



Behavioural adaptations of mosquito vectors to insecticide control

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Behavioural resistance to insecticides may be an important factor restraining the efficacy of vector control against mosquito-transmitted diseases. However, our understanding of the mechanisms underlying such behavioural resistance remains sparse. In this review, we focus on the behavioural adaptations of mosquito vectors in response to the use of insecticides and provide a general framework for guiding future investigations. We present our review of vector behaviour in the field and a conceptual classification of behavioural adaptations to insecticides. We emphasise that behavioural adaptations can result from constitutive or induced (i.e. phenotypically plastic) traits. Lastly, we identify gaps in knowledge limiting a better understanding of how mosquito behavioural adaptations may affect the fight against vector-borne diseases.

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Introduction

Control of mosquito-borne diseases mainly relies on the use of insecticide-based tools. The increased coverage in the use of insecticide-treated nets (ITNs) in sub-Saharan Africa since the year 2000 is an example of a massive and efficient intervention against malaria [1]. Arboviruses outbreaks can also be controlled through insecticide use [2]. However, using such vector control methods reduces mosquito fitness, and in response, mosquitoes have evolved resistance mechanisms threatening the continued efficacy of insecticide-based strategies.

Understanding the mechanisms of insecticide resistance is key to predicting how resistance may emerge, spread

and hinder control interventions. To date, several physiological resistance mechanisms to insecticides, including biochemical (e.g. target site modifications and metabolic resistance) and morphological (e.g. cuticular thickness) have been described, discoveries aiding the design of resistance management strategies [3,4]. Behavioural resistance is also emerging as an important topic of research [5,6] due to its potentially detrimental effect on the efficacy of insecticides in vector control [7–9,10*] and the resulting increase in residual transmission it would induce [5].

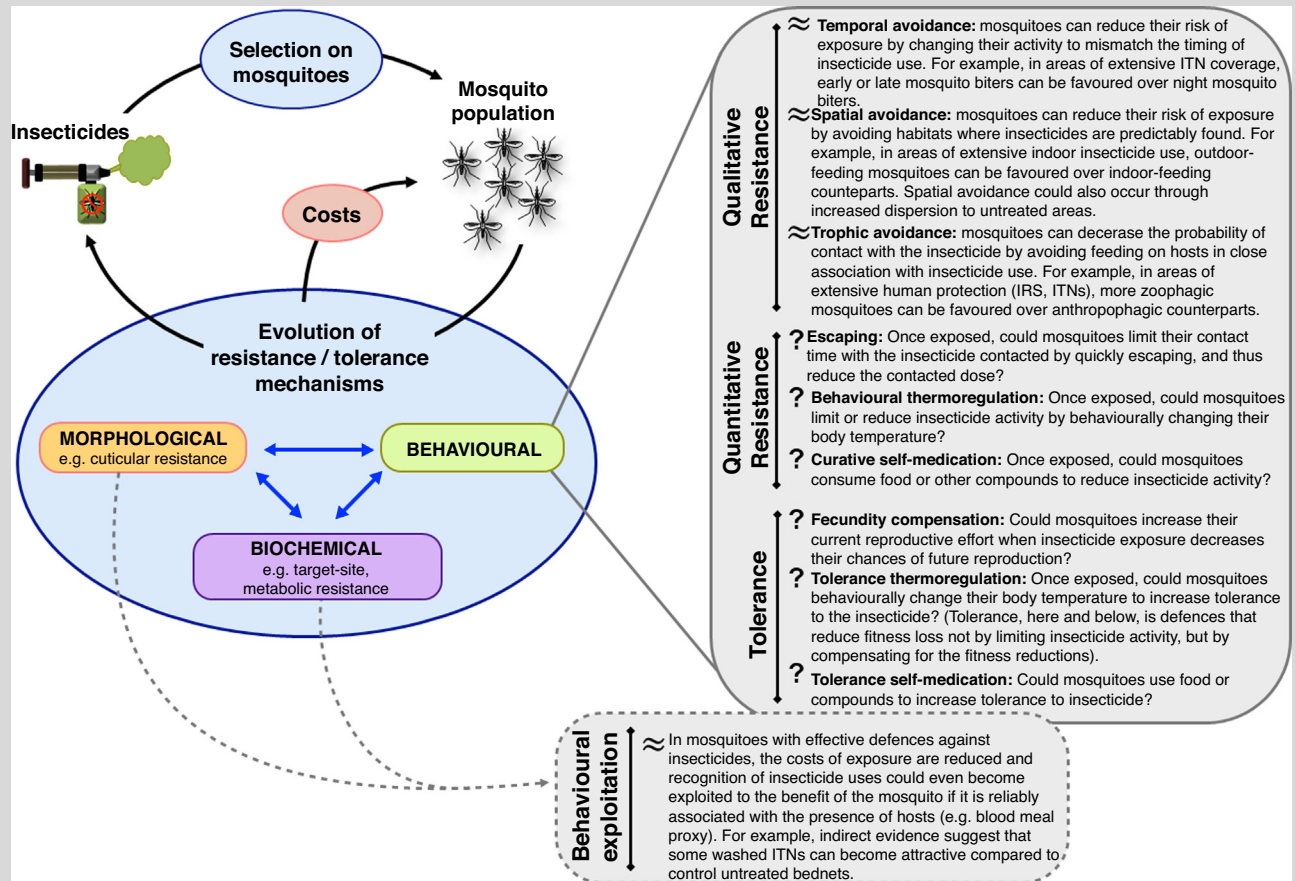
In this review, we focus on the behavioural adaptations of mosquitoes in response to insecticide-based vector control tools. We first propose a framework for organising and investigating such behaviours and review the supporting evidence. Secondly, we highlight that resistance behaviours may be constitutive or phenotypically plastic inducible changes in behaviour, and identify clues for distinguishing between them. Finally, we discuss research perspectives to decipher among behavioural defences in mosquito vectors.

