Status and trends of insecticide resistance in malaria vectors

GMP Entomology and Vector Control and
Imperial College London

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Global **Malaria** Programme

World Health Organization

Background

- **Good news:** Major progress in malaria prevention & control this century, mainly due to insecticidal vector control
- **Bad news**: Insecticide resistance in malaria vectors threatens these gains
- **Potential threat:** Increased morbidity and mortality from malaria
- **Response:** WHO *Global plan for insecticide resistance management in malaria vectors (2012)*

Key resources

Global plan for insecticide resistance management in malaria vectors (2012)

http://www.who.int/malaria/publications/atoz/gpirm/

Test procedures for insecticide resistance monitoring in malaria vector mosquitoes (Second edition) (2016)

http://www.who.int/malaria/publications/atoz/9789241511575/

WEBINAR AVAILABLE

Malaria Threats Map

http://www.who.int/malaria/maps/threats

Framework for a national plan for monitoring and management of insecticide resistance in malaria vectors (2017)

http://www.who.int/malaria/publications/atoz/9789241512138/

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Insecticide resistance monitoring

- Should be conducted annually (minimum)
- **Step 1**: Phenotypic monitoring with discriminating concentration bioassays using either:
  - WHO susceptibility tests OR CDC bottle bioassays

Images: Sven Torfinn/WHO

- **Step 2**: If resistance confirmed -> further investigations
  - Measure resistance intensity
  - Identify resistance mechanisms, such as via:
    - Synergist-insecticide bioassays
    - Other molecular or biochemical assays

Insecticide resistance monitoring: procedures

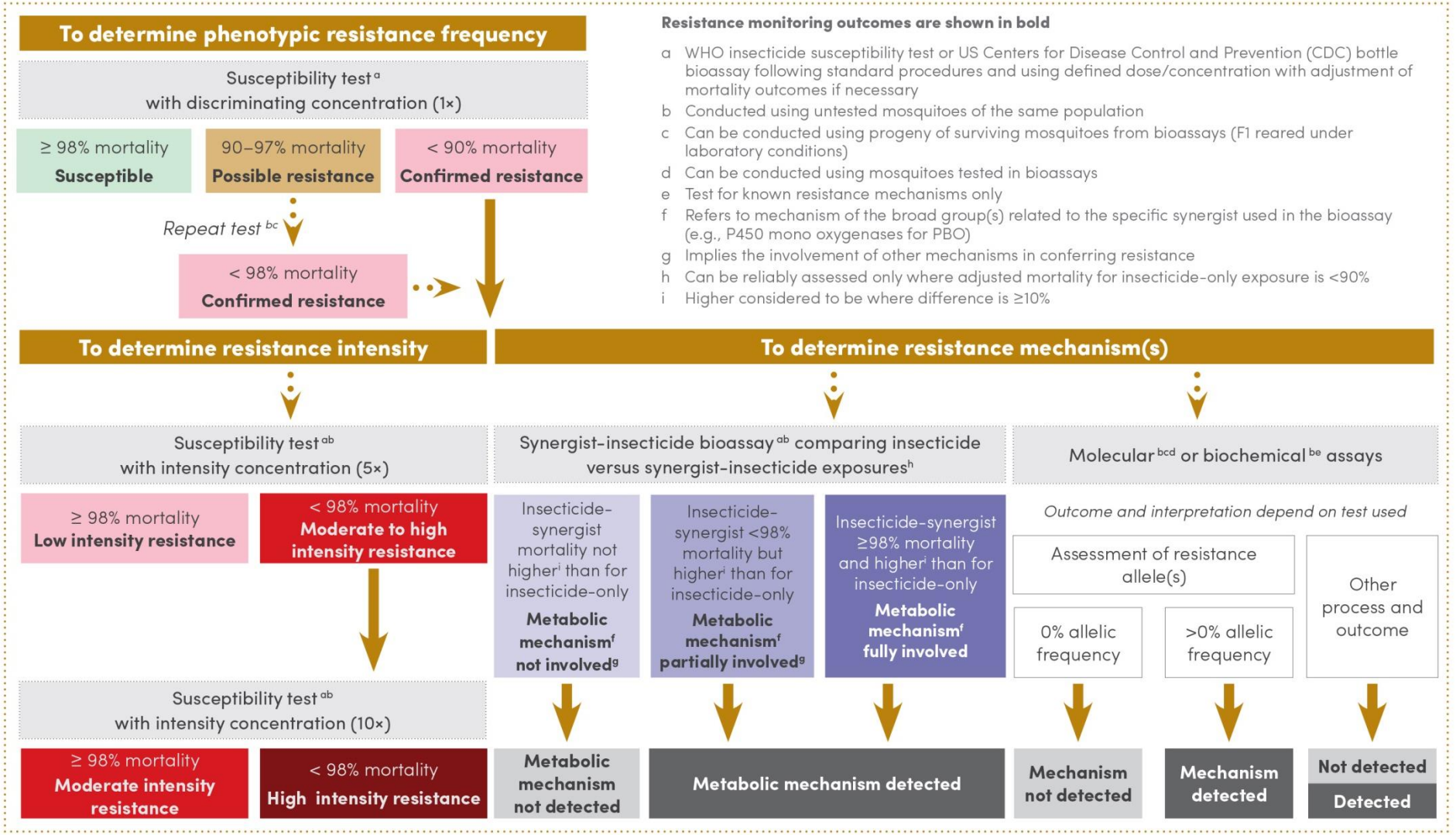


FIG. 3.1

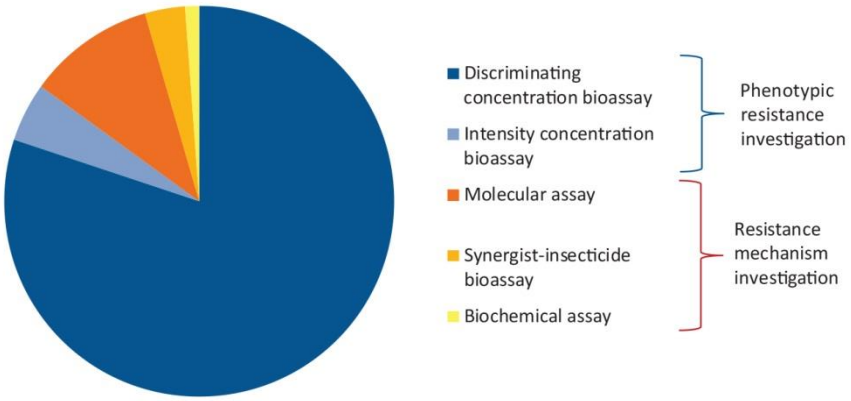
Overview of process and outcomes for insecticide resistance monitoring in malaria vector mosquitoes. Includes measures of: a) phenotypic resistance frequency via discriminating concentration bioassays, b) resistance intensity via intensity concentration bioassays, and c) resistance mechanisms via synergist-insecticide bioassays, molecular and biochemical assays

Global report on insecticide resistance in malaria vectors

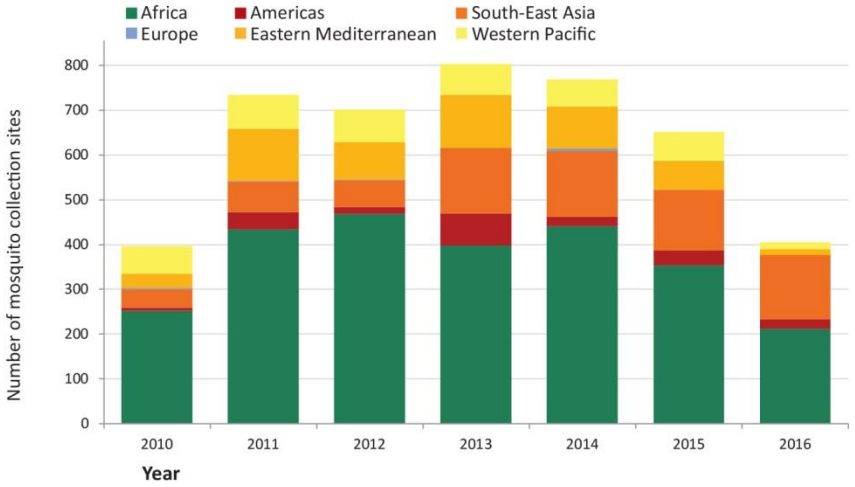
- **Scope:** Summarize *Anopheles* malaria vector insecticide resistance data from WHO database, for standard monitoring procedures for 2010-2016
- **Aim:** To provide status and baseline for subsequent updates, and to identify any temporal trends in resistance
- **Audience:** National programmes and partners involved in malaria vector control planning and implementation

