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RECEIVED 06 September 2024 ACCEPTED 13 January 2025 PUBLISHED 30 January 2025

CITATION

Woldesenbet D, Tegegne Y, Mussema A, Tamene E, Mohamed K, Abebe W, Mekuria M, Bogale K, Geremew H, Shifa MM and Tegegne MA (2025) Can Ethiopia eliminate malaria? Malaria burden: insights from the pre-elimination era, current challenges and perspectives. *Front. Malar.* 3:1492444. doi: 10.3389/fmala.2025.1492444

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Can Ethiopia eliminate malaria? Malaria burden: insights from the pre-elimination era, current challenges and perspectives

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Background: Ethiopia has faced a significant burden of malaria, enduring endemic transmission in various regions. Despite concerted efforts spanning years, malaria remains a persistent public health issue, particularly affecting underserved rural communities. Previous developments in vector control, diagnostic capabilities, and treatment protocols have led to notable reductions in malaria morbidity and mortality. However, challenges persist, including the emergence of drug and insecticide resistance, compounded by environmental and demographic factors. Understanding the historical context and contemporary challenges is crucial for navigating Ethiopia's path toward malaria elimination.

Methods: From October 2023 to January 2024, a systematic search was conducted across open access journals such as PubMed, EMBASE, CINALH, Web of Science, Global Health, and Google Scholar using MeSH and Emtree terms for malaria. The focus was on challenges of malaria elimination in Ethiopia, such as drug resistance, vectors' insecticide resistance and the loss of the diagnostic potential of rapid diagnostic kits.

Main text: Recent trend analyses and World Health Organization reports indicate resurgence in malaria cases in Ethiopia. Factors contributing to this resurgence include emerging drug resistance, insecticide resistance, and genetic mutations such as single nucleotide polymorphisms. Other challenges include the spreading resistance to effective antimalarial drugs, socio-cultural barriers to malaria elimination, the challenge posed by *Plasmodium vivax* in elimination efforts, and the occurrence of imported cases in previously low burden areas. To reverse the rising trend of malaria cases, it is necessary to customize intervention strategies through active community engagement, rigorous healthcare

infrastructure, and learning from countries that have successfully eliminated malaria.

Conclusion: While past successes are notable, they do not guarantee current progress, highlighting the need for rigorous implementation of strategies and adaptation of intervention methods to ensure the success of malaria elimination efforts. However, recent data suggests a concerning resurgence in malaria cases, potentially fueled by emerging drug and insecticide resistance. To achieve sustained success in malaria elimination, there is an urgent need for continued vigilance, customization of intervention strategies, and robust collaboration between stakeholders to address these challenges effectively.

KEYWORDS

malaria, Plasmodium, Ethiopia, trend analysis, elimination

1 Introduction

Malaria, a mosquito-borne infectious disease caused by parasites of the *Plasmodium* genus, remains a significant global health challenge, particularly in tropical and subtropical regions (Kolawole et al., 2023). The disease exacts a heavy toll on human health and socioeconomic development, with millions of cases reported annually worldwide (Chima et al., 2003; Worrall et al., 2005). Malaria manifests clinically with a spectrum of symptoms, including fever, chills, headache, and muscle aches, often mimicking flu-like illness. Moreover, severe cases can progress rapidly, leading to life-threatening complications such as cerebral malaria, severe anemia, respiratory distress, and multi-organ failure (Warrell, 2017; Balaji et al., 2020).

The disease has deep roots in Ethiopia, with evidence of its presence dating back centuries. The country's diverse ecological landscape provides suitable settings for malaria transmission, particularly in lowland areas with abundant mosquito breeding sites (Alelign and Dejene, 2016). Over the years, Ethiopia has implemented various malaria control initiatives, including vector control measures, case management strategies, and communitybased interventions. Despite these efforts, malaria remains endemic in many parts of the country, posing significant health risks to vulnerable populations (Kassa, 2015; Mutero et al., 2020).

Despite substantial progress in malaria control over the years, the disease continues to exert a heavy burden on health systems and populations, contributing to morbidity, mortality, and economic losses. As Ethiopia strives to eliminate malaria by 2030, understanding the historical context, current challenges, and future perspectives is essential for adjustment and customizing effective elimination strategies (Adugna, 2011; Ayele et al., 2012).