Classification of behavioural adaptations to insecticides

There is a wide range of behaviours that mosquitoes could adopt to prevent or reduce the negative consequences of insecticides. We propose a conceptual classification of these behavioural adaptations inspired by the classification of insect responses to natural enemies [11**] (Box 1). The first line of defence is *qualitative behavioural resistance* whereby mosquitoes avoid (either temporally, spatially or trophically) contact with insecticides. In areas with extensive use of ITNs or indoor residual spraying (IRS), selection may favour foraging earlier in the evening or later in the morning, times when the human hosts are not protected by bednets or indoor treatments [7]. Increased outdoor host-seeking and/or zoophagy are also consistent with mosquito behavioural adaptation to the use of ITNs and IRS.

Behavioural observations in the field following implementation of ITNs and IRS have provided support for the existence of such behavioural modifications [5]. Temporal avoidance in the form of a behavioural shift from night to evening aggressiveness has been observed in *Anopheles farauti* on the Solomon Islands [12] and Papua New Guinea [13], *Anopheles funestus* in Tanzania [14], and both *An. funestus* and *Anopheles arabiensis* in Kenya [15]. In

Box 1 Expanding the field of mosquito insecticide resistance



Insecticides reduce mosquito fitness, and in response, selection has favoured genotypes with effective defence mechanisms, including both resistance and tolerance to insecticides. Much work has focused on understanding physiological (biochemical and morphological) defences, but mosquitoes can also express behaviours that protect against insecticides. These 'anti-insecticide' behaviours can be categorised into three possible mechanisms: (1) qualitative resistance which prevents or limits the probability of contact with the insecticide; (2) quantitative resistance, which stops, limits or reduces insecticide action once contact has occurred; and (3) tolerance, which does not prevent *per se* the insecticide exposure or limit its action, but instead alleviates fitness reductions caused by the insecticide. A fourth category of adaptive behavioural response to insecticide use, coined 'behavioural exploitation,' is proposed. This is not a defence mechanism. Instead, behavioural exploitation is envisioned as a secondary behavioural adaptation following the evolution of physiological (i.e. biochemical and morphological) resistance (grey dashed lines) whereby mosquitoes exploit recognition of the insecticide to their benefit. This schematic representation also highlights that the costs of resistance mechanisms (defined as the negative fitness effect of resistance in the absence of the insecticide) should not only focus on biochemical resistance but should also include other defence mechanisms, such as morphological and behavioural defences. The costs qualitative behavioural resistance, for instance, remain currently unquantified. Finally, blue arrows show possible associations between phenotypic defences. For example, if defence is costly, trade-offs between physiological and behavioural defences are expected. For example, individuals with highly efficient behavioural defences may not need physiological resistance, and vice versa. '≈' indicates the existence of field studies providing some, more or less convincing, support to these hypotheses; whereas '?' indicates undescribed cases.

