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Portugal's prominence in malaria research

How a small country became a key player in European research on one of the world's deadliest diseases

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Despite a significant increase that started during the 1990s, Portugal's scientific production remains rather modest compared with the overall research output in the European Union (EU). However, the country's achievements in malaria research are truly remarkable and, in relative terms, far above its EU neighbors in most relevant accounts. The factors to explain this accomplishment include the fact that malaria was autochthonous in Portugal until 1973; the country's colonial history and its close ties with its former colonies; and several outstanding scientists who each inspired generations of malariologists.

> *"... there is one field of research where Portugal has been making significant contributions, even long before 1985: malaria."*

For most of the 20th century, research in Portugal was underfunded, and the country's overall contribution to science was modest at best. This started to change when Portugal joined the European Union (then the European Economic Community) in 1985 and gained further momentum in the 1990s with the creation of a dedicated Ministry of Science. As a consequence, the Portuguese scientific production increased significantly in terms of the number of scientific articles published. Nevertheless, public funding for research has remained well below that of many other EU countries, and far from the target of 3% of the country's GDP, which limits Portugal's overall scientific output. Yet, there is one field of research where Portugal has been making significant contributions, even long before 1985: malaria.

Among many other achievements, Portuguese laboratories have delivered important contributions to malaria research in areas as diverse as drug development, discovery and repurposing, genetic diversity of *Plasmodium* parasites, mechanisms of drug resistance, co-infection between *Plasmodium* and other parasites, host–*Plasmodium* interactions, nutrient sensing and acquisition by malaria parasites, modulation of *Plasmodium* liver infection, immune and inflammatory responses to *Plasmodium* infection, diagnosis, vaccines, the role of microbiota on malaria transmission, pathogenesis of placental and cerebral malaria and acute lung injury, mechanisms of tolerance to malaria, malaria epidemiology, and vector genetics (see Further Reading for examples). Portugal's percentage of scientific papers published in the field of malaria during the past decade relative to the total number of published articles is the highest in the EU (Fig 1A). Naturally, Portugal cannot compete with larger or more affluent countries in terms of the absolute numbers of articles published on malaria. Yet, the country ranks 5th in this regard, closely following the Netherlands, Belgium, Sweden, and Denmark, four countries that have been investing much more and much longer in scientific research (Fig 1B). In fact, if one takes into account the funding for R&D in the EU nations, Portugal ranks ahead of every other country in terms of the number of malaria papers published relative to the investment made in science at the national level (Fig 1C).

This raises the question of why Portugal, a rather small country with only a few decades of research history and an overall moderate scientific performance, fares relatively so well when it comes to research on malaria. I argue that there are three independent, albeit interrelated factors to explain this feat.

A lasting reality demanding an appropriate response

The first factor was the presence of autochthonous malaria in Portugal until the second half of the 20th century and the establishment of research institutions largely dedicated to studying and fighting the disease. Until the end of the World War II, malaria was endemic throughout much of Southern Europe; Italy, Greece, and Portugal were particularly affected. From 1955 to 1969, the WHO conducted its Global Malaria Eradication Programme, which successfully eliminated malaria in several regions of the world, including Southern Europe. The specific history of malaria eradication in Portugal is described in great detail by Bruce-Chwatt (Bruce-Chwatt, 1977) and highlights the intense efforts by multiple state-sponsored institutions dedicated to studying and combating the disease.

> *"... it was not until 1973 that malaria was eventually eliminated in Portugal, three years after Italy, and only one year before Greece."*

Even before the war, in 1931, the Malaria Research Station (Estação Experimental de Combate ao Sezonismo, EECS) was created in Benavente, the goals of which included the collection and analysis of blood samples from infected individuals, treatment of malaria patients, identification of mosquito populations, and malaria prophylaxis. In 1938, the Malaria

