The Eradication of Sustainability?

Global Malaria Strategy and the Neglect of Community-Empowering Interventions

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Global malaria intervention strategy tends to favor biocidal approaches that are intrinsically unsustainable. Insecticides and drugs depend on external resources, manufacturing capacity and distribution networks that do not consistently reach the remote rural communities where malaria transmission is most intense. Research and development pipelines have difficulty keeping pace with the rate at which adaptation of parasites and vectors renders these biocides obsolete.

Research priorities similarly favor novelty over refinements of the tried-and-true. Many methodologies under development (transgenic mosquitoes, recombinant vaccines) will not be deployable for years, if ever.

Little attention or support is afforded locally appropriate and sustainable, community-based interventions against malaria, despite a considerable body of evidence regarding their value and potential. These backyard technologies are as diverse as the ecologies that foster malaria transmission. Many can be implemented with equipment as simple as shovels, stoves, mortars and pestles. Most malarious communities have access to source reduction methods, housing modifications and botanical repellents and insecticides that would allow them to greatly diminish malaria risk on their own, without having to wait for a 'magic bullet' or depend on outside agencies to come to their rescue.

True, many of these sustainable interventions tend to be suppressive rather than eliminatory, and may not seem directly supportive of eradication goals. Ignoring these approaches, however, destroys any potential for synergies to develop between biocidal agents and community-based suppression. Using them together would fulfill the often described but rarely implemented Integrated Vector Management (IVM) model of malaria control.

Furthermore, empowering malarious communities to pursue these neglected intervention approaches would allow them to reduce their risk of severe disease right now on their own, without reliance on external resources and without having to wait for the necessary new vaccines

and insecticides. Where funding falters or turmoil interrupts operations, these measures would remain in place within communities, continuing to protect people from malaria.

This document surveys the status of global malaria intervention strategy and describes some of the neglected but promising community-empowering methods for malaria intervention that could be integrated into a more robust, comprehensive and sustainable approach to malaria suppression, not at all incompatible with the goal of eradication.

A Summary of Current Global Strategies against Malaria

Prior to October 17, 2007, when Bill and Melinda Gates proclaimed malaria eradication the renewed focus of global efforts against malaria (Feachem and Sabot 2008), funding agencies and policy makers seemed to support a broader approach against malaria. Researchers and operatives had more freedom to explore and implement measures aiming to modulate the risk of severe disease and mortality in communities. The Gates proclamation had a profound effect on the focus of malaria control research and operations. Over the next few years, research foci shifted towards prospective 'magic bullets' or at least to methods directly and obviously compatible with eradication, with centralized production, provision and administration of malaria intervention commodities and activities. Non-biocidal methods that do not kill parasites and vectors became marginalized.

While some malariologists protested this drastic change in vision when the proclamation first came out, the malaria intervention community quickly fell into lockstep with the goal of global eradication, using regional eliminations as stepping stones. The tenor of this approach is clear in the latest strategy documents from the leading malaria control institutions:

Bill and Melinda Gates Foundation "Accelerate to Zero" Malaria Strategy (2015)

> *"Our Malaria strategy is based on a core set of foundational principles that support our evolving strategic choices.*
>
> - *Malaria eradication is defined as removing the parasites that cause human malaria from the human population. Simply interrupting transmission is not sufficient to achieve eradication.*
> - *Eradication can be accelerated by new drug regimens and strategies that lead to complete parasitologic cure of the individual. Current artemisinin-based regimens achieve only clinical cure of the individual and do not eliminate the forms of the parasites that are responsible for continued transmission.*
> - *The majority of malaria infections occur in asymptomatic people, who are a source of continued transmission. A successful and accelerated eradication effort will target asymptomatic infections through community-based efforts.*
> - *Emerging resistance to current drugs and insecticides is an immediate threat to recent gains and an obstacle to future progress. Use of current tools and development of new tools should be guided by this evolutionary imperative.*

- *Malaria is biologically and ecologically different throughout the world. Malaria eradication will depend on strategies developed and implemented on a local or regional level."*

Clearly, the updated Gates Foundation approach emphasizes the clinical over the entomological with its emphasis on pharmacological interventions. Although the last 'bullet' listed offers some hope for their recognition of their support for sustainable, local approaches, these do not seem to be significant priorities. In fact, a recent call for proposals for research projects on interventions against outdoor biting mosquitoes specified scientific novelty as a criterion of responsiveness. Refinements of proven non-biocidal approaches were not seen as suitable avenues of research. They were looking for untried methods involving genomic manipulations, new insecticides and new means of getting mosquitoes to contact insecticides.

The World Health Organization and its Roll Back Malaria (RBM) Secretariat mention the term 'Integrated Vector Management' in their 'Global Technical Strategy for Malaria 2016-2030' but do not elaborate on the types of interventions likely to be integrated. Those who originally coined this term intended it to include all matter of activities that suppress malaria, but in practice it has come to mean combinations of insecticidal approaches, for example spraying walls and handing out bed nets in the same households (Pinder et al. 2015).

While their document does mention spatial repellents (insecticidal coils and aerosol dispensers) as viable components of a vector control program, they also emphasize the new and toxic, calling for:

"…new insecticides, formulations or methods of application, new attractants and repellents, new bioactive agents (e.g. fungi or endo-symbionts), new mosquito life cycle targets (e.g. sugar feeding, mating or oviposition phases), and genetically modified mosquitoes."

The term 'new paradigms' appears frequently in this and other documents, which presumes that older paradigms are not possible for anyone to implement effectively. Notably absent from their strategy is the role of proven community-based interventions including environmental management, housing modification and traditional or introduced botanical agents.

The dominant United States government consortium against malaria (USAD/CDC-led President's Malaria Initiative (PMI)) similarly is focused on insecticidal and pharmacological solutions and completely ignoring all other approaches for disrupting malaria transmission. Progress in their main strategy document is depicted solely in terms of program funding levels over time. Their short-term solution to the problem of insecticide resistance is to switch to a new more toxic (to mammals), more expensive, less stable organophosphate insecticide or to rotate between insecticides, an approach that has long been known for its futility in the agricultural sector. Their long term approach calls for more of the same, anticipating new drugs and new insecticides in new combinations, all subject to the same selective forces that rendered their predecessors obsolete.

