

Foci Classification in Malaria Elimination Setting: A Conceptual Framework

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Research

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Abstract

The concept of malaria elimination is becoming more and more important. Among countries with malaria transmission in 2015, eliminating malaria from 35 countries including those in the Great Mekong has been targeted by 2030. In the journey to elimination through the foci classification procedure, a limited number of “hotspots” among a large number of foci should be precisely defined to be covered by effective controlling measures. There is a common consensus that foci and case classification are fundamental principles of malaria elimination and prevention of reintroduction. However, there are numerous ambiguities and controversies in almost all aspects of foci classifications. These uncertainties result in misclassification that, in turn, wastes lives, time, and money thereby violating value for money principles. New progress in the literature such as ignoring “new potential” foci and using the class of “active foci” instead of the two classes of “new active” and “residual active” is in opposition to the philosophy of foci classification. In this paper, we seek to elaborate the controversies and ambiguities around the concept of foci classification and ultimately suggest some solutions. Some of the ways forward include: (a) foci classification should be done by parasite type; (b) a set of foci classes includes “cleared up”, “new potential”, “new active”, “residual active”, and “residual nonactive”; (c) The number and population of various foci classes should be regularly updated and monitored as the basis for measuring progress toward elimination and it can be considered as the basis for needs assessment and planning response; (d) The coverage and completeness of the controlling interventions by foci classes should be regularly monitored; and (e) The criteria for early detection of outbreaks should be defined. Furthermore, two applicable models for foci classification by parasite have been proposed.

Key Messages

Foci and case classification are fundamental principles of malaria elimination; however, there are numerous ambiguities and controversies around this concept that result in wasting lives and violating value for money principles. To address the issue, regular foci classification by parasite using two proposed applicable models in the manuscript is recommended.

Introduction

The arrow that missed the head of its target, as the proverb goes, will never hit the tail. In the battle against malaria, when its elimination is in sight, a few portions of foci as hotspots should be targeted and covered by costly interventions such as vector control and active case finding. Therefore, targeting non-hotspot foci instead of hotspots would waste lives, time, and money thereby violating value for money principles.

The procedure for defining the hotspots is called both micro stratification or foci classification. Micro stratification according to risk of transmission helps to identify and classify areas with active transmission and those with greater transmission potential for planning and prioritizing interventions [18].

There is a common consensus on the necessity of foci and case classification as fundamental principles of malaria elimination and prevention of reintroduction. Furthermore, a complete database of all malaria foci [5] with detailed maps for the last five years is one of the important criteria for certification of elimination [3, 6]. Hence, foci classification has been highlighted in almost all malaria elimination related guidelines as well as regional and national elimination plans, for instance in China, Lao People's Democratic Republic, Myanmar, Nepal, and Iran [4, 24].

To avoid foci misclassification, the criteria for defining various classes of foci and the standard operating procedures (SOPs) of classification should be clearly determined and be harmonized globally. However, there are numerous ambiguities around this topic resulting in huge differences among the foci classification protocols of different countries. Accordingly, comparing the progress of the nominated countries against the elimination targets of the Global Technical Strategy for Malaria (GTS) will be difficult. Given that malaria elimination is becoming more and more considerable, addressing controversies and ambiguities in foci classification as a basis for elimination is crucial.

In this paper, the misunderstandings around the concept of foci classification in the context of malaria elimination are carefully examined and new light is shed on the ambiguity surrounding the topic. Subsequently, the consequences of foci misclassification are reviewed and, eventually, ways are put forth to move forward for correct and precise foci classification. Furthermore, two applicable models by parasite for foci classification have been proposed.

Methods

A comprehensive search and review of the literature was conducted to clarify various dimensions of foci classification including malaria foci classes, their definitions, and the timeline/condition for updating foci classes. Global Health databases, Google, and the WHO website were searched using the following keywords and phrases: malaria, elimination, malaria re-introduction, foci classification, case classification, malaria surveillance, residual active foci, and active foci. Documents covering the keywords were included only if they were published in the past 15 years.

