Chapter 21

Residual Transmission of Malaria: An Old Issue for New Approaches

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Additional information is available at the end of the chapter

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1. Introduction

Malaria is one of the most serious vector-borne diseases, affecting millions of people mainly in the tropics. Recently, a substantial decline in malaria incidence has been observed all over the world. Vector control is one of the key elements in achieving this world-wide malaria decline, with scaling up of Insecticide Treated Nets (ITNs) and the expansion of Indoor Residual Spraying (IRS) programmes contributing significantly. Besides the personal protection, ITNs confer a community protection when wide coverage is assured, meaning that unprotected persons benefit from the large scale intervention [1]. IRS is only meaningful when applied at a large coverage. In the 2011 World Malaria Report [2], the percentage of households owning at least one ITN in sub-Saharan Africa is estimated to have risen from 3% in 2000 to 50% in 2011 while the percentage protected by indoor residual spraying (IRS) rose from less than 5% in 2005 to 11% in 2010. Household surveys indicate that 96% of persons with access to an ITN within the household actually use it [2]. Although these numbers might overestimate the real ITN use, they show that in recent years, several vector control measures were scaled up substantially. Despite these large increases in coverage, a widely held view is that with the currently available tools, namely vector control tools, intermittent preventive treatment, and early diagnosis and treatment, much greater gains could be achieved, including elimination from a number of countries and regions [3].

When considering vector control tools, even when hypothesizing a full coverage of ITNs and IRS, malaria transmission may still continue. Indeed, IRS only affects endophilic[1] mosquitoes and ITNs only target night biting mosquitoes. Moreover both intervention methods will mainly affect anthropophilic[2] mosquitoes that are endophagic[3]. This leaves ample opportunity

1 Endophily is the tendency for mosquitoes to prefer resting indoors

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for more exophilic[4], zoophilic[5] and/or exophagic[6] vectors to escape from contact with insecticide treated surfaces and to maintain a certain level of transmission. Independently of the ITN and/or IRS coverage, outdoor and early malaria transmission occurs in many malaria endemic regions. In the west of Eritrea for example over a two year sampling period 36.4% of infective bites were acquired outdoors [4], in southern Tanzania this was 10% for non ITN users [5]. A study in northeastern Tanzania showed that 12% of the malaria transmission occurred before sleeping time [6]. In Uganda, in 6 sentinel sites throughout the country, up to 36% of indoor transmission and 49 % of outdoor transmission occurred before sleeping time, with the highest proportion of early in- and outdoor transmission in the suburban area of Jinja where *An. gambiae*[7] was the main vector [7]. In central Vietnam, where ITNs are used at large scale, 69% of the infective bites in forest plots were acquired before sleeping time [8]. In a study conducted in the east and west of Cambodia before widespread ITN use, 29% of the bites occurred before sleeping time in villages and forest plots [9]. In North-East India, 21% of the indoor infective bites occurred before 21h [10]. Also in Nicaragua, in an area with mainly Vivax malaria, 50% of the infective bites were acquired before sleeping time [11]. This part of the malaria transmission has the possibility to continue despite high coverage of ITNs and IRS, and is defined for the purpose of this review as 'residual transmission'.

Controlling residual transmission requires a different approach as compared to the currently used vector control measures. This is not new and was already perceived as a major obstacle in the previous malaria eradication era [12]. In 2007 malaria eradication was put as the ultimate goal [3] and renewed attention was given to residual transmission, with vector control models also incorporating outdoor and zoophilic malaria vectors. Recently, an established mathematical model adjusted for human in- and outdoor movements was used to illustrate that even with 50% outdoor biting vectors, transmission suppression can be achieved by a large ITN coverage [13]. However the authors assumed a uniform exposure so that the ITN induced mortality affects equally in- and outdoor biting vectors. When assuming a uniform exposure all individuals of the vector population (belonging to the same or to different species), will exhibit at each gonotrophic cycle a random behaviour (e.g. exo- or endophily, exo-or endophagy, anthropo- or zoophily, early- or late-biting), so that all individual mosquitoes are equally affected by indoor-based vector control measures. In case of non-uniform exposure, two or more subpopulations of vectors (belonging to the same or to different species) are assumed, each exhibiting a specific behaviour. Therefore, each of these subpopulations is affected differently by indoor-based vector control measures [14]. As a result, a fraction of vectors will persist in the presence of these control measures and can be responsible for residual transmission. It was shown that pre-intervention variables reflecting behavior, such as the degree

2 Anthropophily is the tendency for mosquitoes to prefer feeding on human hosts

3 Endophagy is the tendency for mosquitoes to prefer biting indoors

4 Exophily is the tendency for mosquitoes to prefer resting outdoors

5 Zoophily is the tendency for mosquitoes to prefer feeding on animal hosts

6 Exophagy is the tendency for mosquitoes to prefer biting outdoors

7 In this paper, s.l. (sensu lato) is added to the species name when referred to the species complex *(An. gambiae s.l., An. minimus s.l., An. dirus s.l.).* In the absence of s.l., the species is concerned *(e.g. An. gambiae, An. minimus, An. dirus).*

of exophily, may predict the efficacy of a specific intervention [15,16]. Assuming non-uniform exposure, the exophagic fractions of vectors will be less exposed to ITNs, the probability of survival and the vectorial capacity of this subpopulation will be weakly affected, and malaria transmission cannot be reduced further. The model developed in [17] takes into account the non-uniform exposure of the different anopheline species, i.e., the anthropo-endophilic vector species *An. gambiae* and *An. funestus*, and the more zoo-exophilic vector *An. arabiensis*. As would be intuitively expected, this model predicts that even the combination of very effective ITN distribution, twice yearly mass screening and treatment campaigns, and IRS will not succeed in getting the parasite prevalence rate below the 1% threshold if the zoo-exophilic *An. arabiensis* is present. When only *An. gambiae* or *An. funestus* are present, the same combination of interventions are successful in this model [17]. Moreover even within a well-defined species different subpopulations may occur exhibiting different behavioural patterns, resulting in non-uniform exposure within a species.

Therefore, when designing and applying vector control strategies it would be essential to have a good knowledge of the vector behavioural traits particularly those relevant to the chosen control method. However, entomological findings for one region or one anopheline species do not necessarily hold true for the same or different anopheline species encountered in the same or different malaria-endemic regions. In this chapter we will show that even before widespread use of vector control measures, a heterogeneity in behaviour between and within species was present. Because of the heterogeneity in behaviour, mosquitoes have different opportunities to escape from the killing or excito-repellent actions of insecticides used in ITNs or IRS. We will give examples of species shifts, shifts to outdoor- or early biting, shifts to zoophily or to exophily from different malaria endemic regions linked to the use of ITNs and IRS. Although the causes and mechanisms behind these shifts are not yet well understood, we will argue that ITNs and IRS may select for vector populations that predominantly feed early or outdoors, rest outdoors, or that are able to change their behaviour in response to the presence of these insecticides. Therefore, residual transmission will be dominated by vectors that bite outdoors, early or on animals, and that rest outdoors. These vectors require different control strategies, which might also be based on reducing host-vector contact, or target other key environmental resources.

The concept of uniform versus non-uniform exposure is illustrated in Figure 1.

