INFECTIOUS DISEASES

Giovanni Battista Grassi (1854-1925): a forgotten Italian scholar and his fundamental studies on malaria

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Keywords

Giovanni Battista Grassi; history of malaria; infectious diseases; tropical diseases, Charles Louis Alphonse Laveran

Summary

A century ago, on May 4, 1925, an Italian doctor, zoologist, botanist, and entomologist Giovanni Battista Grassi (1854-1925) died in Rome. He was known for his studies on malaria, and he was one of the founders of the "Italian school of malariology". At that time malaria was a main problem in the colonies for the military and in the tropics is a common disease that causes high fever and other symptoms. When the French chemist Louis Pasteur published his germ theory in the 1860s, scientists began to consider that an organism, might be responsible for the malaria disease and the breakthrough came in 1880 with Alphonse Laveran (1845-1922). It was therefore clear that many diseases are caused by microorganisms, and several scholars began to assume that also malaria was caused by a bacterium. Laveran recognized the parasite group that caused the infection in human beings; however, his studies were challenged. In 1889 Laveran showed that malaria is caused by another type of single-celled organism, a protozoan of the Plasmodium family, which attacks red blood cells and also identified other single-celled parasites that cause other diseases: there are four main types of malarial infection caused by four species of parasite plasmodium. In 1898 Grassi began a study that represented a turning point in the study and treatment of the disease. The authors aim to retrace the main steps in the historical evolution of this dangerous, infectious disease and they believe it's important to evoke the scientific personality of the Italian scientist Grassi who is one of the protagonists in the history of medicine and zoology between the 19th and 20th centuries, mainly because of his famous research, about the identification of the vector of human malaria.

Background

Exactly 100 years ago, on May 4, 1925, Giovanni Battista Grassi (1854-1925) (Fig. 1), an Italian doctor, zoologist, botanist and entomologist, known for his studies on malaria, died in Rome.

Grassi was among the scholars who founded the Italian school of malariology, which, after the discovery by the French doctor and army officer working in Algeria Charles Louis Alphonse Laveran (1845-1922) [1, 2] of the protozoan responsible for the infection in the red blood cells of malaria patients, played an important role in the study and prevention of this disease [3].

In 1907, Laveran (Fig. 2) was awarded the Nobel Prize for Medicine for his discovery [4, 5] and established the Laboratory of Tropical Diseases at the Pasteur Institute. In the year following (1908) he also founded the *Société de Pathologie Exotique*.

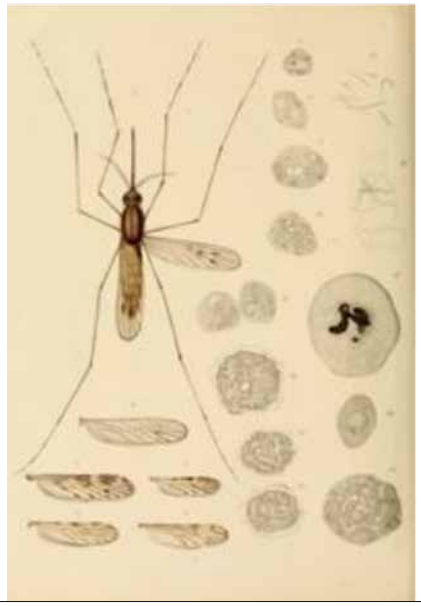
Between the end of the 19th century and the mid-20th century, malaria was endemic in Italy [6]. In the northern regions of the country, except for the coastal areas of Veneto, a mild form of the disease prevailed, while an extremely severe form raged in the southern regions and on the islands. In the Kingdom of Italy, the first public health statistics, which were published in 1887, revealed that malaria was endemic in approximately one third of the country, causing 21,033 deaths – a mortality rate of 710 cases per million inhabitants [7]. In the following decade, malaria killed 15,000 people per year [8]

Fig. 1. Giovanni Battista Grassi (Public Domain - Wikipedia commons).

https://doi.org/10.15167/2421-4248/jpmh2025.66.2.3642

Fig. 2. Charles Louis Alphonse Laveran (Public Domain. Wikipedia commons).

Fig. 3. Original drawing by G.B. Grassi illustrating the cycle of malaria transmitted by the *Anopheles* mosquito (G.B. Grassi, *Studi di uno zoologo sulla malaria*).



and constituted one of the most serious public health problems in Italy at the time [9]. This was the context in which G.B. Grassi worked.

