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Averting a malaria disaster: will insecticide resistance derail malaria control?

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Abstract

World Malaria Day 2015 highlighted the progress made in the development of new methods of prevention (vaccines and insecticides) and treatment (single dose drugs) of the disease. However, increasing drug and insecticide resistance threatens the successes made with existing methods. Insecticide resistance has decreased the efficacy of the most commonly used insecticide class of pyrethroids. This decreased efficacy has increased mosquito survival, which is a prelude to rising incidence of malaria and fatalities. Despite intensive research efforts, new insecticides will not reach the market for at least 5 years. Elimination of malaria is not possible without effective mosquito control. Therefore, to combat the threat of resistance, key stakeholders need to rapidly embrace a multifaceted approach including a reduction in the cost of bringing new resistance

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JH and HR drafted the report; PG collated the data to produce figure 1; all authors commented on the draft and the revised version of the report after reviewers' comments; and MH undertook the commentary on behalf of the Industry Insecticide Resistance Action Committee, which has representatives of all major agrochemical companies.

Declaration of interests

We declare no competing interests. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of organisations they represent.

management methods to market and the streamlining of associated development, policy, and implementation pathways to counter this looming public health catastrophe.

Introduction

In 1999, White and colleagues[1] reported the escalating drug resistance in malaria parasites and the risks associated with the introduction of new malaria treatments as monotherapies. This report was one of the first steps leading to the recommendation by WHO of artemisinin combination therapy as the front-line drug treatment in 2001.[2] These measures to minimise treatment failure, coupled with a massive scale-up in preventing transmission by targeting the mosquito vector with insecticides, have resulted in large reductions in malaria mortality in sub-Saharan Africa in the 21st century,[3] a success highlighted on World Malaria Day 2015. The long-term goal of malaria eradication is not possible without a focused multifaceted approach that combines treatment and prevention. No drug campaign or future vaccine roll-out will succeed without effective vector control.

The necessity of effective drugs for malaria treatment is widely accepted, and reports of suboptimum performance of the combination treatment of artemisinins have elicited a serious international response to curtail the spread of the resistant parasite.[4] Malaria prevention relies mainly on one chemical class of insecticides, the pyrethroids; insecticide resistance is decreasing the efficacy of this treatment. However, the spread of insecticide resistance is insidious. Whereas health workers and patients recognise a failing treatment immediately, it is not as obvious when mosquitoes fail to respond to insecticides. Extensive insecticide resistance is needed before the effect on mosquito survival becomes apparent, and the number of cases of malaria and deaths increase.

Malaria prevention in Africa relies almost entirely on the use of insecticides in the domestic environment in the form of longlasting insecticide-treated bednets or indoor residual spraying. Use of longlasting insecticide-treated bednets reduced under-5 child mortality by more than 20% in both large-scale trials and under routine conditions.[5,6] The distribution of longlasting insecticide-treated bednets has been rapidly scaled up since 2000 with an estimated 54% of African households at risk now possessing at least one net, although coverage and usage are uneven (figure 1). In 2008, Roll Back Malaria, via its Global Malaria Action Plan, set the target of universal population coverage for all people at risk of malaria.[7] National scale indoor residual spraying began in 1946 and was the main prevention strategy of the malaria elimination efforts of the 1960s. With the demise of this effort, most indoor residual spraying programmes stopped in sub-Saharan Africa but many continued in Asia. Largely spearheaded by the US President’s Malaria Initiative, indoor residual spraying has been reintroduced in many African countries. By 2013, 55 million people per year (about 7% of those at risk from malaria) were protected by indoor residual spraying through this programme in Africa.[3]

Increased coverage with these preventive measures has achieved striking results with the estimated malaria burden halving across Africa since 2000. However, the decision to scale up vector control was not accompanied by plans to ensure the sustainability of these insecticide-based methods. Pyrethroids are the only class of insecticide recommended by

WHO for use on longlasting insecticide-treated bednets. When the President's Malaria Initiative launched in 2005, all indoor residual spraying programmes were also using this insecticide class and in 2013, nearly two-thirds of indoor residual spraying programmes worldwide continued to rely on pyrethroids. Thus, for more than a decade, mosquito vectors of malaria have been targeted with a monotherapy. Inevitably, resistance has been selected, and in some parts of Africa pyrethroids no longer kill mosquitoes. With no new insecticide class to replace the pyrethroids expected for a decade, the threat of resistance derailing malaria control has become an issue of urgency that can no longer be ignored without risking a global public health catastrophe.

Current situation

As malaria vector control has escalated across Africa, so too have the number of reports of pyrethroid resistance in both major vector groups, *Anopheles gambiae* sensu lato and *Anopheles funestus* (figure 2), and it is rare to find sites in Africa where one or both these vectors do not show some resistance to pyrethroids.

