Key points and Q&A

Status and trends of insecticide resistance in malaria vectors (2018)

Vector control using insecticides is a key preventive strategy for malaria. Pyrethroid-treated mosquito nets and indoor residual spraying with pyrethroids, organophosphates, carbamates or the organochlorine DDT have contributed significantly to reductions in malaria morbidity and mortality since 2000. The emergence and spread of resistance in malaria vectors presents a threat to the gains made and to continuing progress towards further reduction of the global malaria burden.

Background

- In 2012, WHO released the *Global plan for insecticide resistance management in malaria vectors* (GPIRM) to provide a comprehensive approach to addressing this biological threat to malaria control and elimination. This plan highlighted, among other actions, the need for strengthened resistance monitoring and better management of data, including the establishment of a global database to track the status of insecticide resistance in malaria vectors.

- In 2014, the WHO Global Malaria Programme established a global insecticide resistance database to consolidate the data reported by Member States and their development partners, as well as data extracted from scientific publications.

- In May 2018, WHO released the first *Global report on insecticide resistance in malaria vectors: 2010–2016*. The intention of the first edition of this report was to provide a baseline for regular updates on the global situation of malaria vector resistance to insecticides used in public health. The Global Malaria Programme held a webinar in June 2018 to share the report's key findings; a selection of questions and answers from the webinar appears below.

- The 2018 report summarizes recent data on malaria vector insecticide resistance, with a view to encouraging resistance testing and strengthening the evidence base on which to provide informed communications, advocacy and policy development for malaria control and elimination.

World Health Organization

- The report may also prove useful to programmes and their development partners in developing or refining insecticide resistance management strategies, although this would require more in-depth situation analyses at national and subnational levels.

- An accompanying *Malaria Threats Map* was also developed to enable interactive exploration of available information from the WHO insecticide resistance database and from other databases maintained by the Global Malaria Programme.

Key facts from the report

- The *Global report on insecticide resistance in malaria vectors: 2010–2016* summarizes *Anopheles* malaria vector insecticide resistance data for the WHO database that were derived using standard monitoring procedures for a seven-year period, from 2010 to 2017. This included 17 824 records from 79 of the 91 countries considered malaria-endemic in 2016, with the majority from discriminating concentration bioassays conducted in Africa for *An. gambiae s.l.* and *An. funestus* mosquito populations.

- **Resistance monitoring** – including assessments of malaria vector phenotypic resistance or mechanisms – often was neither conducted nor reported. Where monitoring occurred, it was not conducted consistently, and limited information was available on resistance intensity and resistance mechanisms.

- **Phenotypic resistance** – indicated by mosquito mortality of <90% in standard bioassays – was confirmed in all major vector species, and to the four commonly used insecticide classes. Of the 91 malaria-endemic countries, 62 reported resistance to at least one insecticide class and 50 countries showed resistance to two or more insecticide classes. In particular, confirmed resistance to pyrethroids was common and widespread.

- **Resistance frequency** – indicated by 100% minus the per cent adjusted mortality in phenotypic bioassays – varied across all four insecticide classes, both within and between regions. For pyrethroids, median resistance frequency increased between 2010 and 2016 significantly in *An. funestus s.l.* and moderately in *An. gambiae s.l* mosquito populations. There were small, overall median changes in resistance frequencies to organochlorines, organophosphates and carbamates.

- **Resistance mechanisms** – the means by which insects survive insecticide exposure – are categorised as metabolic, target-site, reduced penetration or behavioural. Although the report reflects insufficient reporting data, it indicates that metabolic and target-site resistance mechanisms often were detected in areas in which they were tested.

- **Key challenges** to understanding the full extent of malaria vector resistance include: limited availability of monitoring data (collected annually from all representative sites); poor quality and incomplete data; reporting not conducted in a timely manner; insufficient data sharing; limited capacity and funding for monitoring; the need for improved methods of surveillance; and suboptimal supply of test kits and test papers.

- To minimize and mitigate the risk of insecticide resistance affecting malaria prevention and control efforts, a pragmatic approach must be taken. Conclusive evidence of control failure should not be the trigger for action; pre-emptive resistance management is required. Existing tools should be deployed strategically, as guided by a national insecticide resistance monitoring and management plan. Up-to-date monitoring information is required to support decision-making processes and planning adjustment.

- Research and development is needed to develop new interventions, such as those that use new insecticide classes or reduce reliance on insecticides. Once the public health value of the new tools has been validated, they should be integrated in malaria control and elimination strategies. Monitoring should measure the impact of the new tools with active ingredients like neonicotinoids and pyrroles on vectors and evaluate their effectiveness in disease control and resistance management.

