

Distribution and trends of insecticide resistance in malaria vectors in Ethiopia (1986 - 2017): a review

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Abstract

Introduction: Malaria vector control intervention relies mainly on long-lasting insecticidal nets and indoor residual spraying. The distribution and frequency of insecticide resistance have increased dramatically and are now threatening the global success of the control program. Resistance to the public health insecticides has been frequently reported in Ethiopia. This review aimed at mapping the spatial and temporal distribution, and the trend of insecticide resistance to different insecticides used for vector control in the Ethiopian populations of *Anopheles arabiensis*.

Objective: To assess the distribution and trends of insecticide resistance, which could help the implementation of Insecticide Resistant Management strategy in the country.

Methods: Relevant published articles and reports on malaria mosquito resistance management were reviewed. The obtained data were organized and the geographical distribution resistance was mapped. For those sites where resistance was reported, but had no GPS coordinates, the coordinates were obtained from Google Earth.

Results: Since 1986, resistance increased from time to time even after the country stopped DDT spraying. The *Anopheles arabiensis* population has developed resistance to pyrethroids and organochlorine class insecticides in most parts of the country. Few vector populations also developed resistance to carbamate insecticides. However, most populations surveyed were fully susceptible to primiphos-methyl and fenthion.

Conclusions: Wild populations of *An. arabiensis* were found resistant to pyrethroid insecticides used for treating nets, therefore there is a need to consider new generation nets to improve the protective effect of nets. As the vector was fully susceptible to primiphos-methyl, it can be used as an alternative insecticide for indoor residual spraying. Moreover, insecticide resistance management strategies should be implemented in the country in such a way that a change in insecticide pattern is ensured before the resistance to a certain insecticide reaches its tipping point.

Key words: *Anopheles arabiensis*, resistance monitoring, insecticide resistance.

Introduction

Malaria is a complex disease caused by a single-celled protozoan parasite that belong to the genus *Plasmodium* and transmitted by the female *Anopheles* mosquito. The disease predominately occurs in tropical and sub-tropical parts of the globe and remained a major public health problem. In 2015, about 88% cases and 90% deaths are estimated to occur in the African Region (WHO 2015a). In fact, malaria shows a declining trend following the scale up of vector control tools and effective treatment as compared to the end of the 1990s. Globally, estimated malaria cases and deaths decreased by 18 % and 48 % respectively, and by 12% and 48 % in Africa from 2000 to 2015 (WHO 2015a). Chemical-based malaria vector control has been a key component of malaria control intervention. With the high coverage of long-lasting insecticidal nets (LLINs), the use of chemicals has been escalated. The world health organization

(WHO) recommends active ingredients of four classes of insecticides, including pyrethroid, organochlorine, organophosphate and carbamate to be used for public health interventions (WHO 2015b). Among those classes of insecticides, pyrethroids are recommended for the treatment of LLINs, due to their safety and effectiveness (WHO 2011a).

A recent review documented that the distribution and frequency of insecticide resistance increased dramatically in the malaria vector population and is now threatening the success of control programs (Ranson and Lissenden 2016). The emergence and the widespread range of insecticide resistance may compromise vector control in malaria endemic areas worldwide and this calls for developing an insecticide resistance management strategy in malaria endemic countries (WHO 2011b). The dependency of the current malaria control on pyrethroids and the development of resistance by malaria vectors to these

products, puts the current global of control efforts at higher risk. Pyrethroid insecticide resistance is spreading and intensifying, reaching levels that threaten the control programs in most malaria endemic African countries (Brogdon et al. 2014). Similarly, insecticide resistant populations of *An. arabiensis* are widespread in Ethiopia. This might also be associated with long standing use of chemical insecticides by the national malaria control program for IRS since the 1950s. Moreover, there has been an increase of indoor residual spraying (IRS) and LLINs since 2005. Subsequently, resistance has been documented in different parts of the country following this intensification of IRS and LLINs (PMI 2016; Abate and Hadis 2011; Yewhalaw et al. 2011). Hence, many studies recommend to monitor insecticide resistance and to implement insecticide resistance management strategies to minimize its impact on vector control (Najera and Zaim 2003; WHO 2014).

Malaria epidemiology: Efforts to control malaria have been boosted in the past few years with increased international funding and greater political commitment. Consequently, the reported malaria burden is being reduced in a number of countries throughout the world, including in some countries in tropical Africa where the burden of malaria is greatest (Mendis et al. 2009). Four human malaria parasite species, namely *Plasmodium falciparum*, *P. vivax*, *P. malariae* and *P. ovale* have been reported in Ethiopia. However, most of the malaria cases are due to *P. falciparum* and *P. vivax* and the remaining two species have low epidemiological significance in the country. *P. falciparum* represents about 65-75% (WHO-Afro 2016) of the total reported malaria cases. Over 42 malaria vector species were recorded in Ethiopia (Authority 1988). However, *An. arabiensis* is the principal vector responsible for malaria transmission (Abeku et al. 2003). The other malaria vector *An. pharoensis* is playing a secondary role in transmission of malaria in the country (White 1982).