Benin, peak biting time in *An. funestus* was delayed to the early morning [16]. Examples of spatial avoidance come from *Anopheles gambiae* s.l. in Bioko Island [17] and *An. funestus* in Tanzania [14], which displayed increased outdoor host-seeking following implementation of IRS and ITNs respectively. Finally, trophic avoidance with a shift towards increased zoophilic behaviours was reported in *Culex quinquefasciatus*, *An. funestus* [18] and in *An. gambiae*

s.s. in areas of high bednet coverage in Kenya [18,19] and in *Anopheles fluviatilis* and *Anopheles culicifacies* in India where IRS had been implemented [20].

As insecticides become more widely implemented, it is likely that mosquitoes may not be able to avoid contact. In this scenario, if mosquitoes are not immediately killed after insecticide exposure (e.g. sublethal doses or

physiologically resistant genotypes), then they could theoretically evolve *quantitative behavioural resistance* (Box 1). As shown in diverse insect species, behavioural quantitative resistance may include escape reactions that reduce contact duration with the insecticide [21], resistance-promoting behavioural thermoregulation [22,23], and/or curative self-medication [24,25] (Box 1). Similar to biochemical metabolic resistance, which lowers the amount of insecticide reaching target sites, these behaviours could limit the insecticide's direct adverse effects following non-lethal exposures.

If mosquitoes cannot avoid exposure (qualitative resistance) or reduce the direct effects of the insecticide when exposure does occur (quantitative resistance), then they could still limit their fitness loss through *behavioural tolerance* (Box 1). This could occur by altering behaviours associated with offspring production that increase their current reproductive effort, such as i) maximising nutrient intake quality (e.g. blood feeding choice), ii) minimising energy expenditure (e.g. feeding rates and resting times), or iii) adjusting egg production and allocation patterns [26]. Similar to quantitative behavioural resistance, tolerance could also occur through behavioural thermoregulation if mosquitoes rest at some specific temperatures [22,23] or by self-medication if mosquitoes feed on specific diets (e.g. nectars) [24,25] that allow them to maintain health despite insecticide exposure.

While we fully concede that the two post-exposure lines of defence (i.e. quantitative behavioural resistance and tolerance to insecticides) have yet to be observed in mosquitoes, they fully deserve to be considered as some evidence has been found in other insect species [11^{••},24,25].

Given the widespread occurrence of physiological resistance in mosquito populations, the study of behavioural defences should not be considered independently. In this context, a fourth category of behavioural adaptation can be introduced: *behavioural exploitation* (Box 1), whereby physiologically resistant mosquitoes may use the recognition of insecticide-based control tools as a proxy for host presence. Some experiments and field observations are consistent with such behavioural exploitation of ITNs by physiologically resistant mosquitoes. In a laboratory study, physiologically resistant mosquitoes were preferentially attracted to hosts under permethrin-treated nets compared to those under untreated nets [27]. Additionally, a retrospective analysis of experimental hut trial studies found evidence that two WHO-recommended ITNs are attractive to wild *An. gambiae s.l.* after multiple washings [28^{••}]. Similarly, a review on the efficacy of ITNs reported 55 deterrence values (defined as the reduction of entry into experimental huts in the presence of an ITN relative to control huts with untreated nets) from 17 articles. Thirteen (24%) of the deterrence values (from seven articles) were negative,

suggesting the possibility of attractiveness [29]. Negative deterrence values have been reported more recently [30,31] suggesting that behavioural exploitation may be associated with different types of ITNs.

