Drug Resistance in Malaria: A Public Delinquent in Low and Middle-Income Countries

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Antimalarial, Agents, Resistance, Mosquito-Borne, Disease, Malaria, Fever, Public Health, Offender, LMICs, Global.

Malaria is considered a disease of poverty [1].

Malaria has affected humans from the Neolithic period, or the New Stone Age [7000 to 1700 Before the Common/ Current Era (BCE)] [2-4]. There is substantiation that malaria was present in different community classes, and, indeed, George Washington, Cesare Borgia, Albrecht Dürer, and Christopher Columbus all underwent this mosquito-borne disease [5-7]. Even Alexander the Great passed away, most possibly because of malaria or typhoid fever or West Nile encephalitis, after suffering from febrile illness for 2 weeks in the city of Babylon on June June 10, 323 BCE [8-10]. It has been reported that around the 3rd century BCE, malaria [11,12,] typhoid fever [13,14,] or West Nile encephalitis were [9] common diseases in Babylon [15,16]. Even today, malaria is common in Iraq and the Middle East Region [17, 18].

Malaria remains a deadly public health issue in Low and Middle Countries of tropical countries [19,20]. World Health Organization reported that "there were 249 million cases of malaria in 2022 compared to 244 million cases in 2021. The estimated number of malaria deaths stood at 608 000 in 2022 compared to 610 000 in 2021 [21]." Nigeria (26.8%), the Democratic Republic of the Congo (12.3%), Uganda (5.1%), and Mozambique (4.2%) account for more than 50% of global deaths [22]. International and African continent deaths from malaria in 2022 by country are depicted in Figures 1 and 2, respectively [23]. WHO reported in 2020 that the mortality caused by malaria was 45 or 0.01% of global deaths in Bangladesh. The age-adjusted fatality frequency is 0.03 per 100,000 of the population. After that, globally, Bangladesh ranks 61 regarding malaria-caused deaths [24]. Furthermore, malaria is one of the predominant causes of death in developing countries [25,26], especially in Sub-Saharan Africa

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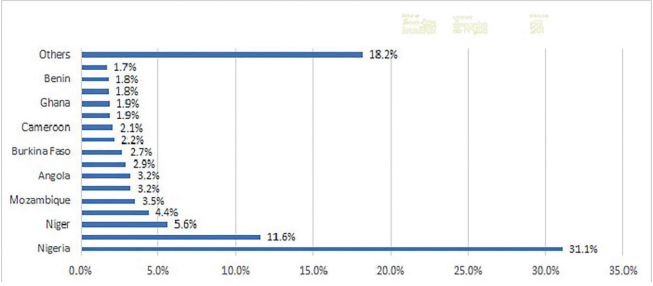

Figure 1: Illustrated Country-Wise Global Death due to Malaria in 2022.

Image Credit: Kona Chowdhury.

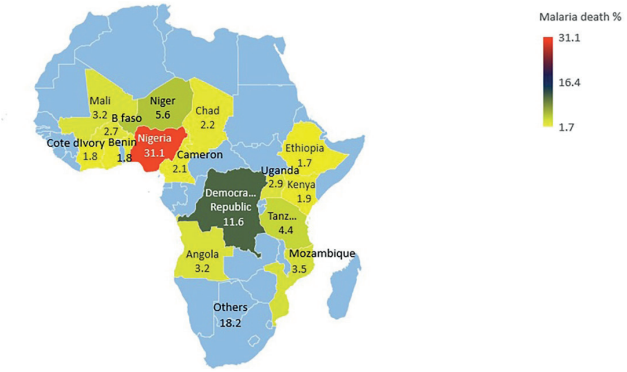

Figure 2: Clarified Death in African Continent due to Malaria in 2022.

Image Credit: Kona Chowdhury.

[27-30]. Nearly one child dies every minute because of Malaria. In 2022, childhood death comprised 76% of total mortality due to this parasitic disease [31].

