

## Moving from Malaria Burden Reduction toward Elimination: An Evaluation of Mass Drug Administration in Southern Province, Zambia

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**Abstract.** From December 2014 to February 2016, a cluster randomized controlled trial was carried out in 60 health facility catchment areas along Lake Kariba in Zambia's Southern Province. The trial sought to evaluate the impact of four rounds of a mass drug administration (MDA) intervention with dihydroartemisinin–piperaquine (DHAP) or focal MDA with DHAP at the household level compared with a control population that received the standard of care. This study was the first randomized controlled trial with DHAP for MDA in sub-Saharan Africa and was conducted through a collaboration between the National Malaria Elimination Programme in the Zambian Ministry of Health, the PATH Malaria Control and Elimination Partnership in Africa, and the Center for Applied Malaria Research and Evaluation at Tulane University. This article serves as an introduction to a collection of articles designed to explore different aspects of the intervention. By describing the recent history of malaria control in Zambia leading up to the trial—from the scale-up of point-of-care diagnosis and treatment, vector control, and indoor residual spraying early in the twenty-first century, to the efforts made to sustain the gains achieved with that approach—it provides a rationale for the implementation of a trial that has informed a new national strategic plan and solidified malaria elimination as Zambia's national goal.

### INTRODUCTION

From December 2014 to February 2016, a cluster randomized controlled trial was carried out in 60 health facility catchment areas along Lake Kariba in Zambia's Southern Province to evaluate the impact of four rounds of a mass treatment intervention with dihydroartemisinin–piperaquine (DHAP). The trial sought to evaluate the relative effectiveness of community-wide mass drug administration (MDA) or focal MDA (fMDA) at the household level (fMDA) with DHAP compared with a control population that received the standard of care (which included good access to case management, including community case management; high coverage of long-lasting insecticide-treated mosquito nets [LLINs] and indoor residual spraying [IRS] with pirimiphos-methyl; and robust surveillance, including rapid reporting and reactive case detection).

This groundbreaking study, the first randomized controlled trial with DHAP for MDA in sub-Saharan Africa, was the result of a collaboration between the National Malaria Control Programme in the Zambian Ministry of Health, the PATH Malaria Control and Elimination Partnership in Africa, and the Center for Applied Malaria Research and Evaluation at Tulane University. Because of the extensive data collection conducted for the trial, many different aspects of the intervention could be addressed in detail. Here, we present a collection of articles designed to explore these topics. This introductory article provides a history of malaria control in Zambia leading up to the trial, a rationale for its implementation, and a brief explanation of the articles found in the supplement.

### ZAMBIA SCALES UP FOR IMPACT

Early in the twenty-first century, Zambia saw its malaria rates tripling over the previous three decades (from 121 per

1,000 population in 1976 to 428 per 1,000 population in 2003).<sup>1</sup> With the global health and malaria community declaring ambitious malaria targets, the Zambian government identified malaria control as one of its main public health priorities. The country was not without existing prevention measures, but although LLIN distribution channels provided a solid base of coverage, they were disproportionately reaching those in urban areas and those with better access to health-care facilities, rather than rural populations most affected by malaria.<sup>2</sup> Thus, with an influx of additional resources planned by the Global Fund to Fight AIDS, Tuberculosis and Malaria and with renewed hope for progress in disease burden reduction, a strategic plan for 2006–2010 was developed emphasizing the scale-up of simplified point-of-care diagnosis with malaria rapid diagnostic tests (RDTs), artemisinin-based combination therapy, vector control with LLINs, and, in selected areas, IRS.<sup>1</sup> Input from the Bill & Melinda Gates Foundation<sup>3,4</sup> made mass distributions of LLINs possible, while support from Zambia's traditional mining centers, the U.S. President's Malaria Initiative (PMI), and the World Bank led to an increase in IRS coverage by the national program that expanded from the more urbanized rail corridor into more rural malarious districts. In addition, intermittent preventive treatment during pregnancy with sulfadoxine–pyrimethamine for malaria prevention among expectant mothers was supported through antenatal clinics.

With this commitment came noticeable results. More than 6 million LLINs were distributed between 2007 and 2010, and more than 1 million households received IRS annually between 2008 and 2010. Between 2003 and 2010, IRS activities expanded from five districts to 54. By 2010, 73% of households in Zambia had either one or more LLINs or had received IRS in the previous year—a 41% increase in household availability of malaria prevention nationally between 2006 and 2010 and a 5-fold increase between 2001/2002 and 2008.<sup>5</sup> In the early part of the decade, changes to Zambia's case management treatment policy, from failing monotherapies to artemether–lumefantrine, were financed to support implementation, although progress in adoption in health facilities

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was slow.<sup>6</sup> Between 2003 and 2008, malaria case management was supported by the increased availability of diagnostic tools, primarily through the expansion of RDTs, which were made available initially to rural health centers and health posts. In 2008, more than 2 million RDTs were distributed.<sup>7</sup>