Results And Discussion

Importance of Micro Stratification

Elimination has been defined as the interruption of the local transmission of a specified malaria parasite in a defined geographical area as a result of deliberate activities [3,7]. A world free of malaria is a major goal of global health, unequivocally embraced by WHO soon after its founding in 1948 [7]. Moreover, in line with Sustainable Development Goals, it has been reemphasized as the vision of GTS for Malaria (2016–2030) [8]. Among the countries with malaria transmission in 2015, eliminating malaria from 21 countries by 2020 and from 35 countries by 2030 have been targeted by WHO [8,9]. Beyond the potential positive impacts of malaria elimination on socioeconomic development, malaria elimination focusing

especially on *P. falciparum* malaria is defined as the main strategy to fight Artemisinin resistance and multidrug resistance in the Great Mekong [10,11].

Fortunately, many countries particularly those with a low or moderate level of transmissions, are approaching the pre-elimination and elimination phase. The number of countries that reported fewer than 10,000 malaria cases increased from 26 in 2000 to 46 in 2019 and, in the same period, the number of the countries with fewer than 100 indigenous cases increased from 6 to 27 [7].

While approaching elimination, there is usually a shift in the populations most at risk of malaria; hence, traditional control interventions are likely to be less effective [16], keeping in mind that the broad coverage of interventions targeting non-hotspots is wasting the resources. Therefore, the operations should be based on epidemiological investigation and classification of each malaria case and focus [17]. This is also a requirement of the prevention of reintroduction while the concentration of the programme is on consolidating transmission-free areas [15, 18].

Thus, for an elimination programme as an essential exercise, a strong surveillance system covering the entire country – preferably information technology-based – is required to identify, investigate, and classify all cases and foci in order to support the implementation of tailor-made responses and targeting appropriate resources and interventions in an aggressive and timely way [2, 3,6, 7, 10, 12, 13, 14, 15].

Stratification should be determined in terms of the intensity of the transmission (number of cases), the level of importation risk (importation of parasite), and the level of receptivity [18]. To have precise foci classification, each confirmed malaria case with parasitaemia should be immediately detected and notified regardless of the presence or absence of clinical symptoms [14]. In addition, a full investigation of each case is undertaken to determine whether it was imported (if so from where) or acquired locally by mosquito-borne transmission (introduced, indigenous, relapsed) or induced [17,2].

A Set of Malaria Foci Classes

The classification of malaria foci depends on their age (residual or new) and the presence of malaria transmission (nonactive, active, or potential). Three different sets of foci classes have been found in the literature which are summarized in Table 1:

Table 1
Classes of malaria foci

	Cleared up	New potential	New active	Residual active	Active	Residual non-active	Endemic
a)	Three classes are defined in a set of foci classes [3]						
b)	Five classes are defined in a Set of foci classes [5]						
c)	Six classes are defined in a set of foci classes [20]						

It seems that there is a strong interest in the simplification of foci classification [3] which is against the concept of foci classification and may result in wasting resources and delays in eliminating malaria. Ignoring “new potential” foci will cause a neglect of the risk of reintroduction and missing opportunities to prevent the occurrence of malaria transmission. Failure in detecting “new potential” foci will result in having more “new active” foci. Besides, having just one class as an “active foci” instead of two classes of “new active” and “residual active” will lead to failure in discovering technical barriers of elimination. It is very important to figure out which one is the main obstacle to achieve elimination: failure to prevent reintroduction in “cleared-up” and “new potential” foci or failure to interrupt transmission in “residual” foci as chronic hotspots. Poor planning, low coverage, the poor quality of interventions, and selection of inappropriate responses are among the underlying causes of existing “residual foci”. The solution to this dilemma is merely formulating operational response(s) in the field.