After graduating in Medicine in Pavia, Grassi became a professor of zoology, anatomy, and comparative physiology at the University of Catania in 1883, where he began to study malaria in birds. In 1890 he published the monograph "*Ueber die Parasiten der Malaria"* (On Malaria Parasites) in the journal "Zentralblatte für Bakteriologie und Parasitenkunde" (Central Journal of Bacteriology and Parasite Science), in which he described the malarial cycle in various species of birds, such as the owl, the pigeon and the sparrow [10].

In 1895, Grassi was appointed Professor of Comparative Anatomy at La Sapienza University in Rome. "In Rome, Grassi came into contact with the group of Roman malariologists, who convinced him of the validity of the transmission of *Plasmodium* via a hematophagous insect, a hypothesis he had until then considered doubtful. The problem was to identify the incriminated insect with certainty" [11, 12].

Subsequently, on studying the case of a patient at the Roman hospital of Santo Spirito in Sassia, together with Amico Bignami and Giuseppe Bastianelli, Grassi managed to demonstrate in 1898 that malaria was transmitted by mosquito bites. On 22 December 1898, he sent a communication to the Accademia dei Lincei in which he described the entire development cycle of *Plasmodium* in the body of *Anopheles claviger* [13]. Thus, the enigma of malaria transmission was solved.

Between 1898 and 1899, by mapping all the mosquito species present in the malarial and non-malarial areas of Italy, Grassi was able to correlate the presence of malaria with a specific genus of mosquito: only *Anopheles* could act as a vector of the human malarial parasite [14]. In this way, Grassi paved the way in the fight against malaria. In his volume *Studi di uno zoologo sulla malaria (A Zoologist's Studies on Malaria)* [15], which was published in 1900 by the *Reale Accademia dei Lincei*, Grassi summarized all the procedures and conclusions of his years of study on the *Anopheles* mosquito and on *Plasmodium* (Fig. 3).

However, his glory was overshadowed and, according to some, usurped by another scholar, the English doctor Ronald Ross (1857-1932). A few years earlier, in 1894, Patrick Manson (1844-1922), who is regarded as the father of tropical medicine, and to whom Grassi had dedicated his volume "*A Zoologist's studies on Malaria*", had hypothesized that mosquitoes played a fundamental role in the transmission of malaria [16].

He had therefore asked his colleague Ronald Ross to examine this thesis. Thus, in 1897-98, while in India, Ross found that an avian *Plasmodium* was transmitted by mosquitoes and hypothesized that human malaria also had a similar cycle.

In the first issue of the *Annales de l'Institut Pasteur* in 1899, Ross published an article entitled *"Calcutta, 31st December 1898: Du rôle des moustiques dans le paludisme (the role of mosquitoes in malaria"* [17].

The vector responsible for the transmission of the disease was indicated as a "moustique d'une nouvelle espèce" ("mosquito of a new species"): a "gray" or "spotted-winged" mosquito, names that are absolutely invalid in terms of Linnaean nomenclature. Not being a zoologist, Ross was obviously unfamiliar with zoological systematics, which Grassi knew very well.

Ross, however, was unable to demonstrate that malaria was transmitted to humans by mosquito bites, nor to establish that only one genus of mosquito, *Anopheles*, could act as a vector of the human malarial parasite, phenomena

which were ascertained by Amico Bignami, Giuseppe Bastianelli and Giovanni Battista Grassi. Indeed, in both humans and mosquitoes, these three Italian researchers described the developmental cycle of the three species of malarial parasites present in Italy [14].

The issue gave rise to a heated controversy between Grassi and Ross, who was awarded the Nobel Prize for Medicine in 1902 "for his work on malaria, by which he has shown how it enters the organism, and thereby has laid the foundation for successful research on this disease and methods of combating it" [18].

It has even been suggested that an English doctor, Thomas Edmonston Charles (1834-1906), who had visited the laboratories of Grassi and the other malariologists at the *Santo Spirito Hospital* in the period 1897-1898, may have reported to Ross the information that he had gathered there. When the dispute arose as to who had first discovered the vector responsible for the transmission of malaria, Ross made public the letters he had received from his colleague Charles [19].