WHO insecticide resistance database

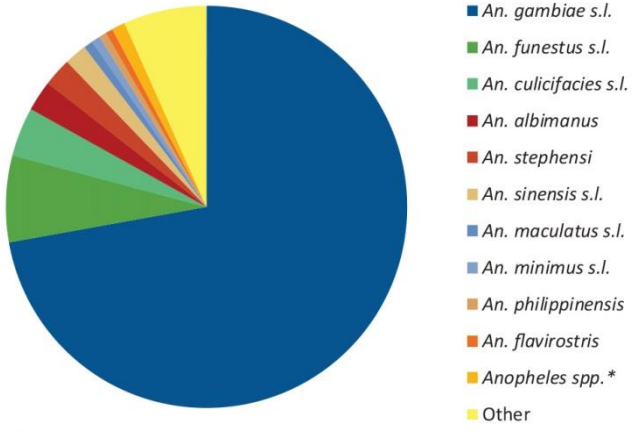
a) Total data by investigation and assay type



b) Total number of collection sites by year and WHO region



c) Total data by vector species



* not identified to species

Data origin (majority): Discriminating concentration bioassays in Africa for An. gambiae s.l. and An. funestus

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Phenotypic resistance: measures

TABLE 2.1.
Overview of common phenotypic resistance indicators, methods, measures and outcomes

INDICATOR	METHODS	MEASURES	OUTCOMES
Resistance status	WHO susceptibility test with discriminating concentration	% mortality of test mosquitoes (adjusted[a])	• Confirmed resistance • Possible resistance • Susceptibility
	CDC bottle bioassay with diagnostic concentration	% incapacitation of test mosquitoes	• Confirmed resistance • Possible resistance • Susceptibility
Resistance frequency[b]	WHO susceptibility test with discriminating concentration	100% minus % mortality of test mosquitoes (adjusted[a])	• % alive
	CDC bottle bioassay with diagnostic concentration	100% minus % incapacitation of test mosquitoes (adjusted[a])	• % not incapacitated.
Resistance intensity	WHO susceptibility test with intensity concentrations	% mortality of test mosquitoes (adjusted[a]), in relation to % mortality for other concentrations tested	• High intensity • Moderate intensity • Low intensity • Could not be reliably assessed
	CDC bottle bioassay with intensity concentrations	% incapacitation of test mosquitoes (adjusted[a]), in relation to % incapacitation for other concentrations tested	• High intensity • Moderate intensity • Low intensity • Could not be reliably assessed

CDC, US Centers for Disease Control and Prevention; WHO, World Health Organization
[a] Using Abbott's formula as required (Abbott, 1925).
[b] This refers to phenotypic resistance only and is different to resistance gene frequency (see Table 2.2)

Indicator helps determine proportion of mosquito population surviving standard insecticide exposure (confirmed resistant)

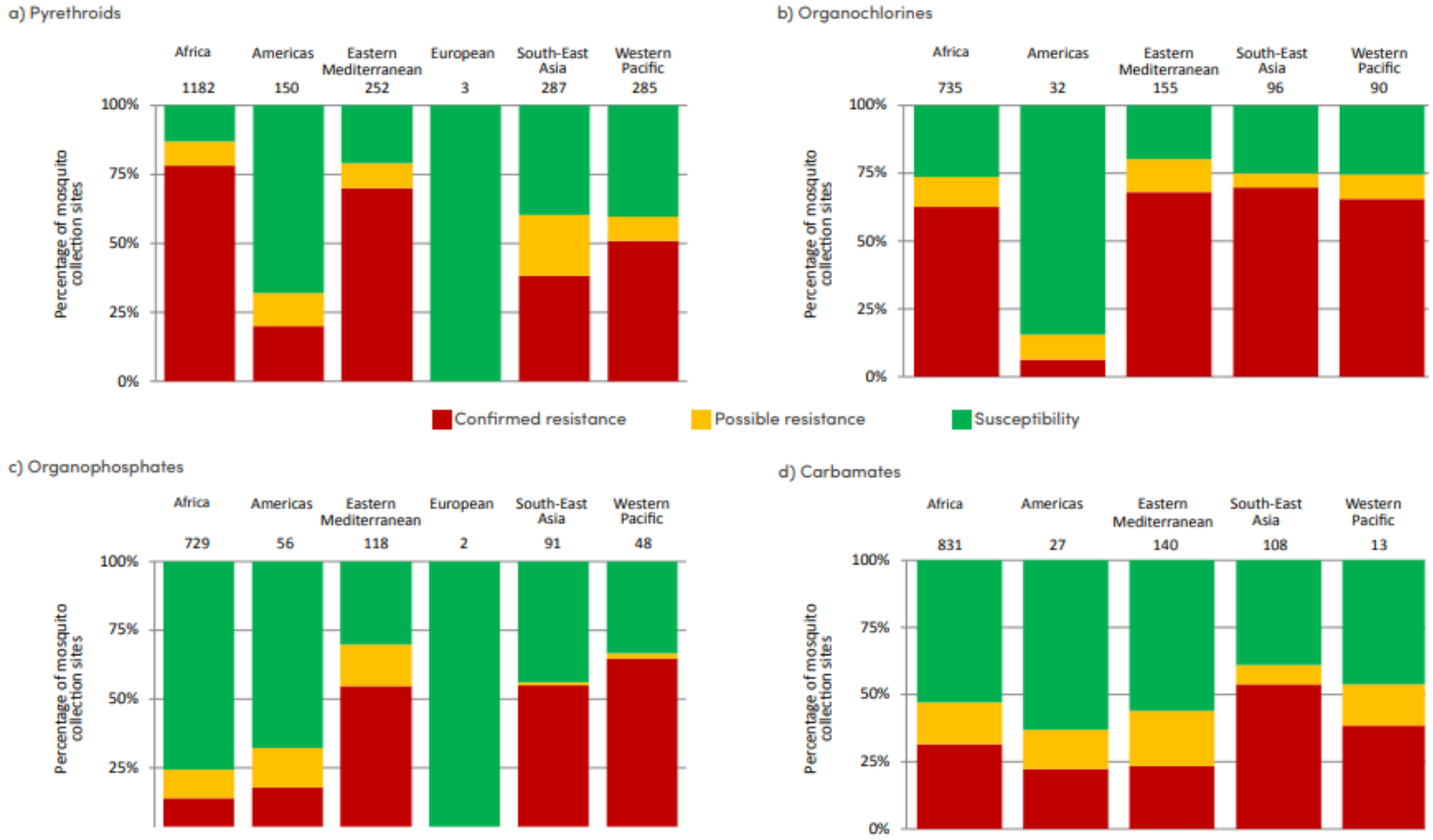
World Health Organization

Phenotypic resistance: status

FIG. 4.2.

