Responding to the threat of *pfhrp2/3* gene deletions

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*Chair of the MESA Community of Practice on *pfhrp2/3* gene deletions

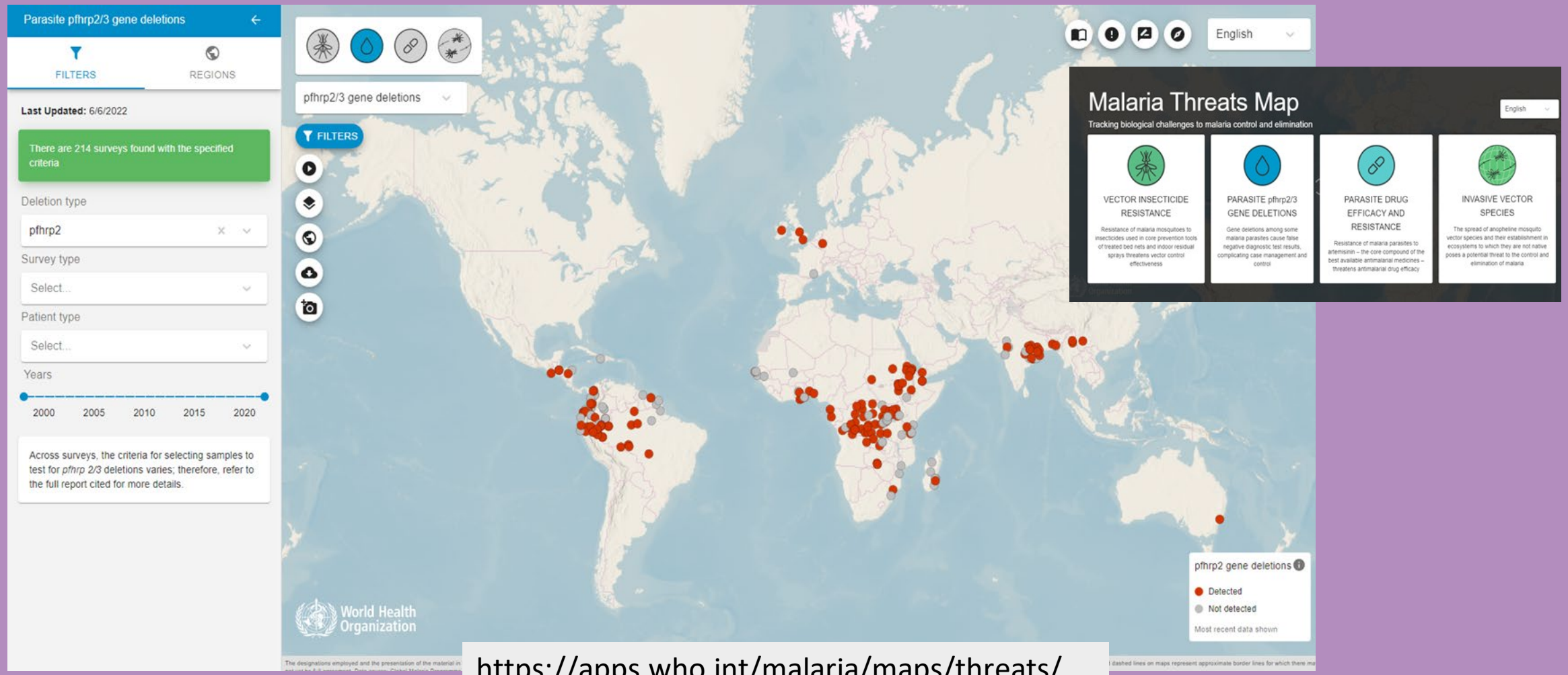
[12th RBM CMWG Annual Meeting, Accra 22nd August, 2023]

Introduction

- **Malaria rapid diagnostic tests** (RDTs) have transformed malaria control, enabling better targeting of treatment and improved surveillance
- The most commonly used RDTs to diagnose *Plasmodium falciparum* infection target one of its antigens, the **Histidine-Rich Protein 2 (HRP2)**
- However, diagnosing *P. falciparum* is under a serious threat because of the emergence of parasites that **do not express the HRP2 protein** (and/or the closely related protein HRP3)
- This is due to **mutations (deletions)** in the genes that encode these antigens and as such result in **false negative results**