In terms of technical approaches, they seem to prefer an intensification of the status quo (ITNs, IRS and IPTp) by "Achieving and Sustaining Scale of Proven Interventions." There is some promise of locally appropriate empowerment suggested in the section on: "Adapting to Changing Epidemiology and Incorporating New Tools." The specific nature of these new tools is not specified, though vaccines are suggested as a possibility. Hope for more community involvement in the process, though, is presented in the following passage:

> *"As countries success in malaria control leads to changes in epidemiology and local strategies and targets evolve in response, PMI will increasingly need to adapt and tailor its approaches and support. This will include testing and scaling up new methods to access the hardest to reach and highest risk populations. Such approaches may include establishing community-based delivery systems; engaging the private sector to reach those who lack access or avoid traditional public health structures; and targeting certain interventions geographically or to hard-to-reach populations (e.g. migrant workers) rather than nationally, for optimal impact with limited resources."*

The UK government, another dominant force in the fight against malaria, follows the same script, emphasizing a more intensified deployment of insecticides and drugs. Their long-term outlook calls for new insecticides and drugs while hoping for a vaccine with enough efficacy and longevity to justify its deployment. Progress in this document is visualized not in terms of outcomes but in processes, as in: "Estimated trend in proportion of households with at least one ITN…." No other interventions are mentioned.

The Integrated Vector Control Consortium (IVCC), of which the Gates Foundation, RBM, PMI and DFID are dominant supporting members, follows suit. A 2014 workshop discussing approaches for dealing with outdoor biting mosquitoes less affected by indoor-deployed anti-vector interventions, such as indoor residual spraying (IRS) and insecticide treated bed nets (ITNs) did not include such proven and obvious modes of protection as topical repellent lotions, a measure that our own CDC recommends for prospective visitors to malarious areas.

The Gates proclamation helped galvanize a surge in funding and interest that led to a marked reduction in malaria morbidity and all-cause mortality around the world. Early success also accompanied the previous malaria eradication campaign in the '50s and '60s. Just like then, sustainability is becoming a concern as biocides begin to fail. Most of the low-hanging fruit have now been plucked. What will happen to these gains if the promised new technologies do not materialize in the nick of time? How will resurgences be prevented?

Thus, the philosophies and prejudices of a select few, dominant funding institutions have come to dictate which malaria intervention tools have become acceptable and which fall into neglect. Despite token representation by highly indoctrinated members of afflicted countries, local knowledge, desires, common sense and science are often secondary concerns. Intervention

strategies become dominated by commodities produced by industries holding considerable sway over policymakers.

Intervention choices are strongly affected by the consensus view of the desired endpoint. Should we strive for sustainably optimizing health in malarious areas or should we attempt to eradicate malaria transmission from the planet? The former tactic, the favored approach in 1980s to early 1990s focused on limiting burdens by suppressing transmission and reducing risk of severe disease in vulnerable populations (pregnant women and children less than five years old) with populations remaining exposed enough to stimulate a partially protective immunity. A broad array of interventions can achieve this end, including modification of housing, local environmental manipulation, topical repellents as well as standard biocidal approaches. However, when the end target becomes eradication, only approaches that aim to exterminate parasites and vectors, only biocidal approaches are favored.

Why is this a bad thing? Wouldn't it be good to rid the earth of malaria? Eradication might be a noble goal if it were achievable within a generation (which is the current timeframe of the mainstream malaria intervention community). But what if the diversion of focus and resources from community suppression to high tech 'magic bullet' solutions merely led to destabilization of malaria transmission? What if resistance compromised the efficacy of drugs and insecticides, reduced community immunity and set the stage for explosive resurgences? Would these ultimately end up killing more people than might have been saved?

Why eradication may not be a viable goal.

Those who don't believe in the validity of complete eradication as a realistic end point might be accused of negativity or a failure of imagination, but there are plenty of good reasons for doubting. *Plasmodium* parasites are extraordinarily resilient organisms, capable of evading immune systems, developing tolerances for multiple classes of drugs and of hiding out in the bloodstreams and livers of asymptomatic people unlikely to visit clinics where there parasitemias might be detected and treated.

The mosquito vectors that carry them are also ineradicable, responding to pesticides via rapid adaptations to multiple agents via multiple mechanisms of resistance. Attempts to eliminate from many island situations have failed. Most notably, a study of genetic diversity after an intensive DDT-based campaign in Sao Tome and Principe in the 1980s showed no evidence of any genetic bottleneck that would have been expected if mosquito populations had been driven to the brink of elimination.

Specifically, my objections to pursuit of eradication are based on the following observations:

1. Lack of an effective malaria vaccine

The creation of an effective malaria vaccine would truly be a game changer. If a vaccine existed that could reliably and sustainably protect newborns and children under five from malaria transmission, eradication might actually be possible, particularly if it were used in conjunction with conventional insecticidal interventions to which vector populations had not yet become resistant.

However, despite a regular succession of modest technical 'breakthroughs' over the past few decades, no vaccine meeting these minimum criteria has ever been developed. The best effort thus far (Butler 2012, Penny et al. 2015; RTS,S 2015) requires multiple inoculations and provides less than complete protection (36.3% in 5-17 month old children) which begins to fade soon after the final booster shot is administered. For maximum efficacy, RTS,S vaccines require three injections plus a booster shot spread over a twenty month long period adding considerably to the complexity and expense of administration. No measurable trace of protection can be detected 18 months after the final inoculation.

There may be situations where a vaccine with such a partial and temporary efficacy might be useful, but it is difficult to make a case for diverting extensive resources to its widespread provision and away from interventions that provide longer lasting and more cost-effective protection. Moreover, this vaccine effort represents the state of the art and has no close competitors. No further breakthroughs appear imminent, despite massive outlays of global research efforts and resources. It can be readily demonstrated that some of the neglected community-based measures that I propose be revisited deliver at least the same level of protection for a tiny fraction of the investment.