Malaria control: Malaria vector control methods focus on the use of insecticides, insecticide-treated materials, environmental management, and personal protection methods against mosquito vectors (WHO 1995). The concept of modifying vector habitat to discourage larval development and/or human-vector contact is generally referred to as environmental management (Singer et al. 2005). The techniques of environmental management are generally grouped into three main categories—environmental modification, environmental manipulation, and modification of

human habitations/behaviors (Ault 1994; WHO 1982). DDT was the first synthetic organic insecticide used for effective vector control with reasonable success. The historic successful eradication of malaria in various parts of the world is achieved mainly by vector control (Harrison 1978). Application of insecticides remains the primary control tool in the majority of vector control programs throughout the world since early nineteenth century (Bremner 2001). However, high coverage of breeding sites is required to achieve significant impact, which is a major operational and logistical challenge in many ecological settings (Pampana 1969). In India, in urban areas, the major vector control strategy is larviciding of breeding habitats with organophosphate insecticides namely temephos and fenthion. However, fenthion has been withdrawn for use in vector control in India due to the recent development of insecticide resistance (Sharma et al. 1996).

Malaria control in Ethiopia started during the 1950s. It is mainly focused on case management and vector control as well as health education. For the treatment of malaria infection, chloroquine was used in the country for over five decades. However, *P. falciparum* developed resistance to chloroquine (Teklehaimanot 1986) and led to use sulphadoxine-pyrimethrin as first line treatment for *P. falciparum*. Currently the first line drug for treatment of uncomplicated malaria infection is artemether lumefantrine, which was introduced in 2004 (FMoH 2004).

The vector control intervention started in Ethiopia during the malaria eradication era in the 1959, and Dichlorodiphenyltrichloroethane (DDT) was used for IRS. It was the insecticide of choice for malaria vector control until 2008. According to FMoH, Malathion was used as an alternative insecticide in areas where vectors had become resistant to DDT. The insecticide was used for both malaria vector control and crop protection in agriculture (PMI 2008). In order to meet the annual needs of the country, Adami Tulu Pesticide Processing Plant located in East Shoa, Central Ethiopia has started formulating insecticides since 2001. In addition, this plant also formulates other insecticides for crop protection. According to Ethiopian FMoH data, DDT was replaced by pyrethroids in 2009, and bendiocarb and propoxur from the same class have been used for IRS in 2011 and 2012, respectively. Up to 2015, the amount of propoxur used in vector control intervention is 3.34 times higher than bendiocarb. The type and amount of insecticide used for IRS shown in Figure 1.

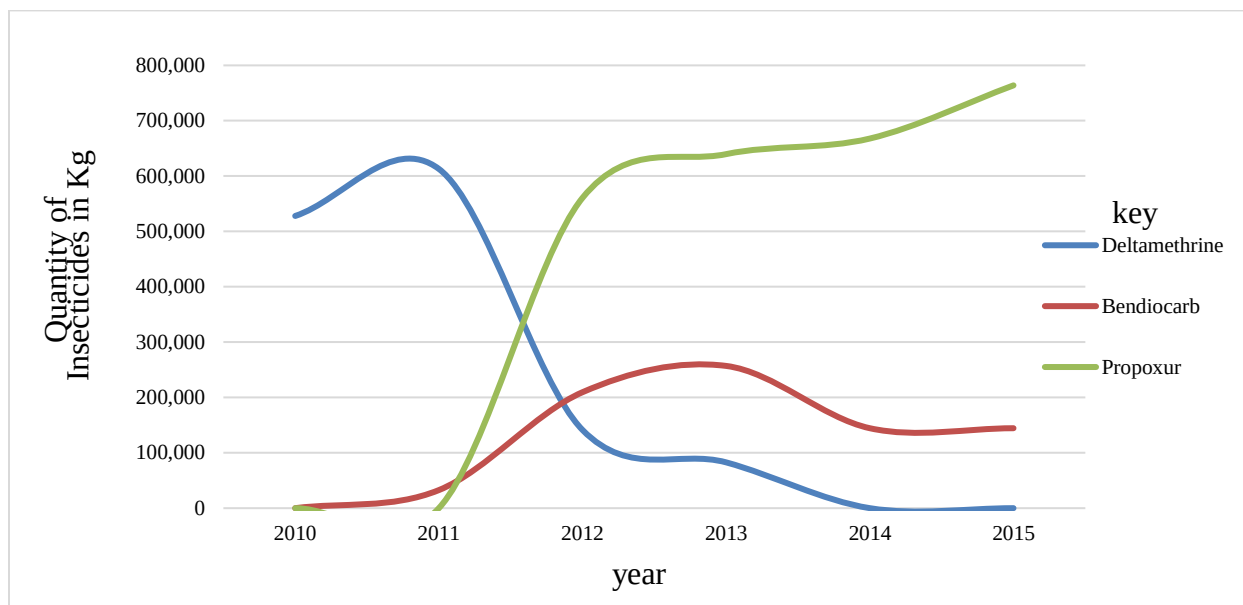


Figure 1: Trends in the quantity (in Kg) of insecticides used for IRS in Ethiopia, 2010- 2015. Source: National malaria control program (NMCP) of Ethiopia 2016