2. Heterogeneity in anopheline behaviour

Heterogeneity in behaviour of anopheline mosquitoes between and within species is present in all malaria endemic regions. In Africa, the two most efficient malaria vector species, *An. gambiae* and *An. funestus*, are very anthropophilic, endophilic, endophagic, and late-night biting [18]. In contrast, *An. arabiensis*, a species belonging to the same complex as *An. gambiae*, is more plastic in its behaviour, exhibiting more often zoophily, exophily, exophagy, and early-night biting as compared to *An. gambiae* and *An. funestus*. However, different factors can influence the behaviour of the anophelines. Host availability for example plays an important

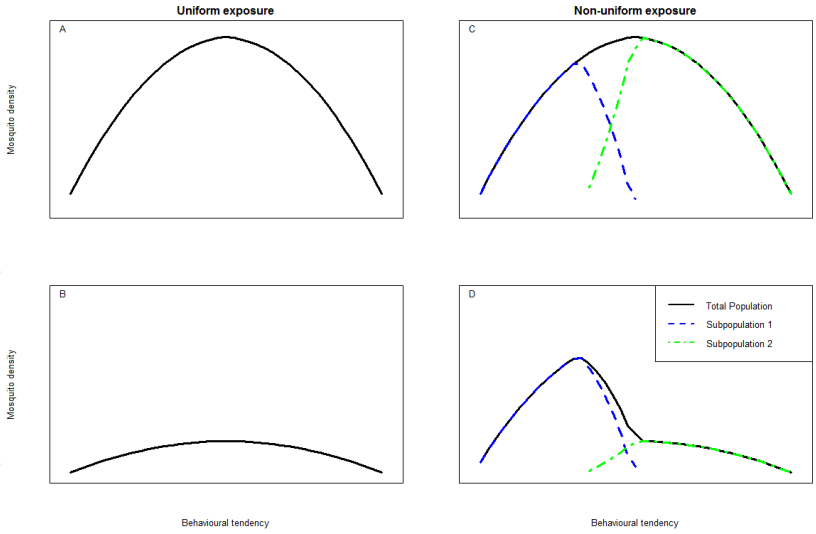

Figure 1. Effect of control measures on mosquito populations in the assumption of uniform exposure and non-uniform exposure. The density of a uniform population (belonging to the same or to different species) A. before applying the control measure. B. after applying the control measure. The control measure reduces the density of the whole population by 80%. The density of a non-uniform population C. before applying the control measure. D. after applying the control measure. The population consists of two subpopulations (Subpopulations 1 and 2, belonging to the same or to different species) each with a different behavioural tendency. Limited contact with the insecticide due to its behavioural tendency makes that Subpopulation 1 is reduced by 20% only, while Subpopulation 2 is reduced by 80% of its initial density. As a result, a fraction of vectors will persist in the presence of these control measures and can be responsible for malaria transmission.

factor in the final host choice of the vector. This has been shown for *An. gambiae* in several study sites. In Burkina Faso for example, a double choice experiment shows that 88% of the *An. gambiae* choose for a human odour baited trap and only 12 % for a cattle odour trap. In contrast, the human blood index of indoor-resting *An. gambiae* collected in the same locality was only 40% [19], showing that this population of *An. gambiae* will adapt its host choice in case of a lower availability of human hosts. *An. gambiae* in São Tomé feeds more on dogs and was observed to be extremely exophagic most probably due to a combination of preference and the ease to reach the dogs sleeping outside under pillar houses [20]. On the Bioko Island (Equatorial Guinea), *An. gambiae* was also observed to be partly exophagic and early-biting [21]. This means that when humans are not available inside, e.g. because of a high bed net use, some populations of *An. gambiae* are observed to feed outside or on animal hosts. In those cases, the frequency of human-vector contact will be lowered although humans will still be bitten in the evening. As a consequence, the longevity of these exophagic or zoophilic vectors will slightly, or not, be affected by ITNs, meaning that the vectorial capacity is not affected and malaria transmission continues.

Also in South-East Asia, heterogeneity of behaviour is observed for the primary and secondary vector species [22]: *An. dirus* is for example very anthropophilic, whereas *An. minimus*,

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depending on the geographical region, has both anthropophilic and zoophilic tendencies. *An. maculatus* has a high tendency for early biting as compared to *An. dirus* or *An. minimus*, but there are large differences between localities. Different populations of *An. minimus* observed in various localities also differ in their endophilic and endophagic tendencies [22]. Whereas *An. dirus* is generally observed to be very exophagic and exophilic, populations in Lao PDR have shown highly endophilic and endophagic trends [23]. Moreover, as reviewed in [24], *An. dirus* s.l. can even take blood-meals during daylight in the jungle.

In Latin-America, one of the most efficient vectors, *An. darlingi* is mainly anthropophilic, whereas the other dominant vectors, such as *An. albimanus*, *An. nuneztovari*, and *An. aquasalis* also have zoophilic tendencies or are more opportunistic. Most of the vectors in Latin America are mainly exophilic, but within each species, the degree of exophily can vary between geographical regions. *An. albimanus* for example is predominantly exophagic and exophilic, as observed in the Dominican Republic, Colombia, and Haiti. However, in Mexico and Central America, 80% of the *An. albimanus* was observed to have an endophilic resting behaviour [25]. Also the time and place of biting differs between sites for most of the species. In some localities for example, *An. darlingi* bites mostly during sleeping hours, or early in the morning [26], whereas in other localities, the main biting peak is early in the evening [27]. In French Guiana, *An. darlingi* was endo-exophagous with a clear predilection for biting outdoors [28].

3. How can the indoor use of insecticides select for exophilic, exophagic, zoophilic and/or early biting mosquito populations?

Insecticides can elicit different actions with different results on mosquitoes [29–31]. These various modes of action are important when talking about selection of 'insecticide avoiding' mosquitoes. Toxic or cidal actions result in knockdown or death after contact with the insecticide. Excito-repellent actions, including contact irritancy and non-contact repellency, result in above-normal levels of undirected movements coupled with loss of responsiveness to host cues. The insecticidal actions and their results depend among others on the insecticidal product used and on the mosquito species present. Large differences in actions of insecticides used in IRS have been observed: dieldrin for example only elicits a cidal action, while alpha-cypermethrin has both contact-irritant and killing actions, and DDT elicits mainly a repellent effect and secondarily a toxic action. [30]. Pyrethroids, the only family of insecticides used on ITNs, have well-documented excito-repellent actions [21] which are dose-dependent, but with for example higher toxic actions of alphacypermethrin as compared to deltamethrin and permethrin [31].

The general concepts of stress-induced variation in evolution [32] can be applied to the effect of insecticides on mosquito populations. Indoor use of insecticides will pose a stress on the female anopheline population, but only when the insecticides present a barrier for indoor feeding or indoor resting. At least three processes can be at the origin of perceived shifts in mosquito behaviour by insecticides:

1. A first protective mechanism can be behavioural plasticity in response to the presence of the insecticide. The ability to actively remove from the insecticide by either relocation or avoidance requires an ability to detect (either by contact or non-contact) or anticipate the presence of the insecticide and the ability to exhibit insecticide avoidance strategies or adjustments [32]. The insecticide, or the unavailability of the host, can then trigger the expression of gene variants that have been accumulated, but were phenotypically neutral under a normal range of environments [32]. Many mosquitoes indeed naturally possess a high degree of irritability or repellency which is evident at the very first exposure of the population to residual insecticides [29]. Where this irritation is such that mosquitoes settling on the insecticide deposit are activated before they have absorbed a lethal dose of insecticide, and are able to avoid further contact and to escape unharmed, the term "protective avoidance" has been suggested. In the presence of a high coverage of IRS or ITNs, mosquitoes exhibiting this protective avoidance should then be able to redirect their behaviour to low-risk behaviour which also can lower their survival. For example, for a species that is normally endophilic changing its behaviour to resting outdoors, the external environment may be unfavourable to the survival of the species [12].