2. Biocides and the Red Queen Dilemma

Organisms do not just sit still and allow themselves to be eradicated. Mosquitoes and parasites are not passive agents. They adapt. The rate at which resistance develops is proportional to the ubiquity and intensity of the use of biocides.

Every class of insecticides currently available has been compromised by at least one mechanism of metabolic resistance, some by multiple, independent resistance mechanisms. This is no surprise. Biocides exert selective pressure on mosquito populations.

This selective pressure has led not only to selection for point mutations, duplications and other genetic modifications that confer physiological resistance, but also has led to an increasing tendency for vector species to spend more time biting outdoors and also to expand their preferred period of biting activity earlier in the evening before people retire under bed nets and in some cases late into the morning after people leave the protection of their bed nets.

'Thought leaders' in the malaria intervention community have coined a novel euphemism for all outdoor biting populations of malaria vectors, whether these behaviors were always present or acquired adaptively through exposure to insecticides. Such mosquitoes are termed 'residual,' as

if they represented remnants of larger from which populations of which all indoor biting members had been successfully exterminated.

The official Gates Foundation definition is as follows:

> *"The term residual transmission is defined as all forms of transmission that persist after universal coverage has been achieved with effective LLIN and IRS interventions."*

While politically expedient, such terminology is an inaccurate portrayal of nature. Coverage is far from universal or universally effective. Many mosquito populations possess natural outdoor biting habits (e.g. *Anopheles darlingi* in South America, *An. dirus* in Southeast Asia.) Due to their highly exophagic and exophilic tendencies, ITNs and IRS do not significantly impact vectors like these. Their populations remain robust and would remain far from 'residual,' even if universal coverage with these interventions could be achieved.

This newly coined term overstates the impact of biocides and minimizes the threat of outdoor-feeding mosquitoes. It also ignores the adaptation of formerly indoor feeding mosquitoes to biting earlier in the evening and out of doors. Such a term is helpful only to those who feel the need to justify disproportionate allocations of effort and resources to commercial, insecticidal interventions.

Resistance to biocides is inevitable and un-manageable. Mosaic ITNs (with panels treated with different insecticides (Corbel et al. 2010)) and insecticide rotations only temporarily delay fixation of resistance genes for each agent in the ensemble. Resistance still progresses like a ratchet, thanks to the recessive nature of the gene expression of the more common mutations. The process can be slowed by combining biocidal agents into a single treatment, but then when resistance arises, you have lost two formerly effective agents, not just one.

This is why the IVCC is proposing research towards the discovery of three new insecticides to be combined in a single product. Existing insecticides cannot be used because none exist that are not compromised by some type of resistance adaptation by some vector in some part of the world. The problem with relying on new insecticidal technologies is that pretty much all of the low-hanging fruit (easy and cheap to produce) have been plucked. The latest generations of insecticides have been getting progressively more and more expensive, while lacking the residual performance and low mammalian toxicity profiles that made moieties like pyrethroids so attractive.

The current status of insecticide resistance in the malarious world is quite patchy and complex. Many areas now show complete fixation for the kdr gene mutations that decrease the sensitivity of mosquito neurons to pyrethroids and DDT. Some areas are now seeing the spread of an additional mutation that amplifies kdr resistance. Numerous other mechanisms of insecticide resistance to these and other insecticides are also emerging and spreading. Reports are beginning to emerge regarding control failures (N'Guessan et al. 2007). While some recent

studies show that ITNs are working just fine, others show no impact on health outcomes correlated with the ownership and use of nets (Mathanga et al. 2015).

But the path towards increasing resistance is inexorable. Areas still experiencing effective responses to insecticidal interventions cannot expect to sustain these outcomes indefinitely. Achieving goals for high rates of net ownership and utilization will only exacerbate the selective forces that induce resistance, leading to more widespread fixation of common resistance mutations and the layering of additional mechanisms conferring additional modes of resistance to vector mosquito populations.

Switching to less widely used insecticides such as carbamates will buy some extra time, but resistance to this toxin is already spreading across parts of West Africa. The insecticide development pipeline is sparse. This is an arms race that cannot be won. The high reproductive potential of mosquitoes ensures that resistance traits spread quickly. Biocides alone cannot be relied upon to achieve eradication. Their efficacy fades proportional to the intensity of their use. Their window of utility is finite (Spielman et al. 1993).

Resistance, of course, is not limited to vectors. Parasites also respond to selective forces and evolve. Several former first-line drugs have already been rendered almost completely useless by resistance. Resistance is now spreading through Southeast Asia for the key component of the current combination therapy of choice, artemisinin. It is only a matter of time before the entire malarious world is affected.

3. High Vectorial Capacity

The daily ability of a vector population to transmit new infections from a single infected person is termed 'vectorial capacity.' It is a component of 'force of infection' or the basic reproduction number (R_0) used to describe the contagiousness of directly transmitted pathogens in human populations. Ebola and the 1928 Spanish influenza pandemic, both considered highly contagious, have R_0s of between 2-3, meaning every sick individual passes on their illness to two or three healthy people. Measles, a pathogen capable of explosive epidemics in unvaccinated populations has an R_0 estimated to range from 12-18.

The involvement of a vector changes everything. The R_0s of vector-borne pathogens are much higher due to the vastly greater abundance and mobility of infected insect vectors relative to person-person transmission. For example, an R_0 of ~40 was once estimated for falciparum malaria in Kankiya, Nigeria (Garrett-Jones and Shidrawi 1969), making it more than three times explosive as measles, and this was after mosquito abundance was drastically reduced by intensive insecticide application. Even after massive interventions (in an era before insecticide resistance had taken hold), malaria's contagiousness could only be reduced to a level of about 15-20 times more explosive than Ebola or Spanish Flu. In this same region, prior to intensive interventions and during peak transmission season, estimated R_0s had reached as high as 1,300.