At the end of 1900, Ross launched a defamatory campaign against the three Italian biologists, claiming that he was the first to discover the mechanism of transmission of malaria, in an attempt to bolster his chance of winning the Nobel Prize. Grassi reacted harshly to the accusations, which, in his opinion, cast doubt on his honor as a scientist. The true nature of the dispute, however, lay in the different ways of approaching research; Grassi's method was characteristic of zoological research – systematic, comparative and experimental – while the approach adopted by Ross was empirical and intuitive. Most probably, we can assert that Ross was the first to conclude that mosquitoes transmitted malaria, while Giovanni Battista Grassi was the first to identify *Anopheles* as the vector of the disease.

Considering this dispute, the Royal Swedish Academy of Sciences wanted to share the prize, but decided to seek arbitration and appointed the great German scientist Robert Koch (1843-1910) as the arbitrator. Unfortunately for Grassi, however, Koch did not prove to be unbiased. Indeed, he did not look favorably upon the Italian scholar, with whom he had argued in the spring of 1898, when he was in Maremma (Tuscany, Italy) to conduct his own studies on malaria.

On that occasion, Grassi had expressed his disagreement with the analytical methods of the German microbiologist. And so it was that the Nobel Prize was awarded only to Ronald Ross, who did not even mention Grassi and his studies in his acceptance speech.

This decision by the Royal Swedish Academy of Sciences was not accepted by Grassi, who decided to abandon his studies on malaria and devote himself to other research topics, only returning to the study of malaria at the end of the First World War, when the disease displayed a severe resurgence. Indeed, owing to the direct and indirect consequences of the war, deaths from malaria rose from 57 per million inhabitants in 1914 to 105 in 1915, to 237 in 1917 and to 325 in 1918 [20].

-Faced with this situation, Grassi resumed his research and in 1918 founded a "Malaria Observatory" in Fiumicino, in the river Tiber delta, where he carried out research on the flying habits of mosquitoes and on the incidence of malaria in the area. He suggested methods of disease control, initiating anti-malaria prophylaxis and saving the lives of hundreds of farmers and workers [21]. He also studied the populations of *Anopheles* in the Naples area, in the Province of Lucca and near Pavia, where the presence of *Anopheles claviger* was not accompanied by malaria. This research enabled him to ascertain the existence of a species of *Anopheles* that does not bite humans but only animals.

Grassi died in 1925, just as Paris Green was beginning to be used against malaria in Italy and Achille Sclavo [22], President of the Italian Association for Hygiene, returned to the subject of malaria in Sardinia by inaugurating the third National Congress on Hygiene [23]. In fact, in 1910, with the pathologist Alessandro Lustig (1856-1937), Sclavo had been the head of the first anti-malaria campaign in Sardinia, promoted by the Government as part of National Healthcare Policies for the prevention of infectious diseases. The campaign supported the reorganization of healthcare with doctors assigned to therapy and prophylaxis by means of State Quinine, but also gave rise to environmental remediation works and hygiene education [24, 25].

Also in 1925, the Italian Association for Hygiene printed its "*People's Instructions against Malaria*", which recommended specific rules of hygiene [26] in order to prevent the disease and the use of quinine [27], to be administered also through "painless injections", as stated in the advertisements for "Gelochin", which was produced by the Tuscan Serotherapy Institute (Fig. 4).

In these few pages of instructions, we can discern the thought of the great hygienist Sclavo, whose note to the text read: "It is strongly recommended that the Municipalities where malaria is present should distribute these instructions widely, especially among Elementary School children, and charge teachers to explain them and to demonstrate, also through visits and experiments, the appropriate means of fighting malaria" [28, 29].

Sclavo was a great believer in so-called "bottom-up education", whereby the young would carry the message of good practices to their elders, parents and relatives, who would then recognize the importance and usefulness of such practices.

In the hundred years that have passed since Grassi's death, Italy and many other countries have been declared free from malaria [30].

From 1944 onwards, the results yielded by the use of DDT (dichlorodiphenyltrichloroethane) were fundamental. When sprayed into the environment, DDT proved effective in reducing the mosquito population and the level of disease transmission [31].

Considerations on the current situation of malaria in the world

Nevertheless, malaria continues to claim lives, though encouraging data are being recorded in many areas [32].

Fig. 4. Advertisement for Gelochin, produced by the Tuscan Serotherapy Institute (Archive of the Gruppo Amici Sclavo).

