Insecticide resistance and mosquito control

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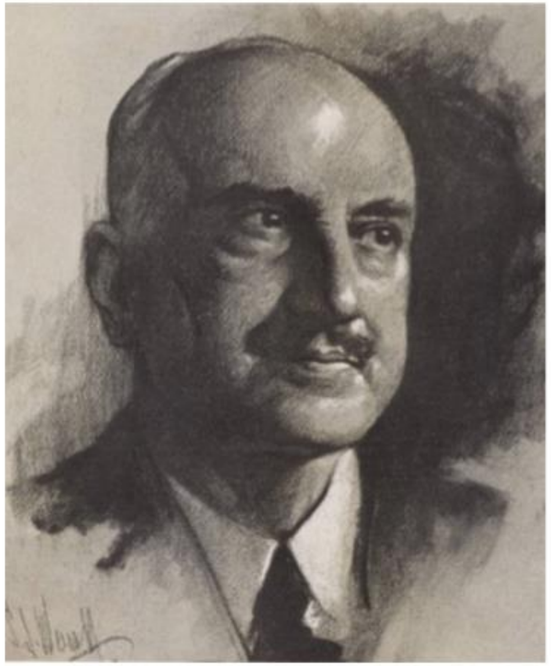
Resistance can be managed if action is taken early….