These numbers are no fluke or relic of the past. Contemporary estimates of malaria's reproductive potential (Smith et al. 2007) show that transmission potentials remain astronomical in some places. The median for 121 African populations was about 115. In Mngeza, Tanzania, R_0 reached 1,600, In Lira Township, Uganda, it ranged between 2,000-5,000. Not all malarious areas exhibit such robust transmission, but such conditions are not uncommon in Africa.

The main operational implication of these large values for malaria R_0 is that even if transmission potentials were reduced by 95% in some areas, they would remain larger and more explosive than most other pathogens we consider very contagious. Thus, it is difficult to see how we can depend on such a limited suite of under-utilized, resistance-compromised intervention methods to accomplish the task of global eradication.

Many instances exist of massive decreases in malaria transmission leading to explosive resurgences when intervention campaigns are interrupted (Nigeria, Kenya, Sudan, Swaziland, etc.—(Cohen et al. 2012)). Partial eradication is only one rainy season removed from disaster, particularly where populations become vulnerable due to loss of immunity.

However, elimination—complete interruption of malaria transmission in countries and regions where climate, geography and ecology conspire to limit vectorial capacity, may be possible in some countries. To achieve even that we will need to find intervention methods that are more robust in the face of adaptation or more ways to combine partially effective interventions into wholes greater than the sum of their parts.

The focus on global eradication diverts attention from many simple and inexpensive measures communities can take to protect themselves from malaria. Eradication goals shift attention from the present to some point decades away. Many community-based interventions focus on the present, using tools already available. Posing such unrealistic but ambitious goals helps garner attention and mobilizes resources to fund high-risk, high-reward research, but it does little for those dealing with intractable malaria today or for those who will suffer when the efficacy of current biocidal agents fades without adequate or timely replacement.

4. Tropical Vectors are Different

Another commonly heard argument in favor of malaria eradication or elimination points to the experiences of the temperate world, where malaria transmission was once a perennial bane. Israel, Sardinia and Southern Italy all used to experience large outbreaks of malaria deep into the twentieth century. These areas are now malaria-free both due to direct public health efforts (DDT, draining marshes) and to the indirect effect of development (industrial pollution, screening, air-conditioning, etc.). These experiences hearten those in favor of eradication, but unfortunately there are some major ecological and biological differences between temperate and tropical mosquito vectors that render these situations incomparable.

The tropics and Africa in particular face a far greater challenge than temperate nations faced in ridding themselves of malaria. The vector species that dominate malaria transmission are highly focused on human biting and thus highly efficient (many fewer bites are diverted to animals unable to incubate human malaria infections).

In Cameroon, for example, *Anopheles funestus* was found to focus their feeding on humans 97.1% of the time. (Tanga et. al. 2011). In *An. quadrimaculatus*, the historically dominant malaria vector in North America, human blood indices (hbi) are much less. Even in the most anthropophilic of Florida's *An. quadrimaculatus* sibling species it measures less than 11% (Jensen et al. 1996). Anthropophilicity ('a') has a powerful effect on the explosiveness of malaria transmission. Mosquitoes must feed twice to acquire and deliver parasites to a human. Transmission efficiency, thus responds to any increase or decrease in this value ('a') as the product (a*a) or square (a^2) of the change in values. Florida's most efficient malaria vector has only 1.3% of the capacity of Cameroonian vectors to transmit malaria.

Thus, North America had a much less daunting task to eliminate malaria than what Africa faces today, based on vector anthropophilicity alone. Many European and North Asian vectors share similar zoophilic tendencies.

Habitats for the dominant malaria vector species also are more difficult to deal with in the tropics. Larvae of *An. quadrimaculatus* and *punctipennis* in North America favor the vegetated shores of rivers, lakes and ponds. Many of the most important tropical vectors are found in habitats that are highly dispersed and ephemeral, namely—puddles. The more stable and concentrated habitats of Europe and North America are much easier to tackle with larvicide applications. Many were also affected by industrial pollution, rendering many highly productive mosquito spawning grounds inhospitable, as an unintended benefit. In the humid tropics, there are also no winters to interrupt and reduce anopheline populations. The temperate world faced a far lesser challenge than the tropics face today.

Alternative Intervention Methods

'Alternative' is an unfortunate descriptor for intervention methods that deserve to have a place in the mainstream of malaria intervention. 'Neglected' might be a more apt label for existing, sometimes traditional technologies that complement conventional approaches to malaria suppression, but due to their locale-specific implementation, their separation from industrial producers of intervention commodities and their non-biocidal effects on parasites and/or vectors, they have fallen by the wayside. Partially suppressive methods are sometimes seen as incompatible with the goal of eradication, but this ignores their potential for filling in the gaps of malaria prevention, protecting those who for whatever reason are not reached by other interventions. Synergies may also derive from certain combinations, with larval interventions creating smaller, feebler adult mosquitoes more susceptible to insecticides. They also serve as a

fail-safe, suppressing vectors and parasites during times when the continuity of conventional interventions becomes interrupted by political instability or resource deficiencies.

A dependency on commercial commodity manufacturers has led to the dominance of commercial, insecticidal approaches to vector control against malaria. The methods described below represent a brief survey of malaria suppression methods available to malarious communities without significant external inputs.

1. Botanical repellents and larvicides

Communities living in malarious areas have long employed traditional means of reducing exposure to mosquito bites, from the use of smoke in enclosed spaces to hanging bruised plants in households to botanical preparations rubbed on skin (Maia and Moore 2011). This is not always done with the express purpose to prevent malaria but sometimes only to reduce nuisance biting as not all rural belief systems support the linkage between mosquito bites and malaria, favoring supernatural or nutritional explanations (green corn) (Okeke et al. 2006; O'Neill et al. 2015). Nevertheless, any measure that leads to reduced biting by insects reduces risk for malaria transmission.

Many partially effective, traditional insect repellents exist across all cultures. A myriad of allelopathic compounds show activity against insects. While these compounds originally evolved as defenses against phytophagous insects, many (volatiles in particular) also show activity against mosquitoes (Maia and Moore 2011). Their modes of action are diverse, but many are toxic or irritating to flying insects.

