Concept Note on Presumptive Treatment for Malaria for Consideration by the E8 Technical Committee May 2016

Current Malaria Elimination Strategies

All malaria endemic countries record cases in which patients (usually symptomatic) passively present and get treated at health facilities. While this identification and surveillance of cases is very important for surveillance, it is restricted to symptomatic treatment-seeking individuals, and thus has little impact on malaria transmission. Where transmission of malaria is very low, strategies for elimination include finding and treating individual infections. In order to have an impact on malaria transmission, it is necessary to identify and clear parasites in all infected individuals - both those who are symptomatic and treatment seeking, as well as those who are asymptomatic and do not present to health facilities. It has been shown that even in low transmission settings, a large proportion, if not the majority of infections, are asymptomatic. In order target the asymptomatic parasite pool and thereby reduce transmission in low endemicity settings, active case detection (ACD) is recommended by WHO for the purpose of malaria elimination, and it is increasingly adopted by malaria control programs in low transmission countries. Various forms of ACD have had a long history in most E8 countries.

Given that it is not feasible to screen entire populations for parasite infections, efforts to trace asymptomatic carriers are generally targeted at geographical foci of transmission ("hotspots"), or demographically defined clusters ("hotpops") in which the reservoir of parasites may be concentrated (Sturrock et al., 2013a). Reactive case detection (RACD) in response to passively reported cases, is based on the premise that parasite infections tend to cluster in the geographical vicinity of passively reported cases, or in well defined populations of individuals (Sturrock et al., 2013b).

There are a variety of ways of practicing RACD with respect to the precise method that is employed. Generally, it is conducted in the vicinity of an index case, but it may vary depending on whether only febrile individuals are screened or whether all residents in a screening radius are tested. The choice of screening radius varies widely. RACD can also be applied demographically by screening networks of individuals who are at risk by virtue of common behaviours or occupations. RACD may be combined with additional targeted deployment of other interventions such as IRS or distribution of LLINs. All forms of RACD rest on the assumption that the people who are being tested for parasites, are at higher risk of infection than the rest of the population. However, a weakness of RACD is that testing is conducted by means of rapid diagnostic tests (RDTs) which fail to detect low density parasitaemia. Molecular diagnostic tools can overcome this limitation, but such methods are more costly, and logistically difficult to deploy in field conditions where RACD occurs, due to the delay between taking a blood sample and obtaining the test result.

There are no published studies that have shown that RACD has any impact on malaria transmission.
Proactive case detection (PACD) or mass screen and treat (MSAT) involves screening of higher risk populations without the trigger of passively detected index cases. Mathematical modeling studies show that PACD may reduce transmission but its effectiveness is dependent on highly sensitive

diagnostic tools and on achieving high coverage. A recent trial in Burkina Faso using RDTs for proactive case detection failed to show any effect of this intervention on malaria prevalence or incidence (Tiono et al., 2013). PACD has, however, been used to reduce transmission in Taiwan, China and Brazil(Yekutiel, 1960, Zizhao et al., 1999, Macauley, 2005). A study in Zambia did achieve reductions in malaria burden after repeated rounds of screening and treating using artemether-lumefantrine, but it was considered unlikely that MSAT would eliminate malaria in this setting(Larsen et al., 2015). In a recent study in Zanzibar, it was reported that there was no significant difference in malaria incidence between districts where focal ACD was applied and control districts (evidence presented to WHO Malaria Policy Advisory Committee Meeting, 16-18 September 2015)(WHO, 2015).

In general, the impact of ACD (whether proactive or reactive) is limited due to the low sensitivity of RDTs, and due to the low yield of positives in elimination settings. Subpatent infections, i.e. those not picked up by RDTs or microscopy, are estimated to make up between 20% and 50% of all human to mosquito transmission in low transmission settings(Okell et al., 2012). Molecular tools such as PCR or LAMP would detect a large proportion of low density infections, but these methods are impractical because of long turnaround times and cost. Using high sensitivity RDTs, which are currently under development, would increase the proportion of infections that are currently detected by ACD. However very low density infections would still be missed, regardless of the diagnostic test used. ***As a result of these limitations, WHO's Malaria Policy Advisory Committee has recently concluded that MSAT and focal screen and treat (FSAT) are not suitable as interventions to interrupt malaria transmission (WHO, 2016).***

Mass drug administration (MDA)