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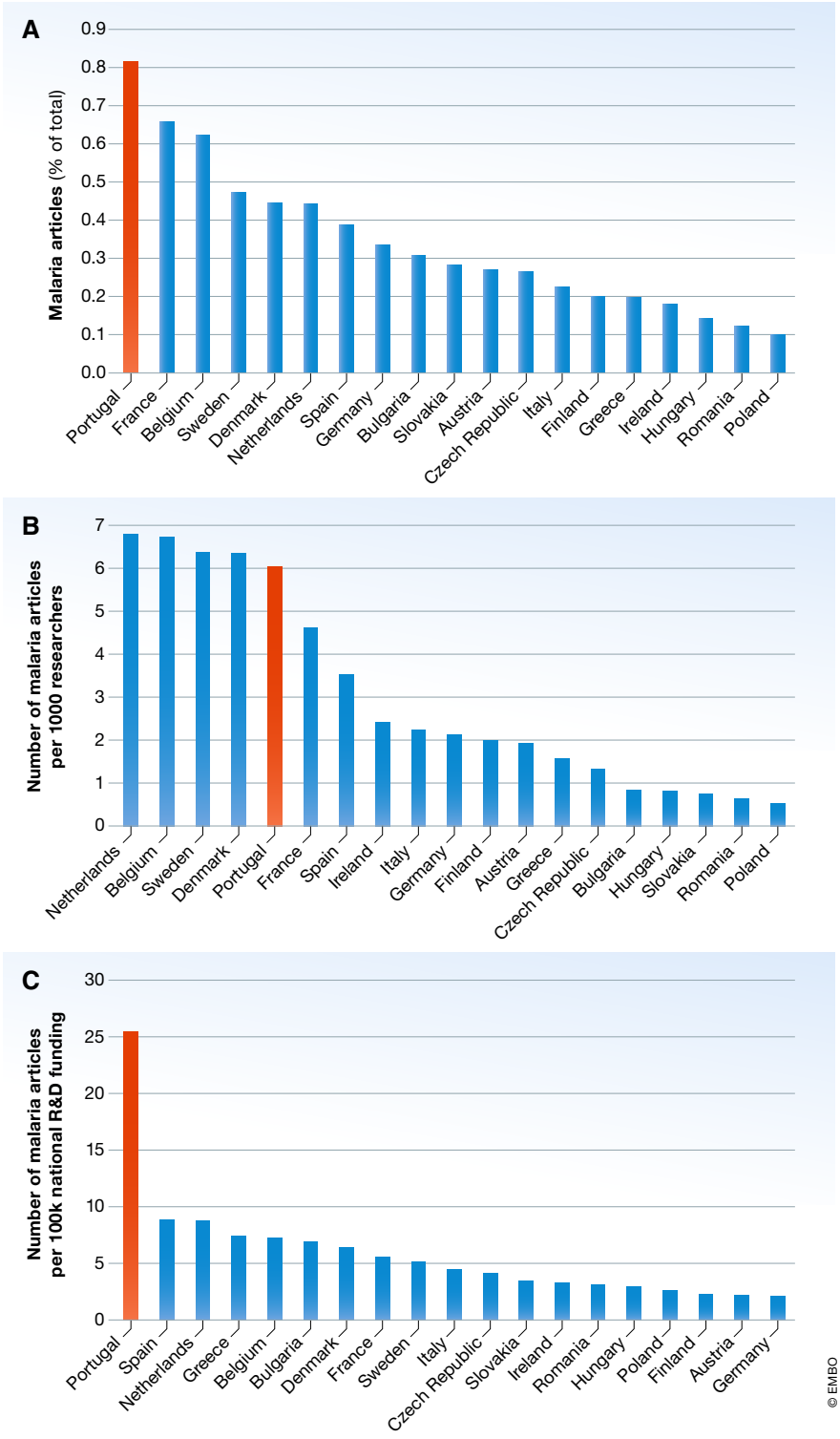

Figure 1. Malaria research in Portugal and in the EU.
(A) Percentage of papers on the subject of malaria relative to the total number of papers from each of the indicated countries from 2009 to present. (B) Number of malaria research articles per 1,000 researchers in each of the indicated countries. (C) Number of malaria research articles per 100,000 Euros of gross domestic expenditure on R&D in each of the indicated countries. Total R&D personnel and intramural R&D expenditure data are from 2017. Papers were quantified through searches of PubMed for articles with affiliation to each of the indicated countries, published from 2009 to present, by use of the terms "malaria" or "*Plasmodium*". Data on R&D investments from Eurostat.