The primary limitation of most crude botanical repellent extracts is the relatively brief duration of their activity against biting insects. Some provide only fleeting relief and few show significant protection beyond four hours. In areas where malaria vectors bite all night long, this means that efficacy fades well before dawn, allowing people to be infected while they are sleeping. Ephemeral repellents still have utility in protecting bed net users while mosquitoes are active before they retire for the night and against outdoor biting vectors.

While most crude repellents are not suitable substitutes for bed net use, the active components of certain plants can be combined and formulated in ways that greatly extend the duration of activity. No Mo, for example, a formulation of PMD, lemongrass oil and vanillin, has been shown to provide more than ten hours of complete protection in laboratory cage tests and at least nine hours of almost 90% protection under field conditions in northern Ghana (Dadzie et al. 2013). This exceeds all reports for duration of efficacy for the current industry gold standard DEET (N,N diethyl-meta-toluamide) against anopheline mosquitoes.

While 'No Mo' is currently manufactured from chemical components that include some synthetic moieties, its active ingredients can also be derived strictly from botanical sources,

offering the potential for it to be formulated from locally grown plants. Lemongrass is already cultivated throughout the tropics.

Lemon eucalyptus (*Corymbia citriodora*), a rich source of citronellal and PMD was introduced to parts of Africa late in the 19th century and is now well established in Brazil, Malaysia, Vietnam, Ethiopia, Ghana, Kenya, Uganda, Zimbabwe and other malarious countries. Eucalyptus trees in general are widely distributed now throughout the malarious world, and despite their invasive properties and conflicts with native flora, are popular for their ability to regrow new boles quick and straight from coppiced trunks. They are a major source of building materials and firewood in certain regions.

Eucalyptus trees strain hydrologically-stressed areas due to their high transpiration rates. This property has actually been exploited to lower water tables and render potential larval breeding sites for malaria vectors uninhabitable. Such applications may not be advisable, however, in drought-prone areas or regions affected by desertification or erosion as eucalypti also inhibit the growth of ground cover due to the release of allelopathic chemicals.

Locally-grown plants can also serve as spatial repellents protecting living spaces when burned or thermally expelled. Leaves of *C. citriodora* were also found to reduce mosquito catches by up to 73% by direct burning in traditional stoves or thermal expulsion on hot sheet metal (78%), thus showing potential as a spatial repellent (Dugassa et al. 2009; Dube et al. 2011).

Despite the availability of several effective topical repellents (botanical and synthetic), policy makers have opted to ignore this approach of protecting those who live in malarious areas from malaria. However, this official neglect of topical repellents contrasts with the behavior and practice of those who visit malarious areas as well as official recommendations for travelers (http://www.cdc.gov/malaria/resources/pdf/travelers.pdf).

The rationale for not promoting topical repellents to prevent malaria in communities at risk appears to be based on three premises:

Topical repellents are:

1) Non-biocidal, thus do not contribute to eradication efforts

2) Poorly tolerated by end-users, thus are under utilized

3) Diversionary, shifting malaria risk from users to non-users.

4) Ineffective at preventing malaria

1. Non-biocidal.

Because topical repellents do not kill mosquitoes, they would not appear to directly address the goal of elimination or eradication. Repellents spare the lives of mosquitoes while IRS and ITNs have a mass-killing effect where vectors have not yet developed resistance that reduces the overall abundance of vectors and thus confers some benefit even to people in the community who are not using bed nets or living in sprayed houses.

Resistance-free zones are rapidly dwindling, however. Increasingly, treated bed nets are becoming non-biocidal, yet this does not seem to influence distribution policies. In such cases, barrier protection and mild repellency suffices to warrant continuation of ITN distribution programs, yet similarly reducing risk for individuals via topical repellents is deemed insufficient.

It would seem that any measure that reduces risk of infection inevitably means that fewer active cases of malaria exist to contribute parasites to transmission cycles. Any activity that suppresses the ability of malaria parasites to infect people and mosquitoes reduces the impact of malaria on a population.

The non-biocidal property of repellents is actually a positive for sustainability because it means that the selective forces that might drive adaptation to render mosquitoes refractory to repellents are much weaker than they would be for a biocide. Selection would be even weaker if a vector species has significant zoophagic (animal feeding) tendencies that would allow for reproductive success after being diverted from a human host.

Although, resistance to repellents was shown to be possible under severe laboratory conditions where caged mosquitoes were given no option but to attempt to bite a repellent-treated human (Stanczyk et al. 2013), these conditions are unlikely to be encountered under field conditions where alternative and unprotected hosts abound. Non-biocidal agents thus do not suffer from the time limitation associated with biocides (Spielman et al. 1993).

2) Low User Acceptance.

It is true that many people find the smell and other negative properties (oiliness, toxicity, plasticizing) of DEET offensive, leading to low user compliance in disease reduction trials (Moore and Debboun 2007). A recent study in Laos, for example experienced compliance rates of only 48-60% (Chen-Hussey et al. 2013). Few dispute the unattractiveness of DEET and some question its safety, particularly in young children, due to its mild neurotoxicity via inhibition of acetylcholinesterase (Dolan and Panella 2011; Swale et al. 2014).

Not all repellents share the negative properties of DEET. Neurotoxicity is not an issue for botanical derivatives like picaridin and PMD. Both alternatives also have more appealing odors and are well tolerated by end users. Trials in Amazonian Peru, Guatemala (Darling, pers. comm.) and Ghana (Dadzie et al. 2013) show user acceptance rates to be much higher than reported for DEET-based trials. In the Ghana study, 85% of users found the odor of a

botanical repellent appealing and 87% reported no inconvenience performing daily applications. Clearly, user compliance issues experienced in studies examining DEET-based repellents are not generalizable to all repellents, and certainly not botanicals.

