Technical assessment of facilities and capacities of countries to conduct routine insecticide resistance monitoring in mosquitoes of public health importance

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by

The Worldwide Insecticide resistance Network (WIN)

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Content

1. Introduction

Vector-borne diseases pose a major threat to the health of societies around the world. They are caused by parasites, viruses and bacteria transmitted to humans by mosquitoes, triatomine bugs, blackflies, sandflies, ticks, tsetse flies, mites and lice. The major global vector-borne diseases of humans include malaria, dengue, lymphatic filariasis, chikungunya, onchocerciases, Chagas disease, leishmaniasis, Zika virus disease, yellow fever and Japanese encephalitis, and account for around 17% of the estimated global burden of communicable diseases and claim more than 700 000 lives every year (WHO, 2018). The burden is highest in tropical and subtropical areas. More than 80% of the global population lives in areas at risk from at least one major vector-borne disease, with more than half at risk from two or more. The risk of infection for certain viral pathogens is particularly high in towns and cities where *Aedes* and *Culex* mosquitoes proliferate, because of favourable habitats and close contact with human beings. Morbidity and mortality rates are often disproportionately high in poorer populations. People who survive these diseases can be left permanently disabled or disfigured, compounding their disadvantage.

Vector control interventions have one of the highest returns on investment in public health. Effective vector control programmes that reduce diseases can advance human and economic development. Aside from direct health benefits, reductions in vector-borne diseases can enable greater productivity and growth, reduce household poverty, increase equity and women's empowerment, and strengthen health systems. Among vector control interventions, insecticide-based vector control is the cornerstone in the fight against malaria and other mosquito borne diseases. For example, malaria morbidity was reduced by 70% due to the massive deployment of vector control tools (LLIN and IRS) since the 2000s (WHO, 2018). Unfortunately, the use of the same insecticide classes for more decades has led to the selection of multiple resistance in mosquito vectors transmitting malaria (Ranson *et al.*, 2016) as well as in the ones transmitting arboviruses such as dengue, Zika and chikungunya (Moyes *et al*., 2016). Effective insecticide resistance monitoring is therefore essential to guide decision making for vector control (WHO, 2016). Sparse information is however available on the capacity of countries affected by mosquito borne diseases to conduct insecticide resistance monitoring. Those gaps strongly impede the implementation of the global plan for insecticide resistance management (GPIRM, 2012) and it is a priority to rapidly identify the countries/territories that will need to strengthen their resistance monitoring capacity.

Over the past year, the WHO Global Malaria Programme (GMP), the WHO Department of Control of Neglected Tropical Diseases (NTD), and the Special Programme for Research and Training in Tropical Diseases (TDR) have developed in collaboration with WHO regional offices, experts and other partners a new strategic approach for the Global Vector Control Response (GVCR), to urgent strengthen vector surveillance and control activities. Following the recommendations of the Member States during the WHA70 in May 2017 and to facilitate the deployment of these activities, an estimate of the capacity and costs for implementing the response at national level is needed.

Noting that insecticide resistance is recognized as a major threat for vector control, the Worldwide Insecticide resistance Network (WIN, https://win-network.ird.fr/) has been commissioned by the TDR/WHO in collaboration with NTD to evaluate the capacity of the countries to monitor insecticide resistance in mosquitoes of public health importance. In this way, an online questionnaire developed by WIN was sent to relevant partners (Ministries of Health, national research institutes, etc.) to assess the country capacities and facilities to perform routine insecticide resistance monitoring at national level. The report summarizes the survey responses obtained from 75 countries located in the 6 WHO regions in order to provide baseline information's to estimate the costs to fulfil the needs in terms of insecticide resistance surveillance at national, regional and international level.

2. Methodology

2.1. Selection of Participants

We first established a list of potential "focal points" in country and territories located in each WHO region (https://www.who.int/healthinfo/global_burden_disease/definition_regions/en/) where vector borne diseases represent a public health threat (EU countries were excluded from the survey). A focal point was defined as "the person (or institution) officially commissioned by the Ministry of Health to conduct routine insecticide resistance monitoring in a given country".

The list of the Country focal points (CFPs) participating to the study is provided in Annex 1. CFPs were obtained from different sources;

- **Global scale**:
- WIN partners (19 institutions located on the 6 continents)
- Personal contacts (IRD network, Institut Pasteur network, WHO, ZIKAlliance and Infravec EU projects, COST-IAM, etc.).

- **Regional scale**
- AFRO: African Network for Vector Resistance (ANVR) ; Elimination 8 (E8); West Africa *Aedes* Surveillance Network (WAASuN); The PMI Vector Link project
- EMRO: Pakistan, Iran, Afghanistan Malaria Network
- PAHO: Caribbean Vector-Borne Diseases Network; Caribbean Public Health Agency (CARPHA) ; Entomology network of Central American countries (EntoNet); The Regional Network for Surveillance and Management of Resistance to Insecticides Used in Public Health
- SEARO & WPRO: Asian Pacific Leaders Malaria Alliance (APLMA) ; Asia Pacific Malaria Elimination Network (APMEN)

CFPs were invited to participate in the survey (see section 2.2) by receiving an e-mail explaining the rationale and objectives of the survey. A cover letter signed jointly by WHO TDR and NTD highlighting the importance of the study was systematically attached to the email (Annex 2). The WHO representative at country level (or at regional level when he/she was absent) was also informed about the study outcomes to promote transparency and facilitate exchanges with the country representatives if needed.

2.2. Questionnaire

An online questionnaire aiming at assessing the country capacity and facility to perform insecticide resistance monitoring at national level has been established by WIN experts. The questionnaire was developed and accessible through a Google form:

https://docs.google.com/forms/d/e/1FAIpQLSf1oUdGhjEygsIYb1H7U8ewdLLpK8ff9p9Kb7Jv_5kwSJB9nQ/viewform.

The questionnaire is made-up of 26 questions divided in 5 categories related to the organization, facilities, human resources, technical capacities, and budget dedicated to vector control and insecticide resistance (Annex 3).

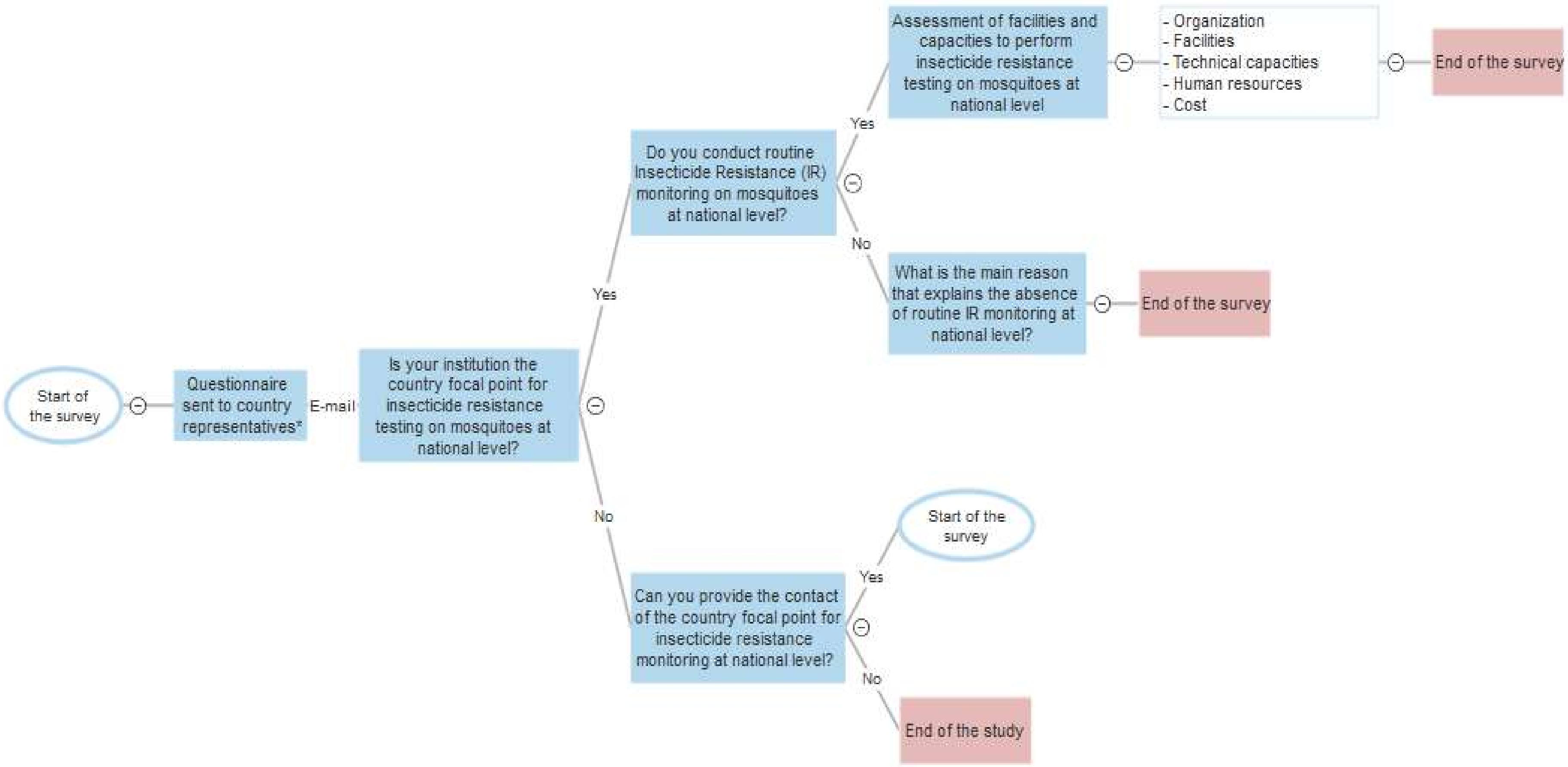
Data were extracted from the questionnaire to produce tables, graphs and maps. All results were provided by an organization or an institution declaring being the Country Focal Point (CFP) for performing routine insecticide resistance monitoring. However, the WIN could not verify the veracity of the declaration and deny any responsibilities in the case of the information submitted by the CFP are not representative of the country situation.

2.3. Study design and inclusion criteria

Simple binary pattern tree was used to collect responses (Figure 1) and to move to the next step. Each person contacted had to respond to 2 preliminary questions before been included in the survey; we had first to ensure that i) the person was the relevant CFP for resistance monitoring activities and ii) Insecticide Resistance Monitoring (IRMo) was implemented in routine in the country. The CFPs received a delay of 1 month to respond to the questionnaire. A first reminder was sent to them after 2 weeks, and a second reminder was sent again 1 week before the deadline. Note that the deadline had to be substantially extended (i.e. weeks or months depending on the country) in order to get enough data coverage to perform the analysis.

In each country, only the institution commissioned by the national authorities to perform routine insecticide resistance testing was included in the analysis. However, in few cases, multiple responses were received from a single country. When multiple responses were obtained from different "institutions" (eg Gabon, Kenya, Nigeria, Philippines, Sudan), we had first to check the "veracity" of CFP responses and include only data coming from the institution "officially" in charge of IRMo. Exceptions were made in Kenya and Nigeria where two institutions were included in the analysis because they both declared being mandated by authorities to perform IRMo. Finally, when multiple responses were sent by different persons within an institution (cases in Egypt and Mozambique), it has been decided to include only one response per institution, i.e. the one coming from the person having the highest position in the institution.

Figure 1. Simple logical pattern tree for the survey on insecticide resistance monitoring



2.4. Indicators and scoring system

Various indicators were used to evaluate the Country Focal Points (CFPs) responses (Table 1). The list of the CFPs contacted is presented in Annex 1.

Table 1. Data, Indicators and definitions

Data & Indicators	Definition
No. of countries and territories listed per region	No. of countries listed per WHO Regional offices AFRO: https://www.afro.who.int/ EMRO: http://www.emro.who.int/fr/index.html PAHO: https://www.paho.org/hq/index.php?lang=en SEARO: http://www.searo.who.int/en/ WPRO: https://www.who.int/westernpacific
No. of countries contacted	No. of Country Focal Points (CFPs) that have received an official invitation to participate in the survey
No. of countries participating in the survey	No. of Country Focal Points (CFPs) that have provided a complete (or even uncompleted) response to the questionnaire (Annex 1)
No. of countries declaring conducting routine Insecticide Resistance Monitoring (IRMo)	No. of Country Focal Points (CFPs) that have declared performing routine Insecticide Resistance monitoring (IRMo) on mosquitoes (Question 6 of the questionnaire)
Country Coverage Rate (CCR)	No. of countries that have participated in the survey / Total No. of countries listed per WHO region * 100
Country Participation Rate (CPR)	No. of countries that have participated in the survey / Total No. of countries contacted * 100
Country Resistance Monitoring Rate (CRMR)	No. of countries declaring conducting routine IRMo / No. of countries that have participated to the survey * 100
Average annual cost per country to perform IRMo (USD)	Average annual budget (USD) per country allocated to insecticide resistance monitoring in the last 3 years (2017, 2018 and 2019). Exchange rate dated of the 24 of April was used when budget was reported in local currency.

The WIN has received the support of Dr. Mariam Otmani del Barrio (otmanidelbarriom@who.int), TDR health economist, for constituting the cost assessment part (see section 3.5).

An arbitrary scoring system to estimate the "representativeness" of the data collected was estimated for each WHO region based on the three following indicators;

- **Country Coverage Rate (CCR),**
- **Country Participation Rate (CPR),** and
- **Country Resistance Monitoring Rate (CRMR).**

Arbitrary Scoring rates for CCR, CPR and CRMR were:

< 20%: insufficient (no analysis performed)

20%-40%: low

40%-60%: average

60%-80%: good

> 80%: excellent

2.5. Mapping

Threat maps were created to address whether data obtained on insecticide resistance monitoring were representative of countries at risk of mosquito transmitted diseases. The WIN addressed the distribution of seven mosquito-borne diseases of global significance; i) malaria (*P. falciparum* and *P. vivax*, including or exlcuding *P. knowlesi*), ii) yellow fever, iii) Zika, iv) chikungunya, v) lymphatic filariasis, vi) Japanese encephalitis, and vii) dengue.

