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Integrated Resistance Management in the control of disease transmitting mosquitoes

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Insecticide Selection for Vector Control

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Overview

- Introduction to IRAC
- Insecticide resistance
- Insecticide Resistance Management
- Insecticide resistance monitoring
- Example from Crop Protection
- Recommendations

Introduction to IRAC

- Insecticide Resistance Action Committee (IRAC)
  - Formed in 1984
  - Specialist technical group of the agrochemical industry association CropLife International.
  - Provides a coordinated industry response to the development of resistance in insect and mite pests.

"Resistance Management for Sustainable Agriculture and Improved Public Health"

Introduction to IRAC Public Health team

- Industry members of the PH team:
  - BASF
  - Bayer Crop Science
  - Dow
  - FMC
  - Sumitomo
  - Syngenta
  - Vestergaard Frandsen

- Special observers/non-industry members:
  - WHO
  - BMGF
  - CDC

Insecticide Resistance

- Insecticide resistance is not new
  - First observed in 1887
    - Scale insects resistant to sprays of kerosene
  - House fly populations were found to be resistant to DDT by 1947
  - Resistance identified to all introduced insecticide groups within 2 – 20 years
  - By 2006 7400 cases in 550 species

Insecticide Resistance

- A decrease in the susceptibility of an insect population due to a genetically controlled mechanism.
  - Altered binding site
  - Elevated or modified metabolism
  - Reduced penetration of cuticle
  - Behavioural modification
  - Multiple mechanisms may be present

Insecticide Resistance Management

- Aim:
  - To take actions that reduce an insect population to an acceptable level, in such a way as to maintain the long term effectiveness of the control interventions employed.
  - Emphasis is on the continuing use of an intervention as part of a VC programme, rather than the continual use of a particular intervention.

Insecticide Resistance Management

- Selection pressure increases the proportion of individuals carrying the gene(s) conferring resistance in a population before field “failure” is observed.

- Selection pressure should be removed when the genes are present at a low prevalence, before field failure is observed.
  - Therefore, we need to identify the presence of resistance at low levels.

Insecticide Resistance Monitoring

- There are a number of resistance monitoring tools available.
- However, before a monitoring programme is instigated, a number of questions must be asked:

Insecticide Resistance Monitoring

- Will the chosen resistance monitoring programme provide enough timely information on which to base the choice of intervention?
  - Can it detect a change in the target population's susceptibility to an insecticide?
  - Does it give an indication of the resistance mechanism?
  - Is it logistically feasible?

Insecticide Resistance Monitoring

- Bioassays are often the most practical in a field setting
  - Requiring little/no access to a laboratory
  - Return fairly rapid results
  - Technicians can be readily trained in methodology
  - Generally robust methodology

Insecticide Resistance Monitoring

- However, bioassays have challenges:
  - If field collected mosquitoes are used
    - Can enough be found?
    - Mixed age, blood fed/non-blood fed
    - Unknown prior exposure to insecticides
  - If f1 adults are used
    - Requires access to lab
    - Less likely to be representative of total population

Insecticide Resistance Monitoring

- Which bioassay method to use?
  - WHO diagnostic assay
    - well established
    - widely used
    - little flexibility, discriminating/diagnostic dose
    - diagnostic dose may be too high
  - Bottle based assays
    - greater flexibility
    - readily available
    - comparison potentially challenging

Insecticide Resistance Monitoring

- Synergists can be used with both methodologies
  - Don’t always give clear results
  - Careful interpretation required

Insecticide Resistance Monitoring

- Molecular methods of resistance monitoring
  - can identify heterozygous resistant individuals which may not be identified in bioassays
  - can identify resistance mechanism in an individual mosquito, or part there of
  - True field kits still in development

Insecticide Resistance Monitoring

- Discriminating dose
  - Ideally generated from a baseline study in a given region against a given insect species
  - Exposure time and assessment interval chosen with a knowledge of the insecticidal mode of action
  - A discriminating dose 2 x lc95 will identify significant changes in susceptibility
  - Survivors examined using molecular techniques to identify probable resistance mechanisms