MDA in targeted populations with high risk factors is an alternative to ACD which would overcome the problem of missed infections. MDA can be defined as ***"the administration of a full dose of antimalarial treatment, irrespective of the knowledge of symptoms or presence of infection, to an entire population in a given area, except those in whom the medicine is contraindicated"*** (WHO Global Malaria Programme Malaria Policy Advisory Committee meeting, November 2015)[1]. MDA has been used in the past to control epidemics, to reduce or interrupt transmission, and more recently in emergency situations such as the Ebola epidemic in West Africa. Generally, it has been more effective in low transmission, near-elimination settings, and on islands where there has been reduced risk of re-introduction of infection. MDA programmes have been more successful where they included vector control, usually IRS, as part of the strategy; where active engagement of communities has been sought by the programme; and where very high levels of coverage and adherence were attained, often through directly observed therapy (Newby et al., 2015). It is not known whether transmission reduction of MDA is caused by the treatment of asymptomatic malaria which would otherwise go untreated and hence contribute towards transmission, or through the prophylaxis against infection that is provided to the population at large, or a combination of both.

Whilst emphasizing that there is a need for research to strengthen the evidence base for the effectiveness of MDA, WHO have recently recommended that MDA should be considered for

[1] Report available on WHO-GMP website at http://www.who.int/malaria/mpac/mpac-sept2015-erg-mda-report.pdf

elimination of *P. falciparum* "in areas approaching interruption of transmission where there is good access to treatment, effective implementation of vector control and surveillance, and a minimal risk of re-introduction of infection"(1 above). It further recommended that medicines for MDA should preferably have a long half-life, and should be different from those used for first line treatment in the area. Emergence of possible drug resistance should be monitored and the effectiveness of MDA implementations should be rigorously evaluated.

MDA is associated with distinct operational challenges. These include: the need for monitoring for concurrent drug interventions to avoid interactions between drugs; difficulty in giving multiday drug regimens to mobile and remote populations; unwillingness of some people to take drugs when they feel well and have not been tested; need to consider pregnancy testing; monitoring for drug resistance markers; ensuring informed consent is given by participants.

Implications for E8

MDA has already been introduced in studies in some E8 countries. Trials in Zambia and in Mozambique have included the evaluation of MDA, and reactive focal MDA in response to index cases is being trialed in Swaziland and in Namibia. Given the considerable potential that MDA offers to eliminate malaria in low endemicity settings, and given WHO's recent recommendations on MDA, the E8 subregion ought to take action towards establishing well-considered policies that allow the E8 countries to benefit from this intervention where appropriate and in conjunction with other interventions such as IRS and LLINs to accelerate the path to elimination in the E8 sub-region. MDA holds significant potential for the current E8 efforts towards elimination, and could further propel the frontline countries closer to zero transmission. For this reason, countries would benefit from adding this tool to their existing options of elimination strategies in settings that meet the criteria for MDA deployment as set out by MPAC recommendations, and to conduct consultations to inform the appropriate introduction into country programmes.

Ongoing work that needs to be undertaken in preparation for the implementation of MDA or focal MDA should include:

1. Continued engagement with WHO to guide the development of policy and informed operational plans where MDA is being introduced into E8 country programs
2. Selection of suitable candidate areas in E8 to be targeted for MDA;
3. Establishing routine movement patterns of communities that can be targeted for MDA, to ensure that the programme is not undermined by parasite importation;
4. Further assessments to determine how mobile migrants can be included in MDA initiatives.
5. Selection of appropriate MDA drug and whether to include Primaquine;
6. Whether MDA initiatives should be proactive targeting particular populations, or whether it should be strictly reactive and highly focal.
7. Ensuring effective safety monitoring and access to treatment by target communities;
8. Evaluation of MDA in the context of E8 national and regional objectives. Genotyping of parasite strains should be considered as part of the surveillance of the MDA scheme to determine the possible routes of parasite importation.

In countries introducing MDA, the strategy can be introduced as a pilot scheme to gain experience and build confidence, but the pilots should be large enough to allow for proper evaluation of the effectiveness of the intervention. Given the current inter-year variation in malaria burden in the Southern African region, before versus after comparisons are likely to be confounded by temporal trends. Therefore, evaluations including contemporaneous control areas for comparison need to be considered.

E8 Action

In order to catalyze action to ensure that E8 countries benefit from this additional tool, the E8 will take the following steps:

- Establishment of a small working group that will support national malaria program managers to assess opportunities and feasibility of the introduction of MDA in each country, in consultation with WHO, and other technical partners
- Develop key messages and action points for national, regional, and global advocacy and resource mobilization
- Draw up the criteria for MDA pilots in the E8, and that draft detailed proposals for the design of a pilot MDA scheme, with input from leading experts in the field.

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