Introduction

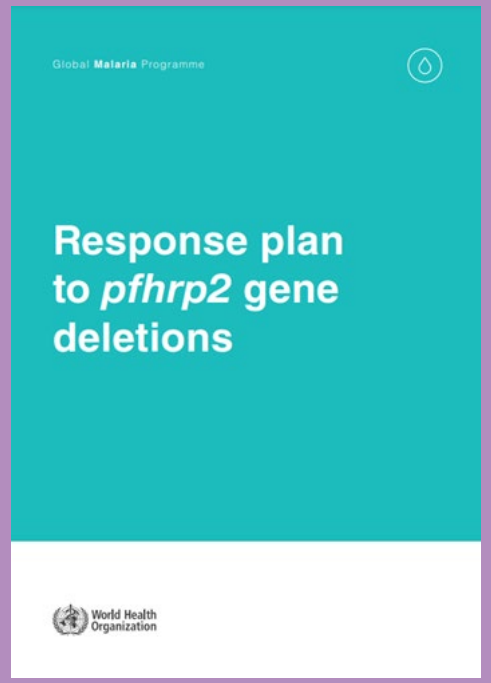
- HRP2 gene deletions were first reported in Peru in 2010, and mutated parasites have now **been reported in more than 35 countries**

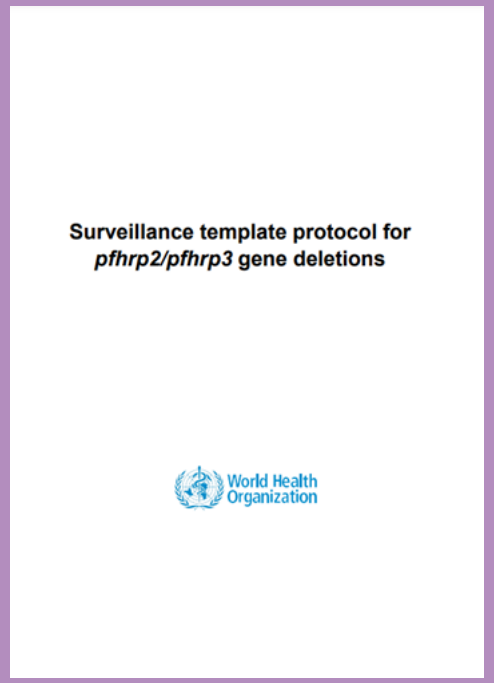


https://apps.who.int/malaria/maps/threats/

Introduction

- WHO has issued **guidance on how to investigate** suspected false-negative RDT results and is encouraging a **harmonised approach** to mapping and reporting *pfhrp2/3* gene deletions.





NOTE:
These documents are currently being updated – new versions to be released by September/October 2023

When should a programme be suspicious ?

- In a programme, the rates of **discordance** between the results of RDTs and microscopy are **systematically ≥ 10–15%** (with higher positivity rates in microscopy)
- When the national malaria control programme receives **multiple formal complaints** or **anecdotal evidence** of RDTs that give false-negative results for *P. falciparum.*
- When *pfhrp2/hrp3* gene **deletions have been reported**, the baseline prevalence should be determined in the affected country and neighbouring countries

Community of Practice (CoP) on *pfhrp2/3* gene deletions

- *Mobilising and providing peer and technical support* -

WHY: rationale for the creation of this CoP

May 2021

- Countries willing to set up surveys, but lack experience and/or technical resources to do it
- Need to raise awareness on this threat

Malaria Policy Advisory Group statement on the **urgent need to address the high prevalence of *pfhrp2/3* deletions** in the Horn of Africa and beyond

World Health Organization

Dec 2021

MESA Resource Compilation: protocols, guidance documents, etc.