To identify countries with a population at risk of each infection, we used a series of predictive maps and WHO classifications as follows:

- **Yellow fever**

We used the predictive map of contemporary annualized yellow fever incidence from https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30024-X/fulltext. This was converted to a binary map of transmission occurrence by converting all incidence values >0 to one. This fine resolution binary map was then overlaid with the UN's national boundaries to identify each country at risk.

- **Zika**

We used the predicted environmental suitability for Zika virus infections from https://elifesciences.org/articles/15272. This was converted to a binary map of transmission occurrence by calculating the suitability threshold value that captured 95% of the confirmed reports of transmission. All predicted values above this threshold were converted to one, and all below were converted to zero. This fine resolution binary map was then overlaid with the UN's national boundaries to identify each country at risk. In this instance, the source data predict suitability for infections with this virus, rather than actual contemporary presence, and this approach can identify very localised areas that may be suitable but are too isolated and small to sustain transmission. For this reason, we also set a 2% of land area threshold below which we assumed this virus was not present in the country unless reports confirmed otherwise.

- **Chikungunya**

We used the predicted environmental suitability for chikungunya virus infections from https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2016.21.20.30234. These data were treated in the same way as the Zika data above.

- **Lymphatic filariasis**

We used the predicted environmental suitability for lymphatic filariasis transmission within the current transmission limits provided by https://parasitesandvectors.biomedcentral.com/articles/10.1186/s13071-014-0466-x. This was converted to a binary map of transmission occurrence by calculating the suitability threshold value that captured 95% of the confirmed reports of transmission. All predicted values above this threshold and within the transmission limits were converted to one, and all below were converted to zero. This fine resolution binary map was then overlaid with the UN's national boundaries to identify each country at risk.

- **Japanese encephalitis**

A binary map of the limits of transmission for JE was obtained from the Centers for Disease Control (2012) *Geographic distribution of Japanese encephalitis virus* (available at http://www.cdc.gov/japaneseencephalitis/maps/index.html). This fine resolution binary map was then overlaid with the UN's national boundaries to identify each country at risk.

- **Dengue**

We used the relative probability of dengue infection occurrence from https://www.nature.com/articles/nature12060. This was converted to a binary map of transmission occurrence by calculating the suitability threshold value that captured 95% of the confirmed reports of transmission. All predicted values above this threshold were converted to one, and all below were converted to zero. This fine resolution binary map was then overlaid with the UN's national boundaries to identify each country at risk.

- **Malaria**

The World Health Organization's annual world malaria reports and certificates of elimination provide the most up-to-date information on which countries have a population at risk of malaria (*P. falciparum* and/or *P. vivax*).

To produce a figure illustrating the fine resolution distribution of risk from all of these infections, each of the above fine resolution, binary maps was overlaid on a single map. In addition, two binary malaria maps were created. The first version used the limits of both *P. falciparum* and *P. vivax* transmission available from https://map.ox.ac.uk/explorer/#/ to create a binary map of the limits of transmission of one or both parasites. The second version included a map of *P. knowlesi* transmission[1] to provide a binary maps of the limits of transmission of one or more of these three malaria parasites.

Data sources for confirmed cases of authochonous transmission (used to calculate thresholds for the binary maps above) can be accessed below;

Zika and chikungunya - https://www.liebertpub.com/doi/full/10.1089/big.2015.0019

Dengue - https://www.nature.com/articles/sdata20144

2.6. Human resources

To evaluate the human resources dedicated to insecticide resistance monitoring, we recorded for each institution the number of staff performing insecticide resistance testing **in full time equivalent (FTE**). FTE is defined as the ratio of working hours actually spent on insecticide resistance testing during a specific reference period (usually a calendar year) divided by the total number of hours conventionally worked in the same period by an individual. For instance, 1 person working full time on resistance test per year, FTE=1. FTE were reported according to the academic levels (under graduate, bachelor, master and PhD degree). Note that the time a staff spent on mosquito rearing before performing resistance testing is included in the FTE.

Example. If 1 employee is spending 8 hours per week (1 day) on IR monitoring over 52 weeks, the time spent on IR testing is 8x52 = 416 hours. A full time employee usually works 8 hours a day, 5 days a week and 52 weeks a year (8x5x52 = 2080 hours). Then the full time equivalent (FTE) for the staff working on IR testing will be 416/2 080= 0.2.Then we add each individual FTE together to obtain the total of FTE for a given institution.

2.7. Cost analysis

Based on the information collected from each CFP on the budget allocated to mosquito control and insecticide resistance in 2017, 2018 and 2019, we tried to estimate an average annual cost for each activity per country. When data were missing for a given year, we adjust the calculation on available data. Exchange rate dated of the 24 of April, 2019 (www.xe.com) was used when budget was reported in local currency.

CFPs could refer to the Resource Needs table (Annex 4) in order to identify country budget needs for insecticide resistance monitoring at national level and to design annual budget for the next year. This document is based on "*the Framework for a national plan for monitoring and management of insecticide resistance in malaria vectors, WHO 2017*" (https://apps.who.int/iris/bitstream/handle/10665/254916/9789241512138-eng.pdf;jsessionid=CB7C2038E8AA42180D9FE35D08418CB0?sequence=1). The template has been updated according to the scope of our study.

[1] The binary *P. knowlesi* malaria map was generated using the methods described for dengue above, and the predicted relative probability of occurrence map from https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0004915.

3. Results

3.1. Key results

Overall, the questionnaire was sent to 119 Country Focal Points (CFPs) among the 169 countries and territories listed by the WHO (https://www.who.int/).

Among the 119 CFPs contacted, 75 responded to the questionnaire which gives a Country Participation Rate (CPR) of 63%. Differences in CPRs were noticed according to the region. The CPR was excellent for EMRO (83%), good for AFRO (71%) and WPRO (67%) and average for PAHO (50%) and SEARO (60%), based on our scoring system (Section 2.4). All countries that have responded to the questionnaire (except Gaza strip) were at risk of one or more transmitted mosquito borne diseases (Figure 2).

The Country Coverage Rate (CCR) was 44% based on our classification (75 out of 169 countries and territories listed by WHO). CCR was average in all regions (40%<x<60%) except in WPRO where only 32% of countries could be surveyed (which is classified as "low"). This could be explained by the large number of islands located in pacific and by the difficulty to identify relevant focal points in each territory.

Among the 75 countries surveyed, 47 of them declare performing routine IRMo at national level (63%). The Country Resistance Monitoring Rate (CRMR) is excellent in AFRO region (84%, 21 of 25) and good in the WPRO (67%, 8 of 12). Interestingly**, the CRMR is excellent (90%) when considering the top 16 "malaria" countries listed by WHO (Malaria report, 2018)**. However, only half of the surveyed countries located in EMRO (5 of 10), PAHO (10 of 22) and SEARO (3 of 6) declared performing routine IRMo at national level. The main reasons for not conducting routine IRMo, according to CFPs, are a lack of i**) trained staff and manpower (41%), ii) adequate facilities (19%)** and **iii) financial resources (20%).**

Overall, most of countries conducting IRMo declare having functional insectarium (100%, except in WPRO) and adequate insecticide testing laboratories (>80%, except in SEARO). The most frequent method in use for testing resistance in mosquitoes are WHO filter papers tests (47%), followed by larval bioassays (26%), CDC bottle assays (23%) and topical applications (4%). Pyrethroids and organophosphate are the two main insecticides classes tested for resistance (100% and 92% respectively) and most of countries (92%) declared performing IRMo on mosquitoes belonging to the *Anopheles* genus.

Among the 47 countries declaring performing IRMo, 88% declare endorsing the Global Plan for Insecticide Resistance Management in Malaria Vectors coordinated by the WHO. However, only half of the surveyed countries declare that the IRM plan is "functional".

Regarding cost assessment data obtained from 43 countries (out of 47), a total of **USD7M are dedicated annually to insecticide resistance monitoring**, with 52% of the total (USD4M) spent in PAHO and 31% (USD2M) in AFRO. Based on the questionnaire, one country in PAHO (Mexico) accounts for 70% of the total annual budget spent in IRMo in the region and then cannot be considered as representative of all Latin American countries.

Table 2. Country participation and data coverage according to WHO region

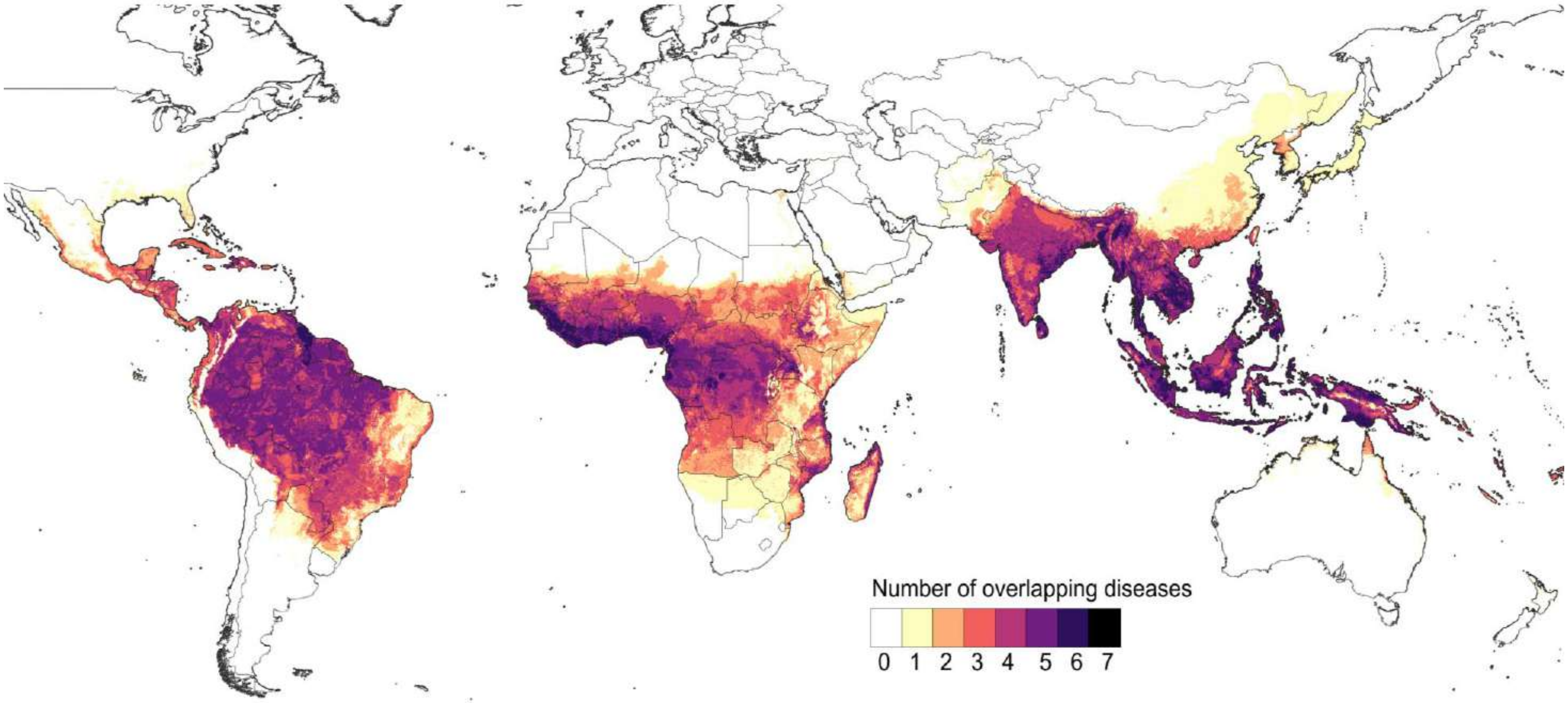
		AFRO	EMRO	PAHO	SEARO	WPRO	TOTAL
A	No. of countries and territories listed per region [a]	**47**	**22**	**52**	**11**	**37**	**169**
B	No. of countries contacted	35	12	44	10	18	119
C	No. of countries that have participated in the survey	25	10	22	6	12	75
D	Country Coverage Rate (CCR)	53%	45%	42%	55%	**32%**	44%
E	Country Participation Rate (CPR)	71%	83%	50%	60%	67%	63%
F	No. of countries declaring implementing IRMo [b]	21	5	10	3	8	47
G	Country Resistance Monitoring Rate (CRMR)	84%	50%	45%	50%	67%	63%
H	Average annual cost by country for IRMo (KUSD)	109,9	63,3	381,5	87,2	158,8	160

[a] As defined by WHO (link to WHO website)

[b] Insecticide Resistance Monitoring

In bold, WHO regions where indicator rates were classified as low (e.g. <40%)

Figure 2. Global map showing the countries with local transmission of mosquito-borne diseases. The map shows the overlap in the predicted geographical distribution of locally transmitted cases of chikungunya, dengue, Japanese encephalitis, lymphatic filariasis, malaria (excluding P. knowlesi), yellow fever and Zika.

