Reports on P*lasmodium Falciparum* Histidine Rich Protein 2/3 Gene Deletions among African Countries Between January 2010 And December 2021 employed different Methodological approaches: A Systematic Review

Keywords: Plasmodium falciparum, gene, deletion, histidine.

ABSTRACT

Background *Plasmodium falciparum* histidine rich protein 2/3 gene deletions (Pfhrp2/3gd) threatens usefulness of mRDT in diagnosing malaria cases. This review was performed to assess the methods used to report findings on those deletions between January 2010 and December 2021.

Methods: Present search was performed using Medline, Google Scholar and PubMed.

Results: Out of 94 articles identified, 19% (n=18) were included. Reviewed articles varied in methods employed to report those deletions.

Conclusion: Methodological approaches for the Reports between January 2010 and December 2021 on Pfhrp2/3gd are varying and this implies that the findings may not be generalized. Prospective studies aiming at assessing Pfhrp2/3gd need to consider WHO guidelines since such studies are important in assessing the magnitude of Pfhrp2/3gd and therefore provide information towards formulating and change of policies aiming at malaria control.

INTRODUCTION

Malaria is a disease of public health importance and affects many people in Africa (1) . In 2015, there were around 429,000 deaths affecting mainly children under five years in African countries (2). The disease causes mortality and morbidity in pregnant women (3,4). In Tanzania, strategies to control malaria include distribution of insecticide treated mosquito bed nets to under-fives, indoor residual spray and intermittent preventive treatment during pregnancy with Sulfadoxine pyrimethamine (IPTp-SP) (5) that aims at reducing poor pregnancy outcomes(6) , and subsequently reduce incidences of congenital malaria in newborns (7,8).

So far, mRDTs are widely used in African countries to diagnose malaria cases such that their accuracy is a prerequisite to successful management of malaria cases (9). However their usefulness has been threatened by reports on pfhrp2/3gd (10–16) which may lead to false negative results paving way to poor management of malaria cases.

This review was performed to assess variation of methodological approaches of studies on Pfhrp2/3gd with a focus on their study design, sample size, study areas, merozoite Surface protein I/II polymerase chain reaction reports, assessment on flanking genes and type of research participants.

METHODS

Searching techniques

Abstracts and paper titles were employed in this review. English language was employed in systematic search. Literature search was performed through Google Scholar, PubMed and MEDLINE. Search items used were 'deletion', '*Plasmodium falciparum*', '*Pfhrp2*', '*Pfhrp3*', 'Malaria Rapid diagnostic tests', 'Africa'.

Review aims

Present review aimed at assessing consistency in methodological approaches for reports between January 2010 and December 2021 on Pfhrp2/3gd.

Inclusion criteria for articles under review

Only findings which met inclusion criteria were reviewed. Inclusion criteria for articles were (a) Primary data published between January 2010 and December 2021 (b) Area of study found in Africa (c) Reporting on Pfhrp2/3gd.

RESULTS

Tentative online search resulted into 94 articles. Out of 94 articles, 19.2% (n=18) met criteria for review while 80.8% (n=76) did not meet criteria for review and these included review articles, articles published outside selected time frame, studies conducted in non-African countries and reports which did not aim at determining those deletions. Detailed information on methods used for reviewed articles are depicted on Table 1.

Table 1: Profile of methodological approaches of Reviewed reports on Pfhrp2/3/gd

African Country	First author	Study design and type of participants	SZ	Pfhrp2/3gd	FG	LM	SGD (%)	Year of publication
Ethiopia (18)	Alemayehu	CSS	218	BR	R	BM1/2N	17.9	2021
Uganda (19)	Sam	CSA	1493	BR	NR	BM1/2N	4.2	2021
Tanzania (17)	Bakari	CSA	7543	BR	NR	BM1/2N	0	2020
Mali (20)	Koita	CSA	480	O2R	NR	MSP2 PCR not reported	2	2012
Kenya(21)	Beshir	CSA	131	BR	NR	BM1/2R	10a	2018
(22)	Nderu	CSS	400	BR	NR	BM1/2N	0	2017
DRC (11)	Parr	CSA	2752	BR	NR	BM1/2N	6.4	2017
Eritrea	Berhane	CSS	50	BR	R	BM1/2R	6.2	2017
(23)(24)	Menegon	CSA	144	BR	NR	BM1/2N	9.7	2018
Rwanda(25)	Kozycki	CSS	3291	O2R	NR	BM1/2N	23a	2017
Mozambique(26)	Gupta	CSS	1162	BR	NR	BM1/2N	1.45a	2017
Senegal (27)	Wurtz	CSS	112	BR	NR	BM1/2N	2.4	2013
Ghana(28)	Amoah	CSA	94	O2R	NR	BM1/2N	36.2	2016
Nigeria (29)	Funwei	PC	309	BR	NR	BM1/2R	17a	2019
Zambia(30)	Kobayashi	CSA	28	BR	NR	BM1/2N	10.7	2019
Angola (16)	Plucinski	CSA	466	BR	NR	BM1/2N	0.4	2019
Ethiopia (31)	Girma	CSA	562	O2R	NR	BM1/2N	4.8a	2019
Ethiopia (32)	Golassa	CSS	189	BR	R	BM1/2R	22	2020