June 2022

- Need to create a space for interaction to mobilize peer support among stakeholders
- Followed-up with experts engaged in the Forum and conceptualized the creation of a new CoP

MESA Forum: *Responding to the threat of malaria parasites evading HRP2-RDTs*

> 450 registrants
> 60 countries
> 90 questions

March 2023

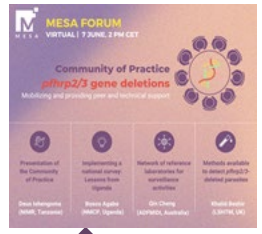
- Analyzed the main interests and requests expressed by the CoP members

Launch of the MESA **Community of Practice on *pfhrp2/3* gene deletions**

Community of Practice
pfhrp2/3 gene deletions
Mobilizing and providing peer and technical support

June 2023

First CoP event: **MESA Forum**
>360 registrants
>70 countries



WHAT we do / HOW we do it

ACTIVITIES

1. Share best practices, reference materials (e.g. protocols, SOPs, training) and relevant **resources** from various stakeholders

IMPLEMENTATION

1. **CoP repository** in MESA **Resource Hub*** (*stay tuned for updates in the new MESA web to be launched soon)

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1. **Provide updates on new developments and advances**

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2. **CoP newsletters and social media**

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1. **Gather questions from NMPs and researchers, and channel these to the pool of experts who have volunteered to support sharing of knowledge within the CoP**

IMPLEMENTATION

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2. CoP newsletters and social media

2. **CoP e-mail address for communication to share questions, concerns and feedback** (hrp2.mesacop@isglobal.org)
   FAQs sheets regularly prepared and/or updated

WHAT we do / HOW we do it

ACTIVITIES

1. Share best practices, reference materials (e.g. protocols, SOPs, training) and relevant resources from various stakeholders

2. Provide updates on new developments and advances

3. Gather questions from NMPs and researchers, and channel these to the pool of experts who have volunteered to support sharing of knowledge within the CoP

4. Organize events to provide updates and facilitate thematic discussions

IMPLEMENTATION

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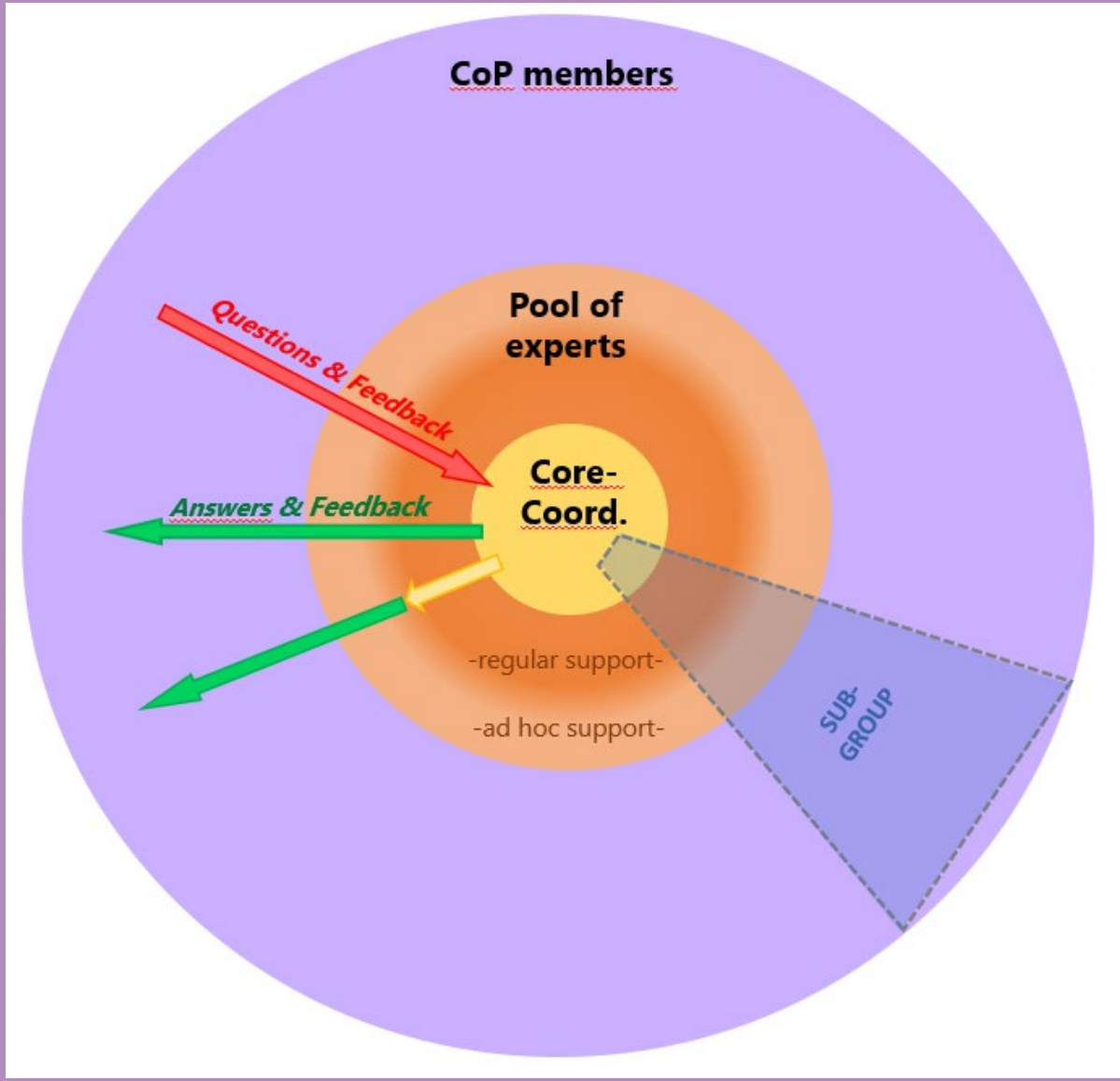
2. CoP newsletters and social media