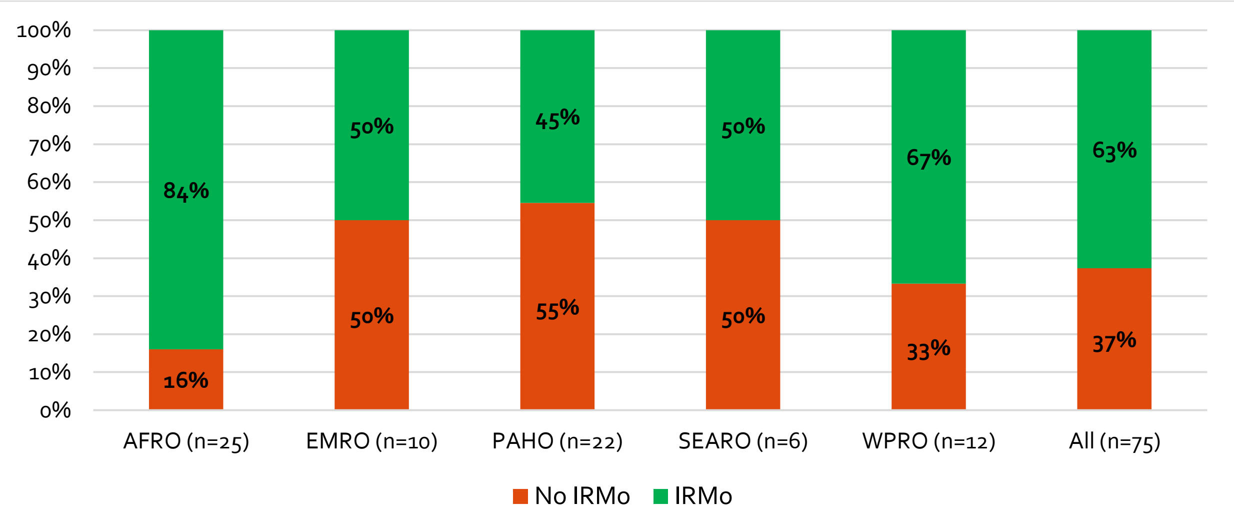


3.2. Organization of Insecticide resistance monitoring (IRMo)

3.2.1. Insecticide resistance monitoring at a global scale

Overall, the proportion of the surveyed countries declaring performing routine IRMo is 63% (47 of 75). Spatial heterogeneity in IRMo coverage exist across and within region especially in Africa, Caribbean and South East Asia. **The proportion of countries implementing IRMo (CRMR) was excellent in AFRO (84%) and good in WPRO (67%). However, only 50% of the countries located in EMRO, PAHO and SEARO declare performing IRMo at national level** (Figure 3). The relative low CRMR in PAHO is explained by the high proportion of Caribbean countries declaring not conducting routine IRMo (see details in section 3.2.2.3). The lack of insecticide resistance surveillance in the Caribbean and SEARO is worrying considering that these regions have experienced resurgence of arboviruses in the recent years.

Figure 3. Proportion of CFPs declaring performing routine Insecticide Resistance monitoring in mosquitoes (CRMR) according to WHO region.



The main reason advanced by the 28 CFPs declaring not conducting routine IRMo was the **i) lack of trained staff and manpower** (41%), **ii) lack of adequate facilities (19%) and iii) lack of financial resources (20%)** (Figure 4). Except Japan, Argentina and Australia, all surveyed countries expressed their will to build IRMo capacity in a near future. Strengthening mosquito surveillance in those regions is key to achieve better control of mosquito transmitted diseases and reach SDGs targets by 2030.

Figure 4. Reasons explaining the absence of routine IRMo

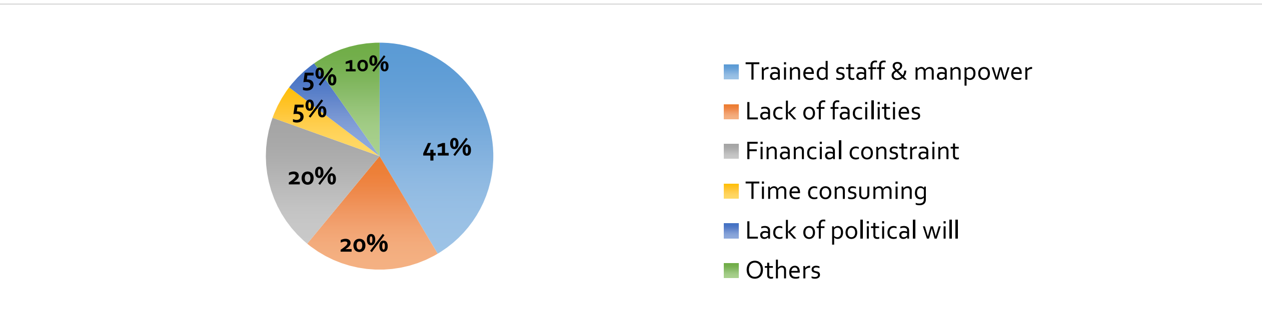
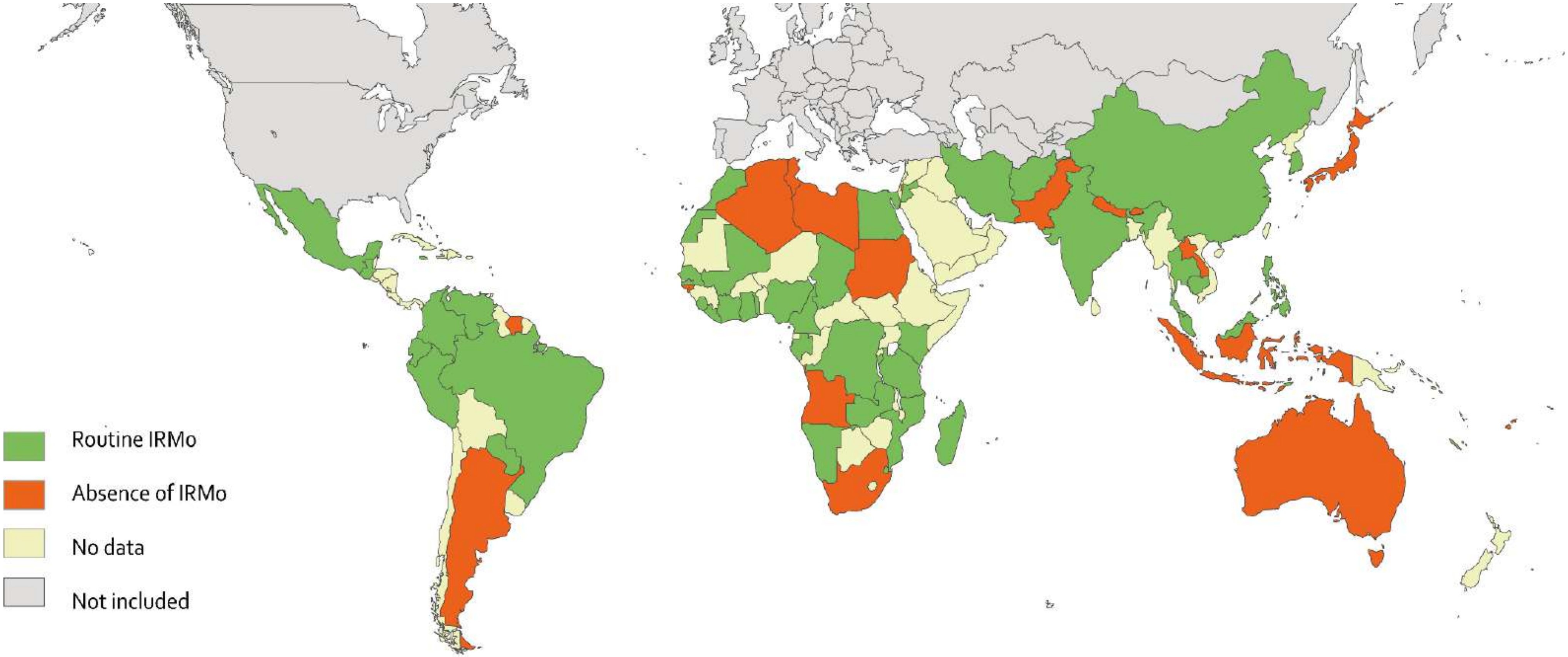


Figure 5. World map showing the spatial distribution of countries performing (or not) routine Insecticide resistance monitoring at national level. Data were analyzed from 75 countries. 47 countries declare performing routing Insecticide resistance monitoring in mosquitoes.



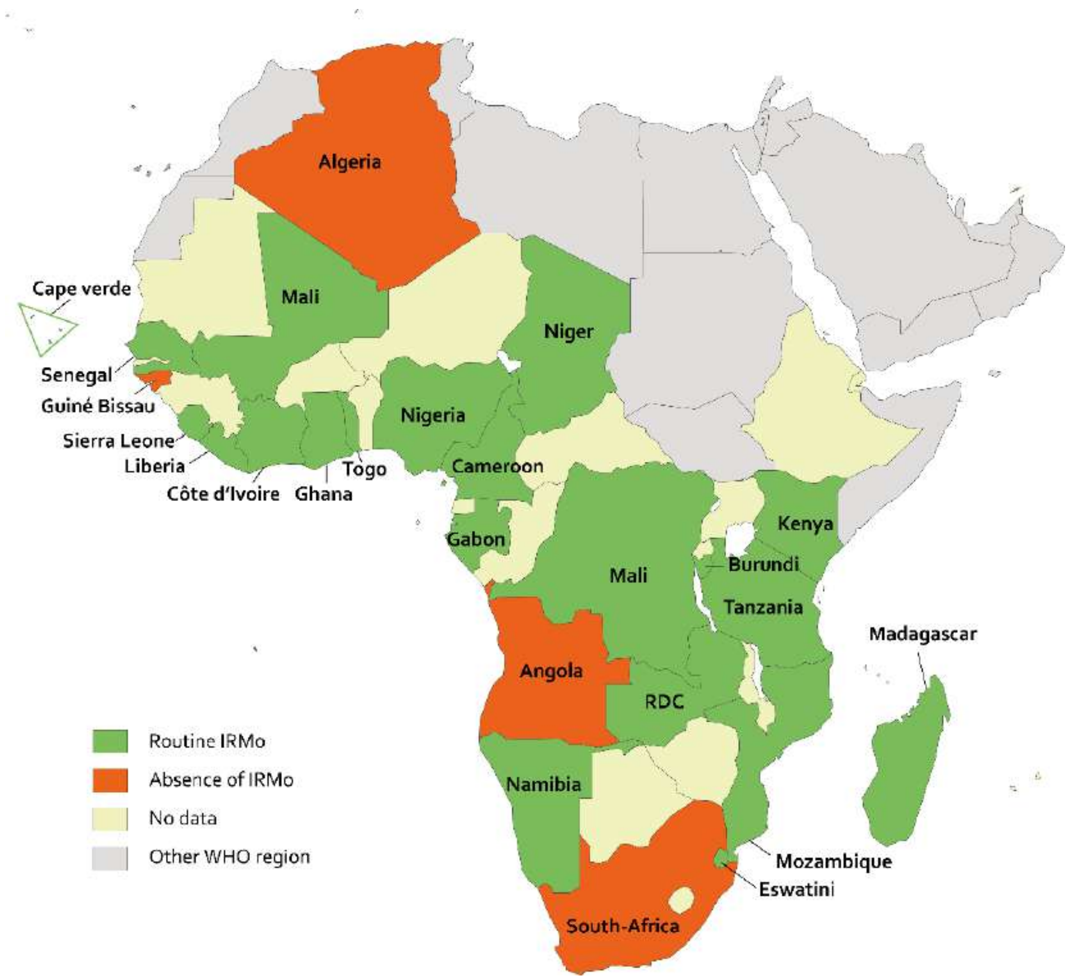
3.2.2. Insecticide resistance monitoring according to WHO region

3.2.2.1. IRMo in the African Region

Countries declaring conducting routine IRMo at national level in the AFRO region is presented in the figure 6. Data were analyzed from 25 countries. Overall, 21 countries declared performing routine IRMo at national level (**84% of the surveyed countries**). Based on the questionnaire's response, only Guinée Bissau, Angola, Algeria and South Africa do not perform regular IRMo at country scale. Some of these countries reported however doing punctual resistance monitoring test according to the need.

Overall, the CRMR in AFRO is excellent (>80% of surveyed countries) and this is promising with the scope to reduce the burden of malaria in Africa that accounts for 93% of all malaria deaths worldwide.

Figure 6. Regional map showing the spatial distribution of countries performing (or not) routine Insecticide resistance monitoring at national level in AFRO.



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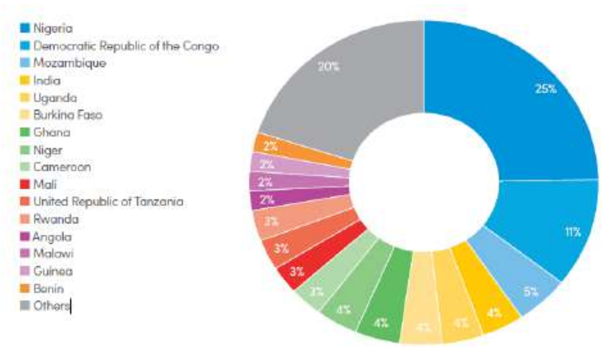
Special focus on the top 16 malaria burden countries:

According to WHO, five countries accounted for nearly half of all malaria cases worldwide: **Nigeria (25%), Democratic Republic of the Congo (11%), Mozambique (5%), India (4%) and Uganda (4%**) (Figure 7). Better understanding of the resistance monitoring capacity in these 16 countries is critical to better tackle malaria transmission.