SELECTED QUESTIONS AND ANSWERS FROM THE WEBINAR

Dr Tessa Knox and Dr Jan Kolaczinski, Global Malaria Programme Entomology and Vector Control unit, and Dr Ben Lambert, Imperial College London

1. If a country does find pyrethroid resistance, how soon should they change the insecticides they are using?

As with drug treatments, resistance management ideally should start before resistance emerges and grows. The *Framework for a national plan for monitoring and management of insecticide resistance in malaria vectors* provides a flowchart that guides users from resistance detection through initial bioassays to determine resistance status and frequency, and then to the second step of determining resistance intensity or mechanisms. At that early stage of documenting resistance, it is good for the national programme to initiate discussions among in-country stakeholders to explore whether resources are sufficient or can be mobilized to deploy alternatives to pyrethroids immediately. This action can mitigate against increasing pyrethroid resistance.

2. Is there any indication that pyrethroid resistance grows at a higher rate where indoor residual spraying (IRS) is used rather than long lasting insecticidal nets (LLINs)?

Currently, there is insufficient coverage data of indoor residual spraying (IRS) to determine whether there is a correlation between the frequency or intensity of resistance (i.e. whether mosquitoes die after exposure to low, intermediate or high doses of insecticide) and the extent to which mosquito population have been exposed to IRS over time, or how this compares to exposure of mosquito populations to LLINs. WHO is encouraging the reporting of higher-resolution IRS data to allow further exploration of these types of potential relationships in the data. In any case, it should be borne in mind that the emergence, spread and intensification of insecticide resistance depends to a considerable extent on the extent of selection pressure. With LLINs being used at a much larger scale, they are more likely to select for resistance than IRS.

3. For pyrethroid resistance, which resistance mechanism plays the most important role?

Pyrethroid resistance in anopheline mosquitoes is due to two key resistance mechanisms, namely target site resistance (point mutations that prevent insecticide from binding with receptor molecules on mosquito neurons) and metabolic resistance (increased level of one or more enzymes capable of detoxifying or sequestering insecticides). In many areas, both of these two mechanisms are present in the same mosquito vector species. The limited data available on the level of pyrethroid resistance – rather than just presence/absence in *Anopheles* vector populations - show that in areas of high resistance enzymes seem to be the cause. More data will be required to further investigate such links.

4. Resistance is growing most in *An. funestus* mosquito populations. Why look at all resistance growth, rather than focusing on those vector species with the highest resistance?

In West Africa, the predominant vector is *An. gambiae* rather than *An. funestus*. In that subregion, high intensity pyrethroid resistance has been identified in many countries. Monitoring cannot consider a sole species and must be holistic and reflective of the entomological and epidemiological situation.

The report, in addition to consolidating data, identified evidence gaps for which information on *An. funestus* resistance is scarce. With Imperial College London and other collaborators, WHO is using this information to guide organizations with the resources and capacity to conduct or fund more work to close such evidence gaps.

5. When resistance challenges are detected, is operational failure dependent on resistance frequencies or on resistance intensity?

The introduction of the intensity assay has been relatively recent. The scarce data currently available prevents reaching a meaningful conclusion on the exact linkage with operational impact. Further investigation is needed to determine whether current monitoring approaches are generating useful data to predict the efficacy of IRS and LLINs.

6. What new methods are proposed for insecticide resistance data collection?

At present, no changes in test methods are proposed as these are clearly outlined in the *Test procedures for insecticide resistance monitoring in malaria vectors*. However, as part of the ongoing collaborations with Imperial College London and Oxford University, we are investigating how to use existing information to inform how and where data are collected and can be best used for decision-making. For example, extrapolating from existing monitoring data could provide spatial predictions of resistance that would inform prioritised deployment of new vector control tools as well as indicate the geographical scale and locations at which to collect new data. This should also allow refinement of recommendations on where to place sentinel sites, and how many, since this is currently informed by best estimates rather than evidence.

7. What about data management?

In terms of data management, DHIS-2 is a powerful tool that countries are using increasingly to track epidemiological data. We can improve our data management by also including reports of insecticide resistance. National programmes and other collaborators, as well as implementing partners, should ensure coordinated data management to support national programme decision-making. To this end, WHO is developing an entomology and vector control module to support countries in standardised reporting and aggregation of the data at the appropriate administrative levels, as well as to enable easier reporting to WHO.

8. The impact of insecticide resistance on vector control effectiveness remains poorly understood. What is GMP doing to increase understanding in this area?