3. CoP e-mail address for communication to share questions, concerns and feedback (hrp2.mesacop@isglobal.org)

FAQs sheets regularly prepared and/or updated

4. Open Forums; CoP working group sessions (thematic, language specific); Trainings

WHO: creation of the CoP



CoP CORE GROUP

Experts who contributed to the creation:

- Deus Ishengoma (NIMR, Tanzania) - *Chair*
- Dionicia Gamboa (UPCH, Peru)
- Eric Rogier (CDC, USA)
- Khalid Beshir (LSHTM, UK)
- Bosco Agaba (NMCP, Uganda)
- Jane Cunningham (WHO, Switzerland)
- Qin Cheng (ADFMIDI, Australia)
- Mateusz Plucinski (CDC/PMI, USA)
- MESA team - *Coordination*

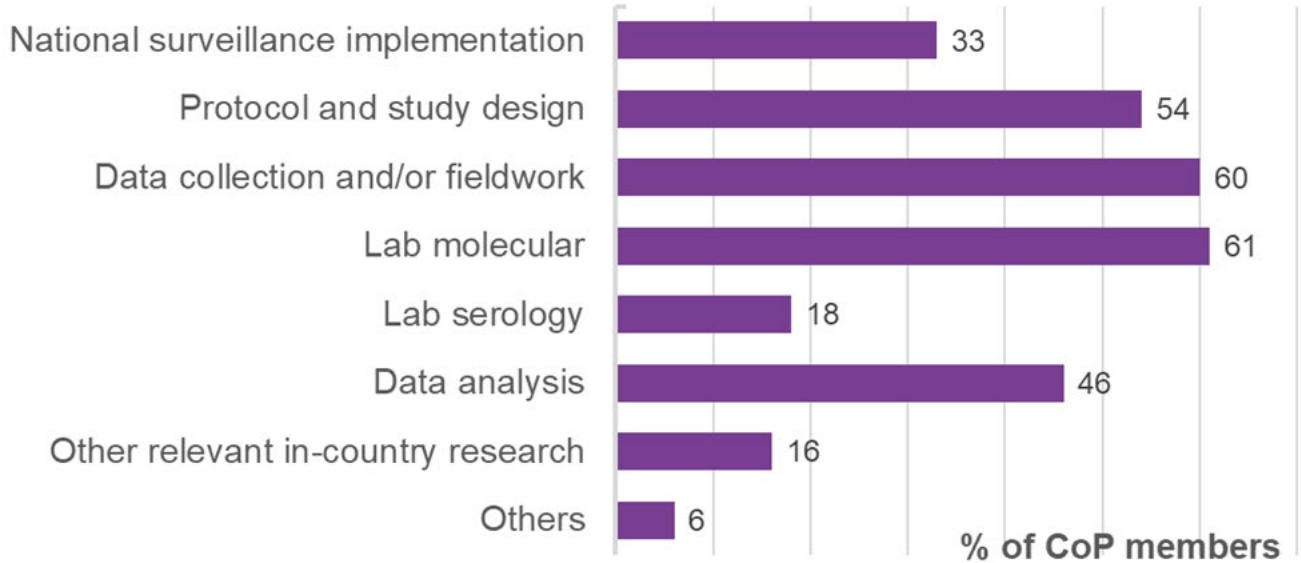
WHO: CoP members profile

- **243 members** from **56 countries***

	N	%		Most represented:
Africa	164	*67%*	➔	Tanzania, Nigeria, Ethiopia, Kenya
Asia	27	*11%*	➔	India, Pakistan
Europe	24	*10%*	➔	Spain, UK, Switzerland
North America	14	*6%*	➔	USA
Latin America	11	*5%*	➔	Peru, Brazil
Oceania	3	*1%*	➔	Australia