2. A second protective mechanism for the mosquito is a consistent "protective behaviour" [29] such as exophily, exophagy, zoophily or early-biting resulting in a minimal contact with the insecticides used indoors. As mentioned above, some mosquito populations naturally exhibit this kind of protective behaviour, which is probably genetically determined (see further). Also differences in responses to the insecticides can result in diverse exposure rates of different species or subpopulations to the insecticide. *An. minimus* for example, shows very strong repellency responses to several insecticides and would have a higher survival chance in the presence of insecticides as compared to *An. harrisoni* which shows a much lower repellency response [33]. In this case, insecticides will favour the (sub) populations of mosquitoes that have this innate preference for protective behaviour or for avoidant strategies by which they will escape the exposure to the insecticide. This is probably the mechanism that is occurring for many of the perceived species shifts that are illustrated below.

3. Where these phenomena of protective avoidance or protective behaviour are not evident at the very first exposure of the population to the insecticides, but develop only gradually, perhaps over several years under continued insecticide pressure, the term "behaviouristic resistance" is employed [29]. The presence of the insecticide will in that case result in the selection of mutations and recombination that favour the survival of the mosquito in the presence of the insecticide, eventually leading to a directional selection. This can be compared to the development of insecticide resistance, although selections of many mutations will probably be required before an appropriate behavioural change may occur. Classification as "behaviouristic resistance" is only valid on the basis of accurate comparisons made before and subsequent to the widespread use of residual insecticides in any particular area. As shown below, very few behaviour shifts observed so far, would fit this definition of behaviouristic resistance.

4. Shifts observed in the presence of indoor insecticidal pressure

In the following paragraphs we will review the shifts that were observed in the presence of IRS and ITNs. For the purpose of this review, a 'shift' means an observed change, including relative changes, with a reasonable link to the indoor use of insecticides (ITNs or IRS). A distinction is made between different kinds of shifts: species shifts describe changes in the species composition which can also be within species complexes, whereas shifts to early biting, exophagy, zoophily or exophily describe changes in biting time, biting place, host, or resting place within a species, or within a species complex if no species information was available. Because a large part of the shifts in literature are described in the Afrotropical region, this region will be handled separately.

5. Afrotropical region

5.1. Species shifts

An IRS campaign resulted in the elimination of *An. funestus* from the South Pare District (at the Tanzania-Kenya border), at the same time reducing the numbers of indoor-resting *An. gambiae* s.l. [34]. In the years immediately following this IRS campaign, populations of endophilic *An. gambiae* s.l. slowly regained their former levels, whereas gradual resurgence of *An. funestus* was not observed until almost 10 years after the campaign was abandoned. IRS campaigns in two Kenyan villages resulted in a large decrease (up to total disappearance) of *An. funestus*, with an increase in the more exophagic *An. rivulorum* [35] or *An. parensis* [36], both not considered as malaria vectors in the study sites. In Niger, nation-wide Long-lasting insecticidal net (LLIN) distribution caused a marked decrease of *An. funestus*, without effect on *An. gambiae* s.l. abundance [37]. Following an IRS campaign, *An. gambiae* was completely eliminated from Pemba Island (Tanzania), leaving the salt-water breeding *An. merus*, an exophilic mosquito with a preference for cattle [38]. In Kenya and Tanzania, large scale ITN use significantly decreased the proportion of indoor-resting *An. funestus* [39] and *An. gambiae* [39–42] while the proportion of *An. arabiensis* increased. The shift from *An. gambiae* to *An. arabiensis* was also observed in the larval collections [40,41]. As larvae of *An. gambiae* and *An. arabiensis* show no habitat segregation, larval sampling reflects true proportions of the two species. The change from sub-populations dominated by *An. gambiae* to those dominated by *An. arabiensis* took about a decade, as would be expected if caused by a constant ITN selection pressure [43].

In contrast, in Kenya and on the Bioko Island (Equatorial Guinea), the same species compositions were observed regardless of the use of ITNs or IRS [21,44]. Moreover, in the north-east of Tanzania, a species shift has been observed in the absence of insecticide selective pressure, in a region without organized vector control activities reported [45]: *An. gambiae*, the most dominant in the past, was replaced by *An. arabiensis* without any known reason.

5.2. Shifts to early-evening or early-morning biting

Studies have shown that widespread ITN use increases the proportion of early bites by *An. gambiae* [46] and *An. funestus* [42,46] in Tanzania. Such shift was not observed for *Culex*

quinquefasciatus which is highly resistant against pyrethroids [46]. According to the authors [46], this suggests that for anophelines, where there is considerable killing by contact with ITNs, several years of selection has begun to produce an upward shift in the proportions of insects biting at a time when people are accessible. Also in southern Benin, a significant change in host seeking behaviour of *An. funestus* was observed after achieving a universal coverage of ITNs. The shift in biting time was here not to the early evening but to the early morning. Moreover in one locality about 26% of the *An. funestus* bites were observed after sunrise [47].

The use of ITNs resulted in a shift towards earlier biting of *An. gambiae* s.l. in Kenya [48] and Tanzania [42,49], possibly [48,49] or certainly [42] related to a species shift from *An. gambiae* to *An. arabiensis*.

In other studies however, no evidence for a shift in biting time after the introduction of ITNs or IRS was obtained for *An. gambiae* s.l. in Tanzania, Kenya, The Gambia and Nigeria [44,50–52], for *An. gambiae* the Bioko Island (Equatorial Guinea) [21], or for *An. funestus* in Kenya [44]. Widespread use of mostly untreated bed nets did not result in more early biting of *An. gambiae* [5].

Country	Vector control measure [a]	Insecticide [b]	Collection methods [c]	Species shift [d]	Shift to early-biting [d]	Shift to exophagy [d]	Shift to zoophily [d]	Reference
Benin	ITN	Deltamethrin	Indoor/ outdoor HLC	ND	Yes	Yes	ND	[47]
Burkina Faso	ITC	Permethrin	Indoor/ outdoor CDC LT	ND	ND	Not observed	Not observed	[53]
Burkina Faso	ITN	Unspecified	IRC, Odour-baited traps	ND	ND	ND	Yes	[19]
Equatorial Guinea	IRS ITN	Deltamethrin, alpha cypermethrin, bendiocarb. Unspecified LLIN	Indoor/ outdoor HLC	Not observed	Not observed	Yes	ND	[21]
Kenya	IRS	Dieldrin	ORC, IRC, LD, HLC	Yes	ND	ND	ND	[35]
Kenya	IRS	DDT	Indoor/ outdoor HLC	Yes	ND	ND	ND	[36]
Kenya	IRS	Dieldrin	IRC, ORC	Yes	ND	ND	Not observed,	[34]
Kenya	ITN	Permethrin	IRC, indoor and outdoor HLC	ND	Yes	Yes	Yes, but not significant	[48]
Kenya	ITN	Permethrin	IRC, ORC	ND	ND	ND	Yes	[54]
Kenya	ITN	Permethrin	WET, IRC, outdoor bed net traps	Not observed	Not observed	ND	ND	[44]
Kenya	ITN	Permethrin,	IRC	Yes	ND	ND	ND	[39]
Kenya	ITN	Permethrin, alpha cypermethrin, Unspecified LLINs	IRC, LD	Yes	ND	ND	Not observed	[41]