Insecticide Resistance Management

- “Ideal” steps of an IRM programme:
  - Baseline study
  - Understand resistance mechanisms where present

  →Chose effective insecticides, with different modes of action, and apply in a temporal or spatial rotation, according to product label
    - Don’t expose consecutive generations to insecticides with the same MoA
    - Don’t expose different life stages to insecticides with the same MoA

Insecticide Resistance Management

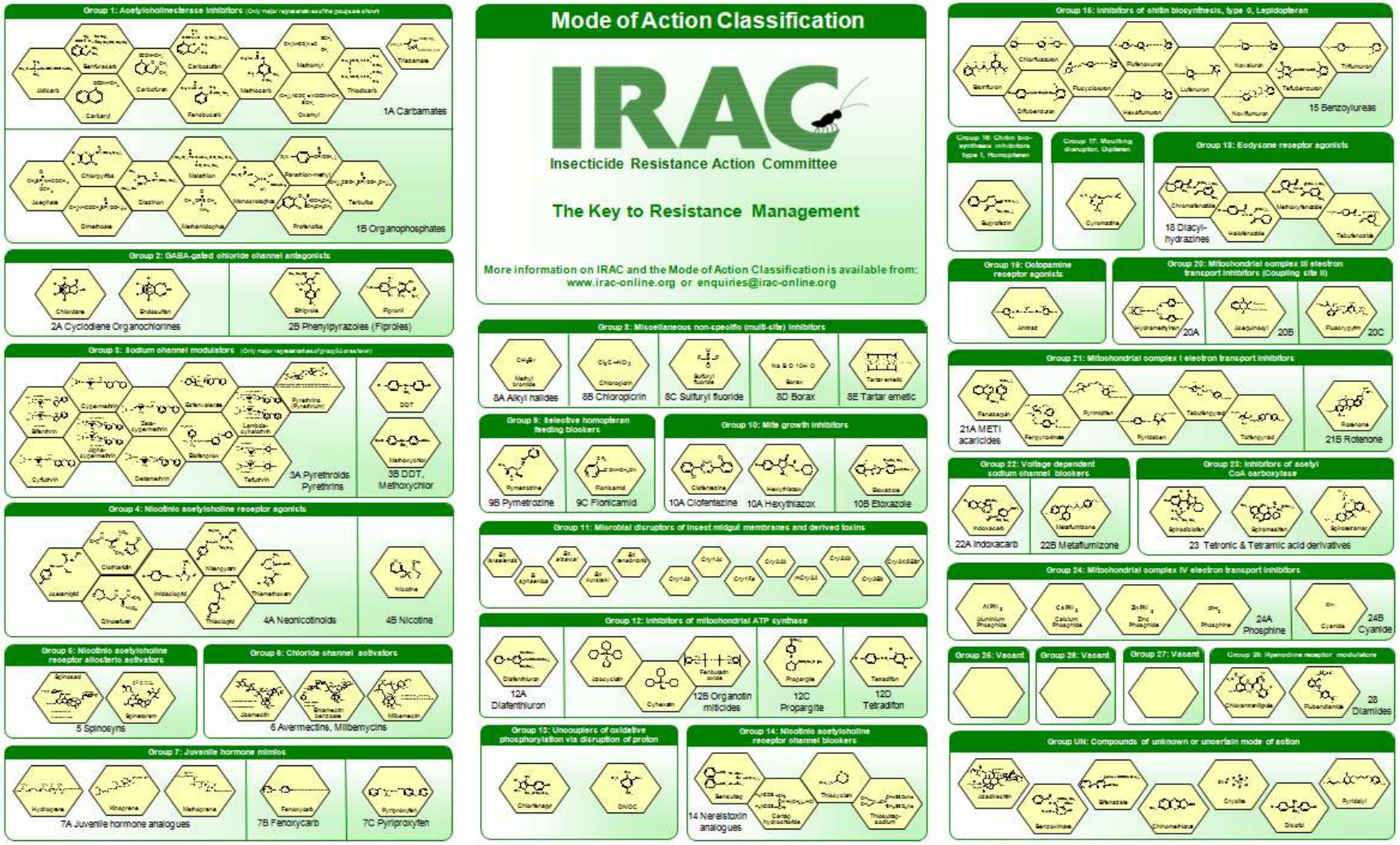
- “Ideal” steps of an IRM programme:
  - Continue monitoring
  - Change rotation partners