- **50.4%** have been (or are currently) involved in *pfhrp2/3* gene deletion surveillance:

Which **type of activities** are the CoP members involved in?



*as of 9th August 2023

FOR WHAT: members' requests & interests

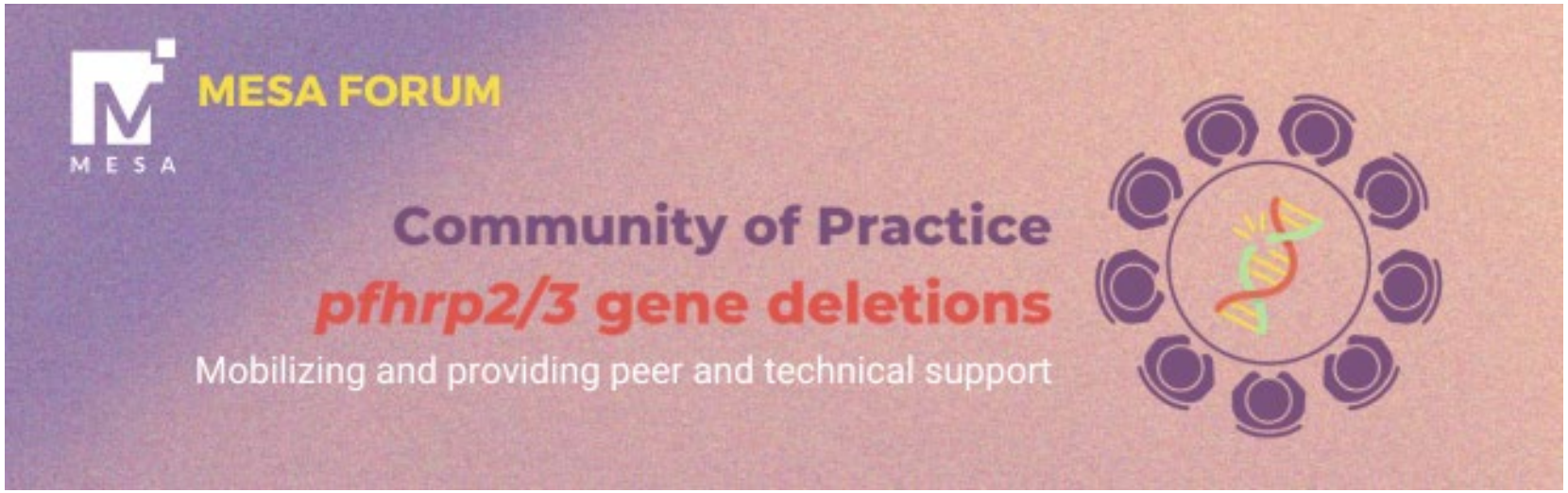
- Suggestions from the CoP members on what the CoP should address:

TOPICS of INTEREST

1. Implementation of surveys
2. Standardized laboratory procedures
3. Genomics/molecular epidemiology
4. Non-HRP2 based RDTs
5. Relation with other surveillance activities (e.g. drug resistance)

REQUESTS / EXPECTATIONS

- ★ Support in interpreting data, policies & guidelines
- ★ Lobby for funding
- ★ Organize (virtual or physical) events for more orientation
- ★ Capacity building
- ★ More involvement of National Programs



Key points and relevant information (CoP MESA Forum, June 2023):

- **Implementing a national survey: Lessons from Uganda**
- **Network of reference laboratories for surveillance activities**

➢ Implementing a national survey: Lessons from Uganda

Sequence of steps followed to implement

- Stakeholder engagement
- Identify survey areas/coverage (if not national survey)
- Quantify the need (resources, supplies, etc)
- Resources mobilization
- Site selection
- Protocol (IRB, investigators, etc)
- Data tools (questionnaires, consent, translations)
- Constitute survey teams
- Site initiations
- Collection-data, samples
- Lab testing – reference Lab if available or shipment
- Data analysis & Report
- Dissemination to NMCP, partnership, publication

