Global **Malaria** Programme

Technical consultation on the use of economics in insecticide resistance management for malaria vector control

Report of a virtual meeting,
14–16 September 2021

World Health Organization

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ABBREVIATIONS

IR	Insecticide resistance
IRM	Insecticide resistance management
NMCP	National Malaria Control Programme
USA	United States of America
WHO	World Health Organization

1. GENERAL BACKGROUND

The problem of mosquito resistance to insecticides is not new. Since the invention and deployment of insecticides, mosquitoes have evolved resistance to them, sometimes within a few generations, and have even been found to be resistant to insecticides never deployed before. Three of the top 16 arthropod species to evolve resistance to pesticides around the world are mosquitoes *(1)*.

Insecticide resistance (IR) is defined in many different ways. The definitions of resistance can be divided into those that are biological and those based on human values *(1)*. Biological definitions focus on genetics and are often based on thresholds for resistance, allele frequency or population mortality when exposed to an insecticide. The presence of a resistance allele in a gene is the basis of biological resistance. According to the World Health Organization (WHO) *(2)*, insecticide resistance is a property of mosquitoes that allows them to survive exposure to a standard dose of insecticide. The emergence of insecticide resistance in a vector population is an evolutionary phenomenon due to either behavioural avoidance (exophily instead of endophily, for example) or physiological factors whereby the insecticide is metabolized, not potentiated, or absorbed less than by susceptible mosquitoes, or is conferred by target site alteration *(2)*.

Note that survival by mosquitoes may or may not be an adequate indicator of even biological resistance, and that ultimately the interest lies in a potential functional loss of insecticidal capacity to reduce transmission. In the context of public health, there is therefore a need to define insecticide resistance as an impact on the effectiveness of an intervention, which implies that while resistance tests (WHO test kits, for example) may indicate a potential problem, they do not necessarily indicate that the effectiveness of an intervention has been lost. Furthermore, mosquitoes categorized as biologically resistant may survive, and therefore be defined by, one dose of insecticide, but killed by a higher dose.

Practical, economic definitions of resistance relevant to public health goes beyond the genetics and the simple bioassay: the economic consequences are also determined by the environment, the abundance of mosquitoes, and all the management interventions deployed. Economic definitions consider the perspective and goals of a stakeholder and the practical consequences of interference with those goals. One example of an economic definition of resistance is the reduction in vector control due to resistance in an *Anopheles* population that causes malaria deaths to exceed a certain number in a country. In this case, it is the control failure which is important, and not the genetics of the mosquito population. It is likely that threshold-based definitions are irrelevant for economic models that account for the evolution of resistance over a time horizon. Note that both biological and economic definitions are subjective.

Integrated vector management is rational decision-making for optimal use of resources for vector control *(2)*. The aim is to improve the efficacy, cost-effectiveness, ecological soundness and sustainability of vector control activities against vector-borne diseases. Insecticide resistance management (IRM) is long-term integrated vector management that helps stakeholders achieve their goals *(1)*. As is the case with Integrated Pest Management in agriculture, the goal is never simply to reduce pest densities or delay evolution of resistance of the pest, but rather to consider wider societal (in this case, public health) benefits. Thus, the evolution of resistance can be delayed by a greater or lesser degree, depending on the economic evaluation. Because economists optimize a benefit to human society when they consider IRM, attempts to limit the evolution of resistance will only be an economically optimal choice if resistance truly and significantly interferes with stakeholders' ability to limit cases

of malaria. The speed of evolution is also a major factor. Complete prevention of evolution is rarely attempted: delaying resistance is the usual approach, if determined to be economical.

Typical approaches to IRM include designing the system so that resistant insects do not bite humans or transmit malaria, designing the system so that vector control is easier or less expensive, and reducing the selection pressure (mortality and repellency) experienced by mosquito populations during vector control. In vector control, examples of design options include various insecticide treated nets, such as insecticide-treated nets, window screens, changes to water resources, and possibly the use of non-human hosts ("baits") for the mosquitoes. Some options for control include changes to concentration of insecticide, use of mixtures of insecticides, variation in scheduling use of multiple insecticides, and integration of insecticidal and non-insecticidal vector control.[1] All alternatives should be evaluated not for how they delay evolution of biological resistance, but for how they improve public health and the use of resources.

Unfortunately, solutions and improvements are usually constrained by the limited insecticide pipelines, the problem of repurposing insecticides used now and in the future by agriculture, and limited budgets. Use of the same class of insecticides in agriculture increases the evolution of resistance by mosquitoes targeted in vector control *(3)*, because the mosquito populations can be exposed to the same insecticides inside and outside of houses. However, developing new insecticides that are different from those used in agriculture will likely increase vector control costs.

The specific goals of each national malaria control programme (NMCP) will determine how each evaluates vector control and the mosquito resistance that may reduce the effectiveness of control. Economic evaluations and planning for the future typically require these goals to be based on effective metrics for benefits and costs, a time horizon, a discount rate, a clear description of the spatial scale being considered, and a prediction with a rational basis. When performing an economic analysis involving prediction of the future, two key decisions must be made about the consideration of time. First, the stakeholders must select a time horizon over which decisions will be made and the economics will be evaluated. Consequences for human health are often evaluated over long time horizons (over 30 years). Technologies that are likely to be useful for only 5–10 years are usually evaluated over shorter time horizons, sometimes as short as donor funding cycles (1–3 years). Time after the end of the chosen horizon is considered to be of no importance at the point when funding/procurement decisions are made. The second concern is the choice of time value of costs and benefits. People typically value goods and services provided in the future less than those provided immediately. Thus, future economic values are discounted relative to current values. In many public investment evaluations discount rates vary from 0–3% per year: the higher the percentage, the lower the future is valued. For example, with a 3% discount rate, expenditure of US$ 100 in the 30th year is valued as US$ 42 in the first year. The same model would impose the same reduction for the discounted value of a human life in the 30th year. Policy-makers may feel more comfortable valuing future human lives much the same as present lives, and thus prefer to use long time horizons and discount rates less than 3%. On the other hand, it may not be realistic to develop models that adequately predict changes in policies, human populations, technologies, mosquito populations, and climate over long time periods – in which case discount rates provide an opportunity to account for greater uncertainty in modelled outcomes. Although the IRM models will explicitly simulate evolution of the mosquito populations, it is not clear how other dynamic factors will be modelled.