LLIN was introduced to Ethiopia as a vector control tool since 1998 (PMI 2008). Then, the NMCP scaled up the distribution of LLIN in 2005 to increase the ownership and utilization of LLINs. This resulted in the reduction of malaria cases and deaths. Unfortunately, the highest coverage of IRS and scaled use of LLINs is believed to enhance the appearance and development of resistance in vector species to

various classes of insecticides (Yewhalaw et al. 2012). Before 2005, ITN were treated with conventional K-O tab® and it serves for one year in the absence of re-treatment. During large scale LLINs distribution, the purpose of global ITN distribution was to deliver two ITNs per household (PMI 2008). The amount of LLINs distributed from 2005 to 2013/14 in Ethiopia shown in Figure 2.

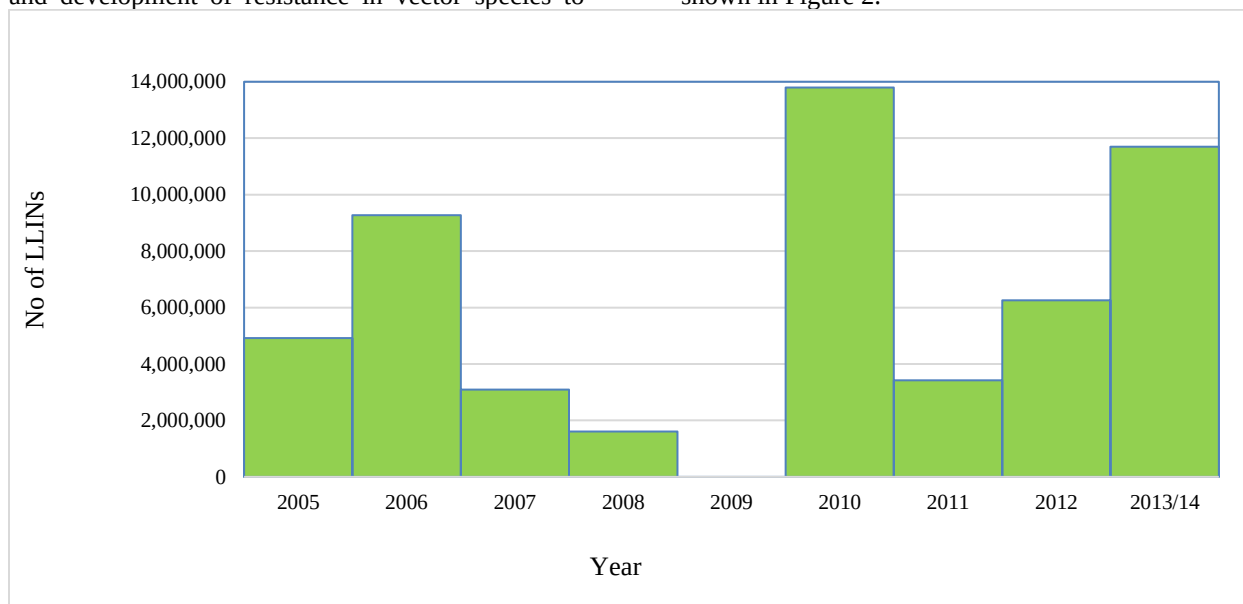


Figure 2: The number of LLINs distributed in Ethiopia from 2005 to 2013/14, Source: National malaria control program (NMCP) of Ethiopia 2016.

Materials and Methods

For this review, relevant published articles and reports on malaria mosquito resistance management were consulted. Graphs and maps were constructed after

data on mosquito mortality obtained from published sources were organized in excel. The database incorporated variables like location, insecticide type, percent mortality, and resistance level, year of study

and GPS location. For those publications that had no GPS coordinates, the coordinates obtained using the Google Earth application by tracing the name of the study site. Key words used to search the literature from Pub-Med and other journals for this review were: insecticide resistance, resistance management, vector control, history of insecticide utilization and impact of resistance. The inclusion criteria considered all manuscripts, reports and publications in English language that report on vector control, insecticide resistance in malaria vectors, the epidemiology of malaria, resistance management and integrated vector management (IVM).

Results

Distribution and trends of *An. gambiae* s.l resistance to DDT: Resistance to DDT was first detected in 1986 at middle wash, central Ethiopia (Abose et al. 1998). From 1986 to 1995, the susceptibility status of wild *Anopheles arabiensis* to DDT was assessed using a WHO tube test in six sites. During this time, mean percent mosquito mortality rates were 80% (range from 67% to 95%) (Abose et al. 1998). Moreover, populations of *An. gambiae* s.l developed resistance to DDT in Metahara and Melka Woror (Balkew et al. 2003). In 2005, Abate and Hadis reported DDT resistant *An. arabiensis* populations at three sites with mean percent mortality 86% (range 80.5% in Finchwuha to 92.2% in Andassa). Balkew (2010) also reported DDT resistance in *An. arabiensis* with mean percent mortality of 44% (range 3.8% to 78.8%). In 2007, resistant to DDT by the same species has been reported in Wondogenet, but population of *An. arabiensis* was susceptible in Pawi (Abate and Hadis 2011).