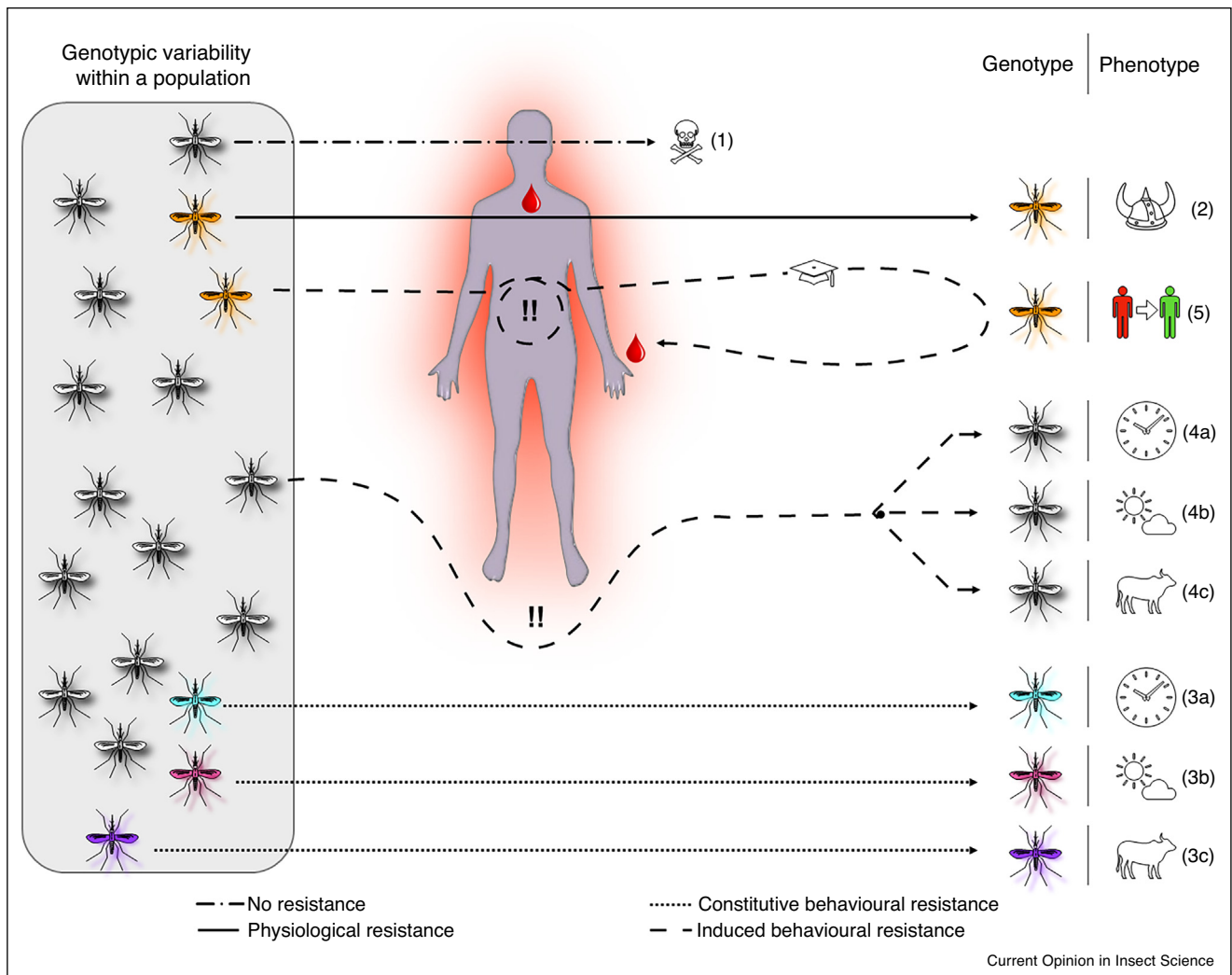
Constitutive versus inducible behavioural resistance traits to insecticide