2 Objective of the review

This review aimed to critically examine the burden of malaria in Ethiopia during the pre-elimination era, focusing on historical trends, current challenges, and future prospects. By analyzing epidemiological data, policy documents, and research studies, we identified key factors influencing malaria transmission dynamics and assess the feasibility of achieving malaria elimination by 2030.

3 Burden of malaria in Ethiopia

3.1 Overview of malaria prevalence in Ethiopia

Malaria continues to impose a significant health burden in Ethiopia, with an estimated 68% of the population living in areas with moderate to high malaria transmission rates (Kassa, 2015). The disease in humans is caused by five *Plasmodium* species globally, but in Ethiopia, *Plasmodium falciparum* and *P. vivax* are the primary parasites contributing to the burden (Girum et al., 2019; Aschale et al., 2023). Parasite transmission in the country is mainly driven by *Anopheles arabiensis*, with other species like *An. pharoensis*, *An. coustani* s.l., *An. nili*, *An. funestus*, *An. stephensi* and *An. demeilloni* playing smaller roles (Aschale et al., 2023).

The disease disproportionately affects rural communities, where access to healthcare services and preventive measures is limited (Abdishu et al., 2022; Graves et al., 2009; Hailu et al., 2017). In 2022, Ethiopia reported approximately 2.4 million confirmed malaria cases, making it one of the highest-burden countries in sub-Saharan Africa (WHO, 2023). In Ethiopia, the burden of malaria

Abbreviations: ACT, Artemisinin Based Combination Therapy; DDT, Dichlorodiphenyltrichloroethane; HRP, Histidine Rich Protein; IRS, Indoor Residual Spraying; LLIN, Long Lasting Insecticidal Net; SNP, Single Nucleotide Polymorphism; WHO, World Health Organization.

varied significantly across different locations. Reports indicated high prevalence rates in various regions, including Kola Diba in Northwest Ethiopia (75%) (Alemu et al., 2012), Benishangul-Gumuz regional state in Western Ethiopia (51.8%) (Alkadir et al., 2020), Woreta town (48%) (Alelign et al., 2018), and the Omo zone of Southern Ethiopia (41.5%).

The economic burden of malaria in Ethiopia is substantial, with direct and indirect costs estimated to exceed \$200 million annually, constituting approximately 10% of its total health expenditure (Jobin, 2014; Eregata et al., 2019). These costs encompass expenses related to diagnosis, treatment, and productivity losses due to illness and absenteeism from work or school. Despite the rising collaboration funding by the Global Fund, PM/USAID, and the government from 2020 to 2022 (WHO, 2023), malaria-related expenditures continue to place a significant strain on household finances and national healthcare budgets, thereby undermining efforts to achieve sustainable development goals.

3.2 History of malaria epidemics in Ethiopia

Malaria has historically been endemic throughout the country, posing significant health risks to its population (Negash et al., 2004; Adugna, 2011; Yukich et al., 2013). Ethiopia commenced its battle against malaria over half a century ago. Initially, malaria control began as a pilot project in the 1950s, subsequently transitioning into a national eradication campaign in the 1960s, followed by a control strategy in the 1970s. This effort has witnessed alternating periods of success and failure. In 1976, the vertical organization known as the National Organization for the Control of Malaria and Other Vector-borne Diseases emerged from the Malaria Eradication Service. As is the case in other regions where malaria is endemic, the disease remains far from being conquered. The causative agent, Plasmodium, has developed resistance to several drugs, while the vector mosquito has evolved mechanisms to resist the chemical interventions (Merida, 1965; Vecchiato, 1991; Gish, 1992; Negash et al., 2004).

3.3 Elimination efforts in Ethiopia

In March 1966, systematic malaria eradication operations began in Ethiopia, with the ambitious goal of eliminating malaria from the country by 1980. These efforts were part of a global initiative led by the World Health Organization (WHO) to eradicate malaria worldwide. Ethiopia's eradication campaign included a combination of vector control measures, such as Indoor Residual Spraying (IRS), and mass drug administration (Tesfaye, 1973; Britanak et al., 1974; Janssens and Wery, 1987).

