies.com/countries/pemba/tanzania-library/files/EliminationZanzibar.pdf. Accessed 13 March 2015.

48. Matola YG, Mwita U, Masoud AE. Malaria in the islands of Zanzibar and Pemba 11 years after the suspension of a malaria eradication programme. Cent Afr J Med. 1984;30(91–92):95–6.

49. Koenker H, Kilian A, Hunter G, Acosta A, Scandurra L, Fagbemi B, et al. Impact of a behaviour change intervention on long-lasting insecticidal net care and repair behaviour and net condition in Nasarawa State, Nigeria. Malar J. 2015;14:18.

50. TACAIDS, ZAC, NBS, OCGS, and Macro International Inc. Tanzania HIV/AIDS and Malaria Indicator Survey 2007–08. 2008. http://tacaids.go.tz/index.php?option=com_docman&task=doc_download&gid=77&Itemid=142. Accessed 12 Jan 2015.

51. TACAIDS, ZAC, NBS, OCGS, and ICF International. Tanzania HIV/AIDS and Malaria Indicator Survey 2011–12. 2013. http://www.dhsprogram.com/pubs/pdf/SR196/SR196.pdf. Accessed 8 Feb 2015.

52. USAID. President's Malaria Initiative Benin malaria operational plan FY 2008. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy08/benin_mop-fy08.pdf?sfvrsn=6. Accessed 12 Jan 2015.

53. Osse RA, Aikpon R, Gbedjissi GL, Gnanguenon V, Sezonlin M, Govoetchan R, et al. A shift from indoor residual spraying (IRS) with bendiocarb to long-lasting insecticidal (mosquito) nets (LLINs) associated with changes in malaria transmission indicators in pyrethroid resistance areas in Benin. Parasit Vectors. 2013;6:73.

54. WHO. World Malaria Report 2015. Geneva: World Health Organization. http://apps.who.int/iris/bitstream/10665/200018/1/9789241565158_eng.pdf?ua=1. Accessed 7 Jan 2016.

55. Chandler C. Malaria burden and impact of control interventions in Uganda. In: The All-Party Parliamentary Group on Malaria and Neglected Tropical Diseases, London; 2016, January.

56. Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. Cochrane Database Syst Rev. 2010;4:CD006657.

57. Fornadel C, Norris L. President's Malaria Initiative country insecticide susceptibility summaries. 2015. http://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/pmi-insecticide-susceptibility-summary-april-2015.pdf?sfvrsn=2. Accessed 12 Sep 2015.

58. Edi CV, Djogbenou L, Jenkins AM, Regna K, Muskavitch MA, et al. CYP6 P450 enzymes and ACE-1 duplication produce extreme and multiple

insecticide resistance in the malaria mosquito *Anopheles gambiae*. PLoS Genet. 2014;10:e1004236.

59. Matowo J, Kitau J, Kaaya R, Kavishe R, Wright A, Kisinza W, et al. Trends in the selection of insecticide resistance in *Anopheles gambiae s.l.* mosquitoes in northwest Tanzania during a community randomized trial of longlasting insecticidal nets and indoor residual spraying. Med Vet Entomol. 2015;29:51–9.

60. WHO. WHO guidance for countries on combining indoor residual spraying and long-lasting insecticidal nets. Geneva: World Health Organization; 2014. http://www.who.int/malaria/publications/atoz/who-guidance-combining-irs_llins-mar2014.pdf. Accessed 14 April 2015.

61. Kleinschmidt I, Schwabe C, Shiva M, Segura JL, Sima V, Mabunda SJ, et al. Combining indoor residual spraying and insecticide-treated net interventions. Am J Trop Med Hyg. 2009;81:519–24.

62. WHO. WHO policy recommendation: Seasonal malaria chemoprevention (SMC) for *Plasmodium falciparum* malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa. Geneva: World Health Organization; 2012. http://www.who.int/entity/malaria/publications/atoz/smc_policy_recommendation_en_032012.pdf?ua=1. Accessed 13 May 2015.