Key: CSS=Cross sectional symptomatic, CSA= Cross sectional Asymptomatic, PC=Prospective cohort, SZ= sample size, FG= Flanking genes, LM =Laboratory method, SGD (%)=percentage of reported deletions, O2R=Only Pfhrp2 gene reported, BR=Both genes reported, NR= Flanking genes not reported, R= Flanking genes reported, BM1/2N=Both MSP1 and MSP2 PCR results not available, BM1/2R= Both MSP1 and MSP2

PCR results available . [a] = means Pfhrp2/3/gd was only estimated on a smaller sample not on all samples.

DISCUSSION

Methodological approaches employed to report Pfhrp2/3/gd between January 2010 and December 2021in African countries were assessed in present review. Generally, the review shows methodological discrepancies as shown in Table 2.

In the year 2018, The World health organization launched a standard guideline for the estimation of Pfhrp2/3gd. In this review, out of 18 reviewed reports 44.4% (n= 8) were reported after the publication of the standard guideline (33) while 55.6% (10=18) were published prior to the guideline. In this review, 5.6% (n=1) of reviewed reports, study designs were prospective cohort study while remaining studies 94.4% (n=17) were cross sectional designs. However, in order to estimate the prevalence of Pfhrp2/3gd in *Plasmodium falciparum* populations, the recommended study design is cross sectional with symptomatic research participants since the parasitemia levels are likely to be higher in symptomatic individuals than asymptomatic individuals (33).

In this review, sample size for study participants ranged from lowest 28 research participants (30) to highest 7543 research participants (17). The WHO guideline recommended at least 370 individuals enrolled from10 randomly selected facilities per survey domain or region. In this regard the domains need to include a combination of low, moderate and high malaria transmission areas. In this review, none of the studies considered a combination of low, moderate and high malaria transmission areas such that estimation of the prevalence of Pfhrp2/3gd in *Plasmodium falciparum* populations was not in agreement with the standard WHO guideline. Studies on Pfhrp2/3/gd which aim at informing on the prevalence of Pfhrp2/3gd in the *Plasmodium falciparum* populations according to the standard guideline should report both Pfhrp2 and Pfhrp3 genes. However, in the reviewed reports, 22.2% (n=4) did not assess both deletions. Furthermore, out of total 18 reviewed reports, flanking genes were assessed in 16.7% (n=3) of the reviewed articles while the rest of the reviewed articles did not report on the flanking genes as shown on Table 2. Such a methodological approach may lead to improper estimation of the Pfhrp2/3gd in *Plasmodium falciparum* populations. Furthermore, in the present

review, 77.8% (n=14) of the reviewed articles did not report both merozoite surface protein I (MSPI) and merozoite surface protein II (MSPII) polymerase chain reaction findings contrary to the recommended WHO guidelines which recommends both MSP1 and MSP2 PCR tests to be performed (33).

Findings of this review imply that researchers employ various methods in reporting Pfhrp2/3gd in African countries and that may have implications on decisions and policy.

CONCLUSION

Reports on P*lasmodium falciparum* histidine rich protein 2/3 gene deletions in African countries between January 2010 and December 2021 vary in methodological approaches such that application of results may not be generalized. Prospective studies aiming at assessing Pfhrp2/3gd need to consider WHO guidelines since such studies are important in assessing the magnitude of Pfhrp2/3gd and therefore provide information towards formulating and change of policies aiming at malaria control.

RECOMMENDATION

Decisions and policies which depend on Pfhrp2/3gd reports, need to take into consideration the variation in research methods from one African country to another and results from one study may not necessarily be generalized to other Countries within the African content

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AUTHOR CONTRIBUTION

B. Sylvester Conducted online research, drafted manuscript, finalized manuscript and approved the manuscript

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