Country	Vector control measure [a]	Insecticide [b]	Collection methods [c]	Species shift [d]	Shift to early-biting [d]	Shift to exophagy [d]	Shift to zoophily [d]	Reference
Kenya	ITN, ITC	Permethrin, alpha cypermethrin, deltamethrin	Bed net traps, IRC, LD	Yes	ND	ND	ND	[43]
Kenya	ITN	Unspecified	IRC, ORC, LD	Yes	ND	ND	Yes, but not significant	[40]
Niger	ITN	Unspecified LLINs	IRC, indoor/ outdoor HLC, indoor/ outdoor CDC LT	ND	ND	Yes	ND	[37]
Nigeria	IRS	Propoxur	Indoor/ outdoor HLC, IRC	ND	ND	Yes	ND	[14]
Nigeria	IRS	Propoxur	Indoor/ outdoor HLC, IRC, ORC, WET	Not observed	Not observed	Yes	Not observed	[52]
Tanzania (Pemba)	IRS	Dieldrin	IRC, ORC, indoor & outdoor HLC	Yes	ND	Not clear	Not clear	[38]
Tanzania	ITN+IRS	Permethrin or lambda cyhalothrin, DDT	Indoor CDC LT, outdoor HLC, IRC, ORC	ND	Inconclusive	Not observed	Inconclusive	[50]
Tanzania	ITN	Lambda cyhalothrin, deltamethrin	IRC, WET, indoor HLC	ND	Yes	ND	ND	[49]
Tanzania	ITN	Majority untreated nets	Indoor/ outdoor HLC	ND	Not observed	Not observed	ND	[5]
Tanzania	ITN	Unspecified	Indoor CDC LTs, Mbita traps	ND	Yes	ND	ND	[46]
Tanzania	ITN	Unspecified	Indoor/ Outdoor HLC	Yes	Yes	Yes	ND	[42]
The Gambia	ITN	Permethrin	Outdoor HLC, IRC, indoor CDC LT, bed net searches	ND	ND	Yes	Not observed	[55]
The Gambia	ITN	Permethrin	Indoor/ outdoor HLC, IRC, WET	ND	Not observed	Not observed	Yes, but not significant	[51]

[a] ITN: Insecticide treated nets; IRC: Indoor residual spraying; ITC: Insecticide treated curtains
[b] LLINs: Long lasting insecticidal nets
[c] IRS: Indoor resting collection; ORC: Outdoor resting collection; CDC LT: Center for Disease Control light trap; HLC: Human landing collection; WET: Window exit trap; LD: Larval dipping; CMR: Capture-Mark-Recapture
[d] ND: Not done

Table 1. Review of the effect of insecticide based indoor vector control measures on malaria vectors in the Afrotropical region

5.3. Shifts to exophagy

In Nigeria, IRS resulted in a threefold increase of the proportion of *An. gambiae* s.l. biting outdoors [14,52]. Several years of vector control by IRS and later ITNs in the Bioko Island, increased the trend for outdoor biting of *An. gambiae* [21] as compared to historical data in the same region of preferred behaviour for indoor biting. Also in Tanzania, high ITN-use resulted in an increased outdoor biting for *An. funestus* [42]. In the latter study the proportion of indoor contact with *An. funestus* bites had dropped to only half of the indoor contact before widespread ITN-use. In southern Benin as well, after achieving universal ITN coverage, a higher proportion of outdoor biting was observed for *An. funestus* [47], although this was only observed in one out of two localities that were studied.

Some studies have shown that distribution of ITNs in Niger, Kenya, and The Gambia decreased the endophagic rate of *An. gambiae* s.l. [37,48,55], and to a lesser extend of *An. funestus* [37]. However, as the species of the *An. gambiae* complex were not determined in these studies, a possible reason for this decrease would be a species shift from *An. gambiae* to *An. arabiensis*.

In other studies however, no evidence for a shift to outdoor biting of *An. gambiae* s.l. due to widespread IRS or ITNs use was found in Tanzania [42,50], Burkina Faso [53] and The Gambia [51]. Also widespread use of mostly untreated bed nets did not result in a higher outdoor biting rate of *An. gambiae* [5].

5.4. Shifts to zoophily

In Kenya, ITN-use caused a shift in host selection of *An. gambiae* s.l. and *An. funestus* [54] from humans towards cattle or other animals. Similar observations were made in Burkina Faso with *An. gambiae* [19]. In other studies in Kenya and The Gambia, the use of ITNs caused only small and insignificant decreases in human blood index (HBI) for *An. gambiae* s.l. [40,48,51] and *An. funestus* [40].

The use of ITNs, IRS, or insecticide treated curtains caused no shift in host selection (or decrease in HBI) for *An. arabiensis* in Zambia [56], for *An. gambiae* s.l. in Nigeria, Burkina Faso, The Gambia, Tanzania and Kenya [34,50,52,53,55], and for *An. funestus* in Tanzania and Kenya [34,50].

5.5. Shifts to exophily

As summarized in [57], different populations of *An. arabiensis*, e.g. in the Pare-Taveta malaria scheme, Mauritius, Madagascar, Zanzibar, Nigeria and other West African localities, became either completely exophilic or, at most, remained only partially endophilic after IRS campaigns. ITN distribution reduced the indoor resting fraction of *An. gambiae* s.l. in Niger and Kenya [37,48], and of *An. funestus* in Kenya [48]. No evidence for a resting place shift after introduction of ITNs or after IRS was observed in Tanzania [50].

6. Australasian, Oriental, and Neotropical Regions

6.1. Species shifts

In the Solomon Islands, IRS in the 1960s has nearly eliminated the major malaria vectors *An. koliensis* and *An. punctulatus*, which are mainly endophagic and late-biters. The density of *An. farauti*, a more exophagic and early-biting malaria vector, remained quite high, particularly in outdoor man-biting situations [58]. The latter species is now the primary vector in the Solomon Islands, with the former major malaria vectors being totally absent. *An. hinesorum*, which is not considered a vector, has now occupied the breeding sites commonly used by *An. koliensis* [59].

In the forested hilly areas of Thailand, IRS resulted in a higher proportional decrease of *An. dirus* s.l. as compared to *An. minimus* s.l. [60]. Widespread use of IRS resulted in a different behaviour of the *An. minimus* s.l. present [61], which probably reflects a species shift from *An. minimus* to *An. harrisoni*, as also observed in Vietnam as a result of widespread use of ITNs [62]. Residual spraying did effectively control indoor resting species in Nepal such as *An. annularis*, *An. culicifacies*, *An. splendidus* and *An. vagus*. The abundance of the partially outdoor resting species, *An. fluviatilis* s.l. and *An. maculatus* s.l. also decreased markedly after the spray application, but then rebounded rapidly within 1 or 2 months after treatment [63]. ITN use in China caused a higher decrease of the endophilic and anthropophilic *An. lesteri* (syn. *An. anthropophagus*) [64] and *An. minimus* s.l. [65] than of the exophagic and zoophilic *An. sinensis*.

In British Guiana, the primary malaria vector *An. darlingi* (both larvae and adults) was rapidly eliminated by IRS, whereas larvae and adults of a zoophilic species, *Anopheles aquasalis*, a possible malaria vector, were completely unaffected [66]. In Guatemala, *An. vestitipennis* decreased in abundance in communities with a wide distribution of ITNs, while *An. albimanus* did not change. Whether this change was an effect of the ITNs could not be concluded as the study was not designed for answering that question [67].

6.2. Shifts to early biting

In Papua New Guinea, ITN distribution immediately changed the biting cycles of both *An. farauti* and *An. koliensis* from a post-midnight peak towards a pre-midnight peak [68]. Also on the Solomon Islands, intervention and longitudinal studies have shown that IRS, ITNs, or a combination of both, changed the biting cycle of *An. farauti* to an earlier biting peak [58,69,70].

IRS changed the indoor biting peak of *An. dirus* s.l. in the forested hilly areas of Thailand to one hour earlier. Outdoors, the peak remained the same, but a higher proportion bite earlier. Also for *An. minimus* s.l., a shift to earlier biting was observed [60]. In the foothills on the other hand, where *An. minimus* s.l. was the main vector, no effect of DDT was seen on the already early biting *An. minimus* s.l. population [71]. Also recent studies in Vietnam have shown that in the prolonged presence of impregnated bed nets, 45% of the *Anopheles* bites are acquired before sleeping time in the forest, and 64% before sleeping time in the village [8]. In Cambodia,

in a period when ITN coverage was still low, already 29% of the *Anopheles* bites were acquired before sleeping time [9].