Malaria often involves kidney [32], liver [33,34], spleen [35,36], and brain [37]. Involvement of any of these organs ended in fatal clinical outcomes. The principal pathology of such severe complications is not well comprehended [38]. Plasmodium falciparum is considered the most lethal among malarial parasites [19, 39,40]. However, multiple studies reported that vivax malaria is developing as a possibly severe malarial infection related to a wide-ranging clinically complex situation and considerable alteration in laboratory indicators denoting a severe form of disease manifestation [41-44]. Multiple studies revealed that cerebral malaria has consistently disastrous clinical outcomes [45,46]. A case fatality rate (CFR) was 15-50% [47]. Another study detected that cerebral malaria causes 20% and 15% of grownup and childhood mortality, respectively [48]. One more study revealed that CFR among pediatric cases of cerebral malaria CFR was CFR ranges from 6-50% [49].

The earliest effective pharmacological intervention, a juice brought out of the aril of the South American cinchona tree, was introduced to Europe by a Roman Catholic Priest named Brother Agostino Salumbrino (1561–1642) sometime amid 1620 and 1630. He was trained as an apothecary [50,51]. Cinchona bark's active antimalarial component was quinine. Cinchona bark fluids administration intravenously was the lone efficient antimalarial medication till 1820. In 1820, the component quinine was discovered [52-54]. The earliest man-made antimalarial two agents (pamaquine and mepacrine) emerge from Germany in the 1920s and 1930s during the First Great War [52,55-57]. The most widely used antimalarial medicine, chloroquine, was synthesized by Johann Andersag (1902-1955) in 1934. He is also known as Hans Andersag and is employed at Bayer IG Farbenindustrie in Elberfeld, Germany. [58,59]. A list of antimalarial medicines discovered is depicted in Table 1.

Serial Number	Medicine Name	Synthesized or Marketed Year	Resistance Developed Year
	Quinine	1820 [60]	1910 [61]
	Mepacrine	1928 [62]	1946 [63]
	Chloroquine	1934 [59]	1989 [64]
	Mefloquine	1984 [65]	1990 [65], 1988 [66]
	Halofantrine	1988 [67,68]	1992 [69,70]
	Artemisinin	1972 [71-74]	2009 [75,76]
	Amodiaquine	1948 [77]	1987 [78]
	Piperaquine	1968 [79,80]	2014 [81]
	Lumefantrine	1976 [82]	2016 [83]
	Pyronaridine	1973 [82]	1988 [84,85]
	Naphthoquine	1986 [82]	2013 [86,87]
	Proguanil	1945 [88,89]	1948 [66]
	Primaquine	1952 [90]	No Genetic Yet Discovered [91]
	Atovaquone	1991 [92]	2002 [93]
	Pyrimethamine	1953 [94]	1962 [66]
	Sulfadoxine	Early 1960s [95]	1994 [96]
	Tafenoquine	2018 [97]	No Genetic Yet Discovered [91]
	Sulfadoxine + Pyrimethamine	1977 [98]	1979 [99]

"Malaria is a difficult disease to control largely due to the highly adaptable nature of the vector and parasites involved [95]."

Malarial parasites have a byzantine life process. Yet malarial infection and the immune response of infected

individuals remain in cloak-and-dagger. Malarial parasites are also inherently convoluted and possess the talent to yield large numbers of effectual antigens [47,100,101]. For over 100 years, malarial parasites have successfully developed resistance against antimalarial medicine [61]. World Health Organization (WHO) has demarcated antimalarial resistance "as the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within the tolerance of the subject "in 1967 [102-104]. Multiple factors determine the development of antimalarial drug resistance among malaria parasites, e.g., *P. falciparum* and *P. vivax,* giving rise to the considerable health hazard [105]. Those include poor diagnosis skills, excessive and imprudent use of antimalarial medicine, inadequate or incomplete therapeutic interventions of active infections, and low-dose antimalarial agents prescribing compared to clinical need. Moreover, it has been observed that malarial parasites have the mastery to modify their genetic and metabolic levels to develop resistance progressively against antimalarial medicine. Additionally, these parasites have an immense reproduction power that empowers resistance among selected populations to spring up comparatively in jet-speed [106].

