**Working Title: Is insect control essential for sustainable control or elimination of infectious diseases?**

Insect control has a massive impact on our ability to reduce human mortality from a range of infectious diseases, but the extent of this is poorly documented and understated. Co-evolution of insects, humans and the parasites, such as malaria, that have established their niche circulating between the two hosts, go back centuries. Other disease agents, many contained within the neglected tropical diseases (NTDs), or arboviruses, such as Zika, are zoonoses that have more recently made the transition from animal reservoirs into man.

Prevention, diagnosis and treatment of these vector borne diseases is complex. Major reductions in transmission require multiple different interventions, especially in the high transmission areas where conditions are optimal, or when epidemics are triggered. It when dealing with a clinical problem to underestimate the role that vector control could, should and does play in preventing human morbidity and mortality. Concerted efforts to reduce malaria in Africa in the last two decades have benefitted from better diagnosis, new combination drug therapy and massive scaling up of pyrethroid insecticide treated nets (LLINs) and indoor residual spraying (IRS). The timing and scale of the changes allowed accurate estimates of the relative contributions of the different interventions. Many were surprised that vector control account for 81% of the gains (1). Similarly, increasing IRS coverage from 60 to 80%, is predicted to have a much greater impact on reducing the time taken to eliminate Visceral leishmaniasis than halving the time taken to start treatment from 40 – 20 days, although the greatest benefit comes from combining the two interventions (2).

It follows that if insect control fails human suffering will increase. Heavy reliance on any single intervention will lead to the selection of resistance. This is true for insecticides and drugs. The international community has adopted the use of malaria combination drug therapy to slow the selection of resistance, but the pyrethroid insecticides have been left exposed to intense selection. Pyrethroid resistance, almost non-existent in the major malaria, Zika and dengue vectors in the 1990s, is now the norm, and the situation is rapidly degenerating.

Four recent international workshops have concluded that our ability to sustain and further reduce child mortality due to malaria will be compromised unless resistance is addressed. The impact that pyrethroid resistance is already having on the efficacy of IRS and malaria prevalence in several countries was highlighted. This includes a resurgence of malaria in South Africa, co-inciding with the re-emergence of pyrethroid resistant *Anopheles funestus* (3).

The problem of resistance management is multifaceted, with a series of issues that need to be tackled. To sustain LLIN and IRS use we need new public health insecticides. The over-reliance on pyrethroids, a class of insecticides first brought to market in the 1970s, is a direct result of market failure. Public health insecticides from 1950 – 1980 were re-purposed from agriculture. When the target product profile for insecticides used on crops switched from rapid acting broad spectrum nerve poisons, used as contact insecticides, to selective stomach poisons delivered through the plants, the pipeline for new public health insecticides stopped. This was recognised in 2005, with the formation of the Innovative Vector Control Consortium (IVCC), which rapidly evolved into a product development partnership between industry and academia [4]. Funded by philanthropic and government donations, the IVCC sought to dramatically improve the longevity of IRS formulations and establish de novo a new pipeline for public health insecticides that could be used for both LLINs and IRS. This initiative has been extremely successful, generating new non-pyrethroid and pyrethroid IRS formulations that last 9 – 12 months [5], and engaging with all the major agrochemical companies involved in insecticide research and development to generate a robust pipeline of potential new insecticide classes.

The introduction of the new long lasting formulation of the organophosphate insecticide pirimiphos methyl in Ghana, triggering a major drop in malaria prevalence. This IRS formulation has subsequently been rolled out in multiple countries where pyrethroid resistance is high with similar results. A WHO led multi-country study on the impact of resistance confirmed that pyrethroid-based IRS was failing in Sudan, after the pyrethroid was replaced with bendiocarb [6]. Resistance also triggered an increase in malaria in Bioko Island, Equatorial Guinea, where pyrethroids were able to control the common ‘kdr’- type pyrethroid resistance, conferred by a sodium channel mutation in the insects’ nervous system, but failed when a second more intense metabolic pyrethroid resistance mechanism was selected in 2015. Attention has now shifted to reducing the market cost of the new insecticide formulations to control programmes through a large UNITAID funded programme, aimed at giving more price and volume certainty for the companies to bring down the unit price [7].