Provided there is sufficient genetic variation in *constitutive behavioural resistance traits* and/or *inducible behavioural resistance traits*, they can adaptively evolve in response to selection pressures imposed by insecticide tool use. Constitutive resistance traits occur when genetic variants spread through the population over generations, whereas induced resistance traits (aka plastic traits) occur within a generation. Phenotypic plasticity, the ability of a given genotype to produce different phenotypes in response to different environmental conditions, can indeed allow organisms to quickly respond to environmental changes by producing better matching phenotypes. Theoretical and experimental studies suggest that when environmental conditions are variable (e.g. the risk of contacting the insecticide is unpredictable or variable, perhaps because of heterogeneous ITN coverage, etc.), the evolution of phenotypic plasticity (here inducible behavioural resistance) is expected; whereas in constant conditions (e.g. high overall risk of contact with an insecticide, widespread ITN coverage, etc.), constitutive traits (here constitutive behavioural resistance) will be favoured [32,33]. Nonetheless, constitutive and induced resistance traits are not mutually exclusive; they can co-exist in a given population. In other words, at the individual level, some behavioural resistance traits can be fixed (e.g. early biting) while others plastic (e.g. zoophagy); and at the population level, some individuals may display constitutive resistance traits while others display plastic resistance traits.

The potential behavioural responses presented above for qualitative and quantitative resistance, behavioural tolerance and exploitation can result from the expression of either constitutive or induced behavioural traits. In Figure 1 we illustrate the constitutive versus induced nature of these behavioural traits in the presence of insecticide-based vector control measures implemented in the field (Figure 1). Most of the behavioural resistance phenotypes thus far observed in the field fall into the category of qualitative behavioural resistance (shifts in biting time/site, shifts of bitten hosts), although some observations are consistent with potential behavioural exploitation of insecticides (cases of negative deterrence of ITNs). While some studies are directly or indirectly informative about the potential constitutive or inducible nature of the resistance traits (see below), in many cases it remains difficult to distinguish the origin of the observed behavioural phenotypes.

Behavioural shifts observed in the field can be grouped in relation to i) changes in spatiotemporal biting behaviour,

Figure 1



Schematic representation of the observed mosquito phenotypic responses against insecticides in the field.

Given a genetically variable mosquito population, host-seeking individuals may express different phenotypes when facing insecticides (red halo) depending on their genetic background and their behavioural plasticity. (1) Mosquitoes sensitive to the insecticide will be killed after exposure/contact. (2) Physiologically resistant mosquitoes will encounter insecticides, but their behaviour will be relatively unaffected, being eventually able to blood feed (red drop). (3) Constitutive behavioural resistance mechanisms will favour individuals with genetically determined behaviours that reduce or eliminate contact with control tools. For instance, a shift in biting time (3a; clock), exophagy (3b; sun/cloud) or preferential zoophagy (3c; cow). (4) Individuals with induced behavioural resistance mechanisms must first recognize (!!) control tools, triggering a deterrence reaction, which is followed by adaptive behavioural modification, for example by modulation of biting time (4a; clock), increased exophagy (4b; sun/cloud) or increased zoophagy (4c; cow). When mosquitoes possess physiological resistance to the insecticide, recognition could trigger an attractive effect, (5) if mosquitoes learn (hat) the presence of the insecticide tool is a reliable indicator of host presence.

ii) changes in host preference, and iii) the sensory detection of the control tools implemented.

The first group (i) refers to changes in biting rhythms and the degree of exophagy or endophagy. These spatiotemporal shifts in biting behaviour are generally observed together because of the confounding effect that humans are usually outdoors in evenings and mornings whereas they are indoors at night, making difficult to distinguish the underlying cause of the behavioural shift. Circadian

activity in mosquito vectors is known to be under genetic regulation [34–36] with olfactory functions, essential for host seeking, being adjusted by daily rhythms [37,38]. These facts provide a plausible scenario for the possible selection of constitutive behavioural resistance traits related to biting-time. However, specific variants associated with biting time have not yet been identified [39], and a potential biting time shift resulting from behavioural plasticity (induced resistance) cannot be excluded. The genetic determinants possibly regulating

shifts from endophagy to exophagy are even less understood and as is the potential role of phenotypic plasticity in spatial behaviour in mosquitoes [40*].