In 2010, Zambia's malaria focus shifted to sustaining the gains from the initial scale-up. As recommended by a program review in 2010<sup>8</sup> and adopted in the country's 2011–2015 strategic plan,<sup>9</sup> three broad malaria epidemiological strata were defined based on the latest prevalence information from national household surveys. Lusaka and environs were the lowest epidemiological burden, eastern and northern areas of Zambia the highest, and all other areas fell in the middle. Notable new activities during this period included the expansion of malaria testing and treatment services at the community level through integrated community case management (iCCM). The launch of the National Human Resources for Health Strategic Plan in 2011 focused on adding an additional 18,000 health workers in various cadres and 5,000 community health workers (CHWs).<sup>10</sup> Early research had demonstrated the cost-effectiveness of engaging CHWs to supplement facility testing and treatment services.<sup>11</sup> Integrated community case management training and funding for implementation ramped up during this period with support from the PMI, the Global Fund, and the Canada International Development Assistance. For the volunteering CHWs offering iCCM services, support was further provided nationally by the roll out of the community health assistant workforce and by increasing the number of health posts in underserved areas.<sup>12,13</sup> Furthermore, the expansion of malaria case management to more rural, malarious areas through iCCM shifted coverage of care to trained CHWs,<sup>14–16</sup> addressing the most significant hurdle to diagnosis and treatment access.

In 2011, Zambia began using the District Health Information System, or DHIS2, an open-source health management information system platform that enabled the ministry of health to strengthen their routine health information systems, harmonize reporting across partners, and introduce a weekly malaria rapid reporting system via mobile phone-based data entry. The increasing timeliness and quality of data facilitated the ability to make strategic, data-driven decisions to improve service delivery. In 2011, Zambia initiated CHW-based passive and reactive case detection, expanding care and treatment access to communities and introducing a case investigation intervention to find additional malaria infections in the community.

#### SUSTAINING MALARIA CONTROL

Despite often achieving high coverage with vector control and other interventions, by 2014, Zambia had not achieved the reduction in transmission it had expected. Malaria indicators surveys in 2010 and 2012 showed that 16% and 15% of children tested positive by microscopy, respectively, an increase from the 10% documented in 2008.<sup>17–19</sup> Of note, many of these infections were in asymptomatic individuals likely because of acquired immunity; thus, passive case detection methods seemed unlikely to substantially reduce the parasite reservoir in the population. These challenges to the “control-only” approach and rising global interest in malaria elimination helped move Zambia toward setting an ambitious malaria elimination target date of 2021. To achieve this, new tools

were needed and various approaches to population-based drug strategies were considered and tested.

Although MDA had been used in many different countries for malaria control in past decades, it had largely fallen out of favor because of concerns about the transient impact and drug resistance. However, as the global progress began to stagnate between 2000 and 2010, the malaria community began looking for alternative tools. Mass drug administration and related activities—mass test and treat (MTAT), mass screen and treat, and fMDA—began to be re-examined as potential solutions. Mass drug administration had a long, successful history of control and elimination for some neglected tropical diseases, and the advent of artemisinin-based combination therapies meant that resistance was less likely.<sup>20,21</sup> However, the evidence surrounding these solutions was incomplete, having mostly been generated decades ago using nonexperimental study designs that limited the evidence generated. In addition, many MDA interventions were one-off research exercises that did not include robust malaria prevention and control activities after cessation of the study.<sup>22</sup> A 2013 Cochrane review concluded that MDA was likely safe but noted the lack of high-quality evidence and called for studies that looked at how the effects of MDA could be sustained past 6 months after administration.<sup>23</sup> Early modeling results also suggested that MDA could have a significant impact when coupled with other interventions such as robust vector control.<sup>24,25</sup>

#### A PIVOT TOWARD ELIMINATION

The decision to launch an MDA trial stemmed from the new focus on elimination and the realization that MTAT, a mass treatment strategy the country had already experimented with, was inadequate to achieve substantial transmission reduction. An MTAT randomized controlled trial conducted in Southern Province, Zambia, from 2011 to 2013 showed a statistically significant effect but one far too small to provide major gains toward elimination.<sup>26</sup> A similar study conducted in Zanzibar showed no effect.<sup>27</sup> At the same time, reports from several studies showed that HRP2 RDTs were missing a significant number of low-density infections, meaning that a substantial component of the parasite reservoir would not be detected by a test-and-treat strategy.<sup>28–30</sup> In this context, therefore, MDA was a promising malaria elimination acceleration strategy to test.

This supplement presents the results of the main trial evaluating four rounds of MDA or fMDA with DHAP, compared with a control of no MDA or fMDA.<sup>31</sup> We also report the findings of several studies conducted concurrently that investigated various aspects of the trial. These include studies on the acceptability of treatment,<sup>32</sup> MDA coverage,<sup>33</sup> DHAP efficacy and adherence to the treatment regimen,<sup>34</sup> RDT performance,<sup>35</sup> infection incidence,<sup>36</sup> parasite genotypes before and after the intervention,<sup>37</sup> human movement and the relationship between travel history and malaria infection status,<sup>38</sup> insecticide resistance and parasite infection in *Anopheles funestus* mosquitoes in the study area,<sup>39</sup> and the cost-effectiveness of adding an MDA or fMDA strategy to the standard-of-care malaria control in Southern Province.<sup>40</sup> Although specific to the trial and study area, many of the issues explored in these articles are germane to consideration of the

potential usefulness of population-based drug strategies in other settings. Moreover, the gains in knowledge from this trial helped usher Zambia into a new era of its malaria efforts, providing key evidence to inform a new national strategic plan and solidifying elimination as the national goal.

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