Institute (Instituto de Malariologia, iMal) was founded in Águas de Moura to investigate the epidemiology of the disease, promoting adequate treatment and implementing vector control measures (Saavedra, 2010). Nonetheless, it was not until 1973 that malaria was eventually eliminated in Portugal, three years after Italy, and only one year before Greece.

Yet, the threat of malaria reemergence meant ongoing vigilance, and iMal paved the way for the creation of the Centre for the Study of Malaria and Parasitology (Centro de Estudos de Malária e Parasitologia), in 1973, later to become the Centre for the Study of Zoonoses (Centro de Estudos de Zoonoses) in 1987, and the Centre for Vector and Infectious Disease Studies (Centro de Estudos de Vetores e Doenças Infeciosas) in 1993. In addition, the Portuguese School of Tropical Medicine (later called National School of Public Health and Tropical Medicine, ENSPMT, now the Institute of Tropical Medicine and Hygiene, IHMT), founded in 1902, was one of only four institution of its kind in the world (Amaral, 2008). Since its inception, its mission has been the teaching and research in tropical medicine, biomedical sciences, and international health and, to this day, a significant part of its research continues to focus on malaria.

A close bond with Africa

Another major factor for Portugal's prominent position in malaria research is its colonial past and the country's close ties with its former colonies. During its period of maritime expansion in the 15th and 16th centuries, Portugal colonized many territories from Asia to the Americas and Africa. Most, if not all, of these territories were, and for a large part still are, endemic for malaria. Former colonies, such as Brazil or the Portuguese territories in India, gained their independence during the 19th century, but maintained close ties with Portugal.

However, several African countries, specifically Angola, Cape Verde, Guinea-Bissau, Mozambique, and S. Tomé & Príncipe, remained under Portuguese rule until well into the second half of the 20th century (Miller, 1975). In fact, while most African nations gained their independence from European countries during the 1950s and 1960s, Portugal's dictatorship held on to and suppressed its African overseas territories, which led to armed uprisings in Angola and Guinea-Bissau

Further Reading

Important contributions to malaria research by Portuguese laboratories during the past decade

Drug development, discovery and repurposing

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Early Portuguese institutions dedicated to malaria investigation and research

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in 1961, and in Mozambique in 1964 (Miller, 1975). During the ensuing colonial wars, thousands of Portuguese soldiers were sent to these countries, where they were exposed not only to the horrors of war, but also to malaria (Campos, 2017). The Portuguese military actions in Africa finally came to an end in 1974 after the peaceful Carnation Revolution, which established democracy in Portugal and ended the colonization of all Portuguese-held African territories.

> *"... even today, many younger people have direct contact with family members or friends who have experienced malaria, bringing the reality of this scourge closer to home than in many other EU countries."*

Over the next few years, hundreds of thousands of military personnel and former residents of the ex-colonies, known as "retornados", moved back to Portugal, leading to an increase in the number of imported malaria cases (Bruce-Chwatt, 1977). Since then, these numbers have subsided, but the close ties that Portugal maintains with its former colonies mean that travel to and from malaria-endemic regions remains high, contributing to the prevalence of imported malaria cases (Piperaki, 2018). It also means that malaria is not such a distant threat for most Portuguese; even today, many younger people have direct contact with family members or friends who have experienced malaria, bringing the reality of this scourge closer to home than in many other EU countries.

Remarkable and inspiring figures

The third and final factor is the enormous and lasting influence of various uniquely inspiring figures from several generations of malaria researchers. Indeed, the history of Portuguese malaria research is rich in prominent scientists who shaped the national research landscape. Attempting to highlight specific names among the many doctors, epidemiologists, and scientists from the past and present is a naturally risky exercise that runs the risk of overlooking important figures. Nevertheless, the crucial contribution of a few representatives of four generations of Portuguese scientists is beyond dispute.