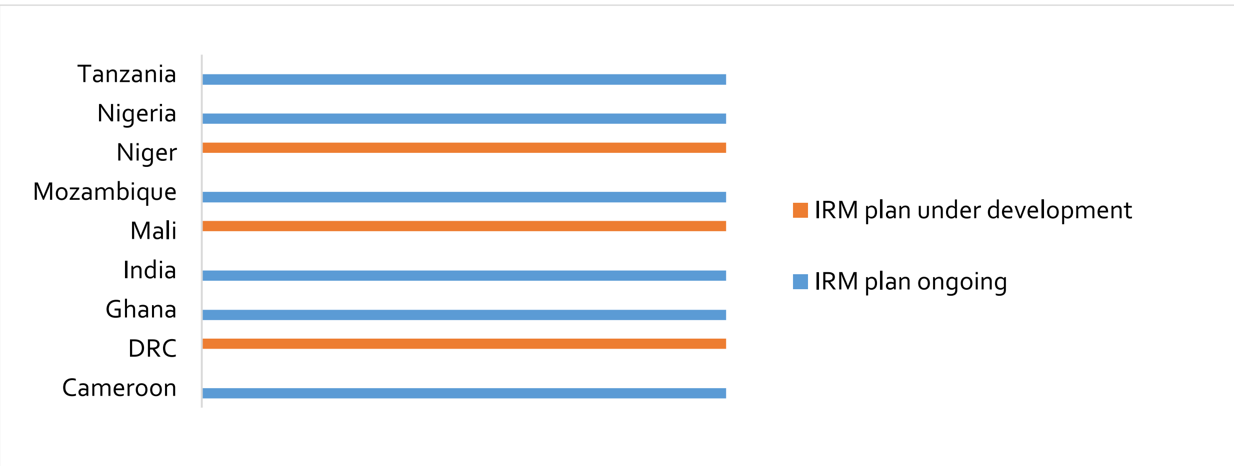
Figure 7. Countries paying the heaviest toll to malaria. Source: WHO malaria report, 2018



In this study, data could be obtained from 10 of the top 16 "malaria" burden countries (data were missing for Benin, Burkina Faso, Guinea, Malawi, Rwanda and Uganda). Based on the questionnaire analysis, **the proportion of malaria-targeted countries declaring performing routine IRMo is excellent (90%**). The unique surveyed country declaring not conducting routine IRMo is Angola. The lack of mosquito resistance surveillance in this country is worrying considering that Angola accounts for 10% of malaria cases in Central Africa (WHO, 2018) and has also experienced yellow fever outbreaks recently.

Among the 9 countries performing routine IRMo, all (100%) declared that their Insecticide Resistance Management (IRM) efforts are aligned with the Global Plan for Insecticide Resistance Management in Malaria Vectors coordinated by the WHO. However the IRM plan is still "under development" in Niger, Mali and Democratic Republic of Congo (DRC).

Figure 8. Status of IRM plan in the top 16 malaria burden countries



3.2.2.2. IRMo in the Eastern European region

The list of countries declaring conducting routine IRMo at national level in the EMRO region is presented in the figure 9. Data were analyzed from 10 countries. **Overall, 5 countries declared performing routine IRMo at national level (50% of the surveyed countries**). Routine IRMo is absent in Libya, Tunisia, North Sudan, Palestinian territory and Pakistan. Conflicts or humanitarian crisis may explain the difficulty to undertake regular entomology activities in some of these countries. Overall, the CRMR in EMRO is average (40<x<60%) and should be strengthened.

Figure 9. Regional map showing the spatial distribution of countries performing (or not) routine Insecticide resistance monitoring at national level in EMRO.

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3.2.2.3. IRMo in the Pan American region

The list of countries declaring conducting routine IRMo at national level in the PAHO is presented in the figure 10. Data were analyzed from 22 countries. **Overall, only 10 countries and territories declared performing routine IRMo at national level (45% of the surveyed countries)**, but important spatial heterogeneity was seen within the region. In South America, IRMo is not conducted in Surinam and Argentina only. In this later country, CFP reported that IRMo is not considered as a public health priority. **When pooling Central and South American regions, the IRMo coverage is good (77% of the surveyed countries**). **In contrast, only 2 countries (Jamaica and Martinique) declared conducting routine IRMo in the Caribbean which is clearly insufficient (CRMR of 15% based on our scoring system).** Surveyed countries where IRMo is not conducted in routine are Grenada, Barbados, Aruba, Dominica, Montserrat, Saint Kitts and Nevis, Sint Eustatius, Sint Maarteen and Anguilla. Clearly, IRMo should be strengthened in the Caribbean considering the increasing risk of mosquito transmitted diseases (especially arboviruses) in the region.

Figure 10. Regional map showing the spatial distribution of countries performing (or not) routine Insecticide resistance monitoring at national level in PAHO.

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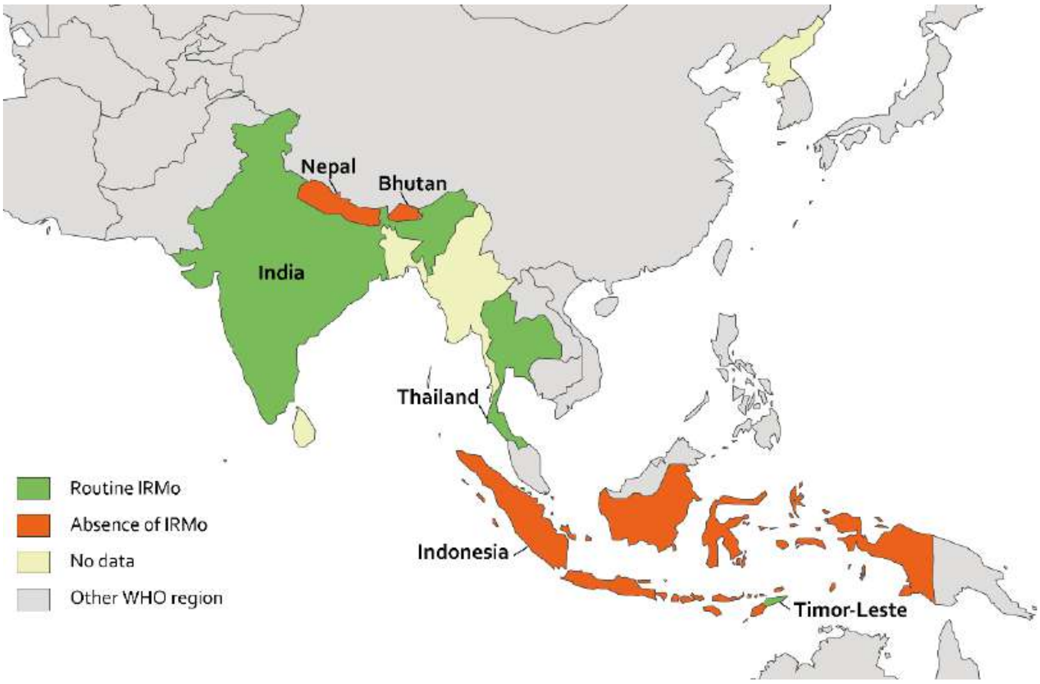
3.2.2.4. IRMo in South East Asia

The list of countries declaring conducting routine IRMo in SEARO is presented in the figure 11. **Data were analyzed from 6 countries, and 3 of them declared performing IRMo at national level (50% of the surveyed countries).** According to CFPs, IRMo is not conducted in routine in Bhutan, Nepal and Indonesia. Knowing that Indonesia accounts for 21% of total malaria cases and 16% of malaria deaths in the region (WHO, 2018), IRMo should be reinforced to achieve malaria elimination goals and reduce the burden cause by arboviral diseases, especially dengue. Overall, the CRMR in SEARO is average (40<x<60%) and should be strengthened.

Figure 11. Regional map showing the spatial distribution of countries performing (or not) routine Insecticide resistance monitoring at national level in SEARO.



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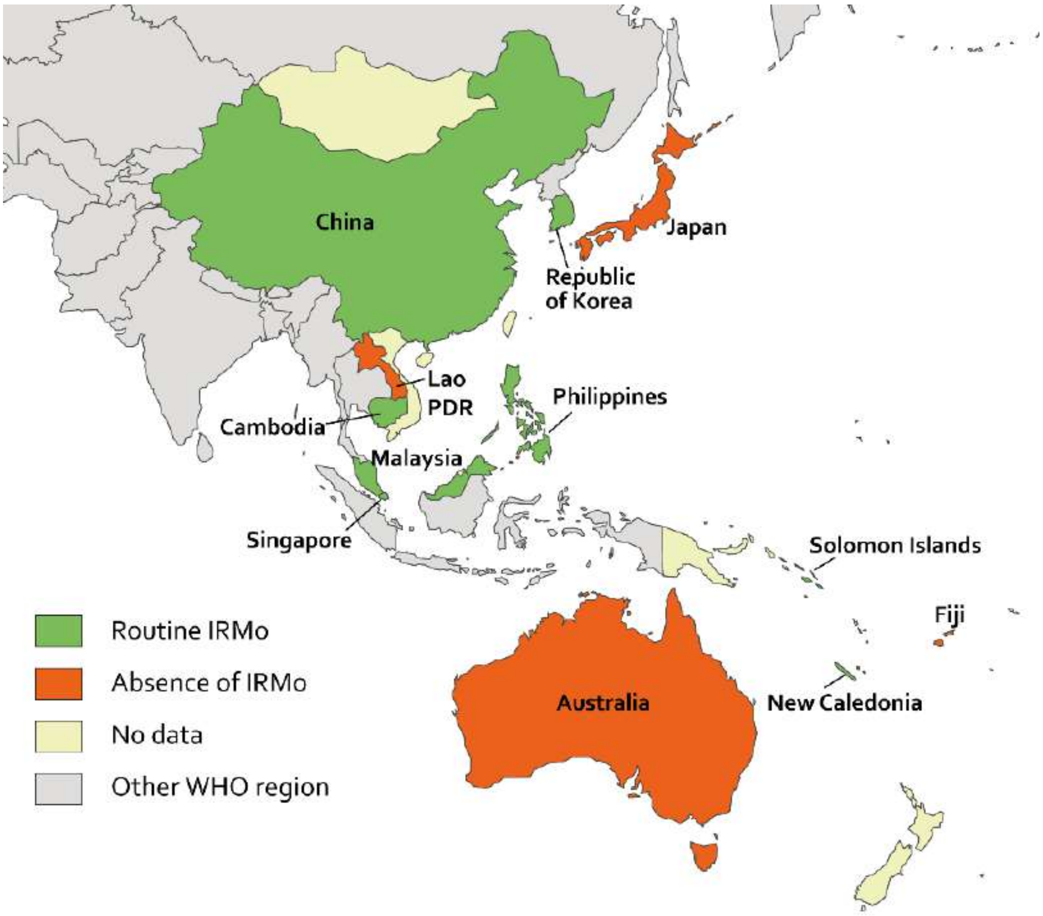
3.2.2.5. IRMo in Western Pacific region

The list of countries declaring conducting routine IRMo at national level in WPRO is presented in the figure 12. Data were analyzed from 12 countries. **Overall, 8 countries or territories (66% of the surveyed countries) declared performing IRMo**. IRMo is not conducted in routine in Lao PDR, Japan and Australia. In Japan and Australia, CFP reported that IRMo is not considered as a public health priority. IRMo should be strengthened in Lao PDR considering the resurgence of dengue outbreak and the persistence of malaria "hotspots" in some parts of the country (especially the southern provinces). Overall, the CRMR in WPRO is good (60<x<80%) but the results have to be taken with caution considering the low country coverage rate (32%).

Figure 12. Regional map showing the spatial distribution of countries performing (or not) routine Insecticide resistance monitoring at national level in WPRO.



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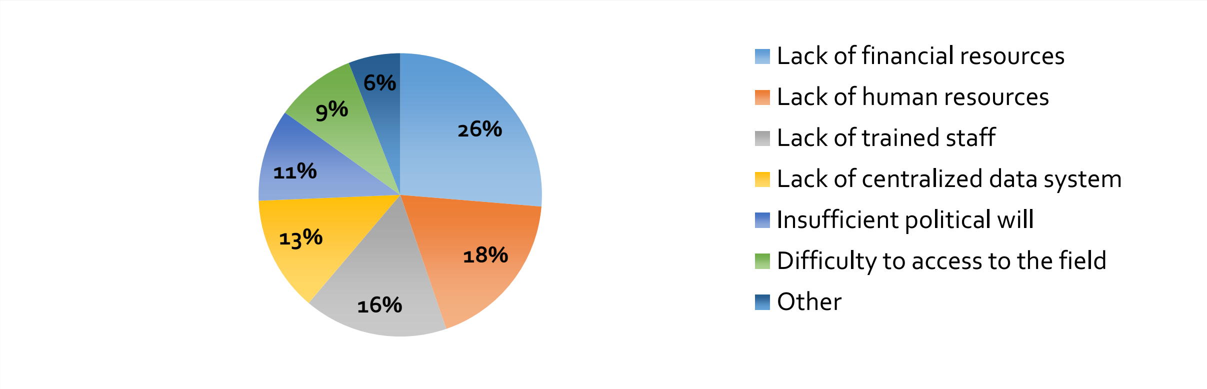
3.2.3. Analysis of country responses with regards to the efficiency/satisfactory of their insecticide resistance monitoring plan

Among all CFPs declaring performing routine IRMo, 29% (14 of 49) declare being satisfied with their resistance monitoring plan. Interestingly, 47% (23 of 49) declare that the IRMo plan is "not optimal" and should be improved. Finally, 24% (12 of 49) declared being not satisfied at all with the resistance monitoring plan. The main reasons explaining the "dissatisfaction" of resistance monitoring are a lack of financial resources (26%), lack of human resources (18%), and lack of trained/qualified staff (16%) (Figure 13).

Figure 13. Main constraints for implementing routine IRMo



3.2.4. Data sharing and management

80% of the surveyed countries declare hosting a centralized insecticide resistance database (39 of 49). When the countries have reported not maintaining an IR database, 50% of them declared that another institution in the country is in charge of data depository and management.