Indeed, in the 25 years since 2000, approximately 2.2 billion cases of malaria and 12.7 million deaths have been avoided as a result of health policies [33]. In the same period, 44 countries and one territory have been certified as malaria-free [34].

Most recently, in October 2024, Egypt was officially declared malaria-free by the World Health Organization (WHO) (Fig. 5).

However, malaria remains a serious threat to public health, as is demonstrated by the highly significant figures released by the World Health Organization in its *2024 World Malaria Report* [35]. Indeed, 263 million cases of malaria were estimated in 2023.

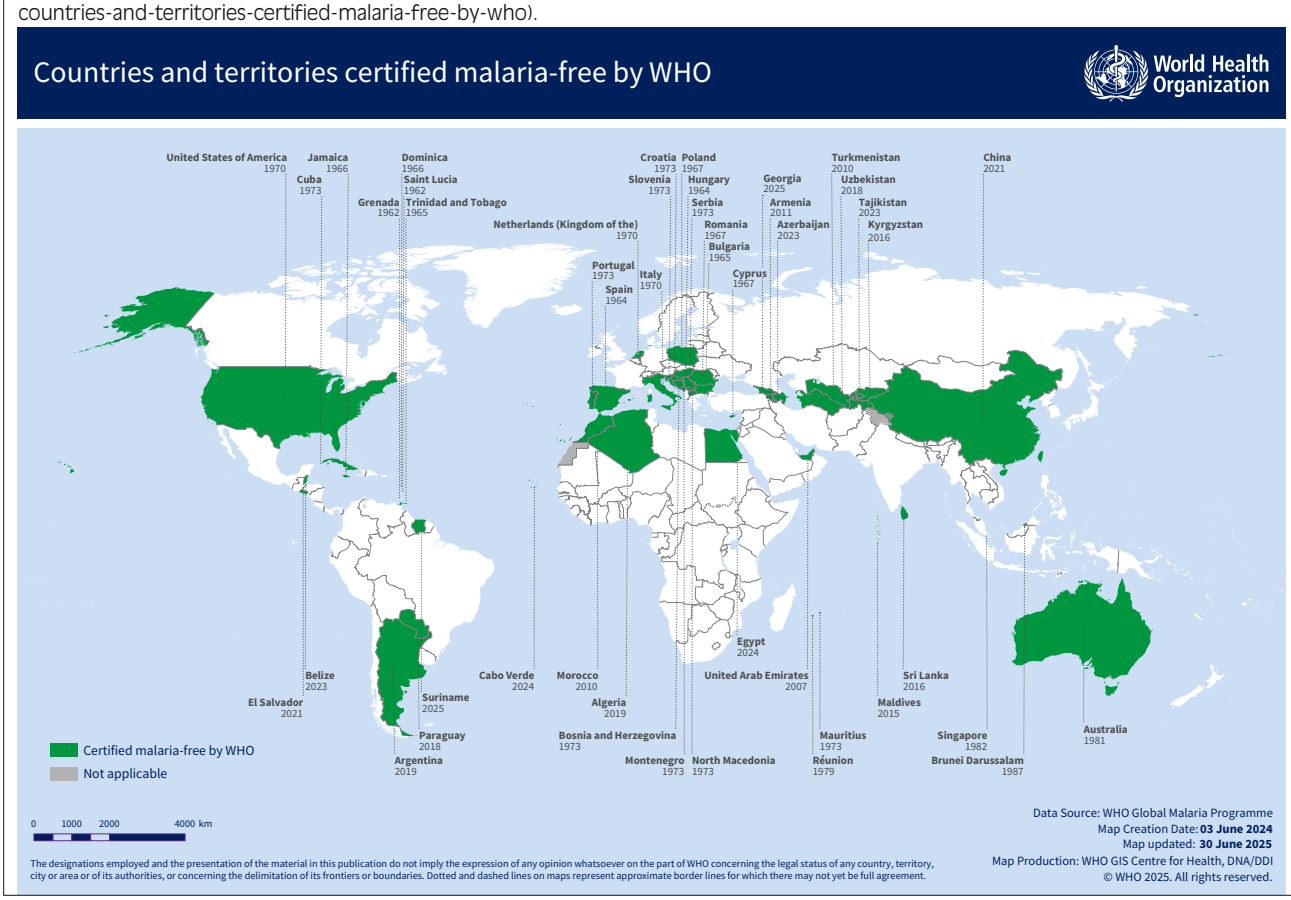
This figure is even more significant in view of the fact that 11 million fewer cases were recorded in 2022. "The WHO African Region continues to carry the heaviest burden of the disease, accounting for an estimated 94% of malaria cases worldwide in 2023" [35].