Potential Challenges

- Integration into routine surveillance
- Capacity
- Surveys largely remain in “project” mode
- Lengthy processes for MTA for those intending to ship
- communicating hrp2 deletion results where prev <5%
- Introduction of alternative tests alongside HRP2 in areas with deletions (guidelines, training, Supply chains, etc)

Deployment of alternative tests alongside HRP2 in requires efficient distribution system

Lessons

- Top-up for health workers motivated government staff
- Use of existing capacity within the region
- Pooled procurement of supplies
- Resources- both grants and domestic resource
- Adhere to WHO protocol
- Inclusion of NMCP investigators on survey protocol

WHO international lab network to support *pfhrp2/3* surveillance

- Set of **geographically diverse labs** with experience characterizing *pfhrp2/3* deletions (currently 7 labs, 2 under consideration)
- Engage in **tripartite agreements** between WHO-Lab-Survey country (MOH, research institute)
- WHO has some **funding** to support molecular and serological analysis and some of the labs also have funding sources
- **Contact WHO** to be directed to a lab, preferably at planning stage
  - Dr Andrea Bosman, bosmana@who.int;
  - Interim: Dr Qin Cheng, qin.cheng@defence.gov.au

Institute		Country	Lead
London School of Hygiene and Tropical Medicine	LSHTM	UK	Khalid Beshir
University of North Carolina	UNC	USA	Jonathan Parr
Australian Defence Force Malaria and Infectious Disease Institute	ADFMIDI	Australia	Qin Cheng
Centres for Disease Control	CDC	USA	Eric Rogier/?
Université Cheikh Anta Diop de Dakar	UCAD	Senegal	Daouda Ndiaye
Universidad Peruana Cayetano Heredia	UPCH	Peru	Dionicia Gamboa
National Institute of Malaria Research	NIMR	India	Praveen Bharti
Amauer Hansen Research Institute	AHRI	Ethiopia	Fitsum Girma
University of Notre Dame	UND	USA	Christian Koepfli

Useful resources

CoP on *pfhrp2/3* gene deletions

Link to join the CoP:
https://ow.ly/iMsy50OY4wJ

CoP page:
https://mesamalaria.org/resource-hub/community-practice-pfhrp23-gene-deletions

MESA Forum CoP:
https://mesamalaria.org/resource-hub/mesa-forum-community-practice-pfhrp23-gene-deletions

MESA Resource compilation

Resource compilation:
Responding to the threat of pfhrp2/3 deletions
http://www.mesamalaria.org/resource-hub/resource-compilation-responding-threat-pfhrp23-deletions

WHO Pfhrp2/3 dashboard (ongoing/planned surveys)

World Health Organization

Pfhrp2/3 dashboard:
https://extranet.who.int/dataformv3/index.php/341317

Acknowledgements

MESA is supported by a grant from the Bill & Melinda Gates Foundation

World Health Organization

Pool of experts who have volunteered to support the activities of the CoP

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When to suspect HRP2 deletions ?

- In a <u>patient</u>
  - negative results on an HRP2 test line of at least two quality-assured malaria RDTs

  And

  - positive on the pan- or pf-pLDH test line, when a combination test is used

  And

  - the sample is confirmed microscopically to be positive for *P. falciparum* by two qualified microscopists.