In most countries (64%), the database is updated annually while the proportion of CFPs declaring updating the database biannually, monthly and less than monthly was 13%, 15% and 8%, respectively. Interestingly, **95% of the countries hosting a database (37 of 39) declare that the IR data are made available to the authorities in order to guide vector control policies**.

Finally, 67% of the surveyed country declared being part of a "mosquito resistance surveillance network" at regional and/or international scale. The list of the networks regularly cited by the CFPs is presented in Table 3.

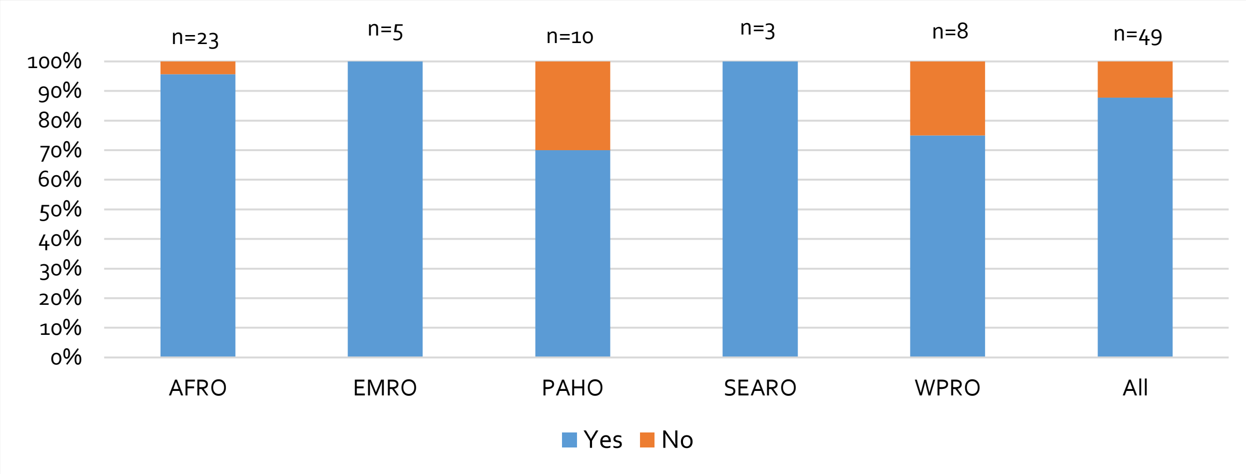
Table 3. Surveillance networks reported in the questionnaire

	Surveillance networks *(No. of countries)*
1	African Network for Vector Resistance (ANVR) *(7 countries)*
2	Centers for Disease Control and Prevention (https://www.cdc.gov/) (1 country)
3	Caribbean Countries Network for Insecticide Resistance Management *(1 country)*
4	Centro de Estudios de Enfermedades Endémicas y Salud Ambiental (CEEESA) *(1 country)*
5	Elimination Eight (E8; https://malariaelimination8.org/) *(1 country)*
6	DDC insecticide resistance network *(1 country)*
7	GAARDian project (https://www.anophelesgenomics.org/gaardian) *(1 country)*
8	EMRO network of Vector Control surveillance *(1 country)*
9	Entomology network of Central American countries (EntoNet) *(1 country)*
10	Macha Research Trust (MRT; https://macharesearch.org/) *(1 country)*
11	Network of the Americas for the Surveillance and Management of Insecticide Resistance *(5 countries)*
12	President Malaria Initiative Network (PMI; https://www.pmi.gov/) *(3 countries)*
13	Pan Africa Mosquito Control Association (PAMCA; https://www.pamca.org/) *(1 country)*
14	PMI AIRS project (operated by Abt associates; http://www.africairs.net/about-airs/) *(1 country)*
15	PMI Vector Link project (https://pmivectorlink.org/) *(2 countries)*
16	USAID (https://www.usaid.gov/) *(1 country)*
17	WAASuN: West African *Aedes* Surveillance Network *(1 country)*
18	WHO Annual World Malaria Report : Insecticides Resistance Monitoring *(1 country)*
19	WHO Regional office *(3 countries)*
20	Worldwide Insecticide resistance Network (WIN; https://win-network.ird.fr/) *(3 countries)*

3.2.5. Insecticide resistance Management (IRM)

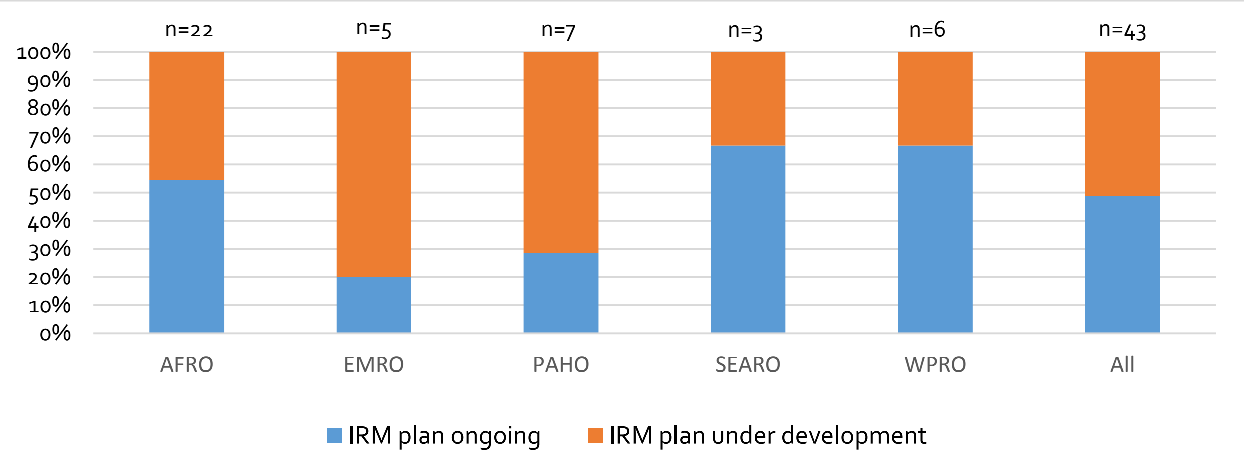
Among the countries performing IRMo, **88% (43 of 49) declare that their efforts are aligned with the Global Plan for Insecticide Resistance Management in Malaria Vectors** coordinated by the WHO (Figure 14). However, 51% of them declare that the IRM plan is "under development" (Figure 15).

Figure 14. Insecticide Resistance Management (IRM) plan aligned with the Global Plan for Insecticide Resistance Management in Malaria Vectors coordinated by the WHO



The proportion of countries having not yet finalized a functional IRM plan is the highest in PAHO and WPRO (80% and 70%, respectively) (Figure 15).

Figure 15. Status of IRM plan per WHO region



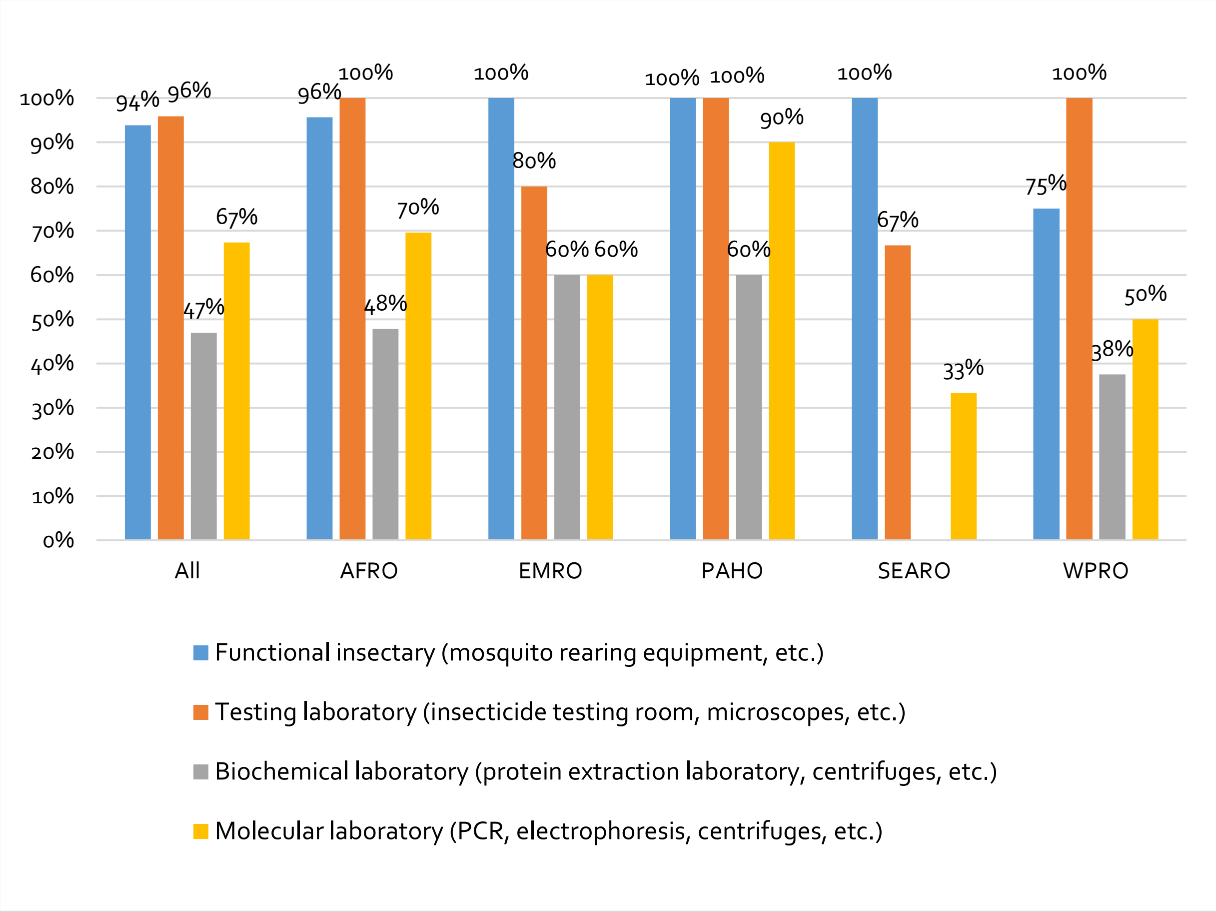
3.3. Facilities and technical capacities for implementing insecticide resistance monitoring

3.3.1. Country facilities for testing insecticides

The figure 16 shows the type of testing facilities available in each WHO region. Most of surveyed countries declare having functional insectarium (100% except in WPRO) and adequate laboratories (>80% except in SEARO) for conducting IRMo.

However, 47% of the surveyed countries (23 of 49) declare having functional facilities for conducting biochemical assays to measure the activity of enzymes involved in insecticide detoxication. Interestingly, 67% (33 of 49) of countries declare having molecular biology facilities to detect insecticide resistance markers in mosquitoes. SEARO, and to a lesser extent WPRO, appear to be the regions where biochemical and molecular capacities need to be particularly strengthened.

Figure 16. Relevant facilities available and in use for IRMo



3.3.2. Laboratory testing capacity

3.3.2.1. Mosquito species targeted

Overall, most of the surveyed countries (92%) declared performing IRMo on mosquitoes belonging to the *Anopheles* genus. 57% and 29% of them reported conducting IR testing on *Aedes* and *Culex*, respectively. As expected, all African countries are monitoring resistance in *Anopheles* species (100% of the surveyed countries) whereas IR testing on *Aedes* (26%) and *Culex* species (9%) remains rare. In PAHO and SEARO, *Aedes* species are monitored in all surveyed countries (100%). Finally, 67% and 80% of surveyed countries located in SEARO and EMRO, respectively declare conducting monitoring resistance in *Culex* mosquitoes (Figure 17).

Finally, 80% of the surveyed countries declare maintaining susceptible mosquito colonies for the conduct of bioassays (used as control). The mosquito species targeted in the framework of insecticide resistance monitoring worldwide are shown in Table 4

