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From evidence to action

Review of mass drug administration and primaquine use

KEY MESSAGES

- Mass drug administration (MDA) for malaria is not new—it has a long history of use in research studies and control and implementation programs.
- MDA has proven effective in interrupting transmission of both *P. falciparum* and *P. vivax* malaria.
- Small operational units of MDA delivery allow for better coverage, adverse event monitoring and community engagement.
- Primaquine has been used extensively in MDA campaigns with few adverse events reported.

WHY MDA?

Mass drug administration (MDA) was a component of many malaria elimination programs during the eradication era, but since then the malaria community has viewed it with skepticism due to concerns about efficacy, logistical feasibility, and fear of accelerating drug resistance. However, in light of the availability of antimalarials that have transmission-reducing effects (e.g. artemisinin-based combination therapies and primaquine), and the limitations of current diagnostic tools in detecting low density infections, the role of MDA as an elimination tool must be reexamined.

Many field studies and programmatic implementaion of MDA have been carried out over the past century with varying degrees of success. Yet the first ever systematic review of published studies analyzing the quantitative effects of malaria MDA was not published until December 2013, a Cochrane review by Eugenie Poirot and colleagues.[1] The Cochrane Review evaluated only 32 studies out of 240 assessed for inclusion, and because of the poor quality of available evidence, only limited conclusions could be made. In order to build on this Cochrane Review and maximize understanding of previous MDA experiences, we conducted a qualitative analysis of published, unpublished, and grey literature, supplemented with key informant interviews. This background paper documents the findings from this qualitative exercise, summarizes remaining knowledge gaps, and provides recommendations to support the use of MDA for malaria elimination and eradication.

Full length background papers can be found at globalhealthsciences.ucsf.edu/news-events/malaria-elimination-background-paper-series

REVIEW FINDINGS

We identified 182 published studies and eight unpublished reviews of programmatic MDA for qualitative analysis. These MDA campaigns span the globe and the past century, with the earliest conducted in 1910 and the most recent in 2010. MDA has been carried out on its own and as part of a package of interventions (e.g. indoor residual spraying, bed net distribution and/or larviciding), targeting a wide range of population sizes and epidemiological settings. It has been implemented with the goals of morbidity reduction or transmission interruption and elimination, and as an outbreak response. As with the Cochrane Review, the published studies were generally of poor quality. The most important additions to our analysis were the unpublished reports of programmatic implementation of MDA, most of which targeted many thousands if not millions of people. In contrast with the published studies, which were most often conducted in high transmission *P. falciparum* settings, most of the programmatic MDA efforts were implemented in areas of low endemic *P. vivax* transmission. This diversity of settings, goals, operational details and study quality makes it difficult to draw firm conclusions and generalize across experiences. However, this research revealed a **wealth of knowledge available to guide future implementation of MDA** as an elimination tool.

A primary finding of the Cochrane Review was that MDA had a larger impact on *P. falciparum* transmission than that of *P. vivax*. In contrast, our qualitative analysis of a much broader range of studies as well as unpublished programmatic MDA presents **strong evidence that MDA is an effective intervention against both species**. "Spring treatment" has been used at massive scale in response to seasonal epidemics of *P. vivax* in China, the Democratic People's Republic of Korea, and several countries in the former Soviet Union, with millions of doses dispensed. When drug coverage was sufficiently high, MDA interventions were successful in interrupting epidemic transmission. Vector control co-interventions are less of a priority in highly seasonal transmission settings such as these, but are essential in all other settings, particularly where *P. falciparum* is endemic.

The most important factor for successful MDA identified through our research is achieving at least 80-90% coverage of the target population with drugs. Such high coverage is facilitated by strong community engagement, directly observed treatment, and limiting the number of rounds and overall duration of the intervention to improve adherence. Evidence indicates that **when the target population is separated into units of no more than 200-300 people with a dedicated MDA delivery team per unit, community participation improves and coverage increases** as a result. Small operational units such as these were deployed in China, where up to 28 million people per year were successfully targeted in *P. vivax* epidemic response campaigns in the 1970s.

Primaquine and other 8-aminoquinolines were used in nearly half of the MDA campaigns that we reviewed dating back to the early 1930s, alone or in combination with blood schizonticides, and targeted population sizes in the millions. Prior to the 1990s, the published studies did not report any glucose-6-phosphate dehydrogenase deficiency data, and only a few reported rare occurrences of hemoglobinuria or hemolysis. In the unpublished work that documented programmatic use of primaquine on a massive scale in several countries, investigators paid close attention to drug safety. Deficiency prevalence was established prior to onset of MDA (prevalence ranged from 2-17%) and the target population was closely monitored for adverse events throughout the interventions. **Despite the enormous scope of primaquine distribution, the incidence of severe adverse events was negligible and no deaths were reported**.

SUMMARY POINTS

- MDA should be carried out with a long-term, contextual view and a holistic approach, drawing upon available evidence and lessons learned from previous MDA experiences.
- Achieving adequate coverage is dependent upon using directly observed treatment and securing a high degree of community participation, particularly when multiple drug rounds are needed.
- MDA drug regimens that include primaquine should always include adverse event monitoring.
- A global research agenda must be established to address the lessons and gaps revealed by this review.

REFERENCES

1. Poirot E, Skarbinski J, Sinclair D, Kachur SP, Slutsker L, Hwang J. Mass drug administration for malaria. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD008846. DOI: 10.1002/14651858.CD008846.pub2.