Pyrethroid resistance was first detected in the African malaria vectors in Sudan in the 1970s and later in west Africa in the early 1990s[8,9] and was probably selected for by exposure of mosquitoes to pyrethroids used to protect agricultural crops against insect damage. This resistance was caused by a target site mutation kdr (knockdown resistance), which spread rapidly across Africa. However, the level of resistance conferred by this mutation alone is low, and this led to complacency with the resistance having little or no operational effect on the efficacy of longlasting insecticide-treated bednets.[10,11] Now, more potent resistance mechanisms have evolved, which have resulted in longlasting insecticide-treated bednets and indoor residual spraying pyrethroid formulations that no longer kill mosquitoes in different settings. These resistant mosquitoes can survive up to 1000 times the concentration of insecticide that kills susceptible mosquitoes, and investigators are increasingly noting blood-fed mosquitoes inside longlasting insecticide-treated bednets or resting on newly sprayed walls.[12–15]

The study of the direct effect of insecticide resistance on malaria transmission is highly complex. A systematic review[16] of experimental hut studies assessing long-lasting insecticide-treated bednets concluded that although some forms of pyrethroid resistance were clearly affecting entomological indicators, such as blood feeding and survival, the quality of the data, variability of experimental design, and inconsistency in methods of resistance measurement made it impossible to assess the effect on malaria transmission. Programmes of indoor residual spraying that have responded to pyrethroid resistance by switching to alternative insecticides have shown a substantial fall in cases of malaria, providing the most compelling evidence that pyrethroid resistance is already resulting in increased malaria deaths in Africa.

What can be done?

In 2012, WHO published the Global Plan for Insecticide Resistance Management in malaria vectors.[17] This report raised awareness of the threats of resistance and put in place a high

level framework to manage it. This plan will soon be supplemented by guidelines for countries to develop their own resistance management plans. However, major operational challenges to implementing many of the recommendations exist. With only one insecticide class available for longlasting insecticide-treated bednets, and Roll Back Malaria advocating universal longlasting insecticide-treated bednet coverage, what should countries do when they detect resistance to this insecticide class? Do they continue to scale up coverage, exerting further selection pressure on the mosquito population? What level does resistance have to reach before the insecticide becomes completely ineffective? Would greater returns on investment be obtained by concentrating on the barrier protection provided by more durable nets? A proactive initiative from the global health community is needed to devise practical guidance on how to respond to pyrethroid resistance. This effort needs to be underpinned by solid evidence, which is urgently needed to guide countries currently relying on increased coverage with longlasting insecticide-treated bednets to reduce their malaria burden.

Advice on when to introduce alternative strategies to maintain control is crucial. Industry is starting to innovate with products designed to combat resistance, such as bi-treated nets and longer lasting non-pyrethroid indoor residual spray formulations with single insecticides or as mixtures. Countries need to know under what resistance scenarios innovative products, including those designed to overcome specific resistance mechanisms, might provide better protection than conventional longlasting insecticide-treated bednets.

Alternative chemical entities for use in indoor residual spraying are available, although resistance to these is increasing too. Here the guidance from WHO is clear, but so far, very few African countries have well developed resistance management plans for indoor residual spraying,[18,19] and for some countries, faced with resistance to all available chemistries, the advice is of theoretical rather than practical relevance. In any case, all insecticide resistance management strategies need the introduction of methods that are more expensive than current interventions. In theory, short-term increases in expenditure are rewarded by long-term gains because the effectiveness of available quality methods is prolonged and the expense (in economic and disease burden terms) of control failure is averted. But how do control programmes, and donors operating on fixed or declining budgets balance the need to maintain coverage levels with the demands to change to more costly insecticide classes to preserve insecticide susceptibility?

Ultimately, the successful implementation of the WHO global plan requires the development and operational deployment of new insecticides. The Product Development Partnership IVCC[20] are working with industry to develop novel public health-specific insecticides and bring these to market. With several of these urgently needed products in the pipeline, a concerted effort has to be made to streamline the developmental, regulatory, and WHO recommendation pathways. Without such steps, entry of these new insecticides to the market is expected to be at least 5 years away. Furthermore, in view of the time, cost, and difficulty associated with operational implementation of new public health insecticides, these new products should never be introduced as large-scale monotherapies for malaria prevention. As with drugs and antibiotics, it is essential that insecticide resistance management starts before

resistance is selected, ideally before the product is released into the market, and not as a reaction to rapidly increasing resistance or increased disease transmission.

It is time to take a more urgent and proactive approach to insecticide resistance. Most immediately, all relevant partners need to stop simply noting the growing resistance trend and work together to ensure that the ability to prevent malaria is maintained. Countries should be helped to develop rational malaria prevention strategies that will prolong the efficacy of current vector control methods, and ensure that these are adequately supported by the major donors. We cannot be paralysed by the absence of data and having to work under resource-constrained conditions. Learning on the job will be crucial to refine recommendations and provide an evidence base for new insecticides, interventions, and resistance management strategies.

In parallel, the global malaria community need to accelerate the development of new insecticides and other non-insecticide-based vector control methods, and their pathway to market. In doing so, researchers need to learn from the lessons from the past and introduce new insecticides in a format that will ensure that they are not rapidly compromised by resistance. To realise these ambitions, and to ensure that vector control continues to save lives, a goals-driven alliance is needed of all key stakeholders (research and implementation funders, government organisations, non-government organisations, academia, industry and other innovators, and WHO), each committed to playing its part. Without this approach, much of the hard won progress in reducing malaria transmission will be lost.