Despite initial hopefulness, Ethiopia's campaign to eliminate malaria encountered numerous challenges and setbacks. During the 1958 epidemic, the estimated number of malaria cases was about three million. The favorable climatic conditions in 1958 facilitated the propagation, longevity, and dispersal of the vector. These circumstances were compounded by the presence of insecticideresistant vectors and Chloroquine-resistant *P. falciparum*, contributing to the severity of the situation. These challenges led to a significant toll, with approximately 150,000 deaths reported in Ethiopia in 1962 alone. The widespread use of dichlorodiphenyltrichloroethane (DDT) for IRS was met with resistance from mosquito populations, limiting its effectiveness. Furthermore, the failure to sustain elimination efforts in target areas, particularly in rural and remote regions, impeded progress toward achieving goals (Pankhurst, 1966; Farvar et al., 1971; Teklehaimanot, 1986).

3.4 Current trends of malaria cases (2019-2022)

Despite on-going control efforts, Ethiopia has witnessed a troubling surge in malaria cases in recent years, marking a reversal of the declining trend observed until 2015 (Liu and Qin, 2023; WHO, 2023). Between 2016 and 2019, the number of confirmed malaria cases decreased by 47%. According to the Health Management Information System reports from 2016 to 2019, malaria-related admissions have significantly decreased. Particularly noteworthy is the decline observed in 2019, with only 15,307 admissions recorded compared to over 30,000 admissions in 2018. Similarly, malaria-attributed deaths have seen an annual decline. Deaths due to malaria were decreased by 58%, from 510 to 213 between 2016 and 2019. However, driven by the continued fallout of pandemic-related program disruptions, armed conflict, and displacement, Ethiopia experienced a 32.5% increase in confirmed malaria cases between 2021 and 2022, rising from 1.1 million to 1.5 million. As of 2023, reported malaria cases have increased by 150% and 120%, respectively, compared to the same periods in 2021 and 2022 (Nureye and Tekalign, 2023; WHO, 2023).

From 2019 to 2022, the number of reported malaria cases has shown a steady increase, indicative of the persistent challenges encountered in disease prevention and control efforts Figure 1 (WHO, 2023).

3.5 Malaria elimination roadmap in Ethiopia

In 2014, Ethiopia's Ministry of Health introduced a Malaria Elimination Roadmap, targeting the elimination of malaria by 2030. By expanding key interventions since 2005, including Long Lasting Insecticidal Net (LLIN) distribution and IRS, malaria cases have notably decreased. This encouraged the Ethiopia Ministry of Health aims for nationwide elimination by 2030 (Aregawi et al., 2014; MoHE, 2017; MOHE, 2021).

The roadmap delineates with global malaria elimination objectives. These objectives comprise reducing malaria incidence, eliminating malaria hotspots, preventing malaria resurgence, and sustaining elimination gains (World Health Organization, 2015; MoHE, 2017). However, Ethiopia currently faces challenges in malaria control, leading to the possibility of failing to achieve the 2030 elimination goal (Yalew, 2022). Identifying the impeding



hurdles and overcoming them requires extensive efforts and strategic improvements. Learning from past efforts and embracing innovative strategies can propel Ethiopia toward its goal of malaria elimination by 2030.

4 Challenges to malaria elimination in Ethiopia

4.1 Artemisinin resistance and single nucleotide polymorphisms

Artemisinin resistance, characterized by delayed parasite clearance following artemisinin treatment, has emerged in some regions of Ethiopia (Jaiteh et al., 2021; Fola et al., 2023). This resistance is associated with Single Nucleotide Polymorphisms (SNPs) in the parasite's genome, particularly the *kelch13* (K13) gene (Volkman et al., 2017).

The presence of the *P. falciparum* carrying the K13 622I mutation, associated with partial resistance to artemisinin, was detected in a significant proportion of samples (Fola et al., 2023). The 622I mutation had only been previously described in northwest Ethiopia, near the Sudan border in 2014 at 2.4% prevalence (Bayih et al., 2016); however, an increase of such mutation was reported in the same location to 9.5% (Alemayehu AA. et al., 2021). Noteworthy is that artemisinin-based combination therapy (ACT), specifically artemether-lumefantrine, has been the primary treatment for uncomplicated falciparum malaria in Ethiopia since 2004 (Ababa, 2004).