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[1] Current guideline recommendations for the use of non-insecticidal vector control tools are not affected by the presence/extent of local insecticide resistance.

Management implies both action now and plans for future actions *(4)*. Thus, making good decisions will require prediction about future realities. Although studies of the past and modelling of idealistic scenarios can contribute to our understanding of useful ideas and strategies, ultimately shorter-term predictions about the future (ex ante economic analyses) will be necessary, using properly validated models and providing uncertainty ranges that are realistic enough for specific decision-makers in a clearly defined region.

Future-oriented adaptive management of resistance has the potential to bring about important population health benefits, but it also involves additional costs, and should therefore be subject to rigorous economic evaluation in comparison with other, potentially less costly strategies. This kind of analysis will require observations to be made at the same frequency over time as the management decisions. The costs of continuous monitoring and frequent implementation should be included in the economic evaluation in order to determine whether adaptive management strategy is indeed cost-effective. Examples of monitored conditions are mosquito density, biting frequency, resistance allele frequency, proportion of mosquitoes dying in bioassay, and net quality and durability. Sequential use of insecticides is an example of an intervention that could be based on monitoring (sequential use is deployment of a single insecticide which is then replaced when its efficacy has declined to unacceptable levels due to IR). It is relevant to mention that in agriculture, such monitoring costs are usually either zero because monitoring is not performed, or are ignored. The value of information and risks associated with low quality or missing data should also be evaluated as part of this analysis.

Questions raised before this technical consultation include:

(i) Is it worthwhile investing resources into maintaining vector susceptibility and delaying resistance in vectors, given limited budgets, and uncertainties in the available data?

(ii) Is it a good idea to spend more on new, more expensive tools/strategies now (assuming they can also delay the development of resistance), or is it better to delay their use until the efficacy of the existing tools has been exhausted, without much regard for insecticide resistance?

(iii) Is preventative IRM always preferable to reactive IRM in malaria vector control?

(iv) How will such solutions account for the trade-offs in malaria management that exist due to limited budgets, such as reductions in programmatic and geographic coverage?

Given that integrated vector management and IRM are fundamentally economic activities, decision-making in this area must be informed by economic and public-health thinking and model-based economic evaluations and predictions. However, limitations and uncertainties in historical data, knowledge, and ongoing data collection make future efforts difficult. The present technical consultation brought together experts in vector control, economics and malaria management to identify key challenges and suggest next steps.

2. OBJECTIVES

The overall objective of the technical consultation was to define and implement a process whereby economic principles are explicitly applied to inform insecticide resistance management (IRM) of malaria.

3. SPECIFIC ACTIVITIES

The identified activities for the technical consultation were as follows:

1. to provide an overview of the current status of insecticide resistance, and of resistance management practices and their likely effectiveness in maintaining susceptibility in malaria vectors;

2. to generate an overview of the ways in which economic principles have been applied to insecticide resistance management in malaria vectors and to valuing insecticide susceptibility;

3. to define next steps in applying economic principles to IRM for malaria vectors and to the deployment of new vector control interventions as part of a resistance management strategy.

4. SPECIFIC OUTPUTS

The anticipated output of the technical consultation is a meeting report providing a summary of the discussion, including both key steps and challenges, on how economic principles can be applied for IRM for malaria vectors and to the deployment of new vector control interventions as part of a resistance management strategy.

No recommendations to WHO were made as a result of this meeting. This consultation forms part of a larger body of work to enhance the decision-making process around malaria vector control interventions, which will serve as a pathfinder to inform further work around resource prioritization for malaria.

5. PROCEEDINGS

Day one: presentations

On the first day of the consultation the focus was on reviewing the present state of knowledge of insecticide resistance, its evolution and its impact on the effectiveness of vector control interventions.

The meeting started with brief opening remarks by Pedro Alonso, Jan Kolaczinski, and Yevgeniy Goryakin of WHO. They welcomed the participants (Annex 1) to the virtual meeting and described the objectives (Annex 2).

The Declarations of Interest (Annex 3) were disclosed. Based on WHO's review of the declared interests, it was decided that none of the declarations constituted a conflict of interest in this context and that the considered experts could participate in the meeting, subject to the public disclosure of their interests. The Statement of Declarations of Interests was read out to the meeting participants and is provided in the Appendix.

Lucía Fernández Montoya and Thomas Churcher began their presentation by describing standard procedures for monitoring insecticide resistance in malaria vectors, and then discussed findings from the WHO global database on insecticide resistance in malaria vectors. The database contains bioassay information on four classes of insecticides (carbamates, pyrethroids, organochlorines, organophosphates) and 65 species of *Anopheles*. Since 2009, vector resistance to insecticides has been increasing significantly. Over the same period, testing for resistance has also increased. Collaborators have confirmed that ten species are currently resistant to four classes of insecticides. With regard to pyrethroids, 86% of countries report resistance and 66% of monitoring sites have confirmed resistance in at least one species.

Montoya and Churcher displayed results demonstrating significant variability in resistance test results across countries and generally over space and time (six years). They mentioned that sampling bias and measurement error may be influencing these findings. In addition, the species tested can change during a year, leading to complicated patterns. Fifty-three countries have completed national insecticide resistance (IRM) plans and that number is expected to increase.