3) Diversionary

Topical repellents are criticized for disrupting the equity of disease risk by diverting infective mosquito bites from users to non-users, thus exacerbating their risk of developing malaria. While this may be true at an individual level, at the community level many studies seem to show a decrease in overall risk for a net or average benefit. Still, this is often viewed as a 'deal-killer' for the inclusion of topical repellents into the intervention agenda.

But few advocate the use of repellents as a stand-alone intervention, but as a complement to current conventional interventions like ITNs that do not address the issue of mosquitoes that are active and biting outdoors or before people retire to bed. Thus, they are intended to fill a protection gap that has long existed in certain areas (South America, Southeast Asia) and that is widening in Africa due to behavioral resistance imposed by indoor application of insecticides. Is diversion really a problem for a secondary, supplemental intervention providing protection in situations where standard interventions are ineffective?

And the evidence for significant diversion is weak and overstated. One recent highly cited study conducted in Tanzania implied that a greater than four-fold increase in resting mosquitoes occurred in the houses of placebo users in a village where over 80% (Maia et al. 2013) of households had been given 15% DEET. But most of the diversion observed in this study occurred in *Culex* mosquitoes which do not transmit malaria. Re-analysis of this data looking only at anopheline vectors showed no significant diversion of *Anopheles gambiae* or *funestus* indoors. *Anopheles* mosquitoes were actually more likely to be found in the houses of repellent users (1.13 mosquitoes per household) than the homes of placebo users (0.87 mosquitoes per household). Outdoors, diversion was apparent only with *An. gambiae*, though the sample size (16 mosquitoes among 23 outdoor locations) was far too small to be compelling. And yet this work, comparing the distribution of fractions of mosquitoes per household, was used to justify intervention policy at a 2014 IVCC workshop.

Furthermore, other interventions also divert mosquitoes to non-users without causing concern or affecting intervention policies. Ideally, ITNs would not divert mosquitoes if vector mosquito populations remained vulnerable to insecticides, but as previously discussed, such favorable situations are becoming less common with every passing year. Increasing resistance confers diminishing benefits to non-users in a community because fewer mosquitoes are killed and net users divert more bites to non-users.

Even in the absence of insecticide resistance, the excito-repellent properties of pyrethroid insecticides would likely divert mosquitoes from households using nets to those who opt not

to use them. No one has ever advocated discontinuing ITN distribution due to the possibility of diversion, not even in high resistance areas where mass killing effects are absent.

The same issue afflicts spatial repellents (mosquito coils, aerosol dispensers) on a household level. Even within a household, heterogeneous air currents are likely to protect certain rooms and portions of rooms more than others. Not all households are likely to comply just as not all people possessing ITNs actually use them. Oddly, diversion is never mentioned as an issue affecting spatial repellents.

One obvious solution to this problem is to ensure universal access to repellents in communities where they make sense as an intervention. Some people will always opt to not use agents that might otherwise protect them from disease. The only thing that can be done is to ensure that as many people as possible are informed of the benefits and to ensure easy and equitable access to all at risk.

4) Low Efficacy.

Several recent studies suggest that certain repellents (DEET) under certain conditions (rural Tanzania) are ineffective at preventing malaria (Chen-Hussey et al. 2013; Wilson et al. 2014). However, the choice of DEET in a malaria prevention trial is questionable given the innate refractoriness of *Anopheles* mosquitoes to this repellent.

Numerous studies have shown that DEET is less efficacious against anopheline vectors of malaria in head to head comparisons with other repellents (Moore et al. 2002; Frances et al. 2004; Costantini et al. 2004; Moore et al. 2007; Frances et al. 2009; Tavassoli et al. 2015). It would be interesting to see how a repellent with high user acceptance and full efficacy against anopheline vectors might fare under similar conditions.

Several recent studies employing botanically-derived repellents in Bolivia, Ethiopia and Ghana have indicated a significant malaria suppressive effect in each community evaluated. In Bolivia, a PMD-based repellent formulation provided an 80% protective effect in households using ITNs and repellent versus those using ITNs plus a placebo (Hill et al. 2007). In Ghana, a village using repellents experiences a 19% decline in overall prevalence of falciparum malaria (Dadzie et al. 2013). In the Ethiopia study, introducing repellents to a community already using ITNs reduced risk of *Plasmodium falciparum* malaria by 47% (Deressa et al. 2014).

Malaria vectors are diverse and thus the ecology and epidemiology of malaria transmission is extremely heterogeneous. It should never be presumed that an intervention that proves successful or unsuccessful in one particular location should be universally useful or useless in all other locales. All interventions should be assessed on their on their relevance for specific situations and their appropriateness for local conditions.

It is human nature to want to simplify and generalize complexity. Policy is easier to craft when it is universal. Unfortunately, top down management that generalizes technical approaches to malaria intervention has the effect of stifling local expertise and leads to allocation of time and resources to interventions that are incompatible with the behavior and ecology of vectors in certain localities and have little chance of being effective. For example, ITNs are still heavily and almost exclusively promoted in parts of Southeast Asia where vectors feed mainly early in the evening and outdoors where up to 61% of infective bites occur before people retire to bed. ITNs provide only partial protection in such situations (van Bortel et al. 2010; Durnez et al. 2013; Suwonkerd et al. 2013).

Spatial repellents appear to be well supported by funding agencies and policy makers. However, local botanical approaches are less preferred than novel industrial commodities (aerosol dispensers) based on insecticides with excito-repellent properties.

The blatant disregard for topical repellents seems puzzling. Certain formulations have been shown to be highly effective in reducing malaria transmission in certain situations. There is little basis for removing them entirely from the intervention agenda. Why not let local stakeholders explore methods that have been shown to work in their unique ecologies?

Botanical larvicides also offer promise for community-based prevention of malaria, but similarly receive little support in the global health arena. For the same reasons that many plants are adapted to produce chemical moieties to repel phytophagous insects, they also produce toxins capable of killing mosquito larvae. Plants already growing in malarious areas can be used to suppress larval development in water bodies.