Although we have not encountered studies in Latin-America with evidence for shifts to earlier biting, some studies indicated that also in this region, early biting vectors can maintain residual transmission. In an area in Brazil covered by IRS for example, blood-feeding of *An. darlingi* started at sunset, remained high during the first half of the night, and decreased gradually until early morning [72]. Also in the Bolivian Amazon, in an area with high ITN use, peak outdoor biting of *An. darlingi* occurred between 19:00 and 21:00 hours, when 48% of the total night's biting took place, and 83% of the night's biting had occurred by 22:00 hours when most local people go to bed [73].

6.3. Shifts to exophagy

On different islands of the Solomon, proportional shifts to outdoor biting (from 47% to 67%) were observed for *An. farauti* after IRS [58]. Moreover, compared to *An. koliensis* and *An. punctulatus*, the exophagic *An. farauti* population recovered completely within nine months after the spraying campaign. However, in other intervention and longitudinal studies on the Solomon Islands, the shift to outdoor biting of *An. farauti* due to ITNs and/or IRS was not so obvious [59,69].

IRS increased the outdoor biting rate of *An. dirus* s.l. [60,74], and of *An. minimus* s.l. in forested and foothill regions in Thailand [60,61]. In contrast, in another foothill region of Thailand, an initial effect of DDT was seen on the malaria transmission, but this was not sustained for this already outdoor biting *An. minimus* s.l. population [71]. Also wide scale use of ITNs caused a higher decrease in the indoor biting populations as compared to the outdoor biting populations of *An. sinensis*, *An. lesteri* (syn. *An. anthropophagus*) and *An. minimus* s.l. in China [64,65]. In Vietnam, after prolonged ITNs distribution, outdoor biting densities of the main vectors, *An. dirus*, *An. maculatus* s.l. and *An. minimus* s.l. were significantly higher than indoor biting density [8]. In Laos, in contrast, the use of ITNs did not stop *An. dirus* from entering the houses [75].

In an IRS area in Brazil, *An. darlingi* fed more frequently outdoors, whereas in earlier years before IRS this species mainly fed indoors [72]. In contrast, in Colombia, IRS did not stop malaria vectors to bite both indoors and outdoors [76]. The combined use of ITNs and IRS has preceded the collapse of a mainly exophagic *An. darlingi* population in Suriname. However, this collapse can also be attributed to an unusual, extensive flooding which coincided with the onset of the control interventions [77].

6.4. Shifts to zoophily

A significant decrease in HBI of *An. farauti* was observed immediately after the distribution of ITNs in Papua New Guinea, although this shift could be due to a slightly changed sampling method [68].

In Thailand, in the prolonged presence of DDT use in IRS, *An. minimus* s.l. exhibited a marked zoophily, whereas in villages with lower DDT pressure, no preference was observed [61],

although this apparent 'change in behaviour' could have been due to a species shift within the *An. minimus* complex as observed in Vietnam [62]. In an intervention study in India, the HBI of *An. culicifacies* was lower in areas with ITNs as compared to areas with untreated bed nets or no nets [78].

In Mexico, a much lower HBI was observed in areas where IRS was implemented as compared to historical data [79]. Also in areas covered by IRS in Brazil, *An. darlingi* was mostly zoophilic [80].

6.5. Shifts to exophily

A very low endophily rate was observed for *An. farauti* after several DDT spraying campaigns in the Solomon Islands [58].

IRS also significantly reduced the indoor resting abundance of all anopheline species except for *An. fluviatilis* s.l. in Nepal [63], and of *An. dirus* s.l. in Thailand [74]. In India, *An. culicifacies* s.l. has been observed to be highly exophilic in areas where residual spraying with DDT was widely used [81]. Also in areas with wide scale use of ITNs in India fewer *An. culicifacies* s.l. were collected indoors (resting collections) as compared to control areas. However, in this area more *An. culicifacies* s.l. were found indoor-resting in individual houses with untreated bed nets as compared to houses with ITNs, both located in the ITN-area [78]. This suggests that this mosquito population did not shift entirely to exophily, but that this behaviour mainly reflects the excito-repellent effect of the permethrin.

IRS has brought the disappearance of *An. darlingi* from the interior of houses in Brazil and French Guiana [28,80]. However, outdoor-resting still persists, either in the vicinity of the houses [80] or outside the peridomestic environment [28]. ITNs as well caused less indoor-resting in an intervention trial in Guatemala [67]. In contrast, in Mexico, after prolonged use of DDT no deterrence was observed anymore for *An. pseudopunctipennis*, with as many mosquitoes seeking shelter in sprayed huts as in unsprayed huts [82].

Country	Vector control measure [a]	Insecticide [b]	Collection methods [c]	Species shift [d]	Shift to early-biting [d]	Shift to exophagy [d]	Shift to zoophily [d]	Reference
Australasian Region								
Papua New Guinea	ITN	Permethrin	Outdoor HLC	Not observed	Yes	ND	Yes?	[68]
Solomon Islands	IRS	DDT	HLC	Yes	Yes	Yes	ND	[58]
Solomon Islands	IRS, ITN	DDT, permethrin	Outdoor HLC, indoor CDC LT, outdoor pig baited traps	ND	Yes	Not clear	ND	[69]
Solomon Islands	IRS, ITN	DDT, lambda cyhalothrin Permethrin, unspecified LLIN	Indoor/ outdoor HLC, LD, animal baited trap	Yes	ND	ND	ND	[59]
Solomon Islands	ITN, IRS	Deltamethrin, lambda cyhalothrin	Indoor/ outdoor HLC, IRC, WET, LD	ND	yes	Yes, small	ND	[59]
Oriental region								

Country	Vector control measure [a]	Insecticide [b]	Collection methods [c]	Species shift [d]	Shift to early-biting [d]	Shift to exophagy [d]	Shift to zoophily [d]	Reference
China	ITN	Deltamethrin	Indoor/ outdoor man-baited nets	Yes	ND	Yes	ND	[64]
China	ITN	Deltamethrin	?	Yes	ND	Yes	ND	In [65]
India	ITN	Lambdacyhalothrin	IRC, Indoor HLC, Outdoor Cattle collection	ND	ND	ND	Yes	[78]
Nepal	IRS	DDT, bendiocarb, malathion	Indoor/ outdoor HLC, IRC, ORC, cattle collections, LD	Yes	ND	?	ND	[63]
Thailand	IRS	DDT	Indoor/ outdoor HLC	Yes	Yes	Yes	ND	[60]
Thailand	IRS	DDT	Indoor/ outdoor HLC	Not observed	Not observed	Not observed	ND	[71]
Thailand	IRS	DDT	Indoor/ outdoor HLC, bovid-baited trap, IRC, ORC	Probably	ND	Yes	Yes	[61]
Thailand	IRS	DDT, fenitrothion	Indoor/ outdoor HLC, IRC	ND	ND	Yes	ND	[74]
Vietnam	ITN	Permethrin	Indoor/ outdoor HLC, IRC, CDC LT	Yes	ND	ND	ND	[62]
Neotropical Region								
Brazil	IRS	DDT	IRC, ORC, animal baited trap,	ND	ND	ND	Yes?	In [80]
Brazil	IRS	DDT	Indoor/ outdoor HLC, outdoor animal baited trap	ND	ND	Yes	ND	[72]
British Guiana	IRS	DDT	IRC, LD	Yes	ND	ND	ND	[66]
Guatemala	ITN	Permethrin	Indoor/ outdoor HLC, IRC, inspection of bed net surfaces, CMR	Yes?	ND	Not observed	ND	[67]
Mexico	IRS	DDT, bendiocarb	IRC, ORC	ND	ND	ND	Yes	[79]
Mexico	IRS	DDT (dieldrin before)	Entry traps, WET	ND	ND	ND	ND	[82]