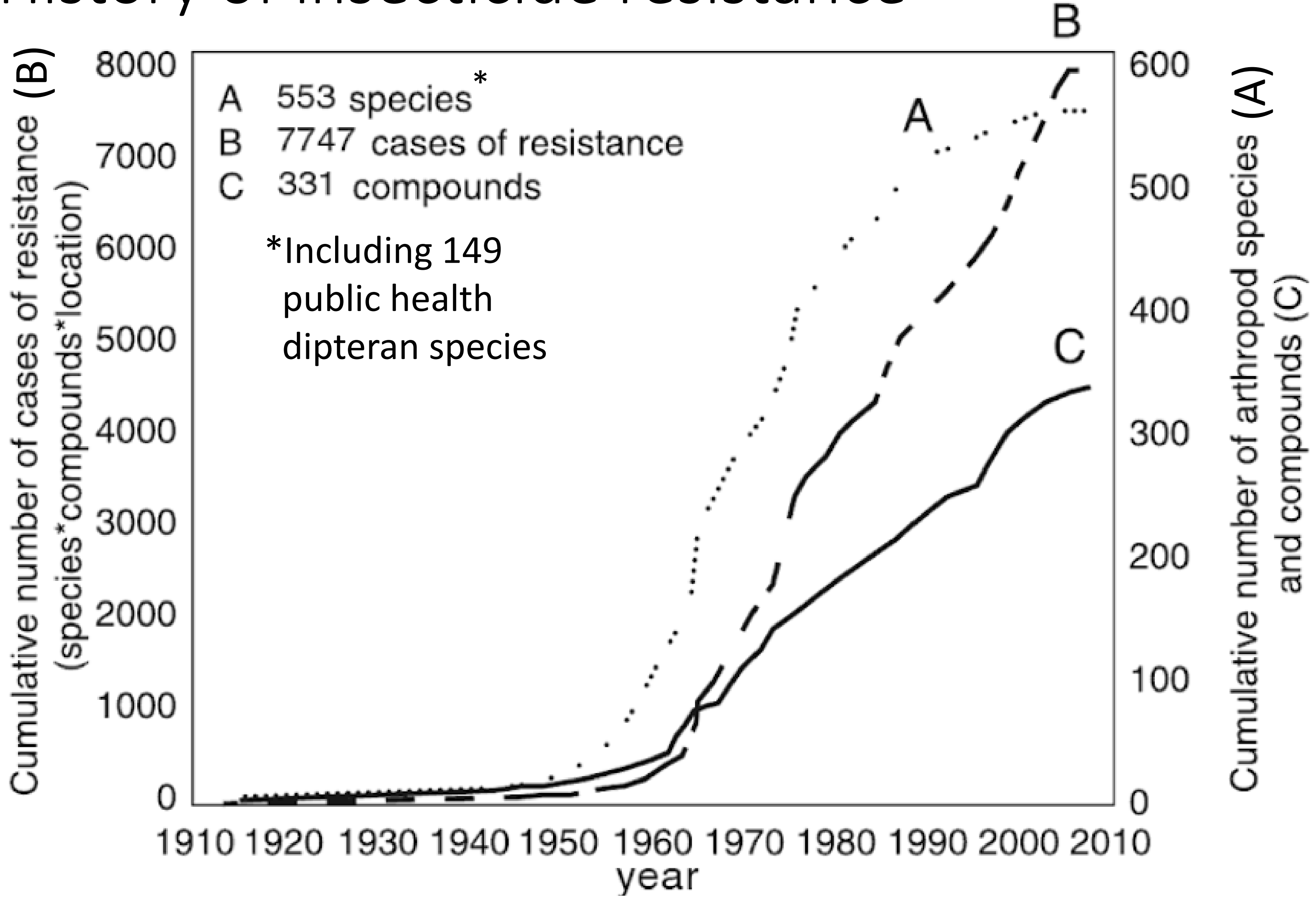


George Santayana
(1863-1952)

"Those who cannot remember the past are condemned to repeat it"

From: V. Corbel (2017) International expert meeting to review vector control options for control of Zika virus, WHO-HQ 23-25 Feb 2017

History of insecticide resistance



Evolution of resistance in arthropods: 1914 – 2007 (Whalon *et al*., 2008)

Resistance marks a genetic change in response to selection

First reported in 1914, field-based resistance remained uncommon until the widespread use of new, very effective, synthetic insecticides, from the 1950s

It can be a major issue for about 25 arthropod species

Factors influencing development of resistance

Biology of pest:
- generation time
- fecundity
- habitat and behaviour [degree of exposure]

Chemical:
- persistence, e.g. pyrethrins $t½$ = hours; DDT $t½$ = years
- rate & frequency of application

Key questions about resistance traits

- Mechanism of Resistance?
    - Altered target site - e.g. altered Acetyl Cholinesterase (Ace) ➤ R to carbamates and organophosphates (OPs); Kdr ➤ R to pyrethroids, DDT
    - Metabolic (increased detoxification) - e.g. cytochrome P450 oxidases ➤ R to pyrethroids, DDT and OPs; esterases ➤ R to wide range, inc. pyrethroids, OPs
    - Penetration - reduced penetration via cuticle
    - Behavioral - avoidance of insecticides
- Cross-resistance?
- Monogenic or polygenic?
- Dominant ------Recessive?
- Fitness cost?

Insecticide MoA

In the many cases, where resistance is due to altered target site, rotation of compounds in different MoA groups is recommended

Target area [MoA group] http://www.irac-online.org/modes-of-action/

- Nerve & Muscle - e.g. carbamates [1A], OPs [1B]; cylcodienes [2A]; pyrethrins-pyrethroids [3A], DDT [3B]; neonicotinoids [4A]; spinosyns [5]
- Growth & development* - e.g. methoprene [7A], pyriproxyfen [7C]; benzoylureas [15]
- Midgut - microbial toxins: *Bacilus thuringiensis* [11A], *Lysinibacillus sphaericus* (syn. *Bacillus sphaericus*) [11B]

*Compounds referred to generically as ‘Insect Growth Regulators’ [IGRs]

Insecticide Resistance Management (IRM)

Low dose strategy

- reduce pesticide applications and rate applied; use short persistence compounds
- leave refugia and/or leave some pest generations untreated
- integrated approach (chemical/non-chemical) and accept higher pest thresholds

Multiple attack strategy

- mixtures of pesticides with different MoA but ideally equal persistence
- rotate pesticides with different MoA

High dose strategy

- kill heterozygotes, making resistance allele functionally recessive
- not recommended except for *Bt* (GM) crops
- ignores the harmful effects nearly all pesticides can have on the environment

Anopheles

- Thirty to 40 *Anopheles* species commonly transmit human *Plasmodium* species
- Some species are also vectors of filarial nematodes and O'nyong-nyong virus
- Most *Anopheles* are crepuscular (active at dusk or dawn) or nocturnal
- Some *Anopheles* feed indoors (endophagic); others are exophagic
- After blood feeding, some species prefer to rest indoors (endophilic); others are exophilic

Anopheles control

Treat larval breeding sites

Physical; Chemical; Biological Control

Attack adults

Spray inside houses with insecticide (Indoor Residual Spaying; IRS) - **endophilic species**

DDT replaced due to environmental concerns

DDT now permitted again by WHO in some parts of Africa

Resistance to insecticides can be a significant issue for mosquito control

Deter adult females

Long-lasting insecticide-treated nets (LLINs) - **nocturnal, endophagic species**