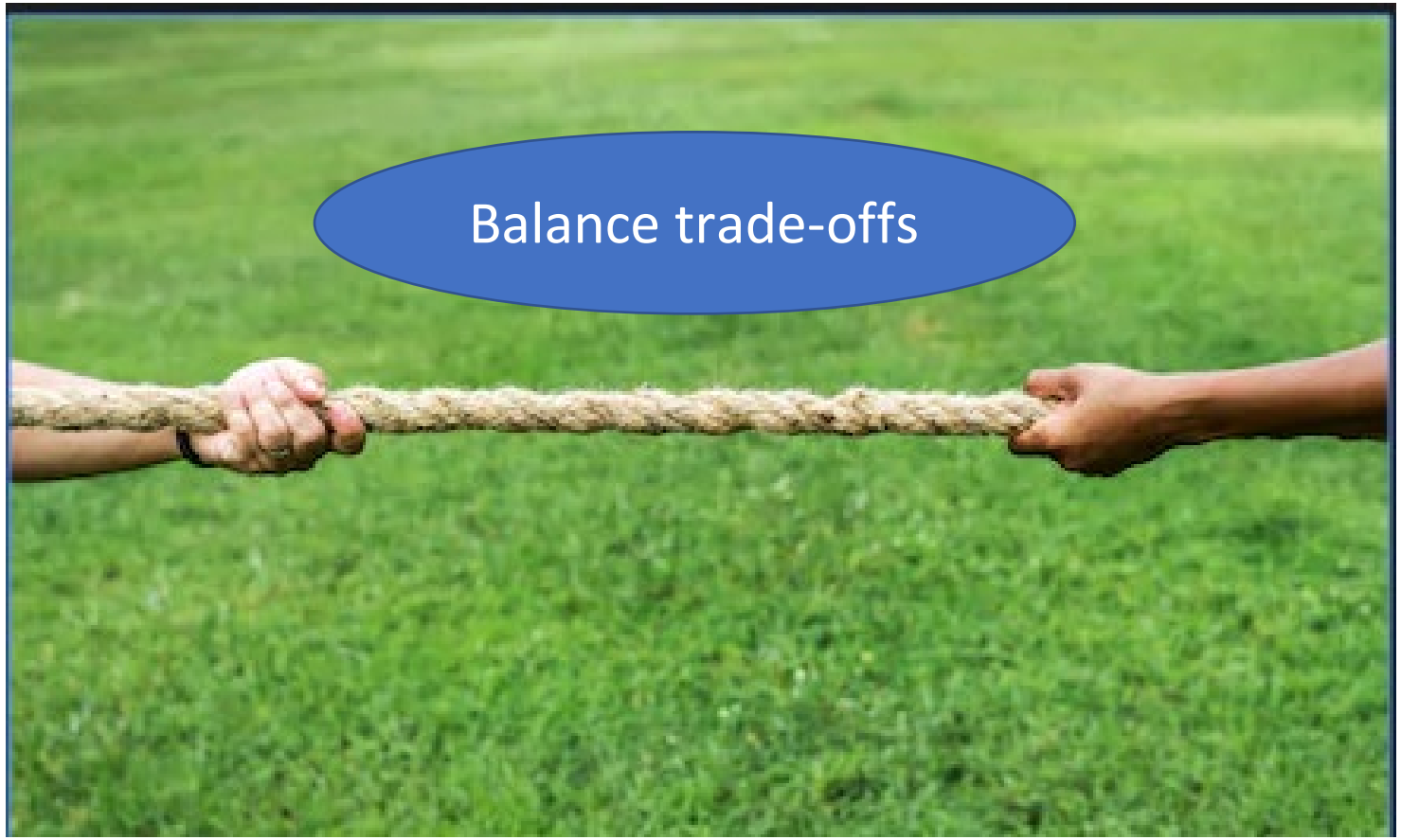
  - Also consider travel history to areas with high prevalence of HRP2 deletions e.g. Peru, Brazil, Eritrea, Djibouti, Ethiopia

https://apps.who.int/iris/bitstream/handle/10665/258972/WHO-HTM-GMP-2017.18-eng.pdf?sequence=1

When to switch away from HRP2 based RDTs

- the prevalence of symptomatic patients carrying pfhrp2-deleted parasites causing false-negative HRP2 RDT results is ≥ 5%
- A threshold of 5% was selected because it somewhere around this point that the proportion of cases missed by HRP2 RDTs due to non-hrp2 expression may be greater than the proportion of cases that would be missed by less-sensitive pLDH-based RDTs
- Comparing sensitivity of HRP2-RDTs and pf-LDH RDTs to microscopy or PCR in several studies the difference is <5-7% amongst symptomatic individuals

What contributes most to missing cases ?