Figure 17. Mosquito species targeted during IRMo according to WHO Region

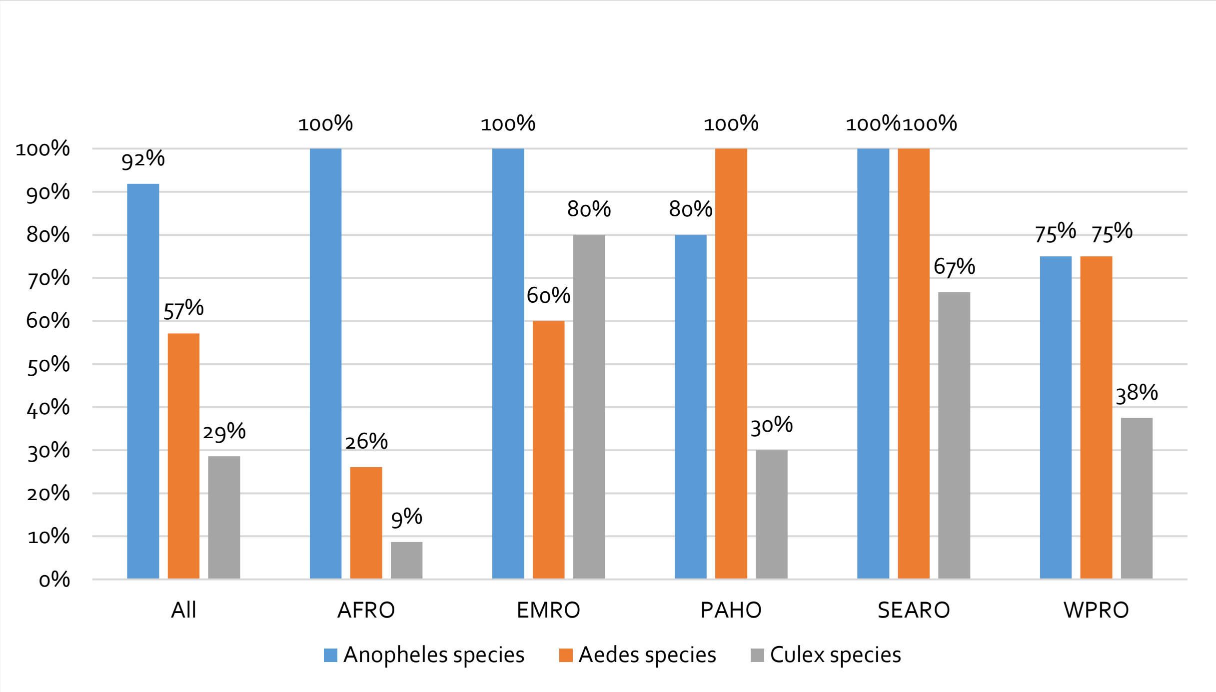


Table 4. Susceptible mosquito colonies maintained in the surveyed countries

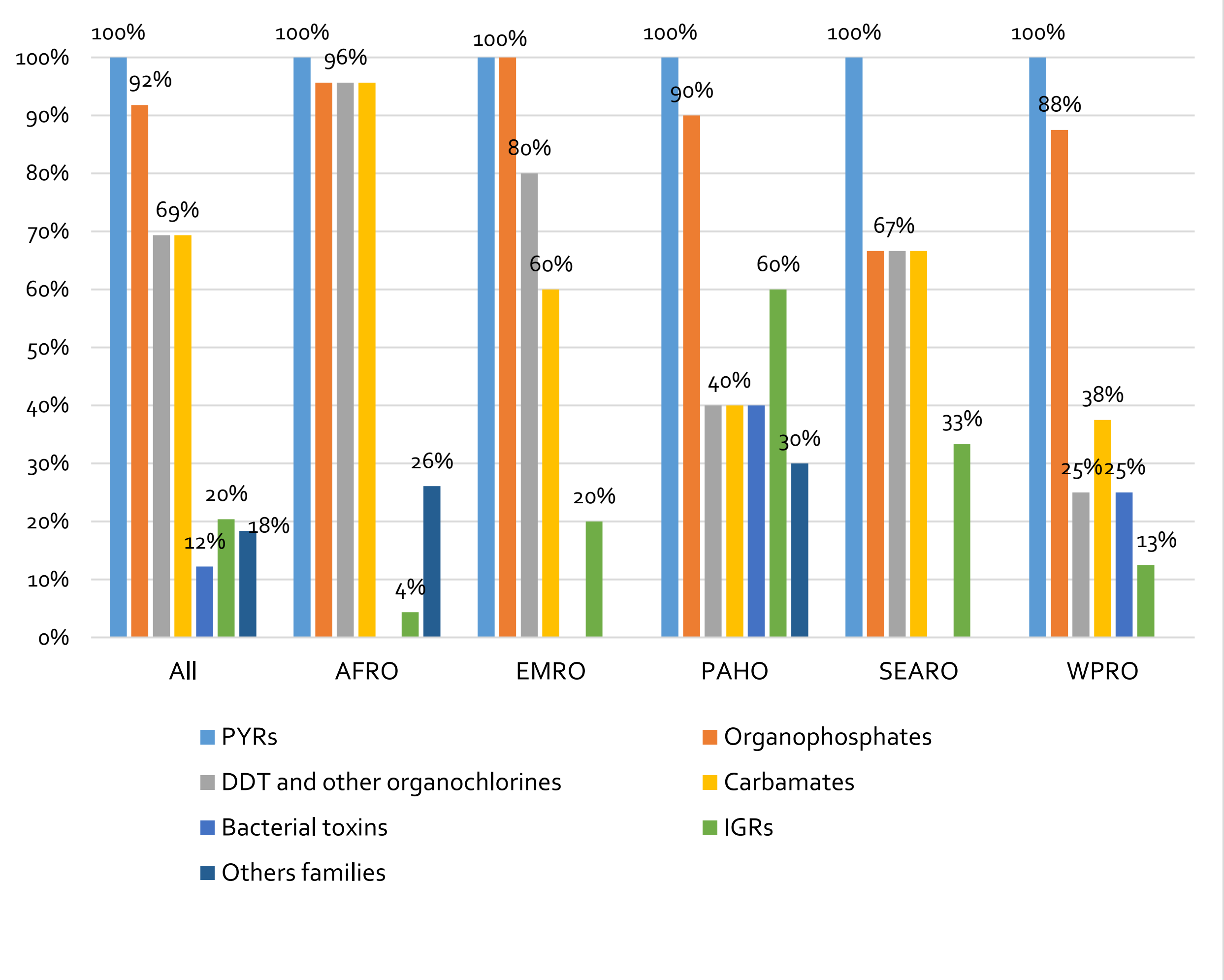
Strains	Institution and country
***Anopheles gambiae* (Kisumu strain)**	Burundi (Abt Associates), Côte d'Ivoire (Institut Pierre Richet), Gabon (Centre de Recherches Médicales de Lambaréné), Ghana (Noguchi Memorial Institute for Medical Research), Kenya (Kenya Medical Research Institute), Liberia (Abt Associates), Madagascar (National Malaria Control Program), Mali (Malaria research and Traing Centre), Nigeria (National Arbovirus and Vectors Research Centre/ Nigerian Institute of Medical Research), Senegal (National Malaria Control Programme), Sierra Leone (National malaria Control programme), Tanzania (National Institute for medical research), Togo (University of Lomé), Zambia (National Malaria Elimination Centre)
***Aedes aegypti* (Local lab strain or not specified)**	Jamaica (MoH), Malaysia (MoH), Nigeria (National Arbovirus and Vectors Research Centre), Paraguay (Servicio Nacional de Erradicación del Paludismo), Thailand (MoH), Singapore (National Environment Agency)
***Aedes aegypti* (Rockefeller strain)**	Brazil (Fiocruz), Colombia (Instituto Nacional de Salud), Ecuador (Instituto Nacional de Salud Pública e Investigación), Guatemala (Universidad del Valle de Guatemala), Mexico (Centro Nacional de Programas Preventivos y Control de Enfermedades), Peru (Instituto Nacional de Salud)
***Aedes aegypti* (Bora-Bora strain)**	Martinique (FR) (Collectivité Territoriale de Martinique/Agence Régionale de Santé), New Caledonia (FR) (Institut Pasteur New Caledonia), Singapore (National Environment Agency)
***Aedes albopictus* (Local lab strain or not specified)**	Guatemala (Universidad del Valle de Guatemala), Jamaica (MoH), Singapore (National Environment Agency)
Anopheles arabiensis	Madagascar (National Malaria Control Program), Tanzania (National Institute for medical research)
***Aedes aegypti* (New Orleans strain)**	Guatemala (Universidad del Valle de Guatemala), Mexico (Centro Nacional de Programas Preventivos y Control de Enfermedades)
***Anopheles albimanus* (Sanarate strain)**	Guatemala (Universidad del Valle de Guatemala), Peru (Instituto Nacional de Salud)
***Anopheles arabiensis* (KGB strain)**	Mozambique (National Malaria Control Program)
Anopheles stephensi	Iran (Tehran University of Medical Sciences)
***Culex quinquefasciatus* (Local lab strain)**	Singapore (National Environment Agency)
***Aedes aegypti* (Hainan strain)**	China (National Institute for Communicable Disease Control and Prevention)
***Aedes albopictus* (Chengdu strain)**	China (National Institute for Communicable Disease Control and Prevention)
***Aedes albopictus* (Sibaté strain)**	Colombia (Instituto Nacional de Salud)
Aedes vexans	Iran (Tehran University of Medical Sciences)

***Anopheles albimanus* (Cartagena strain)**	Colombia (Instituto Nacional de Salud)
***Anopheles albitarsis* (IBEx strain)**	Brazil (Fiocruz)
***Anopheles aquasalis* (IBEx strain)**	Brazil (Fiocruz)
Anopheles cracens	Malaysia (MoH)
Anopheles culicifacies	Afghanistan (National Malaria & Leishmaniasis Control Program)
Anopheles dirus	Cambodia (National Center for Parasitology, Entomology and Malaria Control)
***Anopheles epiroticus* (Local lab strain)**	Singapore (National Environment Agency)
Anopheles gambiae ss	Democratic Republic of the Congo (Institut Nationale de recherche Biomedicale)
Anopheles minimus	Thailand (MoH)
***Anopheles sinensis* (Local lab strain)**	Singapore (National Environment Agency)
Culex pipiens	Iran (Tehran University of Medical Sciences)
***Culex pipiens pallens* (not specified)**	Republic of Korea (Korea Centers for Disease Control and Prevention)
***Culex pipiens pallens* (Beijing strain)**	China (National Institute for Communicable Disease Control and Prevention)
***Culex quinquefasciatus* (IBEx strain)**	Brazil (Fiocruz)
Culex sp.	Egypt (Research Institute of Medical Entomology)
Culex tritaeniorhynchus	Republic of Korea (Korea Centers for Disease Control and Prevention)

3.3.2.2. *Insecticides targeted during IRMo*

According to the questionnaire, 100% and 92% of the surveyed countries (45 of 49) declare testing Pyrethroid and Organophosphate resistance in mosquitoes, respectively. Other insecticide classes tested during IRMo are carbamates and DDT (69%) and to a far lesser extent, Bacterial toxin (Bti, Bs), Insect Growth Regulators (IGRs), neonicotinoids and pyrroles (<20% of the surveyed countries). PAHO is the region where IGRs resistance is more frequently tested (60%), probably because this chemical class is increasingly used for mosquito control because of temephos resistance (Figure 18).

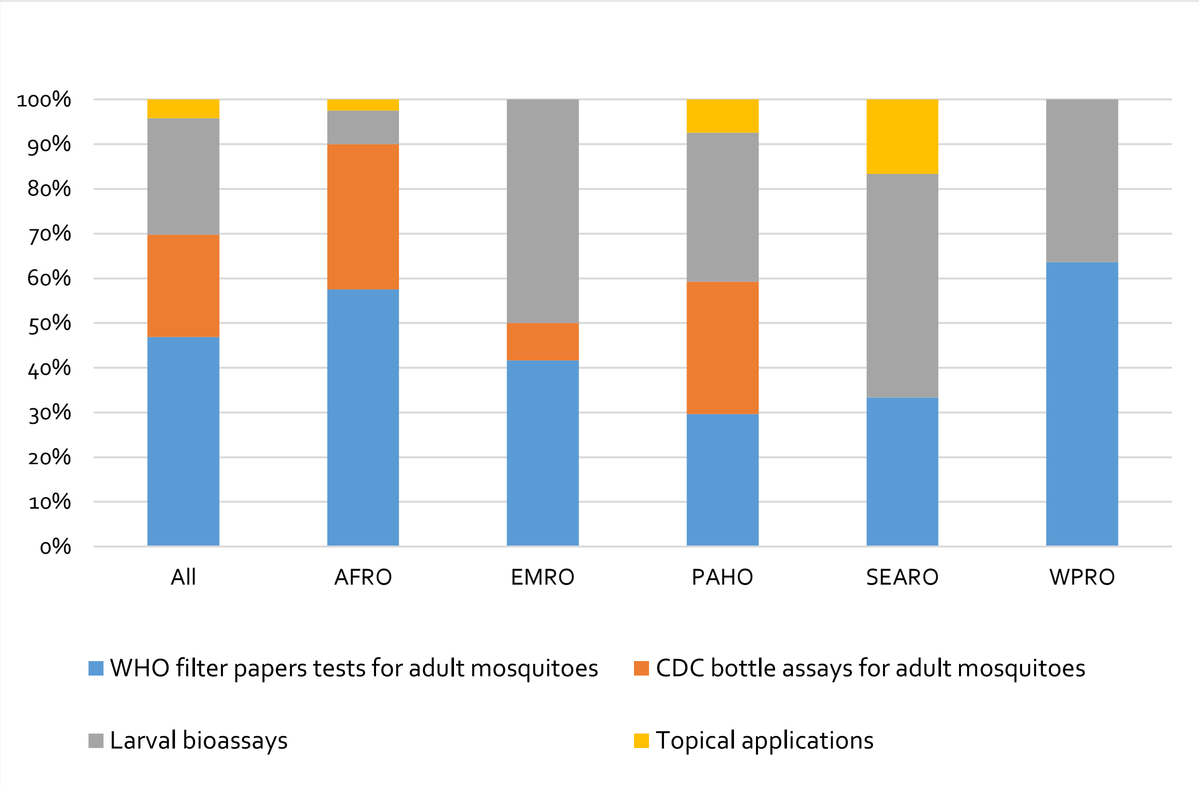
Figure 18. Main insecticide classes tested in the framework of IRMo according to WHO region



3.3.2.3. *Methods for monitoring insecticide resistance*

The most frequent methods in use for testing resistance phenotypes in mosquitoes are WHO filter papers tests (47%), followed by larval bioassays (26%), CDC bottle assays (23%) and topical applications (4%). No surveyed countries located in SEARO and WPRO declared conducting CDC bottle assays in routine for testing adult resistance. Topical applications are labor intensive and require skilled staff and this is probably why very few countries declared using this kind of method during IRMo (Figure 19).