The big question that remains is on the impact of pyrethroid resistance on LLIN effectiveness. The early waves of kdr resistance, that were first selected in African *Anopheles,* generated less than 10-fold resistance, and had little or no impact on LLINs [8], creating complacency. The metabolic mechanisms that were subsequently selected have led to anecdotal reports that nets may be failing, with increasing numbers of live blood fed female mosquitoes being collected inside treated nets [ref]. In contrast to the relatively rapid uptake of new IRS formulations, non-pyrethroid based LLINs or ‘second generation’ combination nets, with a pyrethroid plus a second insecticide or synergist, have had a much harder route to market. There is a circular problem that for the last decade has prevented proper evaluation of any new generation net. The major donors, such as the Global Fund, will not procure nets that do not have a WHO recommendation that they are substantively better than the pyrethroid only nets, to justify the price differential. To generate the data to demonstrate this impact, large randomised control trials over several years are needed, as the efficacy of treated nets is likely to decline gradually as nets start to develop holes and the protection of the net as a physical barrier declines. These are beyond the financial resources of the manufacturers and the capacity of most disease endemic countries to design and run the trials. Unless we can break this cycle, and generate the data needed to assess whether the new generations of nets represent a more effective and sustainable way of preventing malaria, then innovation in this area will cease and eventual major failure of the pyrethroid treated LLINs will be catastrophic.

Ideally mosquito borne disease prevention should use multiple synergistic interventions. Integrated vector management (IVM) has been advocated for many years, as a means of reducing our reliance on chemically based interventions and reducing the selection exerted for resistance from a stand-alone intervention. In principle, this should be the route forward, but in practice disease endemic countries struggle. Take the case of Malawi, a relatively poor land-locked African country with high perennial transmission of malaria. Based on the WHO World Malaria report it had the 9th highest number of global malaria cases (3.7M) in 2012, although data published by the country in collaboration with WHO central and regional office staff suggest there were 4.9M cases that year [9]. An IVM national plan, endorsed by the major donors, based on LLIN mass distribution to achieve coverage of 1 net per 1.8 population, IRS in 12 of 28 districts, larval source management and improved insecticide resistance monitoring and management failed. Malaria cases declined from a peak of 6.75M in 2010, but by 2015 had rebounded again to 1999 levels [10]. The failure was attributed to a range of factors, including the detection of pyrethroid resistance in *An. arabiensis* and *An. funestus* in 2010, only a single district treated by IRS in 2014 due to the increased cost of moving from pyrethroids to OPs, lack of capacity to implement the larval source management and lack of an effective insecticide resistance monitoring and management plan [10]. Malawi is not alone in facing these issues, and we need to be realistic about what can be implemented operationally.

So, what can be done? As with malaria drug treatment and agricultural insecticide resistance management, new compounds, where resistance is not already evident, need to be introduced in combinations. Research can inform operational activity, but only if it is made more accessible to the end users. Advanced genomic analysis can be deployed to look at signatures of selection starting to appear in the mosquito field population genomes, well before operational resistance becomes an issue, giving time for mitigation strategies to be deployed [11]. New insect tracking technologies can be used to refine and optimise product development and placement [12]. Clarity on the route, time and cost to market for products to be used at scale that claim a public health benefit need to be more transparent, efficient and streamlined.

New technologies, including genetic manipulation of the insects to block their ability to transmit disease, should continue to be explored. CRISPR-CAS has the potential to revolutionise our ability to manipulate the insect vector. However, the recent ‘discovery’ of how quickly resistance to this can be selected in population replacement strategies, due to the extreme variability of mosquito genomes, should serve as a warning that this new technology will not be simple technically or logistically to roll out effectively.

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