Jenny Stevenson provided a brief overview of the WHO guideline development process, followed by the discussion of the latest vector control guidelines. WHO guidelines contain general recommendations that are based on the latest, systematically reviewed, available evidence, but each Member State develops its own policies. The first guidelines for vector control were published by WHO in 2019. Revisions were published in 2021, including the publication of consolidated guidelines in a user-friendly MAGICapp web-based platform *(5)*, and more revisions are expected in the future. Recommendations include use of either indoor residual spraying of an insecticide or insecticide-treated nets. For any insecticide-based intervention, WHO recommends that the resistance profile of local vectors is assessed to allow the most appropriate insecticide to be selected. The guidelines also note that there is always a risk that resistance will develop to the selected insecticides. The guidelines provide some background information on prevention, mitigation and management of insecticide resistance. The insecticides applied to nets are pyrethroids. If resistance to pyrethroids is confirmed in an area, WHO conditionally recommends use of piperonyl butoxide plus pyrethroid treated nets. There is currently very limited information in the guidelines on the costs and resource use associated with the vector control intervention deployment. One reason for this technical consultation is to explore if or how economic evidence can contribute to the development of guideline recommendations, including conditional recommendations.

Lauren Carrington then provided a brief overview of new vector control interventions under evaluation by WHO. Current vector control interventions have a number of weaknesses, including in terms of their present efficacy (which may have been partially reduced due to growing resistance to the insecticides being used) and their effectiveness to provide protection to people who are outdoors during peak biting times. Thus, new, more efficacious interventions (strategies, tools, products) are needed, and several are currently being evaluated by WHO (the general WHO vector control evaluation process was described). The Vector Control Advisory Group – responsible for determining whether the new interventions have public health value based on results from two randomized control trials – consists of 15 specialists with expertise in epidemiology, entomology, statistics, product development and regulation. Economic evaluation is outside the scope of the Advisory Group.

Besides new insecticide-treated nets, the Vector Control Advisory Group is considering or will likely consider the following types of interventions, some with the potential to mitigate or manage the evolution of resistance: outdoor bait stations; strategies that repel mosquitoes from houses and lure them into outdoor traps; spatial repellents inside houses; insecticide-containing eave tubes in houses; genetic manipulation of mosquito populations; and systemic treatments such as endectocides (drugs effective against both endoparasites and ectoparasites) and ectocides (drugs without activity against endoparasites that are effective at killing blood-sucking ectoparasites once these have ingested one or more blood meals from a treated human or animal host). Many of these interventions still rely upon the use of insecticides. As is currently common, not all regions or subregions will be represented in trials.

Jan Kolaczinski focused his presentation on emphasizing the importance of strategic information in informing the optimal selection of vector control interventions, as well as their tailoring to a (sub)national context. He started with an overview of various WHO guidance documents where insecticide resistance is considered. The first Global Plan for Insecticide Resistance Management was published in 2012 by WHO *(6)*. In 2017, a framework for resistance monitoring and related management was created *(7)*. As noted above, the Guidelines for Malaria Vector Control were published in 2019, and further updated in 2021 *(5)*. The guidelines contained insecticide resistance testing guidance and tables that related testing results to decision-making, but in general the guidance on resistance management is rather limited, and in any case should be tailored to a sub(national) context. The Malaria Threats Map provides data that can inform decision-making for IRM and the selection of new interventions *(8)*. WHO is developing a new version of its monitoring and intervention-selection document.

As discussed in the previous presentation, there are a number of new interventions with a potential to enter the vector control market in the near future. However, optimal selection of interventions becomes ever more complicated in the context of the stagnant (or even shrinking) malaria budgets. Challenges to the optimal intervention deployment include their expected higher costs, lack of information on their context-specific efficacy/effectiveness and some other relevant factors, including the role played by future evolution of insecticide resistance. According to Kolaczinski, there is therefore a need for strategic information about costs, the impact of resistance on effectiveness in terms of preventing the targeted disease(s), and the links between entomological and epidemiological data (public health benefits) – although better data does not always equal better decisions without a well-designed and transparent decision-making process. A transparent and structured prioritization process is therefore required that considers all intervention options (not just those for vector control) and tailors a management plan to a specific context. Such a process will benefit from local data (costs and effects) and reliable mathematical models to explore the future impact of potential scenarios.

Day one: discussion

One important limitation to the evidence-based decision-making process is that the methods to measure the extent of insecticide resistance are actually quite crude. As was shown in the first presentation, there is significant intertemporal and geographical variability in resistance data, although at least part of this may be due to sampling quality issues rather than any real variations in resistance. If this is indeed the case, it is not clear to what extent decision-makers should interpret limited local data, which has high measurement error, and how this uncertainty ought to be considered in their resource allocation decisions (for example, for procuring nets locally). This lack of reliable resistance data is especially acute on the subnational level.

Having said that, although resource investment decisions should not be driven by small variations across space (for example, procurement decisions should not be made on a village-by-village basis), there is nevertheless a clear trend of increasing resistance over time. Data over a larger geographical area (appropriately averaged) can also be very informative for decision-makers. In any case, procurement is not done for a very small area like separate villages, but rather over provinces or districts.

Given that long-lasting insecticidal nets are generally only replaced every three years, one participant wondered why the Vector Control Advisory Group does not require that public health value is conferred to the target population for three years or more.[2] The answer given was that, although the efficacy is evaluated over a two-year period with the aim of providing faster initial access of new products to the market, WHO does encourage that follow-up evaluation also takes place later (and does encourage trials of three-year duration). In addition, the efficacy of piperonyl butoxide nets may be expected to last less than three years, as piperonyl butoxide is not sufficiently wash-resistant. In any case, two-year trial duration is quite difficult to perform (and might discourage some companies from enrolling in such trials), so this is in a way a compromise.[3]

It is also important to keep in mind that, while the WHO prequalification process is important from the procurement point of view (that is, there is value in receiving the WHO recommendation), it is by no means mandatory. Some manufacturers prefer not to apply for prequalification.