In 2008, susceptibility status of DDT was assessed in 11 sites in north western, western and southern Ethiopia; six sites by Abate and his colleagues (Abate and Hadis 2011), four sites by Presidents Malaria Initiative (PMI) team (PMI 2010), and one site by

Yewhalaw and his colleagues (Yewhalaw et al. 2010). In ten of the eleven sites, populations of *An. arabiensis* were resistant to DDT. The mean percent mortality of *An. arabiensis* to DDT was 20.8% (ranging between 1% in Assendabo to 100 % in Zabatsion). In 2009, the susceptibility status of *An. arabiensis* to DDT was assessed at eight sites in northern, western and southern Ethiopia. The populations of *An. arabiensis* were highly resistant to DDT with the mean percent mortality of 12.86% (range 0.5% to 36.1%) (Yewhalaw et al. 2011; Abate and Hadis 2011). In 2010, the susceptibility status of populations was assessed at 25 sites (Balkew et al. 2012, Massebo et al. 2013). The *An. arabiensis* populations collected from the above sites developed resistance to DDT with mean percent of mortality of 22.5% (range 0 to 82%) (Unpublished-Data; PMI 2016a). In 2011, the susceptibility status of *An. arabiensis* to DDT was assessed in 28 sites. The populations of *An. gambiae* s.l developed resistance in all sites with mean percent of mortality 13.65%, (Asale et al. 2014; Fettene et al. 2013; Unpublished-Data). In 2012, *An. arabiensis* population developed resistance to DDT in all eleven sites with mean percent of mortality 10.24 % (PMI 2014). In 2013, *An. arabiensis* populations were resistant to DDT in eleven sites with mean percent of mortality of 18.3% (PMI 2015) and in 2014 *An. arabiensis* population was resistant to DDT in seven sites with mean percent mortality of 10.5% in 2014 (PMI 2016). Though DDT resistance was first identified in 1986, the trend of insecticide resistance further increased from 2005 to 2015 as shown in Figure 3.

There has been a wide distribution of DDT resistance in the country since 1986 (Abose et al. 1998). However, *An. arabiensis* populations from certain sites of Benishangul Gumuz and Amhara regions was susceptible to DDT in 2007 and 2008 (Abate and Hadis 2011).

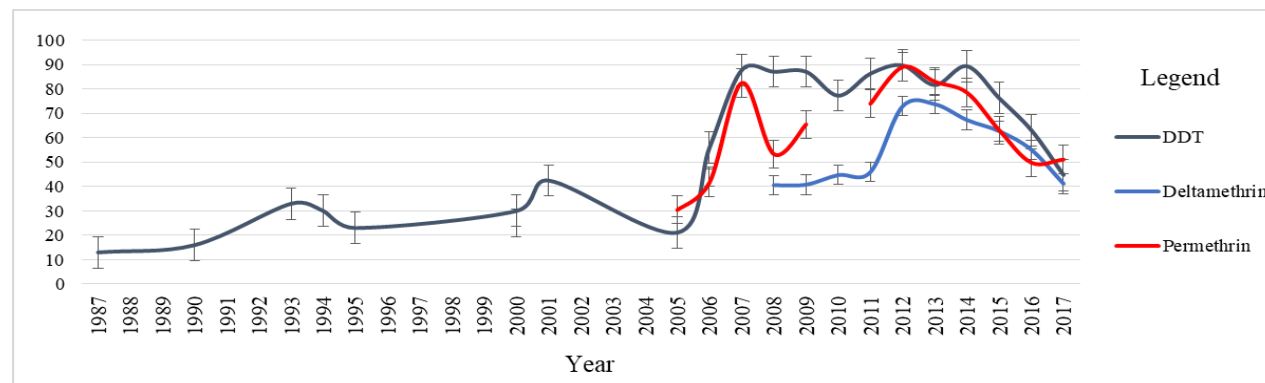


Figure 3: Trends of resistance of *Anopheles arabiensis* populations to DDT, Deltamethrin and Permethrin in Ethiopia (1986 to 2017).

Distribution and trends of *An. gambiae* s.l resistance to organophosphates: The susceptibility status of *An. gambiae* s.l to fenitrothion was assessed from 2011-2017 at 107 localities. Of these sites, *An. gambiae* s.l was susceptible to fenitrothion from 92 sites but

possible resistance and resistance to this insecticide has been reported in 10 and 5 sites, respectively sites (Figure 4) (Balkew et al. 2012, Fettene et al. 2013, PMI 2016; Asale et al. 2014).