Reported insecticide resistance status as a proportion of sites for which monitoring was conducted, 2010–2016, by WHO region

Status was based on mosquito mortality where <90% = confirmed resistance, 90–97% = possible resistance, and ≥98% = susceptibility. Where multiple insecticide classes or types, mosquito species or time points were tested at an individual site, the highest resistance status was considered. Numbers above bars indicate the total number of sites for which data were reported (n).

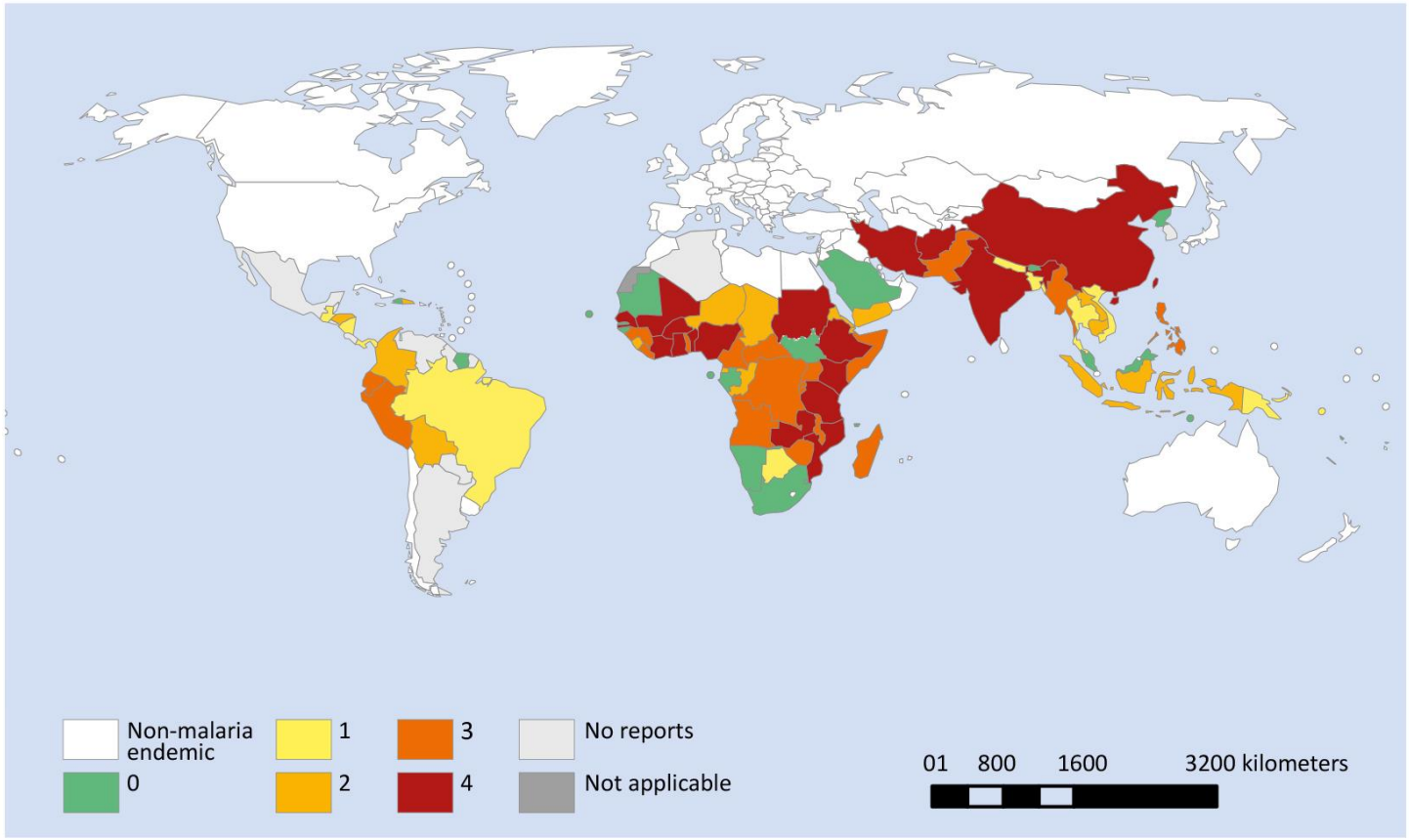


2010 - 2016: Pyrethroid resistance was common and widespread. Resistance to other insecticide classes was also common.

Reported phenotypic resistance: 2010-2016

FIG. 4.1.

Map showing number of insecticide classes to which resistance in malaria vectors was reported, by country, for the period 2010–2016



≥ 1 class = 62 countries

≥ 2 classes = 50 countries

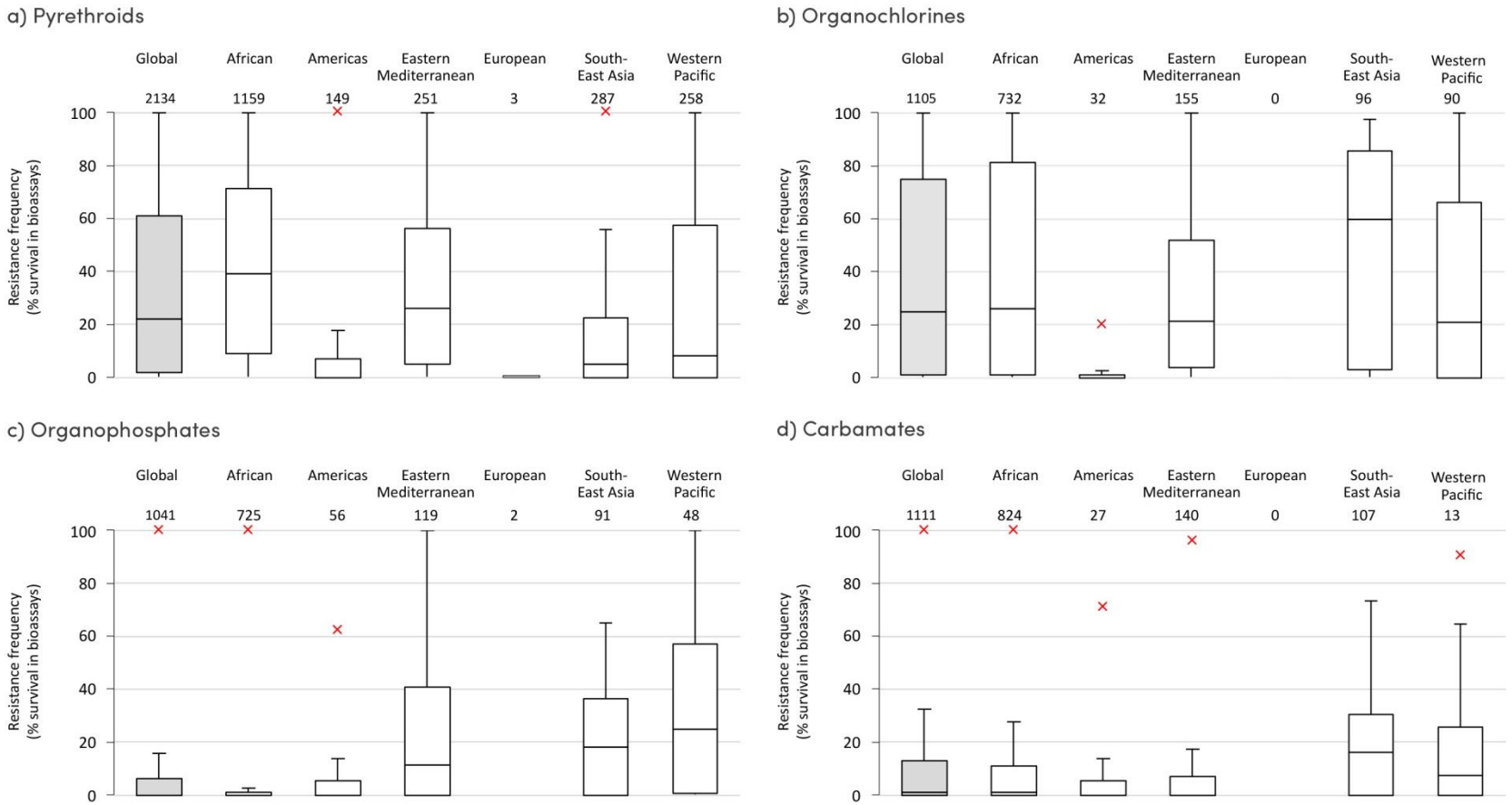
Resistance confirmed in all major vector species, and to the four commonly used insecticide classes.