Improved housing - e.g. window screens - **endophagic species**

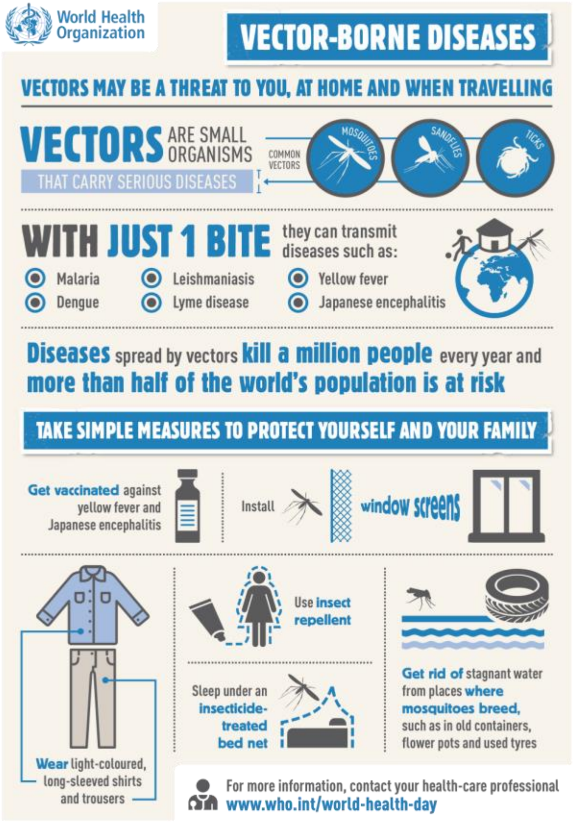
Repellents - e.g. ‘Deet’

Genetic methods (to be considered later)

Anopheles

Known resistance [MoA group]

- Carbamates [1A]
- Organophosphates [1B]
- Cyclodienes [2A]
- Pyrethrins-Pyrethroids [3A]
- DDT [3B]