Examples include neem tree (*Azadirachta indica*) seed powder prepared with mortars and pestles, which were used successfully in Niger to reduce malaria vector *Anopheles gambiae* s.l. populations by almost 50% using twice-weekly applications (Gianotti et al. 2008). Although neem is an introduced exotic species from India, it is widely grown throughout the malarious tropics and numerous other useful medicinal uses including birth control as an anthelminthic.

The complexity of crude botanical extracts offers a major advantage over refined formulations. Insects are much less likely to develop resistance to a complex mixture of active compounds as opposed to a single active moiety. Neem seed kernels, for example, contain about 98 compounds with insecticidal properties besides the most potent component—azadirachtin.

Other common botanicals with similar larvicidal potential include Chinaberry (*Melia azederach*), which was found to inhibit emergence of adult mosquitoes from simulated field habitats in Ethiopia. Inhibition ranged from 93-100% depending on the dose applied (Trudel and Bomblies 2011). Preparation of this natural larvicide was similar to that of neem—simple grinding of dried seeds with a mortar and pestle.

Chinaberry is a type of mahogany native to Southeast Asia but, like neem, has become widely disseminated throughout the tropics and subtropics. It is particularly abundant in the Ethiopian highlands where it is valued as a fast growing source of firewood, lumber and shade. Its fruits are toxic to mammals at high doses, but dilute preparations are sometimes used as traditional medicines.

Cashew pods can also be used to suppress mosquito larvae. Cashews (*Anacardium occidentale*) are native to Brazil, but like many useful plants have become introduced throughout their suitable growing range. Cashew nut shell liquid is prepared from the seed coat or pericarp surrounding the nuts. A trial in India found that a preparation equivalent to 38 ppm reduced late stage larvae and pupae of *Anopheles subpictus* by up to 97.1%.

These few examples represent the tip of the iceberg for plants with suitable larvicidal properties against mosquitoes. Not every community has access to neem, Chinaberry or cashew, but thousands of such species have been identified so the odds are good that some plant species already present within a community could be used to similar effect (Kolcke 1989). If not, and if one of these more promising botanical larvicides is compatible with local ecology, they could always be introduced. The point here is that communities need not be dependent on external inputs for successful malaria vector suppression.

One caveat affecting incomplete application of all larvicides is the possibility of malaria risk increasing due to the release of intraspecific larval competition. Partial killing of larval populations allows survivors to benefit from access to additional nutritional resources, creating larger, more robust and longer lived adult mosquitoes with a greater capacity to transmit malaria (Moller-Jacobs et al. 2014).

Of course, this can be avoided by applying sufficient doses of larvicides to vector breeding habitats. Alternatively, source reduction, another neglected method of community participatory is not prone to such unintended consequences. Reducing the availability of breeding sites imposes crowding, leading to smaller, shorter lived adult mosquitoes with less vectorial capacity (Moller-Jacobs et al. 2014).

Source reduction

There is a long history (in the copper mines of Zambia, the Hula swamps of Palestine, the Pontine Marshes of Italy, the rivers and reservoirs of the Tennessee Valley Authority) of successful environmental management leading to suppression or elimination of malaria transmission (Keiser et al. 2005; Walker and Lynch 2007). Most involved large-scale engineering efforts targeted against vector species breeding in large contiguous habitats such as rivers and marshes. Drainage of wetlands or fluctuation of water levels in large bodies of surface water can render large areas of habitat uninhabitable by mosquitoes.

These examples all involved highly technical and centralized operations that may not be appropriate for the dominant anopheline vector species in the tropics, which tend to favor highly dispersed micro-habitats (puddles, hoof prints, borrow pits, etc.), but not if such efforts are promoted and undertaken at the community level.

In Dar es Salaam, Tanzania, where urban agriculture and irrigation exacerbates malaria risk in adjoining neighborhoods, one such effort proved highly successful (Castro et al. 2009). The primary intervention method (preceded by a community sensitization and mobilization efforts) was simply sending people out daily to walk routes along roadside drainage ditches and ensuring that they flowed freely by removing obstructions by hand. Anopheline mosquito larvae tend only to develop in the still water behind impoundments. This one simple effort reduced malaria risk by 88% as compared to the baseline rate of infection before this community-based effort was undertaken. Adjacent neighborhoods to which the intervention neighborhoods were compared suffered a 70% greater risk of infection by malaria.

Moreover, these efforts showed signs of intrinsic sustainability. Eighteen months after the interventions were begun, the community remained engaged in keeping drains clear of debris.

The same communities later became engaged in efforts to implement community-based microbial larviciding of vector habitats, to further drive down malaria risk (Maheu-Giroux and Castro 2013). These larviciding efforts utilized *Bacillus thuringiensis israelensis* (bti), bacteria that produces a natural biodegradable toxin that affects only mosquitoes and their closest relatives (non-biting gnats). These applications reduced malaria risk by 21% in the wards in which these interventions were implemented, with synergies observed when they were conducted in conjunction with other suppressive measures including mosquito-proofing houses with screening or complete ceilings.

The conventional ‘wisdom’ often heard from global health policymakers, perhaps informed by such urban success stories, is that community level environmental intervention may be appropriate for urban situations where habitats are few and human populations are high, but they are not practical in rural areas for the converse reasons (Fillinger and Lindsay 2011).

In rural areas, people are fewer and puddles are everywhere in the rainy season. But not all collections of water produce malaria vectors. Anopheline mosquitoes are selective regarding habitats in which they will oviposit, responding to environmental cues and kairomones indicative of suitability to foster their larvae. Thus, the dominant vector species avoid shade, overly eutrophic conditions and large, open bodies of water diverse with predators. Unless it rains every day, low volume and thus highly ephemeral collections of

water usually dry out before any larvae hatching in them can develop into adults. This is borne out in assessments of pupal productivity by habitat type.

In the highlands of western Kenya, for example, borrow pits created for the express purpose of harvesting mud to 'plaster' the exterior walls of homes accounted for more than 75% of adult vector mosquitoes despite larvae being present in almost every type of habitat sampled, from cattle hoof prints to roadside ditches (Mutuku et al. 2006; Mala and Irungu 2011).