Phenotypic resistance: frequency

FIG. 4.3.

Resistance frequency (%) as measured in discriminating concentration bioassays (100% minus adjusted mosquito mortality) for most recent data available for each site for 2010–2016 (n=2354 total), using minimum for any insecticide within the class, globally and by WHO region

Boxes show the first and third quartile and whiskers show 1.5× interquartile range (IQR) above third quartile and 1.5× IQR below first quartile. Maximum outliers (red crosses) are shown if outside this range. Horizontal lines in boxes show the median. Numbers above bars indicate the total number of bioassays for which data were reported (n).

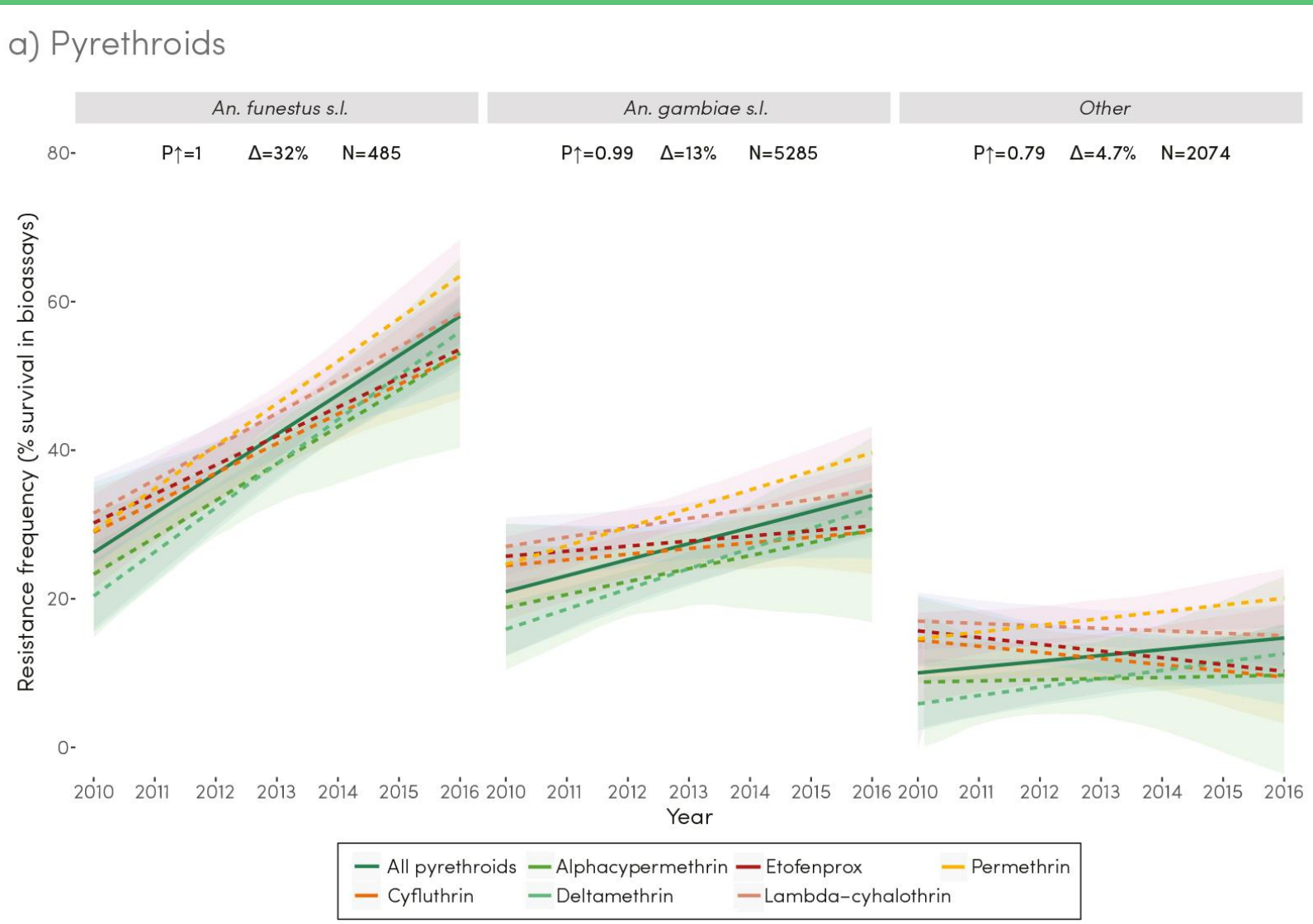


There was variation in resistance frequency across all four insecticide classes, both within and between regions

Phenotypic resistance frequency: trends evaluation

- **How?** Statistical model estimates for average resistance frequency change (mosquito survival for 2010-2016 tests)
- **What?** Across insecticide classes and by WHO regions, subregions, major vector species groupings and individual insecticides
- **Approach?** Linear mixed-effects models were fitted to all data within an insecticide class. Fixed effects:
  - 3 species groupings: *An. funestus s.l., An. gambiae s.l.* and other *Anopheles* malaria vectors
  - insecticide types within a class
- Country of data origin included as a random effect to determine overall temporal trends, taking into account:
  - different starting resistance frequencies between countries
  - variable sampling effort between countries and across time

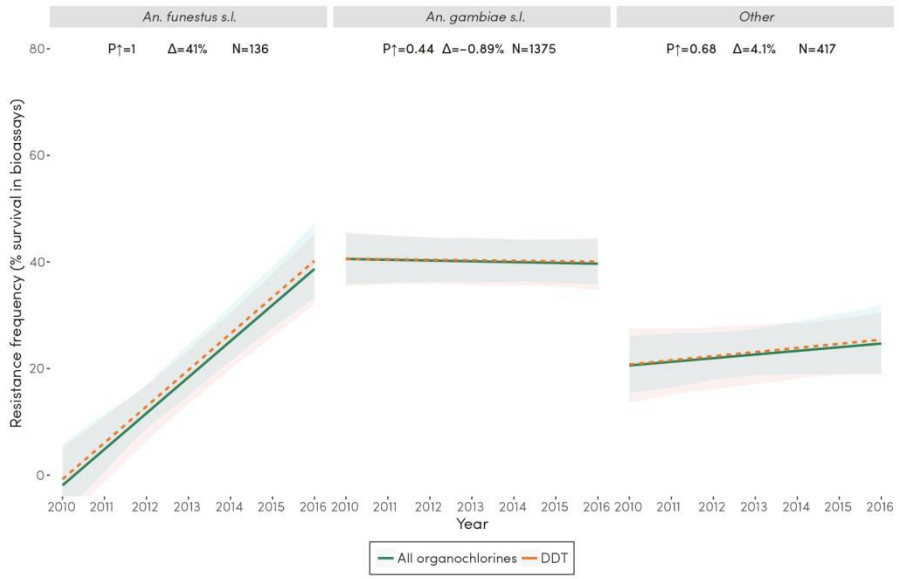
Phenotypic resistance frequency: trends 2010-2016



Pyrethroid resistance increased: significantly in *An. funestus s.l.*, moderately in *An. gambiae s.l.* and slightly in other vector species.