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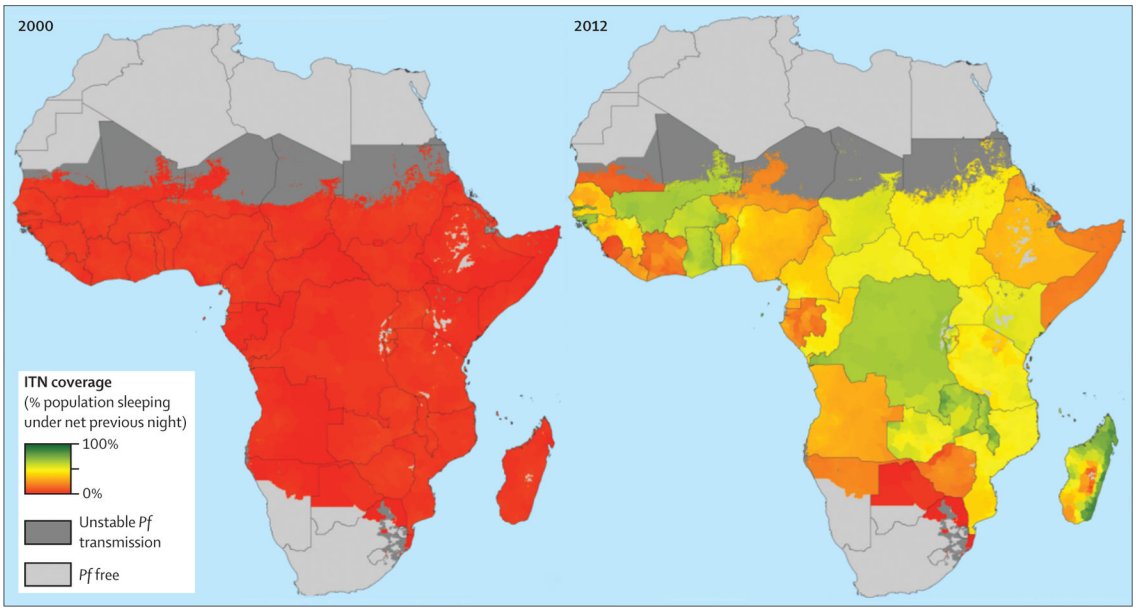

Figure 1: The change in longlasting pyrethroid treated bednet coverage in Africa, 2000–12
ITN=insecticide-treated bednets. Pf=*Plasmodium falciparum*.

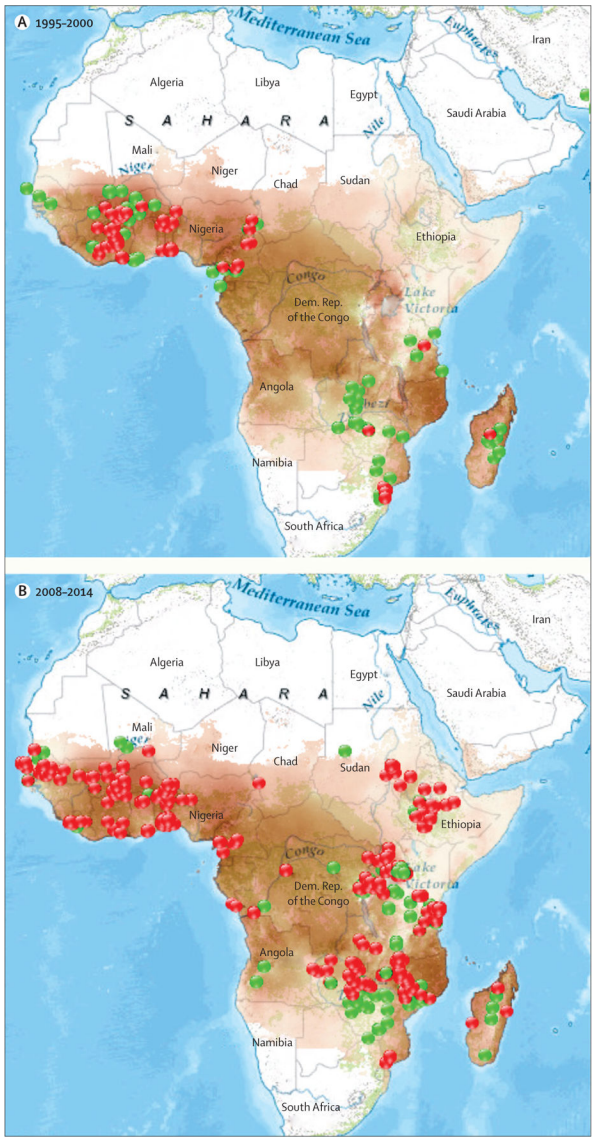

Figure 2: Reports of pyrethroid resistance in African malaria vectors, for (A) 1995–2000 and (B) 2008–14

Red dots show resistant populations according to WHO's definition of less than 90% mortality after exposure to a discriminating dose; green dots show susceptible populations. Base map shows malaria endemicity. Reproduced from IR Mapper, by permission of IR Mapper, October, 2014.