Insecticide Resistance Management

- Currently not practical in Vector Control:
  - Very limited choice of insecticidal MoA
  - Many generations exposed to the same residual deposit of insecticide
  - A favoured intervention uses a single MoA, pyrethroids on nets
  - Extended historical use of available insecticides makes baseline data collection challenging

Insecticide Resistance Management

- In resistance management, it is the insecticides mode of action that is important
  - IRAC Mode of Action Classification categorises all current insecticides into groups according to their mode of action


Mode of Action Classification
IRAC
Insecticide Resistance Action Committee
The Key to Resistance Management
More information on IRAC and the Mode of Action Classification is available from:
www.irac-online.org or enquiries@irac-online.org
Group 1: Acetylcholinesterase inhibitors (Only major representatives of the groups shown)
1A Carbamates
1B Organophosphates
Group 2: GABA-gated chloride channel antagonists
2A Cyclodiene Organochlorines
2B Phenylpyrazoles (Fiproles)
Group 3: Sodium channel modulators (Only major representatives of group(s) shown)
3A Pyrethroids Pyrethrins
3B DDT, Methoxychlor
Group 4: Nicotinic acetylcholine receptor agonists
4A Neonicotinoids
4B Nicotine
Group 5: Nicotinic acetylcholine receptor allosteric activators
5 Spinosyns
Group 6: Chloride channel activators
6 Avermectins, Milbemycins
Group 7: Juvenile hormone mimics
7A Juvenile hormone analogues
7B Fenoxycarb
7C Pyriproxyfen
Group 8: Miscellaneous non-specific (multi-site) inhibitors
8A Alkyl halides
8B Chloropicrin
8C Sulfuryl fluoride
8D Borax
8E Tartar emetic
Group 9: Selective homopteran feeding blockers
9B Pymetrozine
9C Flonicamid
Group 10: Mite growth inhibitors
10A Clofentezine
10A Hexythiazox
10B Etoxazole
Group 11: Microbial disruptors of insect midgut membranes and derived toxins
Group 12: Inhibitors of mitochondrial ATP synthase
12A Diafenthiuron
12B Organotin miticides
12C Propargite
12D Tetradifon
Group 13: Uncouplers of oxidative phosphorylation via disruption of proton
Group 14: Nicotinic acetylcholine receptor channel blockers
14 Nereistoxin analogues
Group 15: Inhibitors of chitin biosynthesis, type 0, Lepidopteran
15 Benzoylureas
Group 16: Chitin biosynthesis inhibitors type 1, Homopteran
Group 17: Moulting disruptor, Dipteran
Group 18: Ecdysone receptor agonists
18 Diacylhydrazines
Group 19: Octopamine receptor agonists
Group 20: Mitochondrial complex III electron transport inhibitors (Coupling site II)
20A
20B
20C
Group 21: Mitochondrial complex I electron transport inhibitors
21A METI acaricides
21B Rotenone
Group 22: Voltage dependent sodium channel blockers
22A Indoxacarb
22B Metaflumizone
Group 23: Inhibitors of acetyl CoA carboxylase
23 Tetronic & Tetramic acid derivatives
Group 24: Mitochondrial complex IV electron transport inhibitors
24A Phosphine
24B Cyanide
Group 25: Vacant
Group 26: Vacant
Group 27: Vacant
Group 28: Ryanodine receptor modulators
28 Diamides
Group UN: Compounds of unknown or uncertain mode of action
Guidance on the use of Sub-Groups:
• Represent distinct structural classes believed to have the same mode of action
• Provides differentiation between compounds that may bind at the same target site
• Are structurally different such that risk of metabolic cross-resistance is lower than for close chemical analogs
• Are likely to be metabolized by different enzymes - may bind differently enough within the target site that the chance of selection for metabolic/target-site resistance is reduced compared to close analogs
• In the absence of other alternatives, it may be possible to rotate compounds between sub-groups if it is clear that cross resistance mechanisms do not exist in the target populations
• Not all of the current groupings are based on knowledge of a shared target protein. For further information please refer to the IRAC Mode of Action Classification document.
•1A & 1B - If there are no other alternatives, compounds may be rotated in situations where cross-resistance mechanisms are known to be absent in the insect populations to be treated.
• 3A & 3B - If there are no other alternatives, compounds may be rotated in situations where cross-resistance mechanisms (e.g. kdr) are known to be absent in the insect populations to be treated. DDT is no longer used in agriculture and therefore this is only applicable for the control of human disease vectors such as mosquitoes, because of a lack of alternatives.
•10A - Clofentezine & Hexythiazox are grouped because they commonly exhibit cross-resistance even though they are structurally distinct, and the target site for neither compound is known.
• 22A & 22B - Although these compounds are believed to have the same target site, they have been sub-grouped because they are chemically distinct, and current evidence indicates that the risk of metabolic cross-resistance is low.
Structures are reproduced from the Pesticide Manual with permission from the British Crop Protection Council
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Poster Version3, September 2009 Based on the Mode of Action Classification- Version 6.1