[a] ITN: Insecticide treated nets; IRS: Indoor residual spraying; ITC: Insecticide treated curtains
[b] LLINs: Long lasting insecticidal nets
[c] IRC: Indoor resting collection; ORC: Outdoor resting collection; CDC LT: Center for Disease Control light trap; HLC: Human landing collection; WET: Window exit trap; LD: Larval dipping; CMR: Capture-Mark-Recapture
[d] ND: Not done

Table 2. Review of the effect of insecticide based indoor vector control measures on malaria vectors in the Australasian, Oriental and Neotropical regions

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7. Discussion

7.1. The importance of residual transmission by outdoor and early biting malaria vectors

In this chapter we have shown that outdoor and early biting malaria vectors are widespread among malaria endemic countries and, as relative shifts to outdoor, early or animal-biting and outdoor resting vectors occur due to the use of IRS and ITNs, these vectors will increasingly contribute to malaria transmission in regions with a high coverage of ITNs and IRS. However the reported shifts are not always well documented: species identification of complexes are often missing, and confounding factors such as changes of the environment, habitat, human behaviour and occupation are not considered.

In Africa, most of the species shifts observed resulted in a large decrease of the important endophagic, endophilic and anthropophilic malaria vectors, *An. funestus* and *An. gambiae*, while the more exophagic, exophilic, and/or zoophilic species *An. arabiensis* persists. Reports on such species shift are recently increasing, with most of these shifts described in East-Africa. But also in the other geographical regions, shifts in species abundances have been observed. It is however important to note that the majority of shifts described are shifts in relative abundances, where the more endophagic, endophilic and/or anthropophilic species declines more (or is being eliminated) while the more exophagic, exophilic and/or zoophilic species maintains at the same density or declines less. Only in some cases, the density of the latter species actually increases (e.g. the non-vector species *An. rivulorum* [35] or *An. parensis* [36]), probably because they take over the breeding sites of the declining species. Moreover, as also mentioned in [83], the vectorial capacity of the species predominating after the intervention does not necessarily increase, but persisting species that are malaria vectors, such as *An. arabiensis*, will be responsible for the residual malaria transmission, while the role of e.g. *An. gambiae* or *An. funestus* decreases.

Therefore, one of the most plausible reasons for species shifts to occur in the presence of ITNs or IRS is the non-uniform exposure of the different species to the insecticides, as described above. This hypothesis is supported by a study in Kenya in which the persisting *An. arabiensis* in an area with high ITN coverage had little to no pyrethroid resistance compared to the declining *An. gambiae*, with moderate to high levels of pyrethroid resistance [41,43]. Moreover, in experimental hut trials on northeast Tanzania, the mortality of *An. arabiensis* measured in experimental huts was consistently lower than that of *An. gambiae* and *An. funestus* [83], which probably is a major contributing factor to the species shifts observed in East Africa following scale up of ITNs. The authors state that, as cone tests on the nets prior to the trials produced rather similar levels of mortality among *An. gambiae* and *An. arabiensis*, the most likely explanation for lower *An. arabiensis* mortality was behavioural avoidance of treated net surfaces. As feeding inhibition in this experiment was similar for *An. arabiensis* and *An. gambiae*, outdoor blood-feeding would be the major mechanism to which *An. arabiensis* avoids contact with the ITN, as opposed to abandoning host-searching when confronted with ITNs.

Besides the species shifts, shifts to earlier-, outdoor-, and animal-biting have been observed for primary vectors such as *An. gambiae*, *An. funestus*, *An. farauti*, *An. koliensis*, *An. dirus* s.l., *An.*

minimus s.l., *An. culicifacies*, and *An. darlingi*. These shifts might also be linked to the non-random exposure of subpopulations of vectors to insecticide treated surfaces (ITNs or IRS). Several studies have indeed shown that the feeding and resting behaviour of anophelines is consistent in certain subpopulations and/or linked to certain genetic markers. Most of the studies on genetic determination of biting and resting behaviour are based on chromosomal inversions. Alleles captured within chromosome rearrangements are protected from recombination and can as such favour local adaptation by capturing sets of locally adapted genes which might lead to reproductive isolated entities or subpopulations [84]. In the Garki District in Nigeria, chromosomal arrangements in *An. arabiensis* and *An. gambiae* have been associated with exophagy and exophily [85,86] and with zoophily [87]. Exophagy and exophily were associated with the standard chromosomal arrangements 2R+^{a} for *An. arabiensis* and 2R+^{b} for *An. gambiae*, and the inverted arrangement 2Rbc for *An. arabiensis*. Moreover, the chromosome arrangements associated with indoor biting or resting are the ones adapted to drier environments, while arrangements more frequent in outdoor collected specimens are those associated with more humid environments [85]. In the Zambesi valley, 2Rc *An. arabiensis* heterozygotes were associated with exophily and zoophily [57]. In Ethiopia *An. arabiensis* heterozygotes of the 2La and/or 2Rb chromosomal arrangements tended to bite later at night than the double homozygotes [88]. Also in laboratory experiments an association between chromosomal arrangements and circadian flight activity has been found [89]: female *An. stephensi* homozygotes for the 2Rb inversion showed more activity following light-on (corresponding to early morning) as compared to homozygous females for the standard 2R+^{b} arrangement. Other field-based evidence on the existence of subpopulations showing consistent behaviour was obtained by studying behaviour of *An. balabacensis* in a capture-mark-recapture experiment in Borneo (Malaysia) [90]. This study revealed significant trends of *An. balabacensis* to be recaptured on the same host or resting site of the original capture. In contrast, a similar capture-mark-recapture study on resting behaviour of *An. gambiae* s.l. in Tanzania showed no faithful tendencies of endo- or exophily [91]: the same individuals within the *An. gambiae* s.l. population mixed indoor and outdoor resting. More recent genetic studies are based on the frequencies of enzyme polymorphisms. In the Malaysian study [90], faithfully indoor and outdoor-resting populations showed significant differences in isozyme frequencies (loci *Est-3* and *Idh-3*). Also in Burundi, isozyme frequencies were significantly different between in- and out-door biting *An. arabiensis* (locus *Mdh-2*) and in- and out-door resting *An. gambiae* (*Mpi* and *Got-2* loci) [92]. Such differences were not observed for *An. gambiae* in Burkina Faso [93]. Moreover, mosquitoes carrying a specific genotype [93] or chromosome karyotypes [87] were found to be significantly more infected with sporozoites, suggesting the occurrence of subpopulations having different vector behaviours. These independent genetic studies, either based on karyotyping or on genotyping, provide evidence that active choice for the best place, time or host to bite, or the best place to rest can be associated with specific genotypes. This suggests the existence of subpopulations characterized by specific behavioural patterns which implies a non-uniform exposure to IRS or ITNs. Selection of specific behavioural patterns can then not be excluded.