Insecticide resistance is complex and we still have limited understanding of how this impacts on the insecticidal tools used to prevent malaria. In May 2018, the full results of a WHO-coordinated multi-country study conducted over multiple years was released. This study was designed to evaluate the impact of insecticide resistance on the effectiveness of nets. The study shows that there is a continuing benefit of insecticide-treated nets despite the presence of resistance. WHO is also in the process of collaborating with scientists to update with newly-available data a 2014 systematic review that examined the impact of insecticide resistance on nets. The update will validate the evidence currently available and also articulate design considerations for future studies.

9. What new vector control tools are coming?

In 2017, WHO prequalified a neonicotinoid indoor residual spray formulation which constitutes a fifth class of insecticide for IRS. Additional developments in process include nets with non-pyrethroid insecticides or insect growth regulators, as well as a broad range of other interventions that are being assessed by the Vector Control Advisory Group. Details on these can be found in the VCAG meeting reports.

10. Why does WHO speak about resistance in a measured way?

The evidence shows that the malaria reductions over the past decade have been substantially driven by vector control. Unquestionably, vector control has and is a very important contributor to malaria burden and mortality reduction. WHO's language regarding insecticide resistance must be fair and measured because there is a risk of undermining the overall key message that vector control is important and should be continued. Recent years have seen extreme and, as yet, unsubstantiated statements regarding insecticide resistance leading to malaria control failure. Assertions that there is widespread failure of interventions due to resistance and that vector control staff should abandon the existing tools have so far not been substantiated.

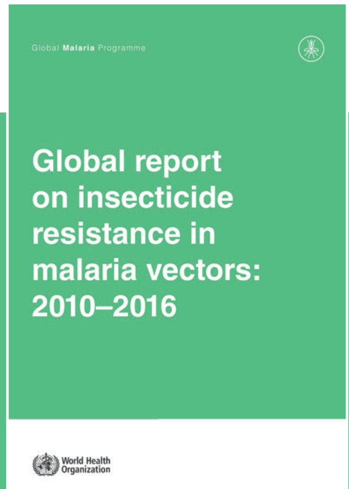
11. What is WHO's position and responsibility with regards to resistance and its management?

WHO's role is to convey evidence-based recommendations. In the absence of good evidence, WHO's first responsibility is to encourage the generation of evidence instead of jumping to conclusions. The recently-published multi-country study coordinated by WHO clearly documents that pyrethroid-treated nets continue to provide protection to users despite resistance. WHO remains open and receptive to reviewing data that clearly demonstrate that the effectiveness of malaria vector control interventions is being undermined, at which point guidance will be reviewed in light of such evidence.

Acknowledgements

- The work presented is the result of extensive contributions by Member States, WHO country and regional offices, and numerous other individuals and partner organizations who collaborated to enhance the global understanding of insecticide resistance in malaria vectors.

- The full list of acknowledgements is included in the report. In particular, the WHO Global Malaria Programme would like to acknowledge the following for their valuable contributions:
  - Formulation and/or review of the *Global report on insecticide resistance in malaria vectors: 2010-2016*: Liverpool School of Tropical Medicine, Imperial College London, WHO Malaria Vector Control Technical Expert Group.
  - Collection and/or validation of data for the WHO insecticide resistance database: national programmes; WHO regional, sub-regional, country and zonal offices; President's Malaria Initiative; and Malaria Atlas Project.
  - Design and/or implementation of the Malaria Threats Map: BlueRaster, LLC; WHO Polio and Emergencies Cluster and WHO Information Management and Technology department.



ONLINE RESOURCES

Global report on insecticide resistance in malaria vectors: 2010-2016. Geneva: World Health Organization; 2018 (http://www.who.int/malaria/publications/atoz/9789241514057/en/)

Global plan for insecticide resistance management in malaria vectors, Geneva: World Health Organization; 2012 (http://www.who.int/malaria/publications/atoz/gpirm/en/)

Framework for a national plan for monitoring and management of insecticide resistance in malaria. Geneva: World Health Organization; 2017 (http://www.who.int/malaria/publications/atoz/9789241512138/en/)

Test procedures for insecticide resistance monitoring in malaria vectors. Second edtion. Geneva: World Health Organization; 2016 (http://www.who.int/malaria/publications/atoz/9789241511575/en/)

WHO insecticide resistance database: http://www.who.int/malaria/areas/vector_control/insecticide_resistance_database/en/

Malaria Threats Map: http://apps.who.int/malaria/maps/threats/

WHO/CDS/GMP/2018.17