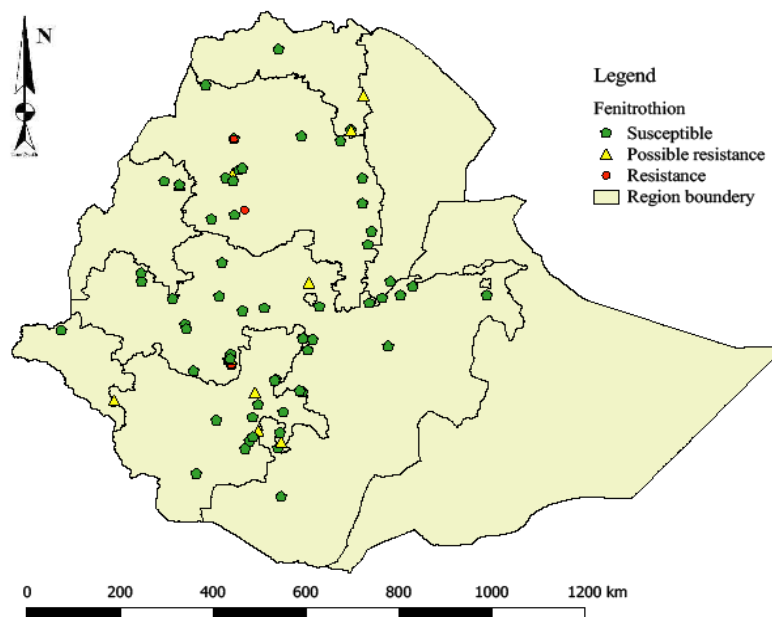


Figure 4: Map showing the distribution of resistance in *Anopheles arabiensis* to fenitrothion in Ethiopia (2011 -2018).

Moreover, susceptibility status of *An. gambiae* s.l to Malathion was monitored in 127 sites from 2005 to 2017. The populations of *An. gambiae* s.l was susceptible at 36 sites, possible resistance at 55 sites and resistance at 36 sites to Malathion. (Balkew et al. 2012; Fettene et al. 2013; PMI 2016; Asale et al. 2014; Yewhalaw et al. 2010; Abate and Hadis 2011). Susceptibility status of wild populations of *An. gambiae* s.l against pirimiphos-methyl assessed in six regions of the country (Figure 5). *Anopheles gambiae* was susceptible to primiphos-methyl in all assessed 51 sites. However, possible resistance and resistance also documented in 4 sites and 1 sites, respectively (Unpublished-Data; PMI 2014; PMI 2015; PMI 2016).

Distribution and trends of *An. gambiae* s.l resistance to pyrethroids: Susceptibility level of wild *An. gambiae* s.l population to alpha-cypermethrin assessed in 12 sites from 2015 to 2017. The population developed resistance to Alpha-cypermethrin in 8 sites. The population was susceptible in 2 sites and, possible resistance was recorded in 2 sites (PMI 2015; Unpublished-Data). In addition, Susceptibility level of wild *An. gambiae* s.l population to Alpha-cyhalothrin assessed in 17 sites from 2010- 2014. The *An. gambiae*

s.l population develops resistance at all monitored sites to the insecticide (Massebo et al. 2013; PMI 2014; PMI 2015). The susceptibility status of *An. gambiae* s.l population to lambda-cyhalothrin was assessed in 62 sites from 2010 to 2015. Of these, twenty-one sites were assessed in 2010. population of *An. gambiae* s.l collected from five sites showed possible resistance, while mosquito populations from the remaining sites was resistant to lambda-cyhalothrin (Massebo et al. 2013; Asale et al. 2014; PMI 2015; PMI 2014). Interestingly populations with possible resistance to the insecticide in 2010 developed resistance the following years in all surveyed sites.

In 2005, populations of *An. gambiae* s.l from Sabure, Andassa and Finchwuha were susceptible to deltamethrin (Abate and Hadis 2011). Mosquito population was also susceptible from Sodere, but resistant to the insecticide from Ghibe and Gorgora (Balkew et al. 2010). Before 2007, among five sites assessed, Populations of *An. gambiae* s.l was susceptible to deltamethrin at two sites in the Amhara region. The resistance frequency of the populations to deltamethrin increased, since 2008. However mean percentage mortality decreased since 2015 (Figure 3).