On a related note, a question arose regarding to what extent trial results on the efficacy of new tools should be extrapolated to other areas, especially if they have not been conducted in similar geographically relevant areas (such as savannah, forest or some other special areas). The answer was that WHO does encourage the trials for Vector Control Advisory Group evaluation to be conducted in epidemiologically separate areas. Realistically, however, it is impossible for such trials to be fully representative, as there are often multiple zones, over which the effect can vary, and it is impossible to conduct trials everywhere.

Managing/delaying insecticide resistance costs money, so at the very least one should be reasonably confident that this will eventually also result in public health benefits. Some participants questioned whether data clearly show a strong link between growing resistance, increases in malaria transmission, and clinical impact; in general, it seems that evidence is not always strong, mostly due to methodological shortcomings. It is apparent that there is gradual decline in efficacy of long-lasting insecticidal nets (with stronger evidence for IRS interventions) in areas of high resistance, but the efficacy does not disappear completely. A related question was whether the efficacy of insecticides is declining more and faster in the areas where insecticide-treated nets have been deployed the longest and with the highest coverage. In this context, a question was also raised as to whether mosquito nets without insecticidal treatment can be used as part of an IRM plan.

A number of other data limitations were also highlighted. For example, the evidence appears limited on how fast susceptibility can recover when the selection pressure is reduced. Some studies show some correlation between the use of insecticide-treated

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[2] This is also relevant in the context of economic evaluations. For example, do we expect that long-lasting insecticidal nets will be replaced every couple of years?

[3] An opinion was voiced that, while conditional recommendations can be made on the basis of short-term results, it is very important to have the longer-term results in order to understand durability and thus to be able to properly compare the cost-effectiveness of alternative strategies.

nets and resistance, but the signal is quite weak. In addition, there is also important lack of economic evidence – and even when such evidence is available, it is not always taken into account in the guideline development process.

The participants debated the choice of time horizon for evaluating benefits and costs, as resistance cannot be delayed indefinitely (see more discussion on this below). Thus, if the goal is to reduce malaria burden cumulatively, over a number of years, then perhaps it is alright to accept some level of resistance by protecting more people now (with less than perfect tools), while also expecting that something may come up later.

An opinion was voiced that it is important to take into account the entire malaria budget, and not focus only on vector control interventions. This is because the use of the more efficacious tools may lead to overall savings from reduced spending on case management, which may to some extent offset the intervention costs, and therefore lead to better cost-effectiveness. Also, a question was raised as to whether the status quo scenario assumes that resistance would stay the same in the future. Again, this can have important implications for cost-effectiveness.

Some participants also emphasized the need for a few common metrics for evaluating outcomes of cluster randomized control trials and using results in decision-making regarding interventions and IRM.

Moving beyond vector control for economic analysis means that there will be a need to define some common outcomes for cross-intervention comparison. This is also very important for moving from more theoretical discussion to more practical modelling steps.

Among some other issues raised during the discussion were modelling time to tradeoff and externalities of resistance, as well as the link between the economics of IRM and vector control and the overall malaria transmission management.

Day two: presentations

Whereas the focus of day one was on reviewing the current state of knowledge, on day two the perspective was more forward-looking. Ian Hastings focused his presentation on describing the modelling done by his team of the effect of various vector-control IRM strategies/interventions (such as mixtures, rotations, sequences, micro-mosaics[4]). The focus of their modelling work was on predicting the effect of IRM choices on insecticide repertoire lifespan, as well as on their longer-term effectiveness in killing mosquitoes; as such, their main assumption was that delaying insecticide resistance was an important goal to be achieved in itself, without considering follow-up questions such as the economic costs of such control efforts, or the public health implications of IRM strategy choices.

Specifically, their deterministic models assume the existence of two mosquito genes, each conferring resistance to one insecticide. Resistance can be complete or incomplete (that is, with less than 100% survival of "resistant" mosquitoes after insecticide contact) and fitness costs due to resistance are also taken into account. The results are evaluated in terms of mosquito mortality and resistance allele frequency. The team compared mixtures, sequential deployment and annual rotations of two insecticides. They concluded that mixtures of two highly efficacious insecticides

[4] See Barbosa et al *(9)* for an earlier study focused on malaria transmission.

perform the best at delaying evolution of resistance. These are also better than micro-mosaics. Rotations are not superior to sequential use. Because of the relatively high cost of mixtures, there is concern that substandard mixtures may be introduced (that is, those that do not consist of adequate concentrations of both chemicals). The team also explored the influence of insecticide residue decay and the importance of heterozygote survival for evolution: heterozygotes typically have advantages over homozygous susceptible mosquitoes as the effective dose of insecticide declines. Ian Hastings also discussed various potential implementation challenges associated with the use of some strategies – for example, how could one tell a manufacturer not to deploy an insecticide until resistance has evolved to the one currently in use?

Thomas Churcher then described his team's new user-friendly tool called MINT (Malaria Intervention Tool), based on the Imperial malaria model, which aims to predict context-specific epidemiological impact of malaria interventions based on data from entomological experimental hut trials (Sherrard-Smith et al. Imperial College, unpublished article, 2020: Optimising the deployment of new vector control tools against malaria). The tool was designed in response to the need for more context-specific data on the effectiveness and cost-effectiveness of vector control interventions. The tool can also calculate costs of interventions per malaria case averted over a three-year time horizon. The model combines entomology and epidemiology but does not model resistance evolution. The team hopes that the software can be used by local decision-makers in the future, as more data becomes available. Conclusions from the Sherrad-Smith document highlight the fundamental aspects of stakeholder goals in an evaluation: "The most cost-effective intervention package will depend on product price and goals of the NMCP" and "... the most impactful interventions might not be cost-effective and goals of NMCPs should be prioritized."