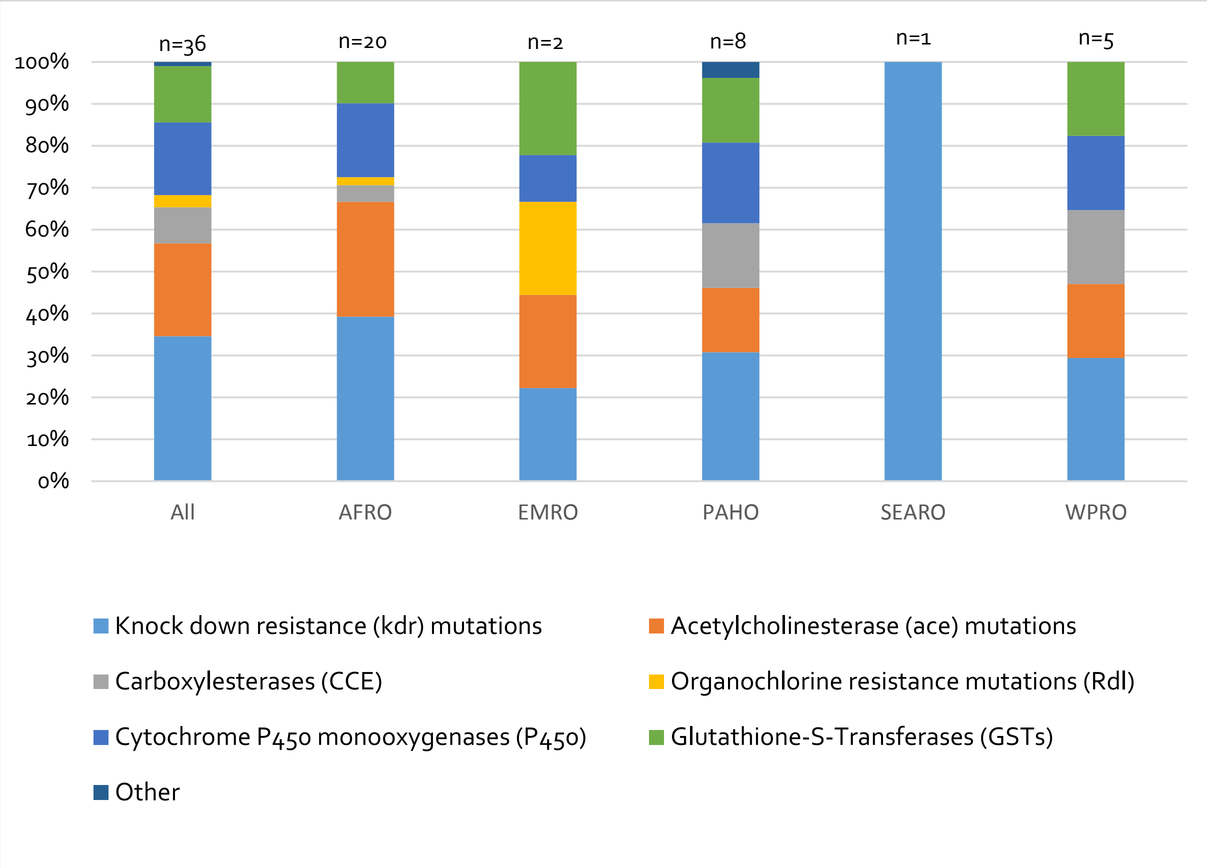
Figure 19. Methods used for resistance monitoring studies



3.3.2.4. *Main resistance mechanisms targeted during IRMo*

73% of the surveyed countries declare investigating "resistance mechanisms" when a phenotypic resistance has been detected in the field. According to country responses, the main resistance mechanisms investigated are the Knock down resistance (kdr) mutations (36%), followed by the insensitive acetylcholinesterase (ace) mutations (22%) and to a lesser extent, Cytochrome p450 monooxygenases (P450) (17%). The lack of simple, reliable diagnostic tools for detecting metabolic resistance genes probably explain the low proportion of countries investigating P450, GST, and Esterases in routine (Figure 20).

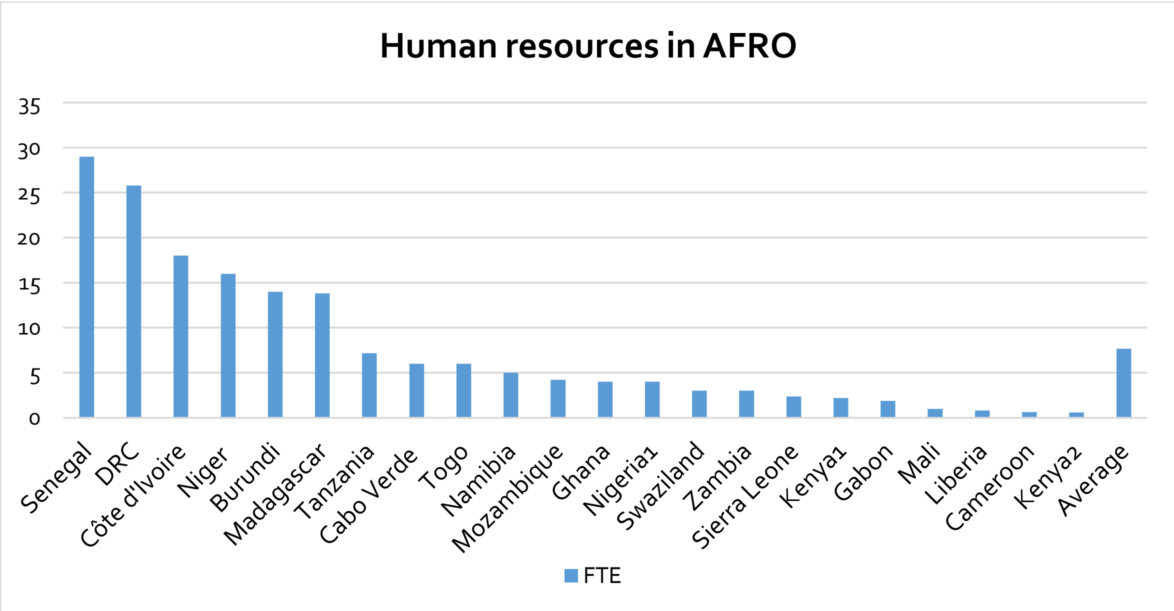
Figure 20. Insecticide resistance mechanisms investigated

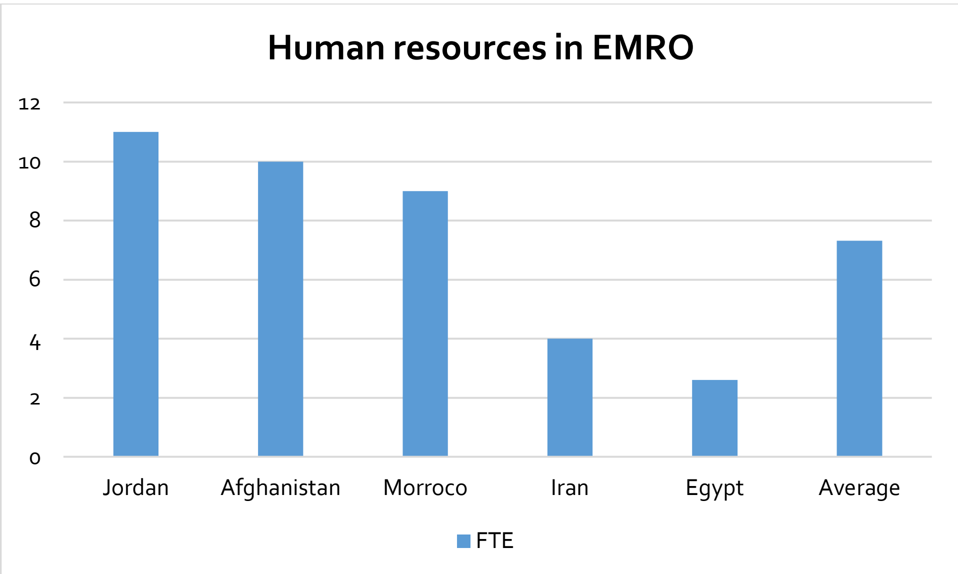


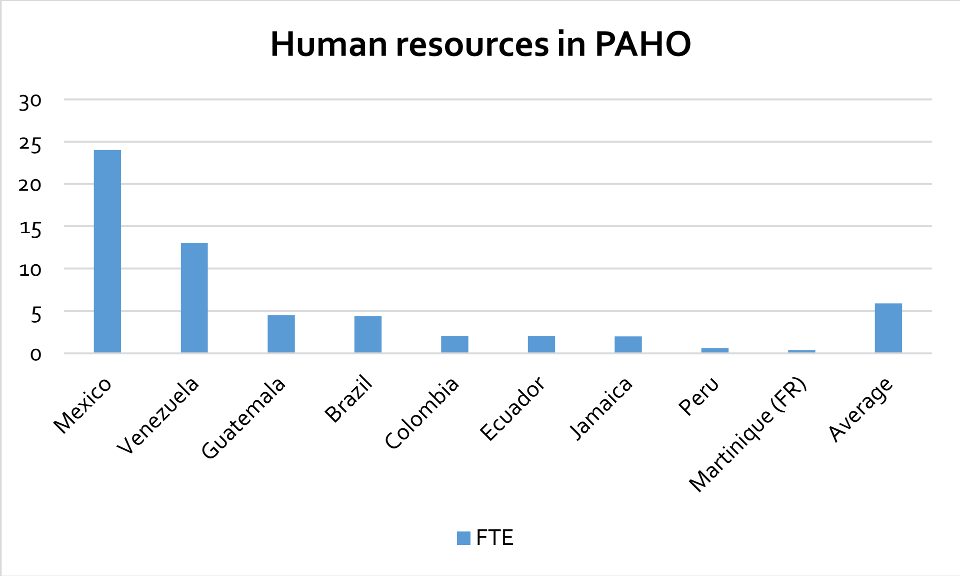
3.4 Human resources available for insecticide resistance monitoring at national level

The figure 21 summarizes the relative number of staff, in full time equivalent (FTE), allocated to resistance testing in mosquitoes according to country and region. A mean number of staff available for IRMo per WHO region has been also calculated. It should be noticed that FTE were calculated based on data coming from a single institution in charge of IRMo in a given country and do not reflect the total human resources potentially available for that activity in the whole country.

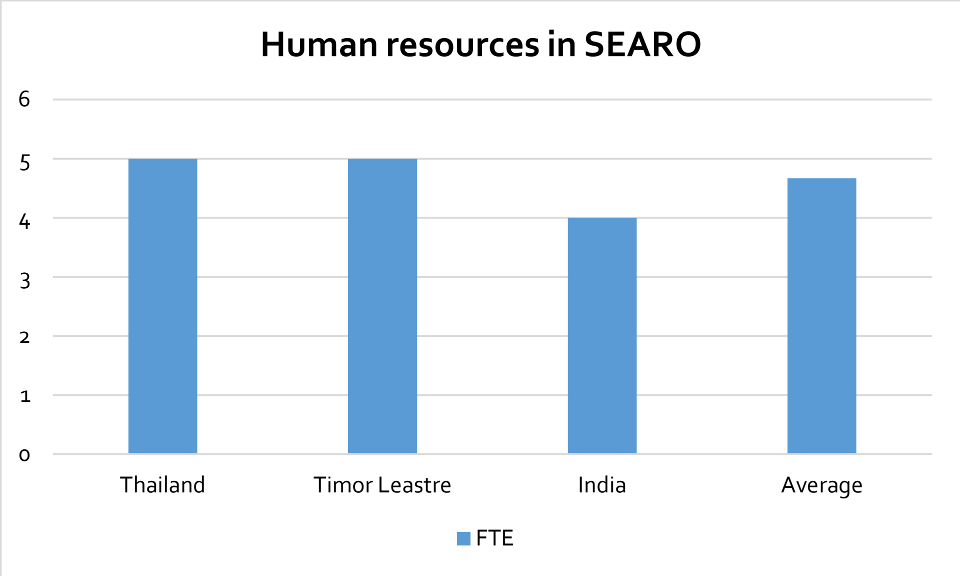
Figure 21. Number of staff, in FTE, available for IR testing per countries and WHO region



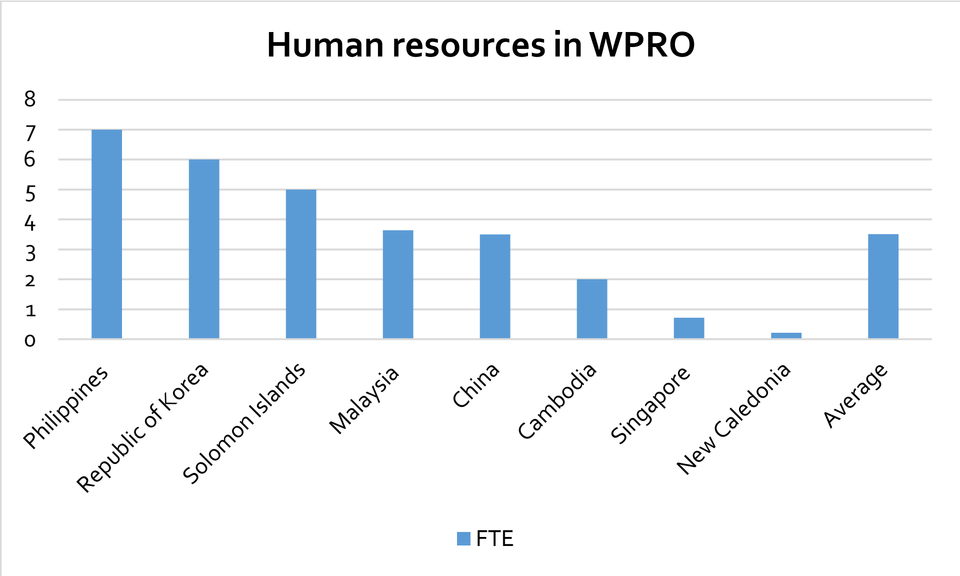




Human resources in PAHO
30
25
20
15
10
5
0
Mexico
Venezuela
Guatemala
Brazil
Colombia
Ecuador
Jamaica
Peru
Martinique (FR)
Average
FTE