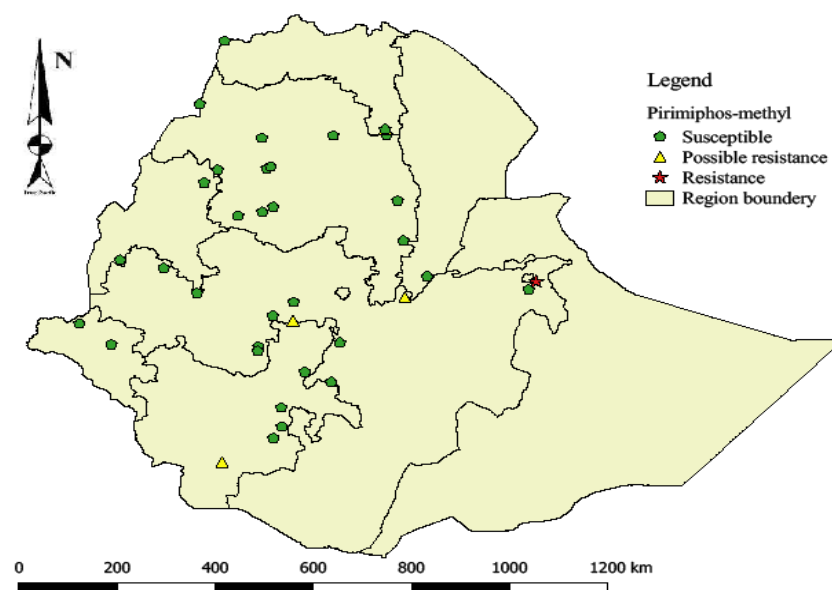


Figure 5: Spatial distribution of *Anopheles arabiensis* population resistance level to pirimiphos- methyl in Ethiopia from 2012 -2017

In 2008, populations of *An. arabiensis* were susceptible at two sites; Gilge Ghibe (Yewhalaw et al. 2010), and Enddo-Kontole and Assendabo (PMI 2010). Later in 2009, *An. arabiensis* population from five sites developed resistance to deltamethrin. (One site from Amhara region, two sites from SNNPs and two sites from Oromia region) (Abate and Hadis 2011; Yewhalaw et al. 2010). In 2010, *An. arabiensis* populations from ten sites were resistant to deltamethrin. However, possible resistance has been reported from this species from seven sites while susceptible populations has been reported at four sites (Massebo et al. 2013; Unpublished-Data).

The susceptibility status of *An. arabiensis* population to deltamethrin was assessed at 24 sites of six regions in 201 (Unpublished-Data; Fettene et al. 2013; Asale et al. 2014). In 2012, of the three regions, mosquito populations developed resistance to deltamethrin at 16 sites with a mean mortality rate of 27% (range 1 % to 61%) (Unpublished-Data; PMI 2014). In 2013, populations, from twelve sites of three regions, developed resistance to the same insecticide with a mean mortality of 26% (range 13%-51%) (PMI 2015; Unpublished-Data). Resistant populations were also reported from 40 sites of seven regions during the period 201-2017 with a mean percent of mortality of 43 (range 11% - 83%) (PMI 2016). Resistance to

etofenprox has been reported between 2012- 2015 from 22 surveyed sites: three sites (i.e. Bahirdar, Zenzlima Robit and Asendabo) in 2012, three sites (i.e. Abaya, Shemen and Zenzlima Robit) in 2013, and sixteen sites (i.e. Alamata, Sedi, Zenzlima Robit, Chewaka, Kurgeng, Osso Billi, Asendabo, Burka and Shemen) in 2014 and 2015 (PMI, 2013 - 2015). From 2000 to 2017, 69 sites surveyed to assess the susceptibility level of populations of *An. gambiae* s.l to permethrin. Insecticide resistance to permethrin has been reported since 2000 (Balkew et al. 2003), however, populations from some sites were susceptible to permethrin in 2008 (Abate and Hadis 2011). In 2008, resistance of this species to permethrin has been reported from 52 sites (Unpublished-Data; Abate and Hadis 2011; Yewhalaw et al. 2010; PMI 2014-2018). The resistance trend of this species to permethrin increased until 2014 as shown in Figure. Distribution and trends of *An. gambiae* s.l resistance to carbamates: The susceptibility status of the malaria vector to bendiocarb was first assessed in 2010 in Ethiopia. From 2010 to 2017, a total of 106 sites were surveyed and, in 2010, wild populations of *An. gambiae* s.l from 22 sites were susceptible to this insecticide (Balkew et al. 2012; PMI 2015). Of the fourteen localities surveyed later in 2011, only populations from five localities were susceptible to this insecticide (Fettene et al. 2013).