Zachary Brown completed the set of day two presentations with a description of two relevant economic models. He first gave an example of how economic analysis, including consideration of marginal user costs, can be used to determine the optimal level of pesticide use in agriculture in order to maximize surplus value to consumers and producers. The important insight of this model is that pesticide use will be optimal up to a point where the profits (and consumer surplus) are maximized, after which economic returns may be negatively affected by growing selection pressure for resistance resulting from pesticide overuse (and therefore depletion of susceptibility). He further provided an example of a dynamic optimization framework, where expected net present value of pest susceptibility is maximized by an optimal choice of IRM interventions. In this dynamic setup, the choice of optimal IRM strategies will depend not only on current levels of insecticide resistance, but also on how current IRM choices will affect future evolution of resistance (appropriately discounted), and therefore future profitability. The model can also accommodate factors such as pest density, fitness costs and dominance/recessiveness of resistance genes.

Brown also discussed some social and institutional challenges to this simplified setup, including potential interregional spread of resistance and the need for collective action to deal with it, which may also be an issue in vector control.[5] One key difference between agriculture and malaria control is that in agriculture, the focus is primarily on profit maximization as a measure of value of susceptibility, whereas the focus of malaria control is on maximizing health benefit (which can be measured by disability-adjusted life years (DALYs) for example).

[5] A relevant point was made during the discussion on this: "the availability of efficacious products now and in future is a natural resource that depletes just as forests, clean air, clean oceans. National policy makers do not have sufficiently long time horizon to protect this natural resource, and so, just as in the environmental debate, it requires an overarching international initiative such as the Paris Agreement on climate to commit national policy-makers to such long-term objectives".

He then discussed adaptive management *(10)*, which incorporates a dynamic value of learning into optimal decision-making. Related approaches for "partially observable Markov decision processes" *(11)* could be applied when genetic frequency of resistance alleles is not measured, especially at very low gene frequencies. Other work has studied the value of monitoring *(12–15)*. Brown ended his presentation with a description of his modelling as part of the Kim et al. study *(16)*, that determined the Value of Information in malaria vector control. Kim et al. *(16)* performed an uncertainty (sensitivity) analysis related to the value of biological information.[6] This type of analysis can be used to make decisions about data collection and reduction in uncertainty.

Day two: discussion

In general, once resistance has developed, it is very hard to eliminate, unless there are very high fitness costs. One possible exception to this rule is potentially provided by gene drives, which can help drive back susceptibility into a vector population *(17)*. While complete pyrethroid resistance may be inevitable, it can still be managed[7] to some extent, such as with a new class of insecticides or IRM strategies. From the economic point of view, the question is whether such efforts are cost-effective *(18)*.

Given the limited malaria budgets, the crux of the matter is to consider economic tradeoffs. For example, the participants discussed whether higher coverage of existing insecticide-treated nets (which are cheaper and protect more people, but continue to select for resistance) was preferable to lower coverage with higher quality (and possibly less resistance-selecting) nets. Some participants advocated for priority to be placed on protecting the users of the insecticide-treated nets, while others advocated for an emphasis on reducing the mosquito population. No consensus was achieved. More generally, with the available data (and methods for modelling), it is rarely possible to answer such questions at the current time. In many cases, such decisions are politically driven. However, this may lead to suboptimal health outcomes.

The lack of evidence hindering the analysis is extensive. For example, it is not always clear how fast resistance develops, and to what extent it reduces the intervention effectiveness in averting malaria cases/deaths.[8] The discussion also revolved around other methodological shortcomings, such as lack of clarity and standardization in defining appropriate time horizons and discount rates. For example, is it always necessary to discount future gains in health? There may be a good argument not to discount, for example, when discounting may create intergenerational inequities. One response to this was that any time horizon acts in the same way as discounting (that is, beyond the end of the selected time horizon, the discounting is complete). One possible compromise can be to use a very low discount rate (not zero).

Participants also discussed the influence of spatial scale on vector control and related policy making. Policies are made at the country level, with implementation at regional or subregional levels. However, heterogeneous landscapes of mosquitoes and people make policy making and implementation difficult (for example, distribution of insecticide-treated nets is not based on village-level resistance data). The challenges

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[6] Their stakeholders used a time horizon of 10 years in a region of villages. The stakeholders chose a discount rate of 3% and chose to value each gain in one disability-adjusted life year (DALY) as worth US$ 7773, which is three times the per capita GDP, a value recommended by the WHO.

[7] Note that piperonyl butoxide nets are actually a resistance mitigation rather than management tool.

[8] It is also a matter of baseline levels of *P. falciparum* entomological inoculation rate (EIR). In areas where there are a lot of infectious bites, increases in biting rates will not make much of a difference, compared to areas where the baseline entomological inoculation rate is low. The impact of resistance will therefore get progressively worse in near-elimination settings.

are even greater when they are based on data from a few trials at a few locations. Interpolation and extrapolation will continue to be used in the near future.

Several economists urged the participants to focus on behavioural economics, including exploring the role played by incentives (for product development or appropriate use, for example), with some others cautioning that such incentives may unnecessarily distort the markets.[9] Economists also emphasized the need to discuss potential implications of diseconomies of scale (for example, in relation to targeting of interventions), and risk (as well as its valuation).

Equity considerations were also mentioned as a necessary complement to the studies on efficiency. It was also suggested that, if equity is of interest when modelling the effect of vector control interventions, then "total cases avoided" might not be the best outcome to consider (deaths may be a better metric to use).

Another discussion point concerned drug (rather than insecticide) resistance in malaria. In general, increasing resistance in drugs usually implies that they are really failing, and therefore must be withdrawn, whereas insecticide resistance in mosquito vectors, as detected by bioassays, does not imply that an intervention no longer works and also leaves some other options. In addition, in malaria drug-resistance management, experts have accepted that we will never have trials giving us evidence for the impact of long-term interventions. Consequently, they use mathematical modelling to predict 10 or 20 years into the future. They have defined outcomes such as (a) cases averted, (b) treatment failures averted, and (c) time until resistance reaches a certain level. They have solid evidence that drug resistance spread leads to increases in cases and prevalence. The experts also trust that drug diversity reduces resistance risk.