Currently, *Plasmodium falciparum* has progressed to resistance to all categories of antimalarial medication, including artemisinin and its' cognate and combination agents with artemisinin or its derivative [107-109]. Other malarial (*Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale curtisi, P. ovale wallikeri* , and *Plasmodium knowlesi*) [110] species affecting human are mostly more sensitive to antimalarial agents than *P. falciparum* [111, 112], although widely reported *P. vivax* resistance towards antimalarial agents including antifolates [113,114]. Multidrug-resistant (MDR) *Plasmodium vivax* and *P. falciparum* malaria progression is increasing at a disquieting degree around the globe [115,116] and has relentless adverse health consequences [117,118], especially among LMICs [119,120]. Pan American Health Organization interprets MDR malaria as resistance to in excess of two antimalarial medicines of non-identical chemical categories [121]. Antimalarial medicine-resistant malaria is responsible for inculpating new geographical areas to spread and revive drug-resistant malaria in those countries where it has been eradicated, mainly tropical and subtropical countries [122]. Resistance against antimalarial agents increases the possibility of an epidemic and a more severe form of malaria [123,124]. Genetic mutations in mosquito-borne malarial parasites are the principal cause of antifolate antimalarial medicine, like chloroquine [125]. It has been reported that six different genes of *Plasmodium falciparum* (*crt, mdr1, dhfr, dhps, ATPase6,* and K-13 propeller) that deliberate resistance to chloroquine, sulphadoxine-pyrimethamine and artemisinin-based combination [126]. Globally, especially in LMICs, there are not many initiatives to control vectors, probably because of poor allocation for preventive healthcare [127,128].

The currently available antimalarial agent's efficacy must be maintained to avoid fatal clinical because of multidrug-resistant malaria (*Plasmodium vivax* and *P. falciparum*) [129,130]. "Mathematical modeling" [123] put forward that administering multiple first-line therapies (MFT) in combination can decelerate the speed of mushrooming MDR malaria [130-132]. It has been reported that a good number of malaria-endemic countries use MFT combination therapy in their policy strategies to retain available antimalarial agents' efficacy [133,134]. Multiple studies reported that antimalarial medications should be prescribed prudently only for confirmed diagnosed cases, and stringent policy should be implemented to curtail haphazard and irrational antimalarial prescribing practices [109,135-137]. There is an urgent need for research and development of novel, inexpensive antimalarial medicine [138,139].

Nevertheless, whilst novel antimalarial research and development goes successfully. These medications to be available in the market will take the next couple of years, and we trust those upcoming antimalarial treatments will have high costs [130, 140]. Additionally, newly developed antimalarial should be highly effective, the low outline of adverse drug reactions, safety profile in pregnancy and pediatric cases well documented, minimum dosing schedule, low cost both individual and community, and have little tendency to acquire resistance [141]. The development of resistance among microbes is a natural phenomenon [142,143]. After being marketed, the pipeline of novel antimalarial drugs will develop resistance because of selective drug pressure by the unnecessary or imprudent use of new agents in healthcare and agricultural locales [124,144]. The only answer remains to combat resistance to develop and implement strict health and drug policies regarding imprudent prescribing of available medicine.

Public and private healthcare authorities should also take the initiative to build awareness to stop irrational prescribing of antimicrobials, including antimalarial medication.

CONSENT FOR PUBLICATION

The author reviewed and approved the final version and has agreed to be accountable for all aspects of the work, including any accuracy or integrity issues.

DISCLOSURE

The author declares that they do not have any financial involvement or affiliations with any organization, association, or entity directly or indirectly related to the subject matter or materials presented in this editorial. This includes honoraria, expert testimony, employment, ownership of stocks or options, patents, or grants received or pending royalties.

DATA AVAILABILITY

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AUTHORSHIP CONTRIBUTION

All authors contributed significantly to the work, whether in the conception, design, utilization, collection, analysis, and interpretation of data or all these areas. They also participated in the paper's drafting, revision, or critical review, gave their final approval for the version that would be published, decided on the journal to which the article would be submitted, and made the responsible decision to be held accountable for all aspects of the work.

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