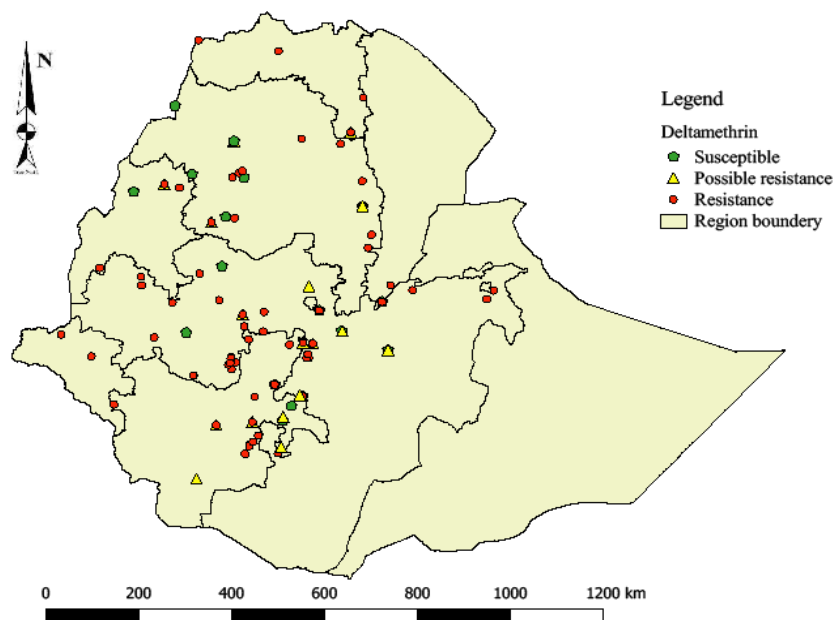


Figure 6: Map showing the distribution of resistance in *Anopheles arabiensis* to deltamethrin in Ethiopia (2005 -2017)

Populations of this species from seven sites in 2012, eight sites in 2013 and four sites in 2014 were susceptible to this insecticide (PMI 2013-2015; PMI Unpublished-Data). From 2015 to 2017, Mosquito populations from 35 sites was assessed for bendiocarb resistance during the period 2015-2017. Of this, populations from 27 sites were susceptible to the

insecticide while, possible resistance and confirmed resistance were documented from two and 6 sites, respectively (PMI 2017-2018; PMI Unpublished-Data). Populations of *An. arabiensis* from the Amhara region developed resistance to this insecticide. The distribution of bendiocarb resistance in populations of *An. arabiensis* in Ethiopia is depicted in figure 7.

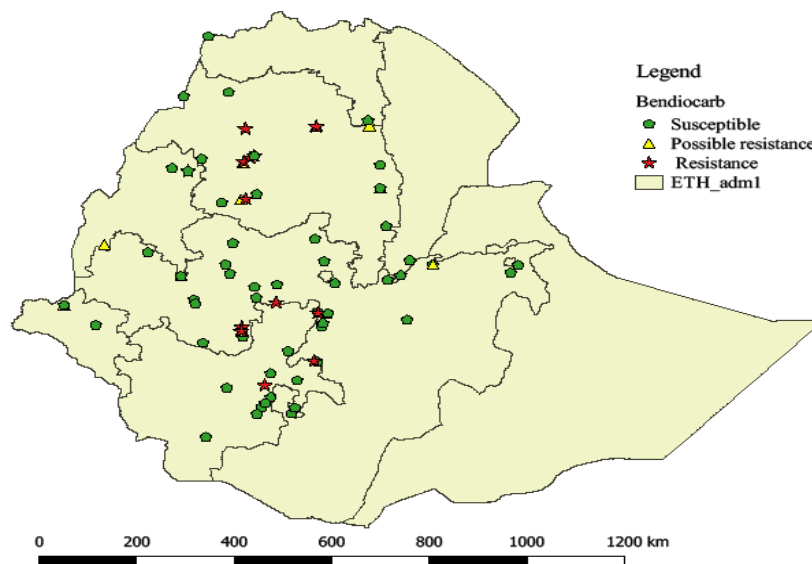


Figure 7: Spatial distribution of *Anopheles arabiensis* population resistance level to bendiocarb in Ethiopia from 2011-2017

Populations of *An. gambiae s.l* was assessed for their susceptibility status to propoxur in 106 localities in Ethiopia from 2010 to 2017. The populations from 91 sites was susceptible to this insecticide and resistance was only developed at populations from six sites (four from Amhara, one from SNNPRs and one from

Tigray) were resistant to the same insecticide. Possible resistance to propoxur was documented from nine sites (Balkew et al. 2003; Balkew et al. 2012; Balkew et al. 2010; Yewhalaw et al. 2010; Fettene et al. 2013; PMI 2016). Spatial distribution *Anopheles arabiensis* resistance to propoxur shown in Figure 8.

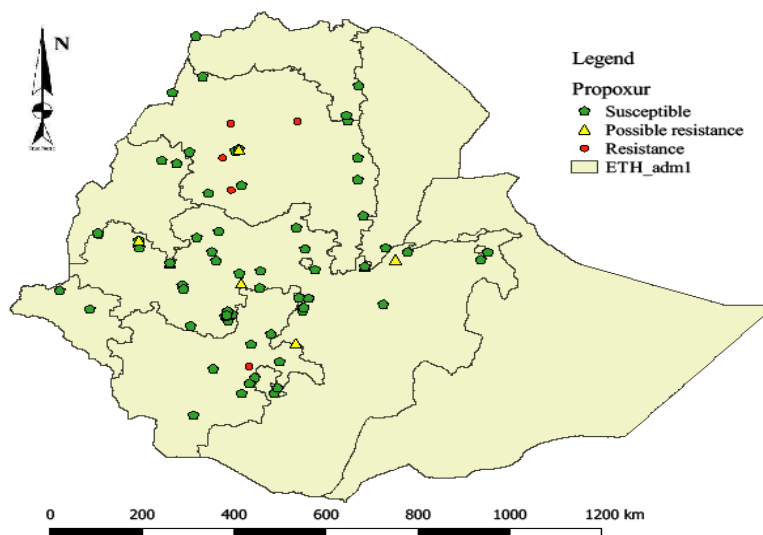


Figure 8: Map showing the distribution resistance in *Anopheles arabiensis* to propoxur in Ethiopia (2000 -2017).