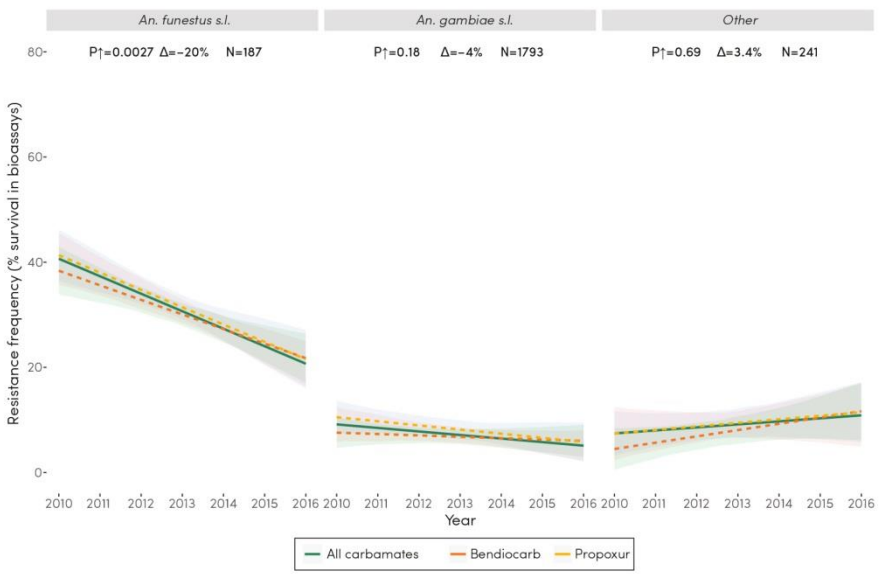
Phenotypic resistance frequency: trends 2010-2016

b) Organochlorines (mostly DDT)[3]

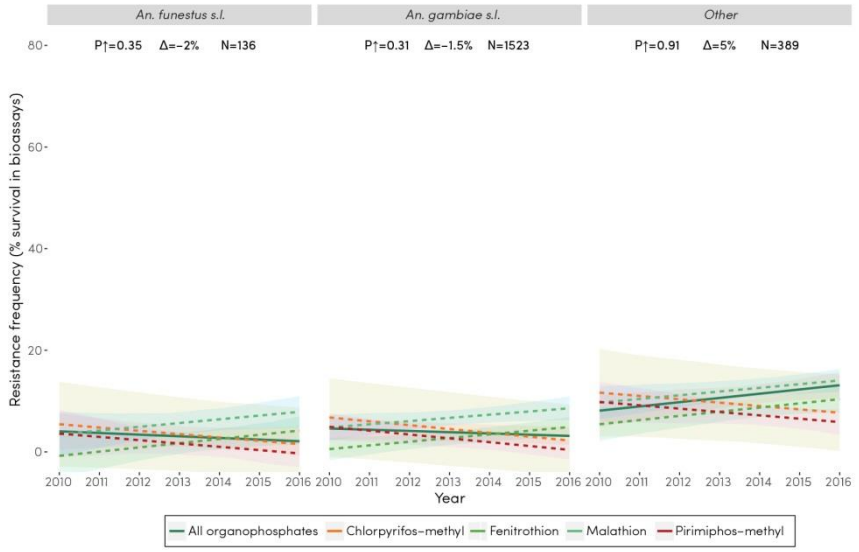


DDT, dichlorodiphenyltrichloroethane[3]

a) Carbamates[4]



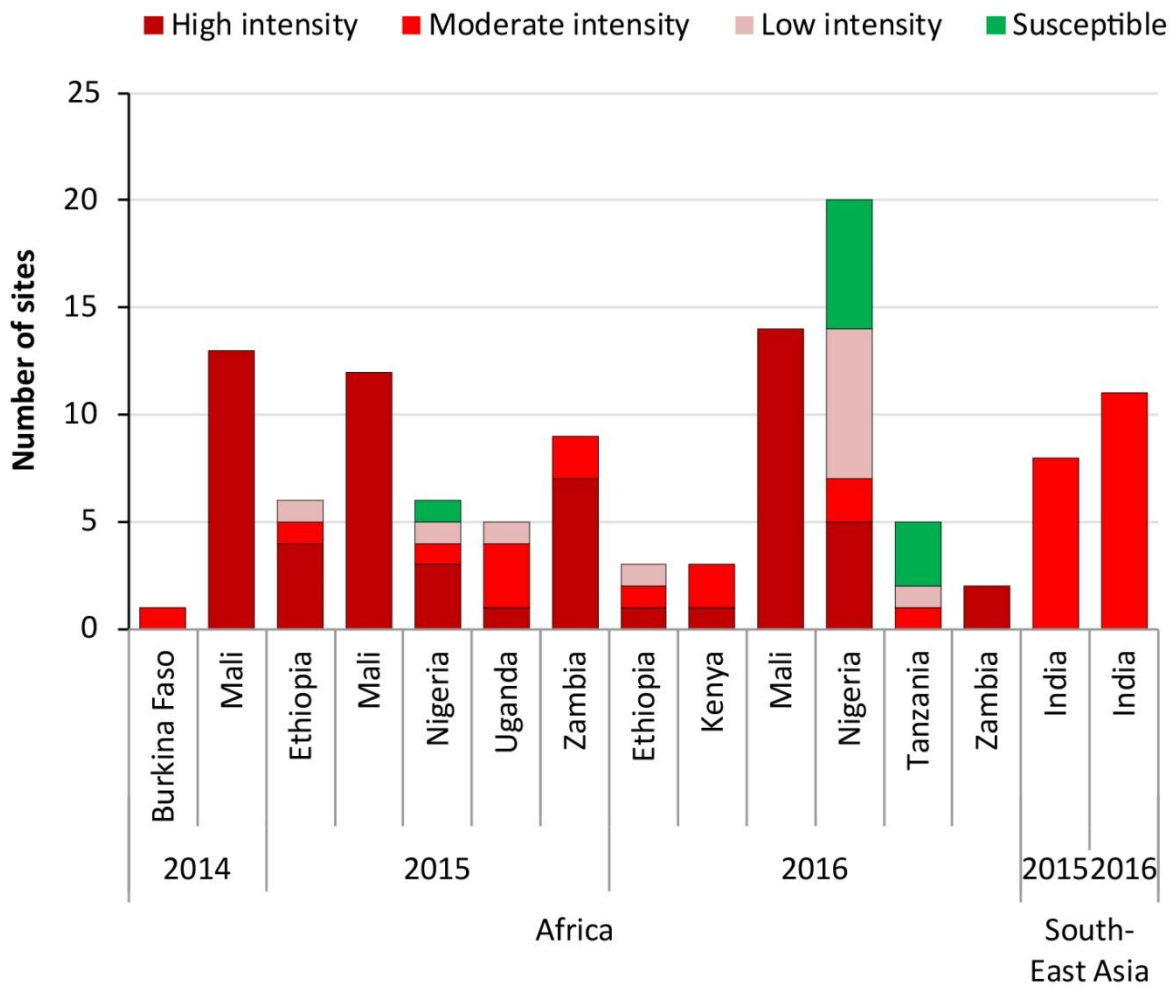
b) Organophosphates



Overall median changes for other insecticide classes were relatively small.
Species cluster-specific changes had too few data points to be well-supported.