The second group of responses expected to be favoured by insecticides (ii) refers to the shifts in host preference. Mosquito species are often described as being either generalists or specialists depending on the fidelity of their host preference [41]. The preference of mosquitos for one particular host over another may be regulated by genes involved in the chemosensory detection of hosts [40*,42,43]. Thus, between-species differences in host preference are genetically based. However, the presence of within-population genetic variation is required for the evolution of potential host shifts following the implementation of insecticides as control measures. It is reasonable to expect that highly specialised anthropophilic individuals will be more exposed to insecticides than individuals searching for animals outdoors. Genetic selection of anthropophilic preference [44] and identification of genetic variants for host preferences [45] provide support for the idea that selection in the context of vector control through insecticides could cause the evolution of a behavioural shift for preference of alternative hosts in natural mosquito populations (i.e. constitutive behavioural resistance). In contrast, there are also studies showing host preference modulation due to changes in environmental conditions (e.g. host availability) [46] and past experiences [47]. The formation of memory as a consequence of past experiences may create a more durable shift in the individual as long as the behaviour is reinforced [48]. Indeed, it has been shown that mosquitoes can modify their behavioural responses to visual and olfactory stimuli thanks to both appetitive and aversive associative learning [49–51,52**,53]. If so, associative learning, a form of phenotypic plasticity, could play an important role in restructuring host choice preferences in response to insecticide exposure.

Lastly (iii), the existence in the population of variation in the ability of individuals to detect and perceive insecticides as noxious will determine their level of exposure. Thus, the adaptive evolution of neurophysiological abilities to detect insecticides, either upon contact or from a certain distance, would significantly reduce the impact of insecticides through qualitative or quantitative behavioural resistance or even behavioural exploitation, and provide a means for the expression of both constitutive (e.g. escaping) and induced behavioural responses (e.g. alternative host choice, etc.) (Box 1, Figure 1). It has been suggested that the olfactory system is capable of detecting some of the most commonly used pyrethroid insecticides used on ITNs from a distance [54–56] although this assertion remains controversial because of the non-volatility of the molecules and the divergence of results depending on the experimental design [57]. If mosquitos are truly capable of smelling insecticides, it is

possible that physiologically resistant individuals may become attracted to insecticides either through learning [53] or through genetic changes of insecticides hedonic sensory valence [58] because of the association with host presence. In contrast, detection of insecticides upon contact is commonly observed through measures of irritancy [59]. Mosquitoes able to escape a treated surface before acquiring a lethal dose are expected to be favoured over counterparts expressing a slower escape reaction. While there are to date no field observations of such quantitative resistance, experimental evolution of quick escapers [21] suggests its potential existence.

Conclusions and perspectives

This review updates our current understanding of behavioural resistance to insecticides in mosquito vectors. The mechanisms underlying the observed behavioural shifts and the extent of their costs remain poorly known. Because behavioural resistance in mosquito vectors may have important and potentially severe epidemiological consequences, it is worth shedding light on these phenotypes and initiating studies deciphering their underlying mechanisms and quantifying their fitness benefits and costs. The proposed theoretical classification of behavioural adaptations offers a framework for investigations. For instance, we list several possible behavioural adaptations that may be expressed in mosquito populations in response to insecticide pressure. While some of these behavioural resistance traits may appear speculative (e.g. quantitative resistance and tolerance), examples have been described in other biological systems and hence may represent promising future research avenues. Moreover, behavioural exploitation could have a potentially dramatic impact on the efficacy of vector control if mosquitoes become able to use insecticides as a proxy for bloodmeal source, resulting in the control intervention having the unintended consequence of heightening contact with vectors.

Behavioural adaptations may result from constitutive or inducible traits and their selection will depend on the constancy and intensity of insecticide use in a given mosquito population. In order to identify the genetic determinants of these traits, genomic analysis searching for signatures of selection in the genomes of mosquito vectors and their sibling species sequenced in the last few years [60**] may become valuable. Regarding the interest of entomologist/epidemiologist community in behavioural resistance, we are optimistic that future research will rapidly provide meaningful insight on the behavioural adaptations of mosquitoes to vector control tools and that these insights will help to adapt control strategies in the fight against vector-borne diseases. Finally, physiological and behavioural resistance may likely coexist in natural mosquito populations and it will be important to study the possible trade-offs and associations between these different protective strategies.

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Conflict of interest statement

Nothing declared.

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