Definitions of Foci Classes (Table 2)

Table 2
Definitions of foci classes in different references

	<i>Cleared-up</i>	<i>New potential</i>	<i>Residual non-active</i>
Various definitions of a specific class in different literature	No local transmission within the previous 36 months [17, 19, 21].	Isolated imported, induced, or relapsing cases are occurring during the transmission seasons in a receptive area that had no transmission in the past 2 years or more [15, 20].	There is no local transmission in an area with a history of local transmission within the past 2 years [15, 20].
	No local transmission during the past 2 years [2,20].	Presence of imported cases with no evidence of transmission but its renewal is possible [5].	There is no local transmission in an area with a history of local transmission within the last 2 transmission seasons [20].
	No cases of any type, including local or imported cases in the previous 2 years [20].		Transmission interrupted, no indigenous cases, but possible occurrence of relapsing ones [5].
	No cases of any type, including local or imported cases in the previous two transmission seasons [20].		Transmission interrupted recently (1–3 years ago) [17, 18].

A focus with Active Malaria Transmission

There are ambiguities about the concept of foci with ongoing transmission, whereas in my view, it is the most important topic in the elimination era. Lack of a clear definition may cause misclassification error which is likely to decrease the accuracy of the estimates of malaria burden and make the identification of high-risk areas for targeted interventions more difficult [23].

For instance, **“new active”**, **“residual active”**, **“active”**, **“endemic”** and foci affected by **“outbreak”** or by **“reestablishment of transmission”** are defined in the literature under this category.

- “New active” focus (NA) is defined as “Transmission in an area that has had transmission for less than two years or has never had local transmission [15, 20, 2].”
- “Residual active” focus (RA) is defined as “Ongoing transmission in an area that has had transmission within the last two years (or the last two transmission seasons) and transmission is controlled [2].”
- There is another class close to “residual active” in the literature as a focus with “Reestablishment of malaria transmission”. It is defined as “Renewed transmission in an area where transmission had

been interrupted and three indigenous malaria cases of the same species in the same focus, for three consecutive years are reported [3].

- Furthermore, to simplify focus classification “Active focus” for covering both active and residual active has been defined. An active focus is defined as a focus where indigenous cases are detected during the current calendar year [3,26]
- In some references, “Endemic class” is added to the classification cycle, that is describing continuing transmission where transmission is not effectively controlled versus residual foci in which transmission is controlled [2].

In my opinion, considering the parasite type in the procedure of focus class definition is crucial. There is a possibility for having *P. vivax* cases with a long incubation period of around 18 months and beyond [2, 18, 25]. In temperate regions, there are usually two transmission seasons in one year. In other words, the local contraction of symptomatic *P. vivax* malaria is, in theory, possible in the second and third transmission seasons after a mosquito bite. It should be noted that as a routine practice, it is not possible to differentiate between *P. vivax* with short and long incubation periods in the field though a simple procedure. Therefore, foci classification by parasite is required. If there were a willingness to have a single classification covering both *P. vivax* and *P. falciparum*, then the possibility of *P. vivax* with a long incubation period should be considered in foci classification and reclassification. That is to say that two transmission seasons is a very short time interval to be considered as the basis for judgment about the last time that transmission happened in the focus.

Furthermore, a WHO certification of malaria elimination requires proof that the local transmission of all human malaria parasites has been interrupted for at least the past three consecutive years [3]. In my view, in line with WHO guidelines, the time duration for changing NA and RA foci to CU should be equal to or more than three years after reporting the last local cases in foci affected by *P. vivax*. Besides, distinguishing “New Active” from “Residual active” foci and determining duration of the transmission is important for monitoring the progress and defining transmission control interventions.

Another ambiguity regarding the definition of “Endemic” foci is that it is not clear how to distinguish between residual foci and endemic foci [2] and the criteria for the control of transmission are not clear, keeping in mind that quantifying local transmissions is a crucial threshold for early detection of outbreak which should be defined [21].

Ambiguities between Foci Classification and Case Classification in the Literature

In the table below, literature review findings have been summarized. “??” means that there is ambiguity or controversy around the case. For instance, there is an ambiguity in the literature whether imported cases can be found in residual foci or not (Table 3).