Some other questions raised during the discussion included the following: Is there a risk that some IRM strategies (sequences, for example) may discourage the development of new insecticides? What would future timeline for IRM be if costs of products decline? What price should be used to estimate the cost of deploying a new intervention?

Day three: discussion

No presentations were made on the third day.

The participants generally agreed that delaying resistance in itself is not the main goal; rather it is the improvement in population health (subject to the available budgets) that is of interest. In this context, conventional economic evaluations can be used as a general framework for assessing the value of malaria vector control interventions (including the value of delaying resistance). Therefore, although it is important to think about how any such benefits, if they exist, can be captured, the discussion should not be framed exclusively around comparing the value of IRM strategies. A few good entomological, epidemiological and management-behaviour models can be combined in several economic analyses to answer a variety of questions about IRM, vector control, and malaria transmission.

[9] One comment in relation to this: "There's a way of doing this without subsidies – a guarantee to buy a large volume at a low cost, which allows the manufacturer to produce at scale, achieving those economies, safe in the knowledge that someone will buy the product. It means the donor agreeing to take on the risk".

For example, the cost-effectiveness of applying sequences can be evaluated by comparing this IRM strategy to the other strategies (such as no IRM at all, mosaics, mixtures, combination nets). The benefit of delaying resistance can then be measured, for example, by the future reduction in the costs of malaria-related case management and disability-adjusted life years (DALYs) avoided. Conversely, the value of susceptibility can be depleted by the excessive use of insecticides, and this can again be linked with the health outcomes. However, it was emphasized more than once that delays in resistance/reductions in vector densities by themselves (without improvements in health) will not be of interest; rather, it is their potential link with future cases avoided that can indicate the value of maintaining susceptibility. In other words, we need to link entomology (that is, resistance level) with epidemiology (changes in infectious bite rate) and its likely clinical consequences in terms of morbidity/mortality. It will therefore be very important to make sure that both the effect of alternative strategies on changes in resistance, and the effect of insecticide resistance on malaria transmission (if it exists) are modelled robustly *(19)*.

In this framework, the issue of defining an appropriate time horizon for analysis to capture the benefit of better managed IR is key. For example, IR mitigation strategies (such as piperonyl butoxide nets) may result in more immediate reduction in cases/deaths, but they may not have a long-term effect on delaying insecticide resistance. In contrast, IR management approaches (such as some integrated vector management strategies) can potentially reduce the extent of resistance in the future, but it may take some time for this effect to appear – and using different endpoints can lead to different conclusions. It was mentioned during the discussions that economists may prefer to apply infinite time horizons[10] in order to avoid time-inconsistent planning (and instead use constant discount rates), but in malaria management this is not really the standard practice. Another relevant comment was that although long-term time horizons can be very important for capturing the benefits of managing resistance, decision-makers may have more immediate needs (their budgets are for much shorter periods of time, for example), and so may be more interested in maximizing health over much shorter periods of time.

The question of whether it would be optimal to invest into delaying resistance then becomes empirical, and only if it results in health benefits. According to the economic framework presented on the previous day, a rational decision-maker will optimize the use of IRM by maximizing net present value of susceptibility as measured by health-related benefits (for example, cases or deaths avoided). In other words, it may well be possible that in some cases the marginal cost of implementing IRM will be greater than the marginal benefit derived from delayed resistance – in which case some alternative, non IRM strategy may be chosen instead. However, susceptibility in itself is of no importance in this framework, as it is the derived health benefits that are of interest, and not the effect on the density of mosquitoes per se.

A number of uncertainties will complicate this analysis. As mentioned before, there is still a lack of robust evidence on the link between insecticide resistance and transmission. New interventions may be easier to deploy in a local, targeted fashion, but more local data may be needed for this. Combining insecticidal and non-insecticidal interventions may be valuable, but there is uncertainty in the effect. Some interventions require more frequent management changes than others, but this may require ongoing data collection. There is also key uncertainty on the effect of the arrival of new products on IR in the future, and a number of other uncertainties. It was proposed during the discussion that this can be addressed with the help of sensitivity analysis, as well as with approaches such as expected value of perfect information, which can help determine the value of collecting additional information for some key parameters.

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[10] In addition, the reference case for economic evaluations proposes the use of lifetime time horizons.

Several parallels were made between IRM approaches in agriculture and in vector control, although some key differences were also mentioned. For example, in contrast to agriculture, it will be the health outcomes that will be subject to maximization rather than profits. It was noted, however, that the public health-oriented framework can be of little relevance to manufacturers, for whom the profit margins are usually very low. One response to this was that it may still be possible to include profit considerations for manufacturers into this framework, as an additional constraint.

The question of economic incentives, such as certain subsidies, was raised several times. For example, it was mentioned that getting a new product into the market is a very time consuming and expensive process, which may discourage product development, especially given the limited profit margins. As a response to this, some incentives for development may be created, although decision-makers should be careful not to create market distortions. A concern was also raised that more thought should be given to incentivizing stewardship of existing tools, rather than relying on the emergence of new ones.

On a related note, cooperation and coordination amongst those implementing and using vector control tactics and interventions is critical to the success of IRM *(1)*. Coordination can be regulated by governments, authorized by farmer cooperatives, encouraged by neighbours, or happen naturally in a crisis. Often, incentives are needed to increase cooperation. Solving vector control problems will likely need integrated combinations of interventions, as the history of agricultural integrated pest management indicates. The economics of alternatives, including incentives, must be explored, but indirect and unanticipated negative effects of incentives should be considered.