Ricardo Jorge (1858–1939) was a renowned epidemiologist responsible for the 1899–1901 National Sanitary Plan, which marked the introduction of modern sanitary concepts in Portugal and changed national public health. In 1903, Jorge was the first to collect reliable and extensive data on the incidence of malaria and its seasonal distribution (JORGE, 1903). He was Portugal's Health Inspector-General from 1899 to 1926, succeeded by José Alberto de Faria (1888–1958), another key figure who, with the support of the Rockefeller Foundation (Saavedra, 2014), created the EECS in Benavente, the first step for advancing knowledge about malaria in Portugal (Bruce-Chwatt, 1977).

Well within the 20th century, Francisco Cambournac (1903–1994) and Fausto Landeiro (1896–1949) were arguably the most important contributors to Portuguese malariology during that period. Following extensive training in some of the most reputed parasitology schools in Europe, Cambournac became Director of Benavente's EECS in 1933, and Landeiro occupied that position from 1938 to 1949. Cambournac founded the iMal in Águas de Moura, serving as its Director from 1939 to 1954, and became Director of the WHO's African region from 1954 to 1964 (Lobo, 2012).

Cambournac and Landeiro published extensively on the epidemiology, entomology, and control of malaria during the 1930s and 1940s, and gave a comprehensive account of the status of the disease in Portugal during that period. Cambournac's 237-page long review (Cambournac, 1942) provided all the epidemiological and other data needed for future planning of control and eradication of malaria in the country, the success of which is widely acknowledged to his immense work (Bruce-Chwatt, 1977).

During the 1960s and early 1970s, the National School of Public Health and Tropical Medicine, ENSPMT, now the Institute of Tropical Medicine and Hygiene, IHMT, played an important role not only in Portuguese research on malaria and other tropical diseases, but also in the cooperation with Portugal's overseas territories at the time. The 1974 revolution and the decolonization

in Africa led to a reshaping of this cooperation, which became increasingly centered on reinforcing the newly independent countries' health systems, on their capacity to carry out research on endemic diseases, and on training programs in tropical and preventive medicine (Havik, 2015). Virgílio do Rosário, professor at the IHMT and, later, head of the Institute's Centre for Malaria and Other Tropical Diseases (CMDT), played a pivotal role in this process. Do Rosário was the founder of several national and international networks for studying malaria and neglected diseases in various regions around the world. He inspired a whole generation of future malaria researchers, making him an inescapable figure among Portuguese malariologists in the second half of the 20th century.

> *"As a great scientist and public advocate for malaria research, Mota has inspired numerous scientists, several of whom have become independent malaria researchers themselves..."*

At the dawn of the 21st century, many Portuguese scientists, who had benefitted from the country's investment in science in the 1980s and 1990s to acquire international training, came back home to set up their own research groups. Among them was Maria Mota, who returned from New York University to Portugal in 2002 to become a group leader, initially at the Instituto Gulbenkian de Ciência (IGC), and subsequently at the Instituto de Medicina Molecular (iMM). Mota's research on the liver stage of infection by *Plasmodium* parasites has had an enormous impact and yielded a plethora of outstanding publications. She became Director of iMM in 2014, and commonly features among the most influential women in Portugal. Mota is also a gifted and engaging communicator, who has helped to garner public attention to malaria research and to the fight against the disease. As a great scientist and public advocate for malaria research, Mota has inspired numerous scientists, several of whom have become independent malaria researchers themselves, both in Portugal and internationally.

These historical, epidemiological, and humane factors have made Portugal an important player in malaria research, from the basic science of the parasite to the pathology of the disease, and from epidemiology to clinical research and drug development. However, these great achievements, and the role played by individual inspiring scientists, should not be taken for granted, but rather serve as an argument for nurturing and supporting research on malaria by future generations of scientists and political decision-makers. A small country with fairly limited financial and human resources cannot reasonably aspire to excel in every area of research, but it can efficiently direct and focus its investment on those that are more likely to generate success. The history of Portuguese malaria research clearly demonstrates this and warrants its continued support as a top priority for national science policies.

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