Selective filling of particularly productive habitats would greatly reduce the labor and resources required to impede mosquito productivity. Effective targeting would only require a simple rubric for when to intervene and when to ignore a potential habitat. Perhaps, the presence of larvae alone would not be a sufficient condition, but the presence of pupae would warrant immediate removal of the habitat. Of course, one would need to balance other needs and desires of the community, including the availability of water in borrow pits for washing and drinking.

However, reducing the abundance and suitability of borrow pits for mosquito breeding does not necessarily require extra shovels or construction equipment. The use of more stable building materials alone can decrease the frequency at which borrow pits need to be dug, allowing ecological succession to render habitats unsuitable for mosquito vectors (Kiszewski et al. 2014).

The specific nature of appropriate community-based environmental interventions will vary with the diverse local ecologies in endemic areas around the world. For example, the high pupal productivity of borrow pits in Kenya is not necessarily generalizable to other locations, such as the Gambia (Fillinger et al. 2009). The design of specific community-based interventions should be guided by local expertise (Mukabana et al. 2006).

Mosquito-proof Housing

Restricting access of mosquitoes to people's homes seems like a common sense means of avoiding bites from vectors that specialize in attacking their hosts where they live. Such interventions are eminently sustainable. No mosquito can adapt to a well-fitted door or window screen. Studies have shown that even partial interference with access by mosquitoes into homes can have a large effect. Minor changes in the configuration of homes can greatly reduce the exposure of residents to infectious mosquito bites.

Few rigorous, larger scale trials have been conducted on the effect of housing, partly due to the lack of institutional support for community-based approaches. But diverse examples of the influence of home construction abound. Living in homes with screening across the ceiling was associated with 48% lower anemia in children in the Gambia (Kirby et al. 2009). In Sao Tome, simply raising houses several meters above ground level on stilts reduced the

abundance of vector mosquitoes resting in homes by about 50% (Charlwood et al. 2003). The use of 'modern' wall materials was associated with an average 25% reduction in the incidence of malaria infection across multiple studies (Tusting et al. 2015). Closed eaves were similarly associated with 25-50% decrease in clinical malaria in children, again averaged across multiple studies (Tusting et al. 2015).

A meta-analysis of 53 studies on the effects of housing configuration on malaria risk showed that 'modern' housing styles were associated with 47% lower malaria risk on average than 'traditional' homes (Tusting et al. 2015). Three quarters of the studies evaluated showed significant epidemiological benefits associated with diverse differences in building materials and construction practices. Given this preponderance of evidence, it is not clear why interventions based on improving housing are not more widely supported by policy makers and funding agencies. Generalizability always seems to be an issue in garnering support and traditional housing methods vary greatly across the malarious world.

Many cultures employ wattle and daub construction employing either rounded or orthogonal floor plans based on timber frames plastered with a mixture of mud and straw with animal manure as a binder. Such methods require the excavation of borrow pits on the edges of wetlands, creating instant malaria vector habitats. On volcanic islands in the Gulf of Guinea where gritty soils are unsuitable for wattle and daub, homes are constructed from planks of timber. In the Amazon, both styles are common as well as homes with walls made of bundled thatch.

One argument sometimes heard against advocating housing modification is that the materials and measurements vary so much in rural areas at risk that it is not possible to use standard sized window screens and doors. I would suggest that on-site fabrication and customization using materials available on site is certainly possible in many situations. Local stakeholders would know better what materials are most available and appropriate, rather than needing to obey prescriptions from afar.

Even subtle modifications of traditional housing methods might make a significant impact. 'Rammed earth' technology has long been promoted for areas in the Sahel where deforestation and desertification have led to a lack of building materials for homes. 'Rammed earth' is simply a more stable form of daub made from a mixture of local soil (mud) combined with a small amount of Portland cement as a stabilizer. The amount of cement required varies according to the properties of local soils. Sandy, friable soils require more; soils with a high clay content less.

A hidden advantage of using rammed or stabilized earth construction is that areas accustomed to annual re-plastering of wattle frames might now be able to go several years or more between re-plasterings. This greatly reduces the rate at which new mosquito breeding

borrow pits are dug, and allows the older pits to become overgrown and unsuitable as vector habitats.

Summary

Sustainable, community-based interventions do not interfere with conventional approaches. Rather, they support standard intervention by adding to, and in some cases, synergizing reductions in the burden of transmission. They also offer a failsafe for when biocides fail, and all biocides inevitably fail. They support mainstream interventions by adding to and in some cases synergizing reductions in the burden of transmission. They fill the gaps, protecting people not reached or non-compliant with mainstream interventions. When funding falters or political instability threatens the flow of aid, communities would remain empowered to continue malaria suppression. While these interventions on their own could not achieve eradication, they would suppress malaria and save many lives even in the absence of outside resources.

Without such a backup, a sudden interruption of current efforts would prove disastrous, as was proven in the prior eradication era and in many localized resurgences since. Interrupting transmission causes the partial immunity accrued from multiple malaria infections since birth to elapse in endemic populations. While this immunity does not suffice to avert future infections it does protect people from the severe and complicated manifestations of acute malaria. The loss of this partial immunity renders communities extraordinarily vulnerable to severe and complicated manifestations of malaria and astronomical mortality rates. Even measures that limit without eliminating malaria transmission would save lives. Multiple, super-imposed infections common in high transmission areas are more likely to overwhelm the immune system and cause severe disease. The presence of sustainable interventions in a community would help buffer such a collapse and explosion.

While policymakers appear to recognize the value of community-based interventions based on committee reports and position statements, this recognition does not often get translated into actions, as opposed to those that rely on externally manufactured commodities involving biocides. This is not too surprising as industries speak louder than local stakeholders. But while biocidal approaches can be powerful early on in campaigns and quite useful in plucking the ‘low hanging fruit’ of an eradication effort, their utility is only temporary. As returns diminish, and the perennial promise of new technologies is once again deferred, perhaps the utility of these simple, common sense approaches will become more apparent.

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