Insecticide Resistance Management

- The IRAC Mode of action scheme is central to developing effective IRM strategies
  - Sequences, rotations or alternations of different MoA groups
    - Do not rotate within a MoA group
  - Knowledge of metabolic resistance mechanisms important
    - Identify cross-resistance
  - Intelligent sequences of MoA groups will always reduce selection pressure, help prevent or delay resistance and help regain susceptibility
  - IRAC strongly supports MoA labelling schemes, e.g. US, Australia, and campaigns for wider use of such schemes

Introduction of a new insecticide: an example from crop protection

- The Diamide insecticides
  - Ryanodine receptor modulators, classified as group 28 in the IRAC mode of action classification.
  - Under the auspices of IRAC, the companies with interests in this area have cooperated in the production of IRM recommendations, before product launch.
  - Implementing IRM as the insecticides are launched will significantly delay development of resistance.
  - This approach should become a model for the introduction of new insecticides.

IRAC recommendations

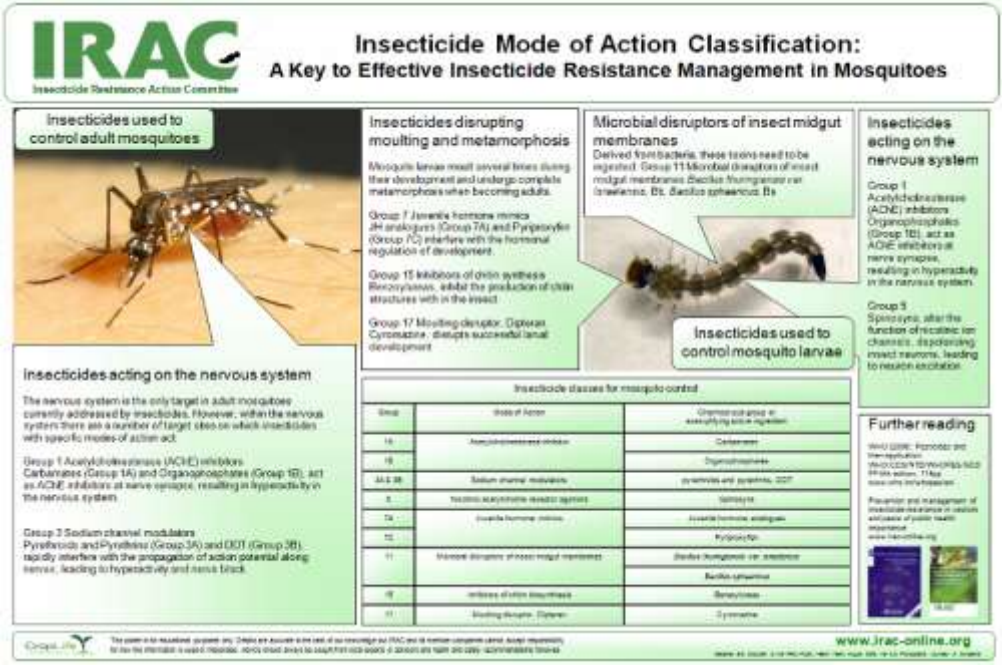
- Best practice Integrated Vector Management
  - Habitat modification
  - Education
  - Minimise non-VC sources of exposure
  - Maintain and calibrate spray equipment
  - Use products that are “fit for purpose”
  - Follow the product label
  - Follow IRM recommendations

