Chapter 13

Malaria Eradication in the European World: Historical Perspective and Imminent Threats

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Additional information is available at the end of the chapter

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Abstract

Malaria was introduced to Europe from the southeast during the Neolithic period and subsequently became established throughout the continent, due to the combination of favorable geomorphological and climatic conditions with the presence of adequately sized human and competent vector populations. *Plasmodium vivax*, *P. malariae* and *P. falciparum* all occurred in various areas of the continent, transmitted by numerous *Anopheles* species, mainly *An. atroparvus* in the northwest, *An. labranchiae* and *An. sacharovi* in the south. The height of malaria endemicity in the Early Modern Age was followed by decline in the twentieth century, particularly in the northwest, owing mainly to man-made contraction of vector breeding sites and improvement of living standards. Eradication was accomplished in 1974 through widespread drug treatment and residual insecticide spraying. Since then, despite the sustained presence of competent vectors and numerous malaria cases imported by travelers and immigrants, autochthonous transmission has been sporadic in Europe, probably due to prompt diagnosis and treatment afforded by robust healthcare services. Current and projected climatic conditions are conducive to malaria transmission, particularly vivax malaria, in several areas of Southern Europe. Moreover, the continuing immigration crisis may facilitate the buildup of an infectious parasite reservoir in the area. Although malaria resurgence is currently unlikely particularly in northwest Europe, it is of crucial importance to maintain disease awareness, diagnostic and clinical competence and robust public health infrastructure for surveillance and vector control to diminish the possibility of malaria transmission in Europe's most vulnerable areas.

Keywords: malaria, Europe, history, resurgence, immigration, mosquito vectors

1. Introduction

Malaria, the most notorious parasitic disease of mankind, has accompanied humanity probably since prehistoric times and has shaped the course of human history over the centuries. It is still a major infectious disease today, causing more deaths by far than all other parasitic diseases combined, while nearly half of the current human population lives in areas of ongoing transmission. According to the World Health Organization (WHO) in 2016, 216 million malaria cases occurred worldwide (uncertainty range 196–263 million) resulting in 445,000 deaths. At present, 90% of all cases and 91% of all malaria deaths (of which 70% are in children under 5 years) occur in the WHO African Region [1]. Five species of the parasitic protozoan *Plasmodium* cause malaria: *P. falciparum*, *P. vivax P. ovale, P. malariae* and *P. knowlesi.* The ecology of human malaria species is closely linked to geomorphology and climatic conditions, particularly temperature and rainfall, which affect both the vector species and the parasites themselves, while malaria epidemiology is influenced by additional factors relating to the human host, such as population density and susceptibility to infection. Ronald Ross developed the original mathematical models for malaria transmission in the early twentieth century and his equations were refined by George McDonald and several mathematicians and other scientists for over 70 years. These models expanded further using epidemiological and entomological data from field studies, eventually evolving into the Ross-MacDonald theory of mosquito-borne disease transmission [2]. These equations still form the basis of our understanding of malaria transmission and, despite some rather simplifying assumptions they contain, they epitomize its most important determinants. In one of them MacDonald defined the concept now called the basic reproduction number R_0 as the expected number of secondary infections resulting from a single infection in a completely susceptible population. He denoted it as follows [3]:

$$R_0 = ma^2 bp^n / -r \ln p \tag{1}$$

where *m* is defined as *Anopheles* mosquito abundance relative to the human population, *a* describes the inclination of a vector to bite a human host, *b* represents the proportion of infective mosquito bites, *p* is defined as the probability the mosquito will survive a day, *n* is defined as the duration of the extrinsic incubation period, that is, time needed for parasite development within the mosquito and *r* is the recovery rate of the human host. If R_0 is greater than one, the number of infected people increases, and if it is less than one, that number declines. In terms of these models, one can surmise that for malaria to invade and remain established in a certain area, where geomorphology, temperature and precipitation favor parasite, and vector survival and development, an adequately sized susceptible human population must coexist with efficient malaria vectors. Efficiency depends on mosquito abundance, life span, predilection for feeding on human host and susceptibility to infection by the various *Plasmodium* species. These determining factors for malaria risk in a given area were described in detail within the definitions of receptivity, vector infectivity and vulnerability. Each of these factors and their respective roles in the establishment and the eradication of malaria from the European World are briefly discussed.

Several *Anopheles* species capable of transmitting malaria exist in Europe. Species belonging to the *Anopheles maculipennis* Subgroup (Diptera, Culicidae) are widely distributed and exhibit

variable susceptibility to infection by *Plasmodium* spp., due to differences in behavioral patterns and feeding preferences. This subgroup includes 10 species among which 3 are important malaria vector species, that is, *An. atroparvus* (van Thiel 1927) in most of western, northern and central Europe, *An. labranchiae* (Falleroni 1926) and *An. sacharovi* (Favre 1903) in the south and southeast. Other species, occurring in Europe that are considered as malaria vectors of minor importance, include *An. messeae, An. maculipennis s.s. and An. melanoon* of the Maculipennis Subgroup, while some are of little significance such as *An. algeriensis, An. claviger, An. plumbeus, An. superpictus* to cite a few [4, 5]. The most important geographical features regarding malaria ecology in Europe were