The five countries with the highest estimated burden of malaria cases in 2023 are listed in the Table I.

Regarding the number of deaths from malaria, the global figure for 2023 is estimated at 597,000, with a mortality rate of 13.7 per 100,000 inhabitants.

The epidemiology of malaria in endemic countries, combined with population movements and international travel, explains the percentage of imported malaria cases in European countries, where malaria has been eradicated

Fig. 5. Countries and territories certified malaria-free by WHO, 2025 (https://www.who.int/teams/global-malaria-programme/elimination/countries-and-territories-certified-malaria-free-by-who).



Tab. I. The five African countries with the highest estimated cases of malaria in 2023 (Data from WHO. World malaria report 2024, available at: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2024).

Country	Estimated burden of malaria cases in 2023 (%)
Nigeria	26%
The Democratic Republic of the Congo	13%
Uganda	5%
Ethiopia	4%
Mozambique	4%

since the 1970s. In these countries, too, the disease constitutes a serious threat to individual and public health. In Italy, "a total of 4,372 cases were reported in the years 2017-2023, with an annual average of 624 cases. The most frequently affected category is that of immigrants legally resident in Italy returning from trips to their countries of origin to visit family members" [36].

Based on these data, *"The Global technical strategy for malaria 2016-2030 (GTS) and Sustainable Development Goal 2025 and 2030 targets for malaria morbidity and mortality are unlikely to be met, as the 2023 global malaria incidence is nearly three times higher than needed to reach the target. Although malaria mortality has decreased, it remains more than twice the target level*" [35].

Indeed, the main objective of the World Health Organization is to significantly reduce the incidence and mortality of malaria, achieving by 2030 a reduction of at least 90% in the numbers of cases and deaths recorded in 2015. Specifically, the WHO's 2016-2030 Global Technical Strategy for Malaria aims to eliminate malaria in at least 35 countries by 2030 (Fig. 6).

To achieve these goals, it is essential to reduce malaria transmission by controlling the vector. Indeed, the main measures implemented focus on reducing contact between mosquitoes and humans. However, it should be pointed out that the increasing global temperatures and changes in rainfall patterns create favorable conditions for the proliferation of *Anopheles* mosquitoes, the vector of the *Plasmodium falciparum* parasite.

This means that previously unaffected areas are becoming vulnerable, while endemic areas are seeing an extension of the transmission period and a potential increase in cases.

New avenues are therefore opening up in the fight against malaria, and these could have an even greater impact than the use of DDT in the middle of the 20th century, which enabled us to combat malaria throughout the world [37].

The use of vaccines and new pesticides, but above all the genetic manipulation of mosquitoes, could yield decisive results, bringing us closer to the goal of eradicating the disease.

With regard to vaccines, the turning point came in 2021, when the World Health Organization recommended the first malaria vaccine (RTS,S/AS01, also known as Mosquirix) for children in sub-Saharan Africa and other regions with moderate-to-high transmission of malaria due to *Plasmodium falciparum* [38].

Indeed, children are particularly vulnerable; the WHO estimates that approximately 432,000 children died of malaria in 2023 in Africa alone, the continent most severely affected by this disease.

A critical factor in successful vaccine implementation is community acceptance [39].

A recent literature review has suggested that acceptance of the RTS,S malaria vaccine is high in low- and middle-income countries, with an average acceptance rate of 95.3% [40].

In October 2023, the WHO added a second malaria vaccine, R21/Matrix-M, to the list of pre-qualified vaccines, in order to expand access to malaria prevention through vaccination [41].

Plasmodium falciparum, a parasite that changes shape during its life-cycle

Malaria has been present since ancient time and remains

Fig. 6. Goals, Milestones and Targets for the 2016-2030 Global Technical Strategy for Malaria (WHO. Global technical strategy for malaria 2016-2030, 2021 update, 19 July 2021 (https://www.who.int/publications/i/item/9789240031357).