Phenotypic resistance: intensity

FIG. 4.6.
Outcomes from intensity concentration bioassays with pyrethroids, 2014–2016

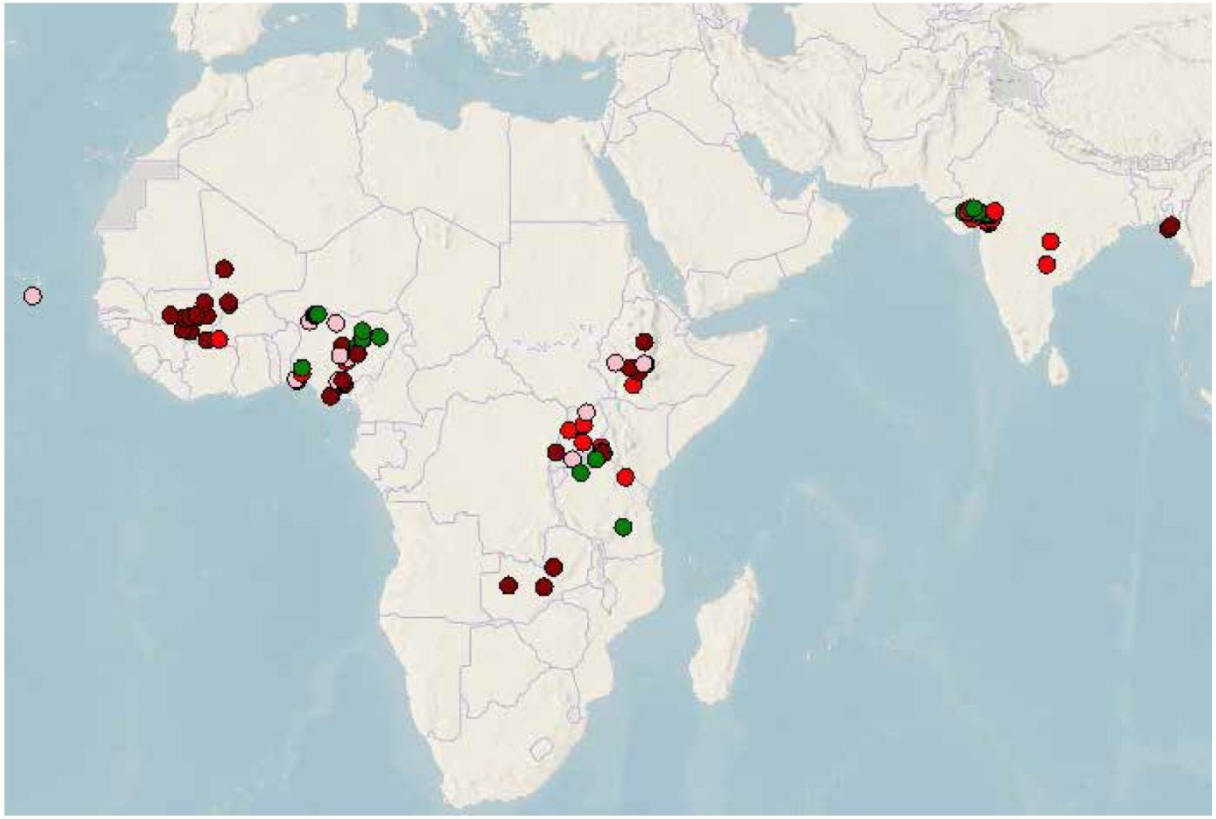


- Limited data
- Further testing needed to understand pyrethroid resistance intensity
- Further investigation needed to determine the value of intensity data for decision-making

Phenotypic resistance: intensity

FIG. 4.7.
Pyrethroid intensity concentration bioassay data reported for the WHO African and South-East Asia regions, 2014–2016

The most recent outcome for any individual site is indicated by colour: dark red = high intensity, red = moderate intensity, pink = low intensity, and green = susceptibility.



- Limited data
- Further testing needed to understand pyrethroid resistance intensity
- Further investigation needed to determine the value of intensity data for decision-making

High-intensity pyrethroid resistance widespread throughout Africa.

Resistance mechanisms: measures

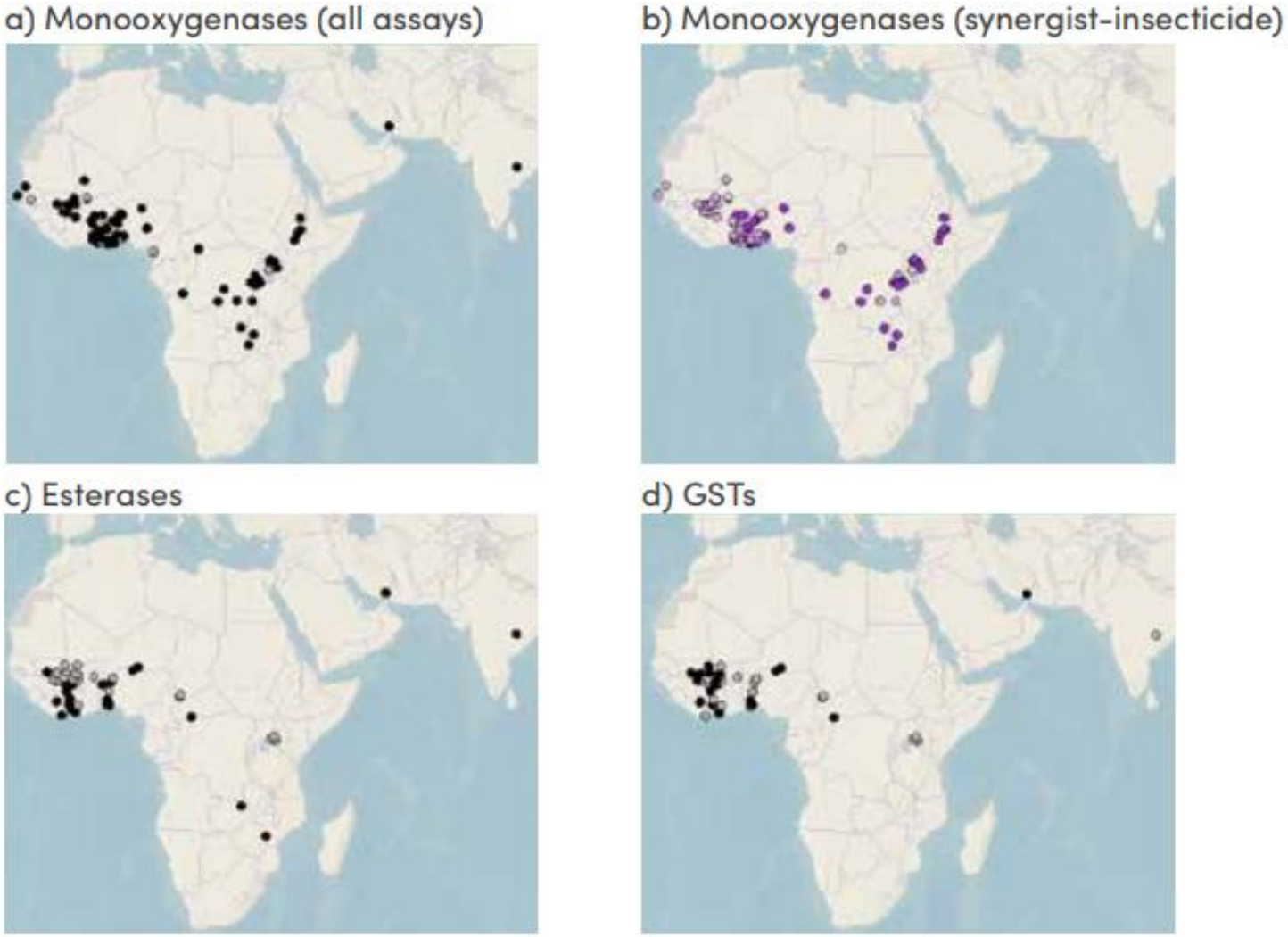
TABLE 2.2.
Overview of common metabolic and target-site resistance mechanism indicators, methods, measures and outcomes

INDICATOR	METHODS	MEASURES	OUTCOMES
Metabolic resistance	WHO synergist-insecticide bioassays	% mortality of test mosquitoes (adjusted[a]) when exposed to synergist and insecticide compared with % mortality when exposed to insecticide only	• Full involvement • Partial involvement • No involvement • Could not be reliably assessed
	CDC bottle synergist-insecticide bioassays	% incapacitation of test mosquitoes (adjusted[a]) when exposed to synergist and insecticide compared with % incapacitation when exposed to insecticide only	• Full involvement • Partial involvement • No involvement • Could not be reliably assessed
	Molecular assays	Upregulation of gene expression[b]	• Present • Absent
	Biochemical assays	Enzymatic activity, in relation to susceptible mosquitoes	• Present (upregulated) • Absent (not upregulated).
Target-site resistance	Molecular assays	% allelic frequency	• Present • Absent
	Biochemical assays	Enzymatic activity, in relation to susceptible population or % allelic frequency (or both)	• Present (upregulated) • Absent (not upregulated)

CDC, US Centers for Disease Control and Prevention; WHO, World Health Organization
[a] Using Abbott's formula as required (Abbott, 1925).
[b] Molecular assays that measure allelic frequencies are also available but are not commonly used.