More broadly, the analysis can go beyond considering exclusively the epidemiologic and economic dimensions of IRM strategies, and take into account a broader, societal perspective. In this context, multi-criteria decision analysis *(20)* could be valuable in evaluations of IRM and vector control, as it can take into account multiple criteria (such as the ethics of reducing coverage levels for some people; logistical challenges and so on, and not just the epidemiology/economics) to help the decision-making process.

Some other questions were raised which may require additional thinking, including whether dynamic optimization should be done from the perspective of an NMCP or from the perspective of global health policy.

6. PROPOSED NEXT STEPS

No recommendations were made to WHO. Instead, the following key next steps were discussed, with WHO Member States in mind as the ultimate target audience. Please note that the steps do not need to be conducted consecutively.

1. Prepare a paper that explains the role and value of economics in informing the need for IRM in malaria

This could be prepared by economists to explain how economics could help with making choices in the area of vector control, including taking into account the value of IRM. The document could also describe relevant lessons from IRM in agriculture and the management of antibiotic resistance in bacteria.

2. Create guidance on the economic evaluation of vector control interventions, including consideration of the value of delaying insecticide resistance (IR) and IRM costs

Better guidance is needed on vector control economic evaluation, including consideration of the value of delaying IR and of IRM costs. Such updated guidance could build on the International Decision Support Initiative Reference Case,[11] which draws on previous insights from WHO and other organizations. The reference case is a set of principles that guide economic evaluations and promote clear thinking about complex public health-related decision-making *(22)*. According to one participant, a major advantage of this approach is that much of the basic framework already exists and is accepted by leading organizations such as WHO. This reference case may be most useful for strategy development. In addition, applicability of some other international guidance documents can be explored, for example the reference case for the global health costing[12] can be adapted to the malaria vector control (and malaria more generally). Such guidance should also be accessible to policy-makers. Ultimately, NMCPs need clear, transparent, simple advice, and therefore good communication of practical guidance on an annual basis is necessary.

As part of such economic evaluation analyses, better modelling methods are needed to predict the impact of vector control interventions, including ability to take into account potential future benefits of managing resistance. So far, modelling has separately focused on IR and on effectiveness of interventions (effectiveness/cost-effectiveness), but the two approaches have not yet been fully integrated.

To enable such analysis, more robust understanding is needed on (i) how resistance will evolve, and what drives it, (ii) to what extent the rate of spread of IR will vary with integrated vector management, and (iii) how these processes are linked to malaria transmission and control. At these early stages of the model development, it is also important to understand the key drivers of the epidemiological impact of IR in order to ensure the best possible data can be collected moving forward.

Linked with this, existing tests provide limited information about the impact of resistance on the malaria transmission potential, and therefore are of limited value to the NMCP decision-makers. More meaningful definitions and measures of resistance therefore need to be developed.

3. Collect more and better data, including standardized accounting of economic benefits and costs

To assist decision-making and enable better modelling, more evidence needs to be available, including on the benefits specific to the IRM strategies, which may include extent of reductions in malaria cases, deaths, lower spending on case management, as well as on the costs of implementing the IRM strategies. Guidance on how to

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11 According to Wilkinson et al. *(21)*,
"A reference case guides the planning, conduct, and reporting of economic evaluations so that both the approach to the analysis and the presentation of the results are coherent, transparent, and consistent. But more than this, a reference case goes beyond recommendations of good practice methodology and analytics and constitutes an explicit position statement on a range of scientific and social values inherent in the practice of economic evaluation. A major motivation for using a reference case is that it enables institutions or individuals wanting to use economic evaluation to inform their decisions to do so in full knowledge of its limitations and relevance to the decision problem at hand."

12 For example, the Global Health Cost Consortium Reference Case has been published, including specific recommendations for the fields of HIV and tuberculosis.

collect such data may also need to be developed (see previous point). In evaluating effectiveness, the data collection can go beyond the traditional RCT approaches and also include quasi-experimental design/programmatic data. The use of common metrics and indices to enable comparison with other malaria interventions will also be important.

There will always be variability in data and uncertainty supporting assumptions about (i) mosquito biology,[13] (ii) human behaviour, and (iii) human values and economic parameters. Therefore, techniques will be needed to understand the impacts of uncertainty and possibly account for risks, which at the moment appear to be limited to the sensitivity analyses. Thus, the translation of large-scale policies to local conditions, especially without local data in many cases, and adaptive management may require extra care to be effective. A common set of metrics or indices will improve evaluation and communication within the scientific community and with NMCPs.

The cost of data collection must be a consideration as well as the value of any data for malaria management beyond vector control.

4. Consider using behavioural economics and incentives in economic models

Several participants proposed various ideas regarding incentives for product development and product acceptance. Others also stated that incentives for insecticide stewardship and other aspects of vector control (better bed nets) should be studied.[14] Incentives require a cautious approach because an incentive on one side of economic market could become a perverse disincentive on another side. Behavioural economics may also be valuable in properly accounting for collective action.

In addition to these four key next steps, three additional steps were also suggested:

5. Evaluate adaptive management and monitoring

It was proposed to explore how and whether it is feasible to use monthly or annual observations to adjust management of malaria vectors. As part of this, it will be necessary to develop simple, inexpensive assays that can be correlated with more meaningful measures of malaria transmission or functional resistance, while also taking into account the additional costs of such efforts.

6. Investigate option-value analysis

Zachary Brown proposed the use of option-value in an economic evaluation *(23, 24)*. Option value is a concept discussed in the Organization for Economic Cooperation and Development (OECD) Guidelines for Benefits-Cost Analysis and the Environment *(25)*. Option value is closely related to adaptive management and decision analysis using value of information. This approach might be particularly useful for investment in pilot projects to deal with insecticide resistance, which exhibit high uncertainty with

[13] For example, there is still little data on what insecticide resistance does to malaria control in the long run and how to parametrize fitness costs, and without this knowledge it is hard to predict what benefits IRM strategies will bring.