AIM & GTS for Malaria Joint Vision: *a world free of malaria*			
Goals	Milestones		Targets
	2020	2025	2030
1. Reduce malaria mortality rates globally compared with 2015	At least 40%	At least 75%	At least 90%
2. Reduce malaria case incidence globally compared with 2015	At least 40%	At least 75%	At least 90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
4. Prevent resurgence of malaria in all countries that are malaria-free	Resurgence prevented	Resurgence prevented	Resurgence prevented

a major global health problem in developing countries. Human malaria is an ancient tropical disease caused by infection with protozoan parasites belonging to the genus *Plasmodium* and is transmitted by female mosquitoes of the genus Anopheles.

Although malaria has been known since ancient times, the protozoan responsible for the disease was identified in the blood of affected individuals only in 1880.

Among the various species of *Plasmodium* parasites, four are the most widespread. The most dangerous, however, is *Plasmodium falciparum*, which is responsible for most cases of human malaria worldwide (80%) and is deeply entrenched in tropical Africa [42] and is responsible for the highest mortality rate among infected subjects. *Plasmodium falciparum* is the etiological agent of malaria tropica, the leading cause of death due to a vector-borne infectious disease, claiming 0.5 million lives every year [43].

It lives and reproduces, in different stages, in human blood and in some species of mosquitoes belonging to the genus *Anopheles*.

When the mosquito bites a human, it inoculates sporozoites, the infectious forms of *Plasmodium*, which are able to evade the immune system.

The parasite develops inside the human organism. First, it reaches the liver, where it invades the hepatocytes. There, it multiplies by producing merozoites (pre-erythrocytic phase). It then infects the red blood cells, multiplying further (erythrocytic phase).

After a few cycles of asexual development, the *Plasmodium* produces gametocytes, sexuate forms of the parasite that remain in the blood of sick persons for a few weeks and are thus able to infect other mosquitoes that bite them.

The different gene expression of *Plasmodium* in different phases of its life-cycle [44] and the considerable polymorphism of its antigens constitute a major problem from the epidemiological standpoint; the different variants enable the parasite to evade the human immune system, making it difficult to target with vaccines and treatments.

While the vaccines currently in use block the replication of the parasite in the pre-erythrocytic phase, the latest studies aim to use the genetically attenuated whole sporozoite.

Is genetic mutation the solution to malaria?

In the early 2000s, genetic engineering techniques began to be used in an attempt to combat malaria. Genetic engineering may enable us to modify entire populations of mosquitoes and to control the transmission of malaria. One of the most futuristic techniques being studied involves modifying the DNA of mosquitoes in order to render them sterile. Some of the studies being conducted in this area aim to target a very specific gene in the mosquito genome.

The technology called "gene drive" enables the genome of an organism to be modified through the use of a "drive", usually an enzyme, that cuts the DNA at the genes involved in the transmission of the malaria parasite [45]. This mutation renders females sterile, as it prevents the formation of eggs. It has been predicted that introducing genetically modified mosquitoes into a population would halt its reproductive capacity within a few generations, resulting in the collapse of the population [46, 47].

This innovative genetic engineering technique may therefore be able to eliminate malaria-carrying mosquitoes permanently.

Another recent study has led scientists to create a genetically weakened version of the parasite, called GA2, which is unable to cause disease but capable of eliciting a robust immune response. When a genetically modified mosquito bites a human, the modified parasite reaches the liver, where, however, it develops more slowly than an unmodified *Plasmodium*.

This delay allows the immune system to recognize and fight the parasite, preparing the body to repel any future infections [48].

These and other possibilities may prove to be alternative preventive strategies that have the potential to improve protection against malaria and offer great hope of a definitive solution to this disease.

Data availability statement

Not applicable.

Informed consent statement

Not applicable.

Funding

This research received no external funding.

Conflicts of interest statement

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.

Authors' contributions

DO: conceived the study; DO & MM: designed the study; drafted the manuscript; performed a search of the literature; revised the manuscript; conceptualization and methodology; investigation and data curation; original draft preparation; review; editing. All authors have read and approved the latest version of the paper for publication.

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Received on June 10, 2025. Accepted on June 30, 2025.

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How to cite this article: Martini M, Orsini D. Giovanni Battista Grassi (1854-1925): a forgotten Italian scholar and his fundamental studies on malaria. J Prev Med Hyg 2025;66:E194-E201. https://doi.org/10.15167/2421-4248/jpmh2025.66.2.3642