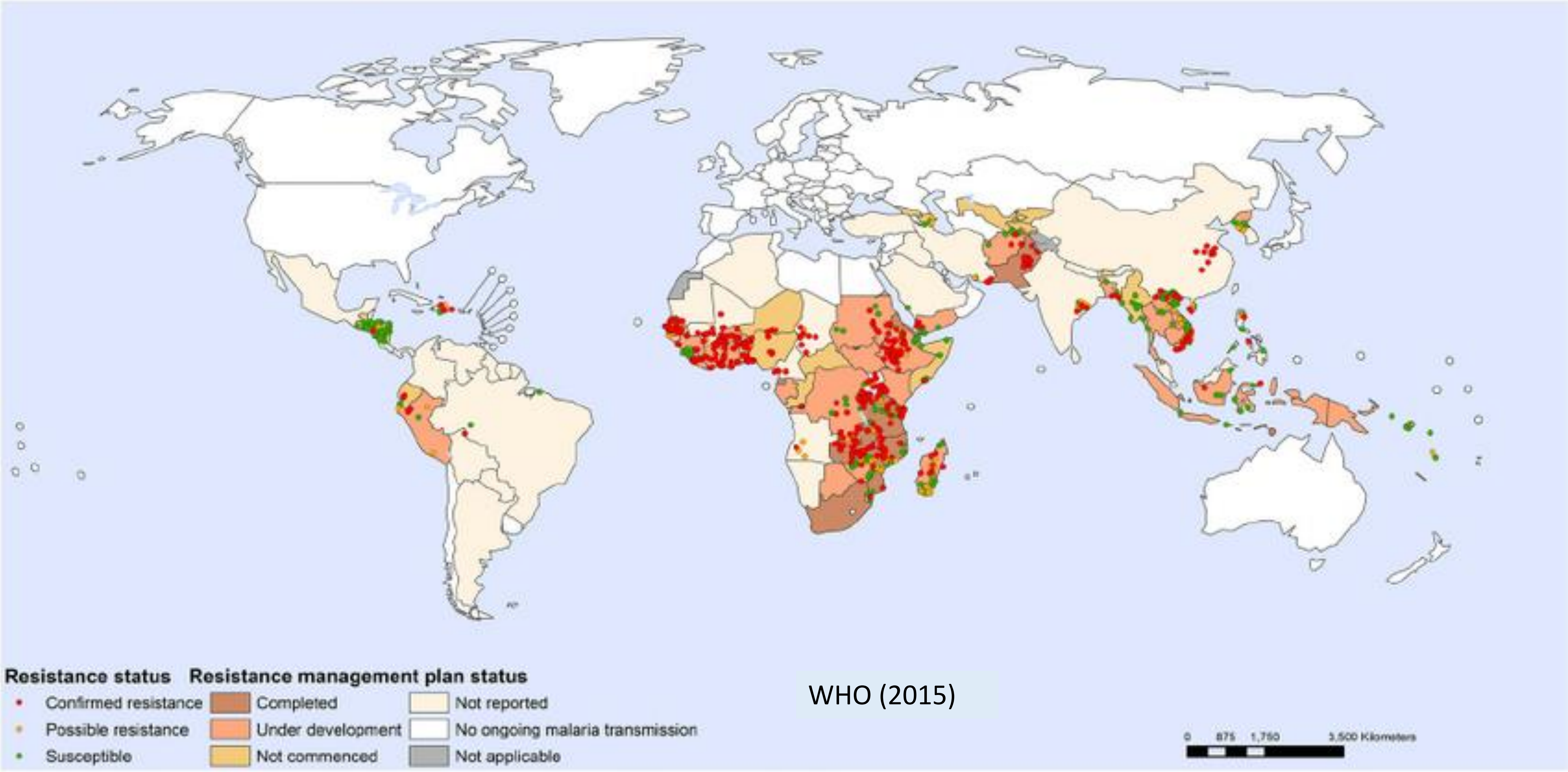


Chemical control

- LLINs (pyrethroid*) and IRS (DDT still needed in high transmission areas);*some nets now have added piperonyl butoxide to combat cyt. P450 oxidase R to pyrethroids
- Larvicides, e.g. *B. thuringiensis subsp. israeliensis* [*Bti*], pyriproxyfen

Resistance monitoring and management plans established in some countries

Reported pyrethroid susceptibility status for malaria vectors (2010-2014) and status of national insecticide resistance monitoring and management plan (2014)



WHO (2015)

Aedes aegypti and *A. albopictus*

*V*ectors of dengue, yellow fever, chikungunya & zika viruses

Vector control

- primarily outdoor space spraying/fogging/ misting [mostly exophilic] [pyrethroids, OPs, *Bti*]
- remove or treat breeding sites [*Bti*, IGRs, OP]
- mosquito traps for monitoring and control, e.g. lethal ovitraps with *Bti*

In endemic areas also advisable to wear long clothing, apply insect repellent outdoors; screen houses; use LLINs. IRS has limited impact