Table 3: Controversies and ambiguities between foci classification and case classification in the literature [2, 15,17,25, 26]:						Personal opinion
	Cleared-up	New potential	New active	Residual active	Residual non-active	
Imported case	No	Yes	??	??	??	Imported cases in NA, RA and RNA can be detected. It is difficult to distinguish local cases from imported cases in NA and RA.
Introduced case	No	No	Yes	??	No	Introduced cases can be seen in RA focus.
Indigenous case	No	No	Yes	Yes	No	
Relapse case	??	No	??	??	Yes	Relapse cases can be seen in CU, NA, and RA. However, in NA and RA it is difficult to distinguish local cases from relapse.
Induced case	??	??	??	??	??	Induced cases can be seen in all types of foci.

Ambiguities in Turning Various Classes of Foci to Each Other

In the following table, literature review findings on conditions for turning one focus class to another have been summarized. “??” means that there is ambiguity or controversy around that concept – for instance, on the condition that a new potential focus turns to a cleared-up focus (Table 4).

Table 4: Turning direction and in the time that a focus classes turns to another one [3,2]

	Cleared-up	New potential	New active	Residual active	Residual non-active
Cleared-up		a	b	No	No
New potential	c ??		d	No	No
New active	e??	No		f??	g
Residual active	No	No	No		h
Residual non-active	i??		No	j??	

- a:** The focus should be recategorized from CU into NP if the conditions for malaria transmission exist during the presence of the cases in the focus; however, there is no evidence for transmission [3,2].
- b:** The focus should be recategorized from CU into NA if the transmission started recently [3,2].
- c:** The focus should be recategorized from NP into CU if there is no evidence in favor of transmission in the previous calendar year (after one year) [3,2] or after two years [25].
- d:** The focus should be recategorized from NP to NA in case of a confirmed transmission in the focus [3,2].
- e:** Based on the literature, the focus should be recategorized from NA to CU in case of reporting no local transmissions in the last three years in areas with the risk of PV [18] or after one year [2].
- f:** The focus should be recategorized from NA to RA if malaria transmission has been seen in two consecutive years or the past two transmission seasons [3,2].
- g:** The focus should be recategorized from NA to RNA after two years if there is no local case [25].
- h:** The focus should be recategorized from RA to RNA if the last indigenous case were detected 1–3 years ago.
- i:** The focus should be recategorized from RNA into CU if without evidence of transmission after one or two years [25] or after three years [26].
- j:** There is ambiguity about the possibility of reclassification from RNA to RA in the literature.

In my opinion, time is the most essential variable for reclassification. In many scenarios such as turning RNA to CU, RA to RNA, NA to RA, NA to CU, the time is not clear in the literature and there is controversy in different resources.

Controversy in the Timeline/Condition for Updating Foci Classification

There is controversy over when the classification of a specific focus should be reclassified. To have updated focus classification, the following frequencies have been recommended: at the end of each calendar year [3,17]; at the end of each transmission season [3]; periodically (every six months, for example) [2,18]; immediately after detecting the cases [2,17].

In my opinion, after detecting any new case(s), the class of the focus should be reviewed and, if need be, reclassified. In addition, the respective focus where the case traveled during a certain period should be reclassified.

The following models are proposed for foci classification (Figs. 1 and 2):

Conclusion

Malaria elimination should be planned based on the results-based management approach and this can be happening merely through precise foci and case classification. Therefore, the progress towards elimination should be regularly monitored using well-defined indicators inter alia, case and foci-based indicators such as the proportion of cases and foci investigated and classified in a timely manner, number of people and percentage of the population living in various classes of foci, and percentage of active and residual nonactive foci protected disaggregated by intervention and year [3, 5, 11, 22]. In line with value for money principles, foci classification can be used as the basis for needs assessment of supplies and equipment.

Abbreviations

CU: Cleared-up; NA: NP: New potential; New active; RA: Residual active; RNA: Residual non-active

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Ethical approval for this type of study is not required by our institute.

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Figures