Several significant mutations were discovered in the *P. falciparum* multidrug resistance gene 1 (pfmdr1), including N86Y (wild), Y184F (mutant), and D1246Y (wild), as well as in other genes linked to lumefantrine resistance, the partner drug of artemisinin (Malmberg et al., 2013; Fola et al., 2023). A single case study reported a patient with *P. falciparum* malaria resistant to

Ethiopia's intended use of the longer half-life drug Dihydroartemisinin-Piperaquine (Russo et al., 2018).

4.2 Vector insecticide resistance

Mosquitoes, primarily *Anopheles* species, have developed resistance to commonly used insecticides, reducing the effectiveness of IRS and LLIN. In Ethiopia, resistance among vectors to insecticides has continued to rise despite the cessation of DDT spraying. *An. arabiensis* populations exhibit resistance to pyrethroids and organochlorine insecticides across much of the country. Additionally, wild populations of *An. arabiensis* have shown resistance to pyrethroid insecticides commonly used for net treatment (Messenger et al., 2017; Mekuriaw et al., 2019; Chanyalew et al., 2022; Demissew et al., 2022). Reduced susceptibility of *An. arabiensis* to malathion, pirimiphos-methyl, propoxur, and bendiocarb was also reported elsewhere. Knockdown resistance (kdr L1014F) was detected in all mosquito populations, with allele frequencies ranging from 42% to 91% (Alemayehu et al., 2017).

4.3 The spread of Anopheles stephensi

Since its detection in Djibouti in 2012, *An. stephensi* has spread to the Horn of Africa, including Ethiopia (Faulde et al., 2014). In eastern Ethiopia since 2016, additional locations of *An. stephensi* have been discovered in subsequent surveys (Balkew et al., 2020; Balkew et al., 2021). From 2021 to 2023, entomological monitoring in 26 urban areas revealed that *An. stephensi*, comprising 7.7%, was the second leading *Anopheles* species following *An. arabiensis* (79.5%). It has also continued to be identified in new areas for the first time in western Ethiopia, suggesting a possible on-going expansion of its distribution (Ashine et al., 2023).

Anopheles stephensi is a potent malaria vector in urban areas, thriving in artificial and contaminated water sources for breeding. Its spread poses a significant challenge to malaria control efforts. A high SNP was detected that confer resistance against insecticides (Acford-Palmer et al., 2023; Ashine et al., 2023; Whittaker et al., 2023). Every *An. stephensi* specimen gathered near Metehara exhibited resistance to all insecticides tested, including those utilized in IRS and LLINs (Teshome et al., 2023).

A study reported that all *An. stephensi* samples displayed resistance to carbamates, resulting in mortality rates of 23% for bendiocarb and 21% for propoxur. Moreover, adult *An. stephensi* exhibited resistance to pyrethroid insecticides, with mortality rates of 67% for deltamethrin and 53% for permethrin. Additionally, resistance to DDT and malathion was evident, with mortality rates of 32%, alongside resistance to pirimiphos-methyl, with a mortality rate of 14%. Notably, these resistances were observed in the absence of the kdr L1014F and L1014S mutations, as well as the ace1R G119S mutation (Yared et al., 2020).

4.4 Histidine-rich protein deletion

The deletion of the histidine-rich protein 2 (HRP2) genes, poses challenges to malaria diagnosis (Jejaw Zeleke et al., 2022). The deletions of the Pfhrp2/3 gene undoubtedly affect the accuracy of malaria diagnosis. The deletion is found in multiple areas and rising (Girma et al., 2019; Golassa et al., 2020; Alemayehu GS. et al., 2021; Tafa et al., 2023) and it undoubtedly hampers the effectiveness of current malaria control and elimination efforts in Ethiopia (Golassa et al., 2020; Alemayehu GS. et al., 2021; Feleke et al., 2021). The study conducted in Adama, Ethiopia, reported 100% deletions in both the pfhrp2 and pfhrp3 genes. In the pfhrp2 gene, deletions extended to the flanking region gene 228 in 4% of samples, while the flanking region gene 230 displayed deletions in 22% of the samples. According to the study, 95% of samples showed deletions around pfhrp3 gene 475, while 40% exhibited deletions around pfhrp3 gene 485 (Golassa et al., 2020).