Resistance mechanisms: metabolic

- Insufficient testing/ reporting precludes further analyses.

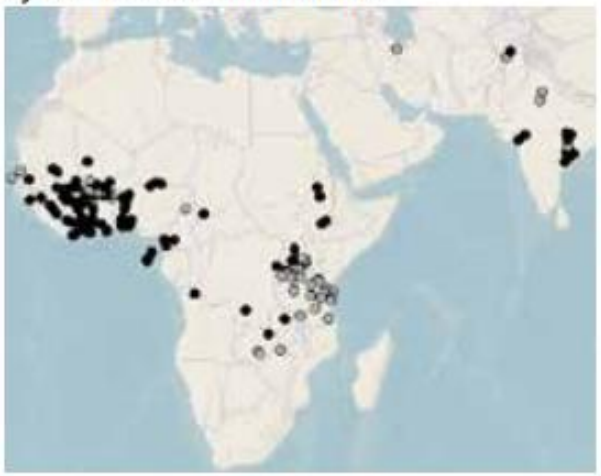


In areas where metabolic resistance mechanisms were tested for, they were often detected.

Resistance mechanisms: target-site

- Insufficient testing/ reporting precludes further analyses.

e) *kdr L1014F* mutations



f) *kdr L1014S* mutations

g) *kdr* mutations (type not specified)

h) *Ace-1R*

In areas where target-site resistance mechanisms were tested for, they were often detected.

Considerations

Key challenges

- Availability of data (annual, representative sites)
- Quality and completeness of data
- Timely reporting
- Data sharing
- Capacity
- Funding
- Need for improved methods of surveillance
- Supply of test kits

Conclusions

- Resistance to four insecticide classes is widespread and increasing (especially to pyrethroids and in *An. funestus s.l.*)
- Complete extent of resistance unknown because:
  - many countries do not carry out routine monitoring
  - countries collecting data do not report or share data in a timely manner
  - no data yet for new insecticides (e.g. neonicotinoids - IRS product PQ listed 2017)
- Impact of insecticide resistance on effectiveness of vector-control tools remains poorly-understood
- **BUT**

  … the potential that increasing resistance may reduce the efficacy of insecticidal interventions remains concerning

Outlook

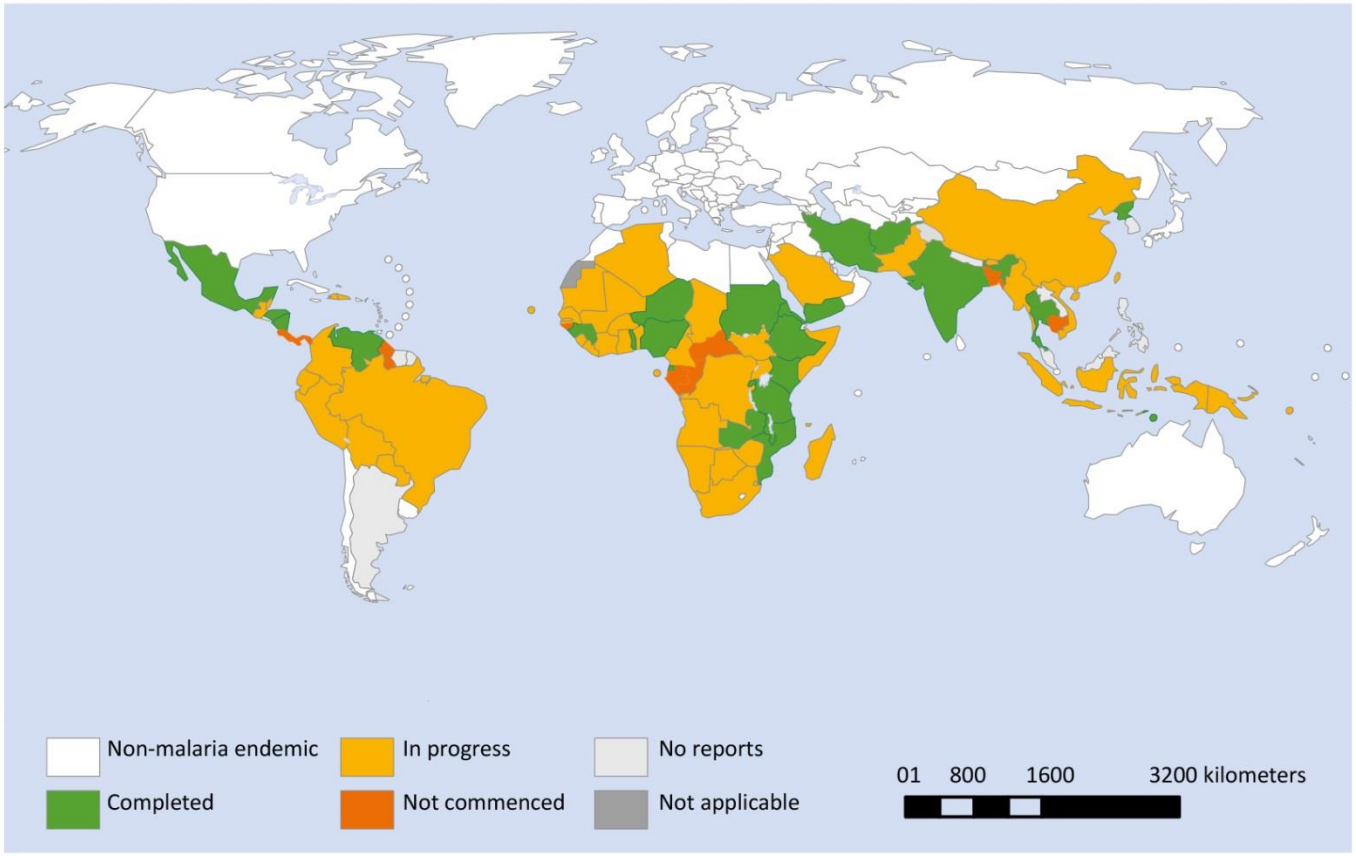
- Conclusive evidence of control failure should not be the trigger for action; pre-emptive resistance management is required
- Existing tools should be strategically deployed, as guided by a national insecticide resistance monitoring and management plan
- New tools are needed - once public health value has been validated these must be incorporated in a timely manner
- Extended monitoring required to measure vector susceptibility to those active ingredients anticipated in new tools (e.g. neonicotinoids and pyrroles)

Priority action

Resistance monitoring & management plans needed.

These must leverage available interventions proactively & appropriately.