Human resources in SEARO
6
5
4
3
2
1
0
Thailand
Timor Leastre
India
Average
FTE

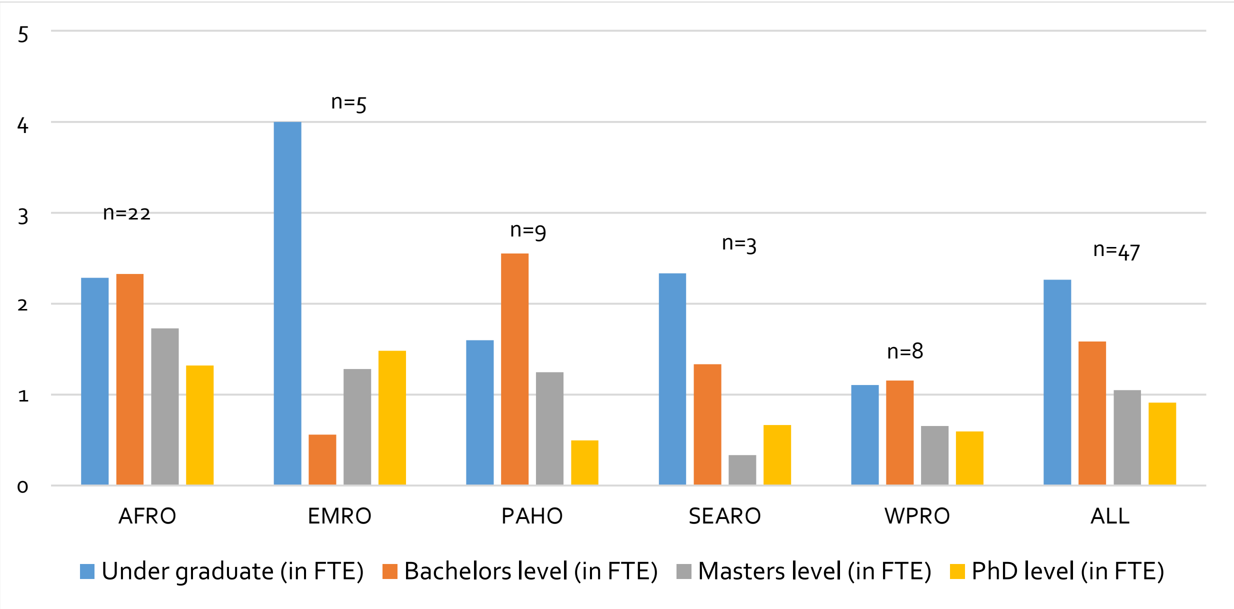


Human resources in WPRO
8
7
6
5
4
3
2
1
0
Philippines
Republic of Korea
Solomon Islands
Malaysia
China
Cambodia
Singapore
New Caledonia
Average
FTE

According to CFPs response, the average number of FTE allocated for IRMo per year and per country are 7.7, 7.3, 5.9, 4.6 and 3.5 in AFRO, EMRO, PAHO, SEARO and WPRO, respectively. More human resources are involved in IRMo in Africa than in other regions, with Senegal and Democratic Republic of Congo spending the highest number of staff in IRMo (>25 FTE) in the region (Figure 21).

Overall, more under graduate and bachelor's degree are involved in IRMo (2.3 and 1.6 FTE respectively) than people having a master degree or a PhD (≤1 FTE). The relative proportion of master and PhD involved in resistance monitoring is higher in AFRO and EMRO than in PAHO, SEARO and WPRO (Figure 22).

Figure 22. Average human resources (FTE) available per country according to the academic levels (under graduate, bachelor's level, master's level and PhD level staffs)



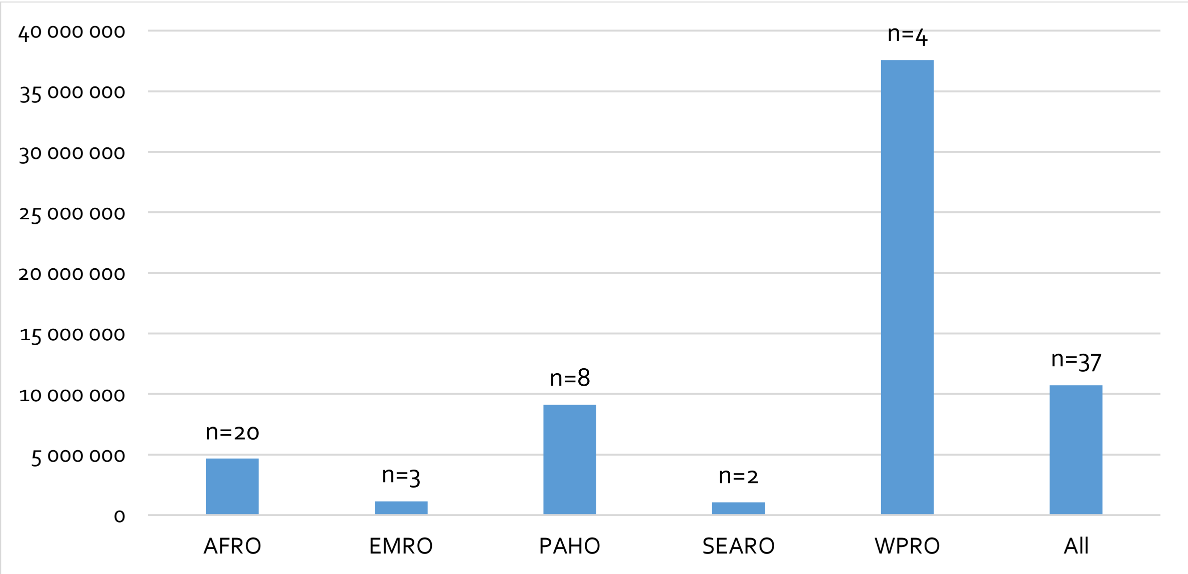
3.5 Cost for conducting mosquito control and insecticide resistance monitoring

3.5.1. Annual cost for conducting mosquito control activities

First of all, 22% of the surveyed country did not provide complete data on cost allocated to vector control (12 of 49) and 4 countries did not provided data at all. This may be explained by the fact that questions related to budget can be sensitive for some countries. For the rest of countries that provided information on cost, 65% declare that their budget for vector control was dedicated to mosquito control only.

The mean budget allocated to mosquito control at national level over the 3 past years (2017, 2018 and 2019) was USD 10.7M (Figure 23). The cost for mosquito control was 3.5 times higher in WPRO (37.6M) than in all other WHO regions. However, this finding has to be taken with caution considering that Malaysia accounts for 85% of all WPRO budget.

Figure 23. Budget allocated to mosquito control (USD)

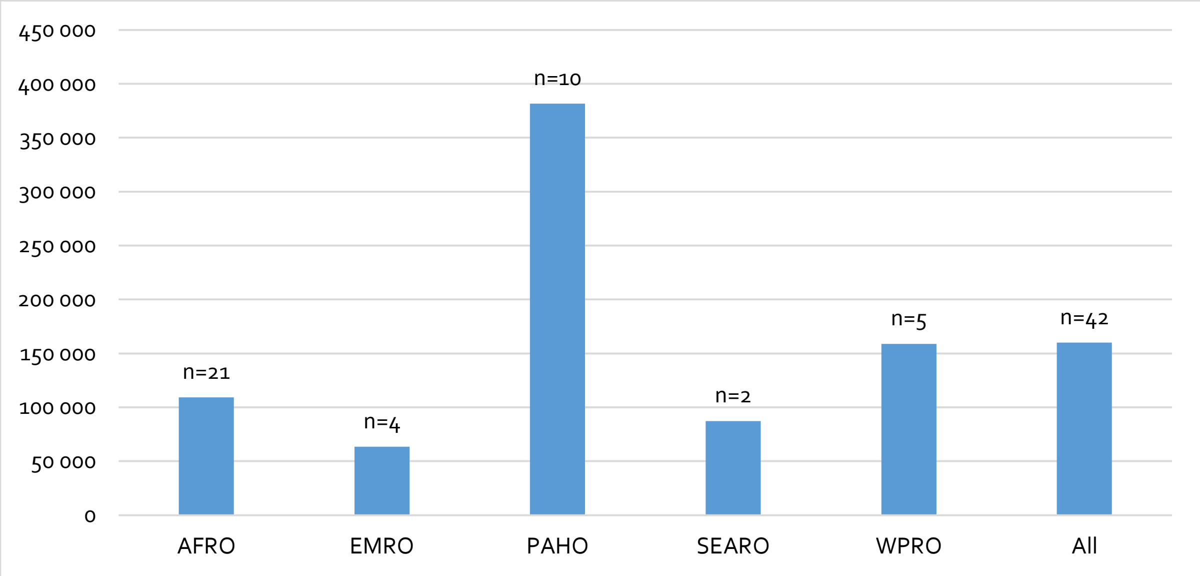


3.5.2. Annual cost for conducting insecticide resistance monitoring

Regarding IRMo budget, data were missing for 7 countries: 2 in AFRO (Cabo Verde and Swaziland); 1 in EMRO (Jordan); 1 in SEARO (India) and 3 in WPRO (Cambodia, New Caledonia and Singapore).

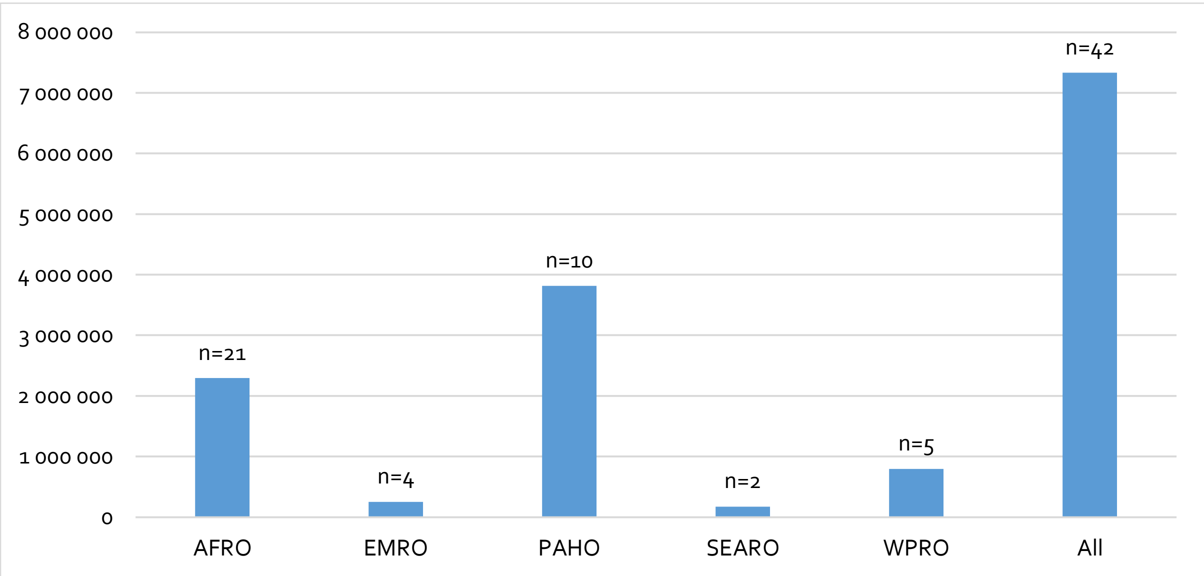
The mean budget allocated to insecticide resistance monitoring per country over the past 3 years (2017, 2018 and 2019) is USD160K (Figure 24). The average cost per region is 2.4 times higher in PAHO (USD382K) than in other regions. It should be notice however that Mexico accounts for 70% of the whole IRMo budget and cannot be representative of all Latin America countries.

Figure 24. Average annual cost dedicated to IRMo (USD) per country



Based on data coming from 42 surveyed countries/territories, a total of USD7M is dedicated to insecticide resistance monitoring yearly, with 52% of the total budget spent in PAHO and 31% in AFRO (Figure 25). Note that this costing assessment has been conducted on data obtained from 21 and 10 countries in AFRO and PAHO, respectively.

Figure 25. Total annual cost dedicated to IRMo (in USD)



4. Discussion

This study provides the first information on facilities and capacities available at country level for conducting routine insecticide resistance monitoring in mosquitoes of public health importance. Overall, country participation was good in all WHO regions (60%<x<80%) and all countries responding to the questionnaire (except Gaza strip) were at risk of one or more transmitted mosquito borne diseases. Data coverage ("representativeness") was however "average" (40%<x<60% of total countries listed by WHO), except in WPRO where only 32% of the countries were surveyed.

Difficulties to obtain country responses should be reported. In some countries, we could not identify the right focal points (CFPs) while in others, no CFPs were commissioned by the Ministries of Health for implementing/coordinating resistance testing activities. In some cases, no responses were obtained from the relevant CFP despite several reminders. In some cases, we had the impression that CFPs were not always familiar with English and we suspect that they may have had difficulties to understand the scope of the study. Translating the questionnaire in different language (Spanish, Arabic, and French) may contribute to increase the country coverage/participation rates in some parts of the world. Finally, some CFPs were reluctant to provide "sensitive" data such as cost for mosquito control and/or IRMo. For example, 22% of the participating countries (n=12) performing routine IRMo did not provide complete data on cost. Data obtained in this study, although incomplete, can serve as a basis to estimate the cost to fulfil the needs for IRMo. The next step should be to increase the country coverage by identifying and including more CFPs.

Overall, data collected on insecticide resistance are important to help national authorities to select the most judicious, locally-adapted tools for mosquito control. Strengthening the country capacities and facilities to conduct insecticide resistance monitoring is a priority with the scope to increase the surveillance and control of mosquito borne diseases by 2030 (SDG3.3).

5. List of Annexes

Annex 1: Country focal points list

Annex 2: WHO TDR and NTD cover letter

Annex 3: Questionnaire

Annex 4: Resource needs table