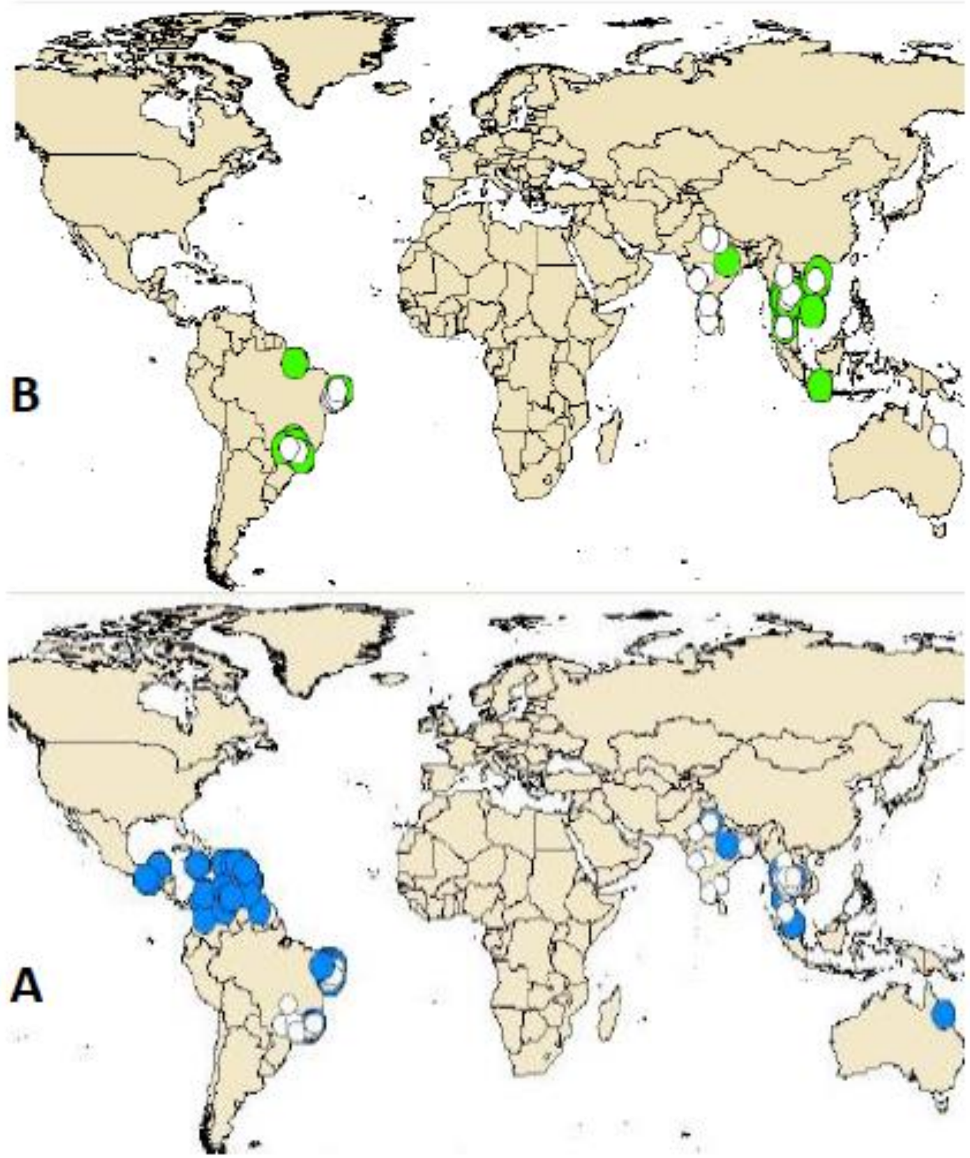
Aedes

Known resistance [MoA group]

- Carbamates[1A: AChE inhibitors]
- Organophosphates [1B: AChE inhibitors]
- Cylodienes [2A: GABA-gated Cl- channel blockers]
- Pyrethrins-Pyrethroids [3A: Na+ channel modulators]

Resistance to the Juvenile Hormone analogue, methoprene [7A] reported in *Ochlerotatus nigromaculis* (*Aedes nigromaculis*) populations in central California

Aedes: Insecticide resistance

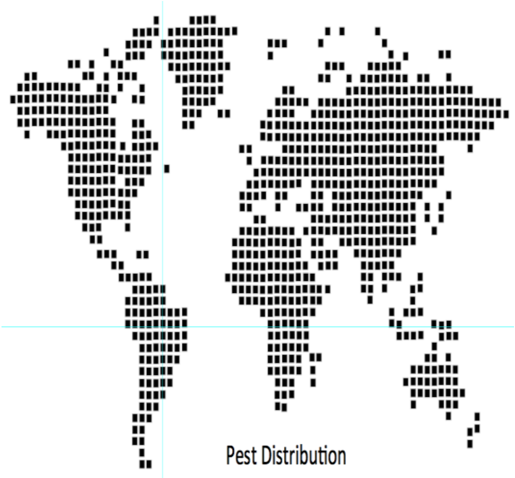


Resistance to pyrethroids (A) and OPs (B) in *Aedes aegypti* (Ransom *et al.* 2010)

The Worldwide Insecticide resistance Network (WIN) http://win-network.ird.fr
tracking insecticide resistance in mosquito vectors of arboviruses around the world

Implementation of IRM strategies required

Culex species



e.g. *Culex quinquefasciatus* and *Culex pipiens pipiens*

Vectors of filariasis, and of viruses that cause various encephalitis diseases, Rift-Valley fever and West Nile fever

OPs and IGRs used as larvicides, also *Bti* or *L. sphaericus* [*Ls*] products

Reduce risk of being bitten (as *Anopheles*, *Aedes*); IRS rarely used

Culex

Known resistance [MoA Group]

- Carbamates[1A]
- Organophosphates [1B]
- Cyclodienes [2A]
- Pyrethrins-Pyrethroids[3A]
- *Lysinibacillus sphaericus* [11B]
- Benzoylureas [15; chitin synthesis inhibitors]