- HRP2-RDT negative due to pfhrp2/3 deletions

pf-LDH (or pan-LDH) RDT negative or faint line missed due to low density infection

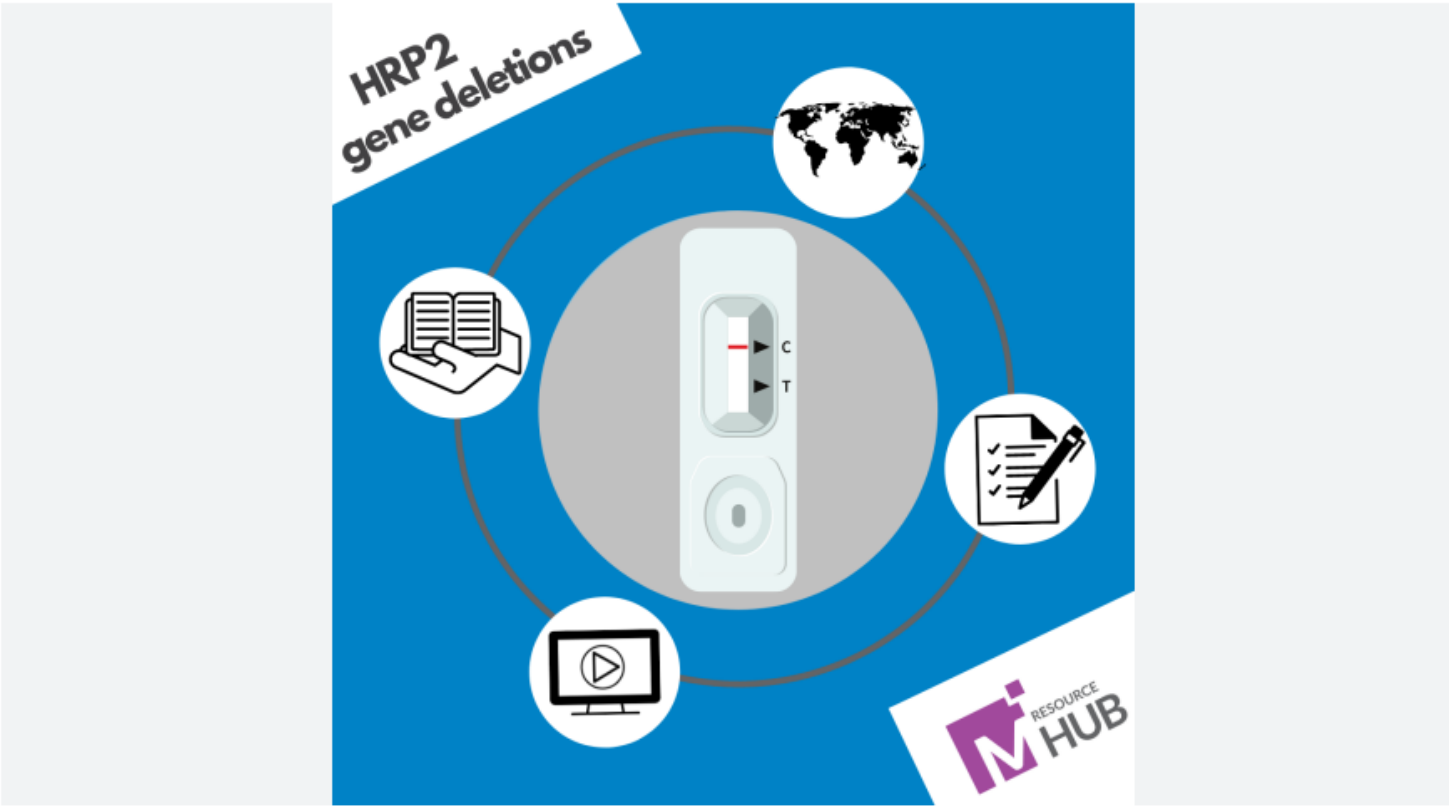
Conclusions

- Health providers and NMCPs need to be aware and responsive to threat of pfhrp2/3 deletions
- Strengthen communication for reporting problems and implement surveillance
- Use WHO protocol templates to develop surveys that are designed and powered to inform policy change.
  - Surveillance approach and using existing health workforce <<< expensive than research
- With continued HRP2 RDT pressure expect problem to grow
- An alternative RDTs not entirely reliant on HRP2 for Pf detection are limited but available (in PQ pipeline and GF ERPD approved) and more going into field trials in 2022 combo test that does rely on HRP2 is available

Resources

Last Updated 12 May 2022

Resource compilation: Responding to the threat of pfhrp2/3 deletions



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World Health Organization