Insecticide resistance management in malaria vector control:

Insecticide resistance monitoring and management (IRMM) strategic plan developed and endorsed by the Ethiopian FMOH in collaboration with stakeholders. For this purpose, 25 malaria sentinel sites identified to generate both entomological and epidemiological data for evidence-based decision making to sustain control and enhance elimination efforts. In high malaria transmission, two type of intervention (i.e. LNNs and IRS) from different class of insecticides will implemented. However, in moderate malaria transmission area rotate IRS insecticides from different classes recommended yearly. The remaining two insecticide resistance managements (i.e. mixture and mosaic) are not operationally feasible in Ethiopia (IRMM).

Future prospects for malaria control: For the success of the goal of malaria elimination in Ethiopia set by 2030, innovation of vector control tools to counteract the emergence of drug and insecticide resistance is crucial (WHO 2016a; Yewhalaw and Kweka 2016). For this, ivermectin became a potential tool receiving attention to be used as a malaria control tool (Carlos et al. 2013; Chaccour et al. 2015; WHO 2016b). The residual insecticides in insecticide-treated wall lining (ITWL) are durable and maintain control of insects

significantly longer than IRS and may provide an effective alternative or additional vector control tool to ITNs and IRS (Munga et al. 2009).

Since the discovery of the mosquito larvicidal activity of *Bacillus thuringiensis israelensis* (serotype H-14) in 1977, several formulations of Bti have used against different mosquito species (Mittal 2003). Moreover, there is a growing interest in the use of very safe insect growth regulator (IGRs) that are emerging as promising vector control compounds for mosquito control with specific action and are relatively safe to non-target organisms (Mulla and Darwazeh 1979; Morrison et al. 2008). Transmission blocking vaccines (TBVs) are being assessed as a way to control the spread of malaria (Wu et al. 2015). Genetic engineering of mosquito's transgenic technology acts as an alternative strategy to the conventional vector control methods (Catteruccia et al. 2000).

Discussion

DDT were used in the country for four decades to malaria control. Since 1986, resistance increased from time to time even after the country stopped DDT spraying. This might be due to cross-resistance with other insecticides used to impregnate LLINs. In the country, DDT and pyrethroids resistance are

widespread, which is constancy with study conducted in western Kenya (Mulamba et al. 2014). Similarly *An.gambiae* s.l. was developed resistant to DDT and pyrethroid in central and eastern Uganda (Verhaeghen et al. 2010). However, *An. arabiensis* was susceptible to DDT in Zanzibar (Haji et al. 2013). Resistance to pyrethroids by *An. gambiae* s.s. and *An. arabiensis* also reported from several districts of the mainland of Tanzania (Kabula et al. 2014; Matowo et al. 2010). *An. gambiae* s.l. showed different levels of resistance to deltamethrin, lambdacyhalothrin and bendiocarb at different study sites of Ethiopia, which is consistence with study conducted in Kilifi, Malindi and Taveta districts in coastal Kenya (Stump et al. 2004) and in Zanzibar (Haji et al. 2013). Moreover, pyrethroid resistance has been also reported in *An. gambiae* s.s and *An. arabiensis* from four districts of Western Kenya. (Stump et al. 2004). In Ethiopia, *An. Arabiensis* were fully susceptible to bendiocarb, fenitrothion and Pirimiphos-methyl until 2011. Similarly, *An. gambiae* s.s and *An. arabiensis* were fully susceptible to bendiocarb and fenitrothion from eastern Uganda (Mawejje et al. 2013) And In Zanzibar, *An. arabiensis* was susceptible to carbamates (bendiocarb). Moreover, in a similar *An. gambiae* s.s to was susceptible to bendiocarb, and malathion (Haji et al. 2013).

Conclusion and recommendations

The development of resistance in *An. arabiensis* to DDT substantially increased after 2006 following the large-scale distribution of LLINs. Even if utilization of DDT for IRS discontinued in 2009, the populations of *An. arabiensis* remains resistant to DDT in the country. This might be because of cross-resistance between organochlorine and pyrethroids. A large proportion of the *An. arabiensis* population developed resistance to pyrethroids class insecticides which are used to impregnate nets, and therefore the use of new generation bed nets might be important to enhance the killing effect of nets. Though the amount of bendiocarb used for vector control is lower than propoxur, a large proportion of the wild *An. arabiensis* population developed resistance for bendiocarb compared to propoxur. *Anopheles arabiensis* was susceptible to primiphos-methyl, and hence it may be used for IRS instead of carbamates in the country to limit the resistance from reaching its tipping point. In addition, considering non-insecticidal vector control method is important to regain vectors susceptibility for carbamate class, like screening of doors and windows and environmental managements.

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