[14] Assuming the provision of such stewardship is indeed socially suboptimal (if this is indeed the case or not, may still need to be established empirically).

irreversibility (both from sunk costs and potentially in the evolution of resistance as well as epidemiological dynamics).

7. Develop a budget impact model for procurement decisions

In addition to the reference case for economic evaluation, some guidance would be useful to inform more practical, procurement-level decisions.

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ANNEX 2. AGENDA

DAY 1 - TUESDAY 14 SEPTEMBER 2021		
Open Session (Participants and WHO Staff)		
15:00 - 15:10	Opening remarks and welcome	Dr Pedro Alonso
15:10 - 15:15	Declaration of interest	Dr Jan Kolaczinski
15:15 - 15:25	Background, objectives and expected outcomes	Dr Yevgeniy Goryakin
PART I: UNDERSTANDING THE CURRENT STATE OF INSECTICIDE RESISTANCE, INCLUDING THE OVERVIEW OF THE CURRENT INTERVENTION OPTIONS		
Open Session (Participants and WHO Staff)		
15:25 - 16:00	Current insecticide resistance status in *Anopheles* vectors	Ms Lucía Fernández Montoya, Dr Tom Churcher
16:00 - 16:30	Brief overview of the WHO malaria vector control guidelines	Dr Jenny Stevenson
16:30 - 17:00	Brief overview of new malaria vector control interventions under evaluation by WHO	Dr Lauren Carrington
17:00 - 17:30	Linking resistance data to the selection of intervention options	Dr Jan Kolaczinski
17:30 - 18:00	Q&A session	All presenters
DAY 2 - WEDNESDAY 15 SEPTEMBER 2021		
Open Session (Participants and WHO Staff)		
PART II: PREDICTING THE LIKELY EVOLUTION OF INSECTICIDE RESISTANCE, AND DISCUSSING THE DATA NEEDS		
15:00 - 15:30	Update on approaches to modelling insecticide resistance in malaria	Dr Ian Hastings
15:30 - 16:00	Application of principles of economics in resistance management in malaria with the help of the MINT decision tool	Dr Thomas Churcher
16:00 - 16:30	Comparing the economics of insecticide resistance management between agriculture and public health	Dr Zachary Brown
16:30 - 17:00	Q&A session	Previous presenters
17:00 - 18:00	General discussion	Chair
DAY 3 - THURSDAY 16 SEPTEMBER 2021		
Open Session (Participants and WHO Staff)		
PART III: CONCLUSIONS AND NEXT STEPS		
15:00 - 18:00	Finalization of meeting conclusions and formulation of next steps to WHO	Chair

ANNEX 3. DECLARATIONS OF INTEREST

All members completed and submitted their Declaration of Interest and Confidentiality Undertaking forms. The review of the completed Declaration of Interest forms identified eight members as having declared a potential conflict of interest; the interest and its management by the Global Malaria Programme are outlined below.

Dr Maciej F Boni is employed by the Pennsylvania State University. He declared having received research grants from the Bill & Melinda Gates Foundation over the last four years.

Dr Ian Hastings is employed by the Liverpool School of Tropical Medicine. He reported receiving grant funding to model evolution of insecticide resistance from the Innovative Vector Control Consortium (IVCC), which ended in May 2021.

Dr Thomas Churcher is employed by Imperial College London. He reported receiving an ongoing research funding going to his employer to investigate public health significance of insecticide resistant mosquitoes from the Innovative Vector Control Consortium (IVCC).

Dr Nakul Chitnis is employed by the Swiss Tropical and Public Health Institute. He reported receiving several research grants for modelling malaria vector control; for modelling push-pull systems; for modelling new interventions to reduce mosquito exposure from the Bill & Melinda Gates Foundation and from the Innovative Vector Control Consortium (IVCC).

Dr Martin Donnelly is employed by the Liverpool School of Tropical Medicine. He reported receiving various renumeration related to the subject of the meeting through his employment in his academic institution.

Dr Katharina Hauck is employed by Imperial College London. She reported receiving various renumeration related to the subject of the meeting through her employment in her academic institution, as well as receiving research and non-monetary support, such as a malaria elimination grant from the Wellcome Trust.

Dr Fredros Okumu reported receiving renumeration through his employment at the Ifakara Health Institute; various grant funding, including from the Bill & Melinda Gates Foundation; consulting engagement with WHO Vector Control Product Prequalification; two patents with the World Intellectual Property Organization (WIPO) (on modifying odorant mixture for malaria mosquitoes and on complex of structures for delivering pesticidal agents to arthropods); participation in the Malaria Strategic Advisory Panel for the Bill & Melinda Gates Foundation; being a co-chair of malERA Refresh Consultative Panel on Tools for Malaria Elimination; participation in the Scientific Working Group providing recommendations for the Pathway to Deployment of Gene Drive Mosquitoes as a Potential Biocontrol Tool for Elimination of Malaria in Sub-Saharan Africa.

Dr Catherine Pitt reported being a lead economist on a trial in Misungwi, United Republic of Tanzania, which compares the effectiveness and cost-effectiveness of Interceptor, Interceptor G2, Royal Guard, and Olyset Plus nets in an area of high insecticide resistance. The trial is paid for by the Medical Research Council/Department for International Development/Wellcome Joint Global Health Trials Scheme and the Bill & Melinda Gates Foundation. She reported that neither her, nor her research group (to her knowledge) had been funded by any groups with a financial interest in the outcomes of this consultation. She also reported being named as a co-investigator on two studies in Uganda on which she did not draw salary. She was also named on the Resilience Against Future Threats (RAFT) research consortium grant, which is funded by the United Kingdom's Foreign, Commonwealth, and Development Office.

Conclusion: Given that no WHO recommendations will be formulated during the meeting, and that no financial and non-financial gains are expected to be generated as a result of the participation, the declared potential conflicts of interest were judged not to present an actual conflict with respect to the content of the present meeting.

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