However, other mechanisms can also explain these kinds of shifts. More early biting could occur as females that fail to obtain a blood meal during the previous night, might be more likely to commence host seeking in the early evening [44]. By disrupting the feeding behaviour,

the ITNs would increase the length of the oviposition cycle of the overall population [68]. This mechanism could explain the immediate change in biting cycles of both *An. farauti* and *An. koliensis* after ITN distribution in Papua New Guinea. Both species shifted from a post-midnight biting peak towards a pre-midnight peak [68], with an extended oviposition cycle. Also in the Solomon Islands, the oviposition cycle was extended from 3 to 4 days due to ITN use, possibly explaining the higher tendency for early biting observed in the village with ITN use [69]. Shifts to outdoor biting by *An. farauti* also occurred immediately after DDT spraying [58]. This first effect would be caused by the deterrent effect of DDT, while only in second instance the endophilic fraction of *An. farauti* is being killed. Moreover, compared to *An. koliensis* and *An. punctulatus*, the *An. farauti* population recovered completely within nine months after the spraying campaign, indicating that this change of behaviour is due to a plastic response to the deterrent effect of DDT. Moreover, it has been shown that the occurrence of a shift in host selection does not necessarily reflect a selection of a more zoophilic vector subpopulation, but can also indicate plasticity in host selection. The *An. gambiae* population in Burkina Faso that showed a high proportion of cattle feeding (HBI of only 40%), had an innate preference for humans (88%) in a choice experiment using an odour-baited trap [19]. The weak accessibility of humans due to the use of ITNs, forces the mosquitoes to feed on cattle. According to the authors of the study, this suggests that in this area a plastic foraging strategy could provide greater benefits than a specialist strategy for this species.

Regardless of the mechanism that causes these behavioural shifts, the case studies show that in several areas the proportion of outdoor-, early- and/or animal biting primary vectors are relatively increasing, which will then be responsible for residual transmission. Moreover, in a similar way, transmission by 'secondary' vectors that have outdoor or early biting behaviour might become more important than transmission by primary vectors in contexts of high coverage of ITNs and IRS. In a malaria endemic region of Thailand, one specimen of the Barbirostris Subgroup (*An. barbirostris*/*campestris*) was found to contain *Plasmodium* oocysts, in the prolonged absence of the main malaria vectors, showing that *An. barbirostris* s.l., an outdoor biting mosquito [94], might be responsible for maintaining malaria transmission in the absence of the main vectors [95]. As secondary vectors are often less anthropophilic, and might be more exophagic and early biting, planning of vector control should also take into account their behaviour. Moreover, as pointed out in [8], secondary vectors might be better vectors of *P. vivax* as compared to *P. falciparum*, as the extrinsic incubation period of *P. vivax* is shorter. In British Guiana, for example, *An. aquasalis*, a mostly zoophilic and exophilic mosquito species breeding in brackish water, was vector of several Vivax malaria outbreaks after *An. darlingi* was eliminated by DDT spraying [96]. Also more recently in Vietnam, *An. sawadwongporni*, a very early biting secondary vector, was found positive for *P. vivax* [8].

7.2. ITNs and IRS are very effective, but additional measures are needed for reaching malaria elimination

ITNs and IRS have been shown to have a large impact on malaria infection and disease [97,98]. Moreover, several entomological studies have also shown that where the vectors are mostly endophagic, endophilic and anthropophilic, ITNs and IRS are very effective in reducing their

population density. This was for example shown for *An. minimus* in India [99] and for *An. dirus* in Laos [100], both of them being anthropophilic, indoor- and late-biting in the respective study sites. A recent study in Zambia also showed that even at a high coverage of ITNs and IRS, the highest probability for malaria transmission based on human and vector behaviour, still occurs indoors [101], making ITNs and IRS valuable tools.

ITNs can also have an effect on malaria transmitted by more zoophilic and exophagic mosquitoes. In Sao Tomé for example, where *An. gambiae* is zoophilic and very exophagic, increased bed net use decreased the malaria prevalence in both bed net users and non-users [102]. The differences in prevalence between users and non-users were greatest in children under 5 years old, who are more likely to use the bed nets in the evening, showing that indeed the bed nets were the cause of the decrease. However, in older age groups, that are more likely to remain outside in the evening, no such difference was observed. Moreover, even at an almost 80% ITN coverage, still a 30% malaria prevalence was observed among bed net users. This means that, as expected, a part of transmission by these zoophilic and exophagic mosquitoes could not be prevented by ITNs [102]. Also in other parts of the world it has been shown that ITNs are less performing in areas with outdoor biting or resting vectors, for example in Peru and Nicaragua [11]. In the Garki District (Nigeria), the impact of the IRS campaign with propoxur was related to the prespraying ratio between the man-biting density and the indoor-resting density and to intraspecific cytogenetic variation [52]. Moreover, as reviewed in [103], even low levels of exophagy, exophily or zoophily may attenuate the impact of ITNs and IRS because this allows mosquitoes to obtain blood while avoiding fatal contact with insecticides.

As we have shown that outdoor-, animal- and early biting behaviour, as well as outdoor resting behaviour is widespread among malaria vectors all over the world and might be increasing as a result of widespread IRS or ITN use, there is an urgent need for additional control measures tackling malaria transmission by these vector populations [103–106]. In other words, there is a 'gap' in protection, not only before sleeping time, but also for people that remain outdoors during the night (Figure 2) and this gap needs to be tackled by additional vector control measures. There are many ways of additionally reducing host-vector contact, including the use of topical repellents, spatial repellents, insecticide treated clothing, long lasting insecticidal hammocks, etc. Recently much research is carried out on the effectiveness of these kind of tools. For example, in the Bolivian Amazon, where the primary vectors *An. darlingi* has a peak biting activity before sleeping time, a household based cluster randomized trial has shown that the combined use of a topical repellent (para-menthane-3,8-diol, PMD) and ITNs can reduce the incidence of malaria by 80%, which was only significant for *P. vivax* and not for *P. falciparum*, as compared to the use of ITNs alone [107]. DEET-based repellents also had an additional protective efficacy against malaria disease in a small scale community based trial in India [108], and DEET-based repellent soap against *P. falciparum* malaria in a household randomized trial in a refugee camp in Pakistan [109]. In an ongoing study in Cambodia, Picaridin based repellents are shown to provide a protection of more than 90% against the bites of the main malaria vectors *An. dirus* and *An. minimus* (MalaResT project led by ITM-Antwerp, preliminary results). Whether the mass use of this repellent will result in a decrease of malaria infection is currently under investigation using a cluster-randomized controlled trial in

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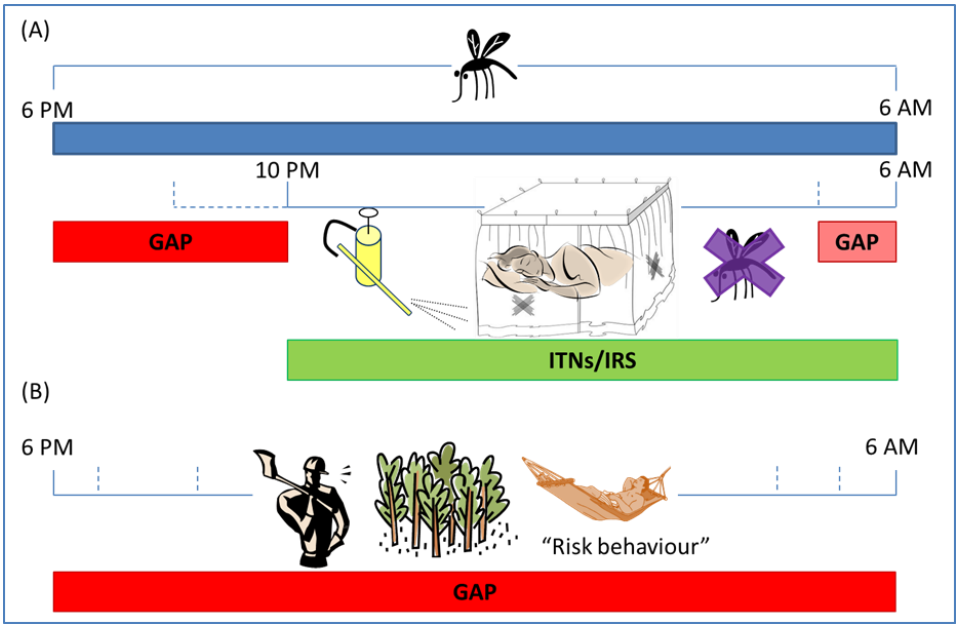

Figure 2. Protection 'gap' when only indoor insecticide-based vector control measures are applied. Anophelines generally bite between 6pm and 6am. ITNs will only protect from infective bites that are acquired indoors, and during sleeping time. IRS only target mosquitoes that rest indoors. Therefore, there is a gap in protection both indoors and outdoors before and after people go to bed (A), but also for people conducting outdoor activities during the night (i.e. 'risk behaviour') (B).