4.5 Rise of *Plasmodium vivax* in high altitude areas

Eliminating *P. vivax* poses significant challenges due to its ability to form dormant liver stages, causing relapses even after treatment. Targeting these dormant forms requires specialized approaches, making its elimination more challenging compared to other malaria species (Habtamu et al., 2022). In addition, the evolution of *P. vivax* to infect Duffy-negative red blood cells was reported in Jimma, Ethiopia. The report indicated that two out of 94 Duffy-negative patients tested positive for vivax malaria (Lo et al., 2015).

Traditionally considered less prevalent in high-altitude areas, *P. vivax* malaria is increasingly being reported in such regions of Ethiopia (Tadesse et al., 2018; Ketema et al., 2021). The unique biology of *P. vivax*, including its preference for cooler temperatures, presents challenges for malaria control and elimination efforts (Hulden and Hulden, 2011; Schäfer et al., 2021).

4.6 Malaria resurgence in previously low burden areas

Despite progress in malaria control, certain regions of Ethiopia that previously experienced low malaria burden are witnessing a resurgence of the disease. Factors contributing to this resurgence include population movement, ecological changes, and weakened healthcare infrastructure (DePina et al., 2018; Endo and Eltahir, 2020; Ewnetu and Lemma, 2022).

5 Perspectives against the challenges

5.1 Case studies: successful malaria elimination strategies

In recent years, remarkable strides have been made in the global fight against malaria, with several countries showcasing successful elimination efforts. Among these exemplars, Azerbaijan, Tajikistan, Belize, El Salvador, and Cabo Verde stand out for their effective strategies in eliminating malaria and certified malaria free by WHO in 2023 (WHO, 2023).

Azerbaijan achieved malaria elimination after years of dedicated control initiatives. Central to its success was a robust commitment from political leaders to prioritize malaria elimination. The country implemented comprehensive vector control programs, ensuring access to healthcare services even in remote areas, and engaged in collaborative efforts with neighboring nations to combat crossborder transmission (Mammadov et al., 2016; Li et al., 2023; WHO, 2023; World Health Organization, 2023).

Tajikistan, has accomplished malaria elimination through strengthened surveillance systems, targeted interventions, crosssectoral collaboration, and active community participation (Matthys et al., 2008; Kondrashin et al., 2017; WHO, 2023). Belize eliminate malaria via strategic planning, active case detection, vector control, and cross-border collaboration were instrumental in its success (Roberts and Rodriguez, 1994; World Health Organization, 2021; WHO, 2023).

El Salvador, eliminate malaria, propelled by strong political will, enhanced surveillance systems, integrated vector management, and health system strengthening efforts (Bennett and Smith, 2018; Burton et al., 2018; Gardellini et al., 2023; WHO, 2023). Meanwhile, Cabo Verde, an island nation off West Africa's coast, attained malaria elimination certified in 2023, leveraging its geographic isolation, integrated surveillance and response systems, health promotion, and cross-sectoral collaboration (DePina et al., 2018; DePina et al., 2019; WHO, 2023; Kokori et al., 2024).

These case studies underscore several key lessons applicable to Ethiopia's malaria elimination efforts, including the importance of strong political commitment, integrated approaches, crosssectoral collaboration, and community participation. By adopting evidence-based strategies and leveraging successful experiences, Ethiopia can accelerate progress toward its goal of malaria elimination by 2030.

5.2 Strengthening healthcare infrastructure

In Ethiopia, the cornerstone of malaria elimination lies in augmenting healthcare infrastructure to ensure universal access to diagnosis and treatment services. This comprehensive endeavor encompasses upgrading health facilities with improved infrastructure, equipment, and personnel training. Additionally, it involves the critical aspect of human resource development, with a focus on training and deploying more healthcare workers, especially in rural and underserved regions. Furthermore, effective supply chain management is imperative to guarantee a consistent flow of essential malaria commodities, including diagnostic tests and antimalarial drugs, thus preventing stock outs and ensuring uninterrupted service delivery.