IRAC recommendations

- Rotation of insecticidal MoA (temporal or spatial), where possible
- Base choice of intervention on IRM principles
- Communication, mosquitoes don’t stop at regional boarders

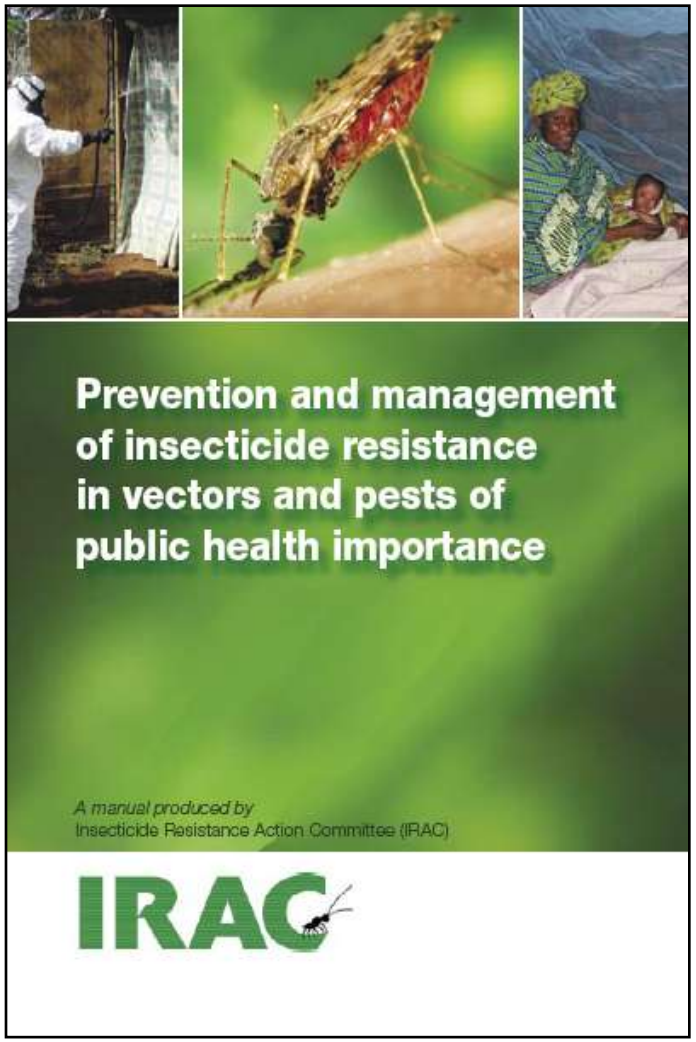
Further information

- Further information, educational material and a newsletter can be found at the IRAC website: www.irac-online.org



Further information

- The “Vector manual”
  - 3,000 hard copies distributed
  - Available for download from IRAC website
  - Collaborative achievement:
    - Content produced by IRAC PH team
    - Layout and design by WHO
    - Printing organised by CropLife
    - The publication was generously funded by the Bill and Melinda Gates Foundation
  - Updated and expanded second edition available early 2010



Conclusions

- IRM should be an integral part of all VC programmes.
- IRM is a stewardship responsibility of the commercial companies that market VC insecticides.
- IRM is a stewardship duty of those who design and implement VC programmes.

Thank you for your attention