63. Tine RC, Ndour CT, Faye B, Cairns M, Sylla K, Ndiaye M, et al. Feasibility, safety and effectiveness of combining home based malaria management and seasonal malaria chemoprevention in children less than 10 years in Senegal: a cluster-randomised trial. Trans R Soc Trop Med Hyg. 2014;108:13–21.

64. West PA, Protopopoff N, Rowland MW, Kirby MJ, Oxborough RM, Mosha FW, et al. Evaluation of a national universal coverage campaign of long-lasting insecticidal nets in a rural district in north-west Tanzania. Malar J. 2012;11:273.

65. Zhou G, Li JS, Ototo EN, Atieli HE, Githeko AK, Yan G. Evaluation of universal coverage of insecticide-treated nets in western Kenya: field surveys. Malar J. 2014;13:351.

66. WHOPES. Report of the twelth WHOPES working group meeting. Review of Bioflash GR, Permanet 2.0, Permanet 2.5, Permanet 3.0, Lambdacyhalothrin LN. WHO/HQ, Geneva 2008, WHO/HTM/NTD/WHOPES/2009.1.

67. WHOPES. Report of the Fifteenth WHOPES Working Group Meeting. Review of: Olyset Plus, Interceptor, Malathion 440EW, Vectobac GR. WHO/HQ, Geneva 2012, WHO/HTM/NTD/WHOPES/2012.5.

68. Mnzava AP, Knox TB, Temu EA, Trett A, Fornadel C, Hemingway J, et al. Implementation of the global plan for insecticide resistance management in malaria vectors: progress, challenges and the way forward. Malar J. 2015;14:173.

69. Oxborough RM, Kitau J, Matowo J, Mndeme R, Feston E, Boko P, et al. Evaluation of indoor residual spraying with the pyrrole insecticide chlorfenapyr against pyrethroid-susceptible *Anopheles arabiensis* and pyrethroid-resistant *Culex quinquefasciatus* mosquitoes. Trans R Soc Trop Med Hyg. 2010;104:639–45.

70. WHO. Pesticide products under WHOPES laboratory and or field testing and evaluation. Geneva: World Health Organization; 2015. http://www.who.int/whopes/Products_Under_WHOPES_Evaluation_May_2015.pdf. Accessed 13 Feb 2016.

71. Hemingway J, Beaty BJ, Rowland M, Scott TW, Sharp BL. The Innovative Vector Control Consortium: improved control of mosquito-borne diseases. Trends Parasitol. 2006;22:308–12.

72. IVCC. To fight malaria, UNITAID is making insecticides cheaper. 2016. http://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/to-fight-malaria-unitaid-is-making-insecticides-cheaper.pdf?sfvrsn=4. Accessed 15 Feb 2016.

73. Walker K. Cost-comparison of DDT and alternative insecticides for malaria control. Med Vet Entomol. 2000;14:345–54.

74. Cohen JM, Smith DL, Cotter C, Ward A, Yamey G, Sabot OJ, et al. Malaria resurgence: a systematic review and assessment of its causes. Malar J. 2012;11:122.

75. USAID. President's Malaria Initiative Madagascar malaria operational plan FY 2015. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/fy-2015-madagascar-malaria-operational-plan.pdf?sfvrsn=3. Accessed 22 Jan 2015.

76. USAID. President's Malaria Initiative Mali malaria operational plan FY 2015. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/fy-2015-mali-malaria-operational-plan.pdf?sfvrsn=3. Accessed 22 Jan 2015.

77. USAID. President's Malaria Initiative Mozambique malaria operational plan FY. 2015. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/fy-2015-mozambique-malaria-operational-plan.pdf?sfvrsn=4. Accessed 22 Jan 2015.

78. USAID. President's Malaria Initiative Rwanda malaria operational plan FY 2015. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/fy-2015-rwanda-malaria-operational-plan.pdf?sfvrsn=3. Accessed 22 Jan 2015.

79. USAID. President's Malaria Initiative Senegal malaria operational plan FY 2015. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/senegal_mop_fy15.pdf?sfvrsn=4. Accessed 22 Jan 2015.

80. USAID. President's Malaria Initiative Zimbabwe malaria operational plan FY 2015. http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/fy-2015-zimbabwe-malaria-operational-plan.pdf?sfvrsn=3. Accessed 22 Jan 2015.