Implementation of IRM strategies required

Bti and *Ls*

Microbial insecticides based on *Bti* and *Ls* marketed for mosquito larval control

- widely used in USA and Europe
- *Ls* used against *Culex* in C. & S. America and Asia due to its good residual activity in polluted water; not effective against *Aedes aegypti*
- high level of safety for non-target organisms, including humans
- the relatively high cost of *Bt* products limits their use in the world's poorest areas

***Bti* products are a low resistance risk as they contain three toxins (Cry4A, Cry4B, Cry11A) with different binding sites, and a cytolytic toxin, Cyt1A**

- little evidence of significant field resistance
- studies have shown 8 to 10-fold natural variation in *Bti* LC_{50} values in *Culex pipiens* field populations from Cyprus [Wirth *et al*. 2001; Vasquez *et al.* 2009]

***Ls* toxins share the same binding site; altered target site resistance is thus a greater risk**

- field resistance has been reported

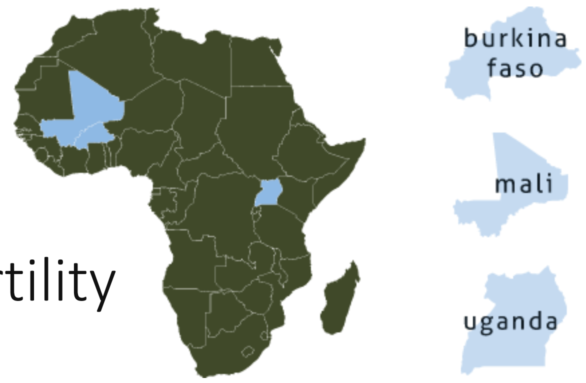
Prospects: genetic control methods

RIDL® - **R**elease of **I**nsects with **D**ominant **L**ethality [Oxitec]

Developed for *Aedes* [2002] but applicable to other insects; genetically engineered males [OX513A] released and mate with wild females, producing offspring which die as larvae; trial programmes in Brazil, Cayman Islands and Panama have been reported to achieve >90% *Aedes* control; expensive, requires repeat introductions

'Target Malaria' [https://targetmalaria.org/]

Heritable strategy; based on 'Homing Endonuclease Gene' concept;
Two current approaches: biasing sex ratio towards ♂s, reducing ♀ fertility



Wolbachia - bacterial endosymbionts, e.g.

5-year EPA registration (Nov 2017) for release of male *A. albopictus* (ZAP Males®) in 20 US states; ♂s infected with *Wolbachia* strain which causes ♀s to produce non-viable offspring

Wolbachia strains have also been associated with antiviral protection and resistance to *Plasmodium* in mosquitoes

Prospects: other methods

Chemical/Physical, e.g.

- introduction of neonicotinoids and spinosad for mosquito control
- monomolecular films, e.g. AGNIQUE® MMF, a biodegradable surfactant, which can spread to completely cover water surfaces - has been combined with use of *Bti*
- insecticidal paints (slow-release microcapsules)
- electrostatic coated insecticide nets
- attractive toxic sugar baits for males and females; have been combined with LLINs

Biological, e.g.

- Mermithid nematodes, e.g. *Romanomermis iyengari*

Application technology

Innovative Vector Control Consortium and US Armed Forces Pest Management Board - areas to improve application technology include:

- ensuring IRS programmes use constant flow valves and erosion resistant (ceramic) tips for compression sprayers to prevent under/overdosing
- new larval management methods:
  - thermal fogging of *Bti* proving highly effective in container habitats
  - next generation technology, e.g. ‘smart’ spray systems for larval control - Drone/GPS precision spraying with systems capable of carrying >50 kg of insecticide

Knapp et al (2015) https://malariajournal.biomedcentral.com/articles/10.1186/s12936-015-0907-9

Management of mosquitoes in natural wetlands

Akrotiri salt marsh spp (potential vectors) e.g.
Ochlerotatus (*Aedes*) *detritus* (JEV and WNV)
Aedes caspius (Tahyna & RVFV)

Very vulnerable environments

Bti [Vectobac 12 AS™] used as larvicidal spray, fogging trials [A Martinou pers com]
Environmentally safe, low risk of resistance; IGRs might also be relatively safe

Spraying neuroactive compounds to control adult mosquitoes in/near wetland areas is potentially very damaging; especially pyrethroids, which are highly toxic to aquatic organisms

Thank you