5.3 Enhanced surveillance and monitoring systems

The implementation of robust surveillance and monitoring systems is vital for detecting malaria cases, tracking transmission trends, and guiding targeted interventions. This involves the establishment of real-time reporting mechanisms to facilitate prompt data collection, analysis, and response to malaria outbreaks and hotspots. Active case detection activities, such as communitybased surveillance and mobile health units, should be deployed to identify and treat malaria cases promptly. Furthermore, sentinel site surveillance networks should be established to monitor drug resistance, vector behavior, and malaria transmission dynamics in high-risk areas, enabling proactive intervention strategies.

5.4 Community engagement and education

Engaging communities and raising awareness about malaria prevention and control measures are pivotal for fostering behavior change and ownership of elimination efforts. To achieve this, targeted health education campaigns should be conducted to promote the use of preventive measures. Mobilizing community leaders, volunteers, and local organizations is essential to actively participate in malaria control activities, including environmental clean-up campaigns and distribution of preventive tools. Innovative communication strategies, such as radio broadcasts, community-theater, and mobile messaging, should be employed to disseminate malaria-related information and encourage positive health behaviors.

5.5 Vector control strategies

Conducting targeted campaigns to eliminate mosquito breeding sites and reduce vector density in malaria-endemic areas is vital. Additionally, distributing LLINs to vulnerable populations, particularly pregnant women and children, provides personal protection against mosquito bites. Implementing larval source management interventions, such as environmental modifications and biological control measures, further reduces mosquito breeding habitats and larval populations, contributing to overall vector control efforts.

5.6 Drug resistance prevention

Managing drug resistance and exploring alternative treatment options are critical components of malaria elimination strategy. Monitoring drug efficacy through therapeutic efficacy studies and molecular surveillance helps detect emerging resistance patterns and guides treatment policies. Promoting treatment adherence and the utilization of ACTs ensures effective treatment and helps prevent the spread of drug resistance.

5.7 Introducing malaria vaccine

Introducing the RTS,S/AS01 malaria vaccine, currently utilized in countries like Ghana, Kenya, Malawi, and Tanzania, could be a significant breakthrough for Ethiopia's malaria elimination efforts. This vaccine has shown promise in reducing malaria cases among young children, providing an additional tool in the fight against the disease. By incorporating RTS,S/AS01 into its malaria control strategies, Ethiopia can bolster its efforts to achieve elimination targets and improve public health outcomes.

6 Conclusion

Ethiopia continues to tackle with a significant burden of malaria, especially in lowland regions where transmission rates remain high. Recent years have witnessed a concerning uptick in malaria cases, underscoring persistent challenges in control efforts, exacerbated by factors like climate variability and limited access to preventive measures and healthcare services. Despite these successes, Ethiopia faces overwhelming challenges, including drug and vector resistance, diagnostic limitations, and the emergence of Plasmodium vivax in high-altitude areas, alongside malaria resurgence in previously low-burden regions. Mobilizing communities and raising awareness through targeted health education campaigns. In addition, intensifying vector control strategies to reduce mosquito populations and interrupt transmission. Likewise, managing drug resistance effectively through monitoring, promotion of combination therapies, and research should be reinforced. Furthermore, fostering innovations in diagnostics and treatment to enhance malaria case management and surveillance should be strengthened. By implementing these recommendations in a coordinated and sustained manner, Ethiopia can conquer the challenges of malaria elimination and work toward a malaria-free future.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

DW: Conceptualization, Formal analysis, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing, Supervision. YT: Methodology, Supervision, Writing – review & editing. AM: Project administration, Supervision, Writing – review & editing. ET: Conceptualization, Writing – review & editing. KM: Project administration, Writing – review & editing. WA: Methodology, Writing – review & editing. WA: Methodology, Writing – review & editing. KB: Methodology, Writing – review & editing. HG: Methodology, Writing – review & editing. MS: Writing – review & editing, Project administration. MT: Conceptualization, Project administration, Supervision, Writing – review & editing.

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Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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