Ratanakkiri province in Cambodia. In a refugee camp in Kenya, permethrin treated clothing and blankets reduced malaria infection significantly [110]. In Southeast Asia, long lasting insecticidal hammocks have been shown to be effective against malaria disease [111] and against *An. minimus* bites, but not *An. dirus* bites [112]. For zoophilic mosquitoes, intervening in the host-vector contact could be more efficient by focusing on its preferred hosts, e.g. by insecticide treatment of cattle. However, killing partly zoophilic mosquitoes in sufficient numbers to suppress malaria transmission would require high protective coverage of both human and animal blood sources [104]. Moreover, it has been observed in Ethiopia that more than 90% of the blood meals taken by zoophilic vectors were taken from the legs of cattle [113], which are more difficult to treat.

Alternative personal protection measures are also of interest for people that work or reside in the forest, a risk area of malaria transmission in Southeast Asia [114]. For temporary shelters in the forest, insecticide treated plastic sheeting could be useful as this has proven to be effective in protecting against malaria disease in emergency camps [115]. Their effectiveness will rely both on their repelling effect and their killing effect, and whether mosquitoes will rest on this sheeting. Alternatively, other more accepted insecticide treated bed net-designs (V-shaped

Tool	Mosquito behaviour that is targeted				Personal (P) or community (C)[b] protection
	Time of biting (E/N)[a]	Host preference (A/Z)[a]	Place of biting (I/O)[a]	Place of resting (I/O)[a]	
Tools relying on host-vector contact					
ITNs	N	A	I	I	P & C
Long lasting insecticidal hammocks & other net designs adapted to outdoor conditions	(E &) N	A	O	O	P & C
Insecticide treated plastic sheeting for shelters in the forest	E & N	A & Z	I & O	O	P
Personal protection including Topical & spatial repellents, Insecticide treated clothing	E & N	A	I & O	I & O	P & C*
Insecticide treatment of cattle	E & N	Z	I & O	I & O	C*
Tools not relying on vector-host contact					
IRS	E & N	A & Z	I & O	I	C
Larval source management	E & N	A & Z	I & O	I & O	C*
Toxic sugar baits	E & N	A & Z	I & O	I & O	C*
Treatment of outdoor resting places, e.g. with fungal biopesticides	E & N	A & Z	I & O	O	C*

[a] E: Early evening & morning biting; N: Night biting; A: Antropophilic; Z: Zoophilic; I: Indoor; O: Outdoor
[b] Community protection can only be achieved if the coverage of the intervention is large enough.
* Community protection is assumed or shown in a limited number of studies, but more evidence is required for confirmation of community protection.

Table 3. Vector control tools and their targets.

nets, long lasting insecticidal hammocks, etc.), could provide protection for people staying in the forest during the night.

The more zoophilic, exophagic, or early biting a mosquito species or population, the more personal protection will act simply by blocking host-vector contact (through lethal or repellent effects). As shown by a mathematical model, malaria transmission involving zoophilic vectors (with 10% feeding on humans) can only be significantly decreased if the personal protection measures confer high levels of individual protection to users (80%) and be used by the majority of human population (80%) [116]. Therefore, the success of any intervention in this context will depend on its entomological efficacy, but also on the human behaviour, including acceptance and adherence to the preventive measures within the community. In São Tomé for example, many people watch communal television outdoors, posing them at risk for early-evening malaria transmission [117]. In Thailand, people do not take their ITN from the village to their farm plot [118]. Also in Vietnam, people often combine living in the village with a second home at their fields located in the forest [119], creating other malaria control needs, such as, for example, long lasting insecticidal hammocks. Taking into account human behaviour when adapting vector control strategies will then be crucial. In Bioko Island (Equatorial Guinea) for example, an increased trend of outdoor biting was observed for the main malaria vector *An. gambiae* [21]. However, the main malaria risk group, namely children under 15 years old, rarely

stay outdoors when it is dark, and there is no evidence that children who report to stay outdoors during the night are at higher risk for malaria infection as compared to those who do not [120]. Implementing control measures that target outdoor biting mosquitoes in this age group would then provide no additional benefit and would be a waste of resources, as personal protection tools might be very expensive to implement.

Also other tools not relying on the host-vector contact can supplement ITNs and IRS as they are not specific for indoor biting and indoor resting mosquito populations [105,106]. Vector control tools could for example target key environmental resources such as the aquatic larval habitat, sugar sources, and resting behaviour. Very little is known about how to manipulate these environmental resources so that malaria transmission is interrupted [105]. Knowledge on vector ecology and behaviour therefore remains crucial. However, despite large knowledge gaps, several examples exist of malaria control by targeting non-blood meal related steps of the mosquito cycle. Larval source management has indeed shown to be effective where vectors breed in large water bodies [121]. However, when larval habitats are more dispersed and not permanent, this approach is considered less feasible. Renewed attention has been given to larval source management as complementary tool to ITNs as recent studies in Africa have shown that it provides substantial additional protection with a high cost-effectiveness in specific settings [122]. Moreover, other innovative ideas combined with knowledge on the vector behaviour can lead to successful vector control. Toxic sugar baits for example were successfully used in a targeted way for the control of the cistern dwelling malaria vector *An. claviger* in the desert oases of Israel [123]. Fungal biopesticides also have the potential to significantly reduce densities of malaria vectors [124] as well as associated malaria transmission [125]. These fungi could be delivered through outdoor odour-baited stations, and in this way slowly eliminate a high proportion of outdoor-resting vectors [126].

8. Conclusion

For malaria eradication to succeed, all elements in the transmission cycle must be sufficiently targeted. With the current vector control tools, only indoor- and late-biting, and indoor-resting vectors are tackled. In this paper, we have shown that there is a 'gap' in protection, not only before sleeping time, but also for people that remain outdoors during the night. Moreover, by describing different shifts in vector species, and vector behaviour within species or species complexes, we have shown that the importance of this gap can increase as a result of widespread ITN or IRS use. Therefore, to eliminate residual malaria transmission, additional vector control tools will be needed. These new vector control tools should be designed to target outdoor and early feeding mosquitoes. Moreover, they should be accessible and acceptable for the populations at risk. A specific mosquito behaviour assuring its vectorial status is only relevant in relation to a specific human behaviour and the relation people have with their surrounding environment. Interrupting malaria transmission may than require different combinations of mosquito control methods addressing each mosquito behaviour at risk for transmission, but also taking into account possible changes in soil occupation, housing conditions, sleeping habits, and outdoor occupation. In conclusion, there is no 'silver bullet'

in vector control and malaria prevention. New paradigms for controlling and/or interrupting malaria transmission should then be explored for their protective efficacy and adapted to the local context for a good efficiency. Although implementation of such new approaches might be very expensive, they will be crucial if malaria elimination is the final aim.

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