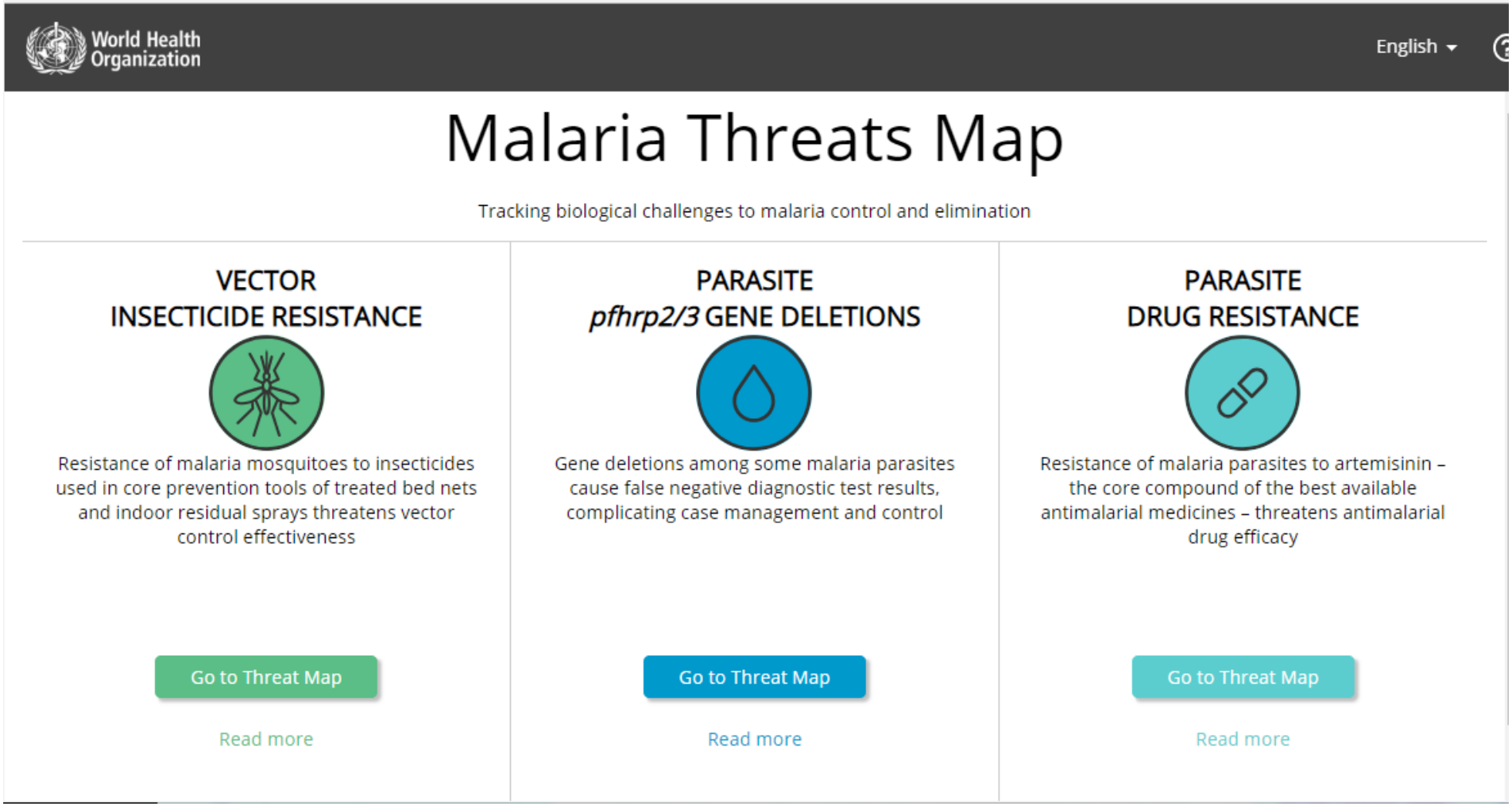
FIG. 7.1.
Status of national insecticide resistance monitoring and management plans, as of October 2017



Data source: WHO (2017e)

Some progress has been made. Further effort is required.

More information: Malaria Threats Map



www.who.int/malaria/maps/threats

Ongoing work, through collaboration

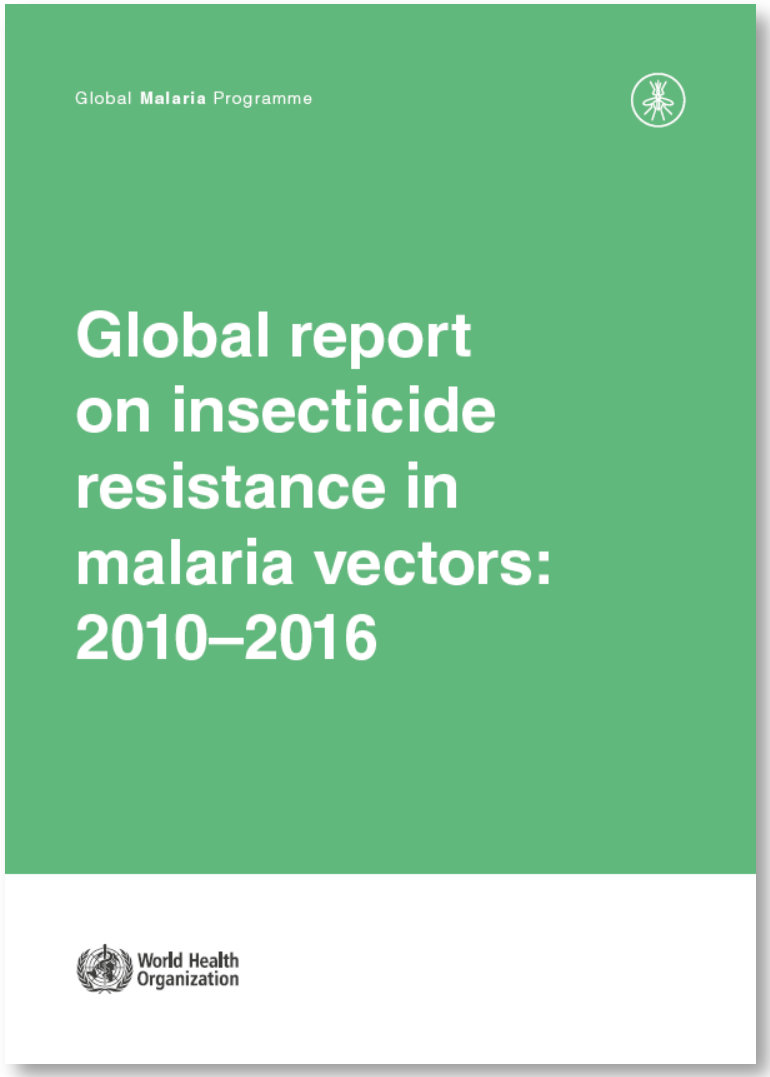
- Build a **nonlinear statistical model** for temporal analyses and examine correlations (within and between insecticide classes; between vector species)
- Test for **relationships** between resistance indicators (frequency, intensity and mechanisms)
- Map **spatial variability** in resistance indicators to guide surveillance and control (e.g. to identify areas for potential deployment of pyrethroid-PBO nets)
- Develop **decision framework** to link epidemiology and resistance data to selection of vector control interventions
- Identify **relationships** between resistance and LLIN/IRS coverage
- Assess the **epidemiological implications** of trends in resistance

Key contributors

Full acknowledgements are listed in the report. In brief:

Global report on insecticide resistance in malaria vectors: 2010-2016	*Formulation and/or review of report:* • WHO Global Malaria Programme • Liverpool School of Tropical Medicine • Imperial College London • WHO Malaria Vector Control Technical Expert Group
WHO insecticide resistance database	*Collection and/or validation of data:* • All national programmes • WHO regional, subregional, country and zonal offices • Other partners (PMI, MAP) • WHO Global Malaria Programme
Malaria Threats Map	*Design and/or implementation:* • WHO Global Malaria Programme • BlueRaster LLC • WHO Polio department • WHO ITC department

Thank you for your attention



Available on WHO website: http://www.who.int/malaria/publications/atoz/9789241514057/

Photo story

Targeting mosquitoes to tackle malaria:
http://www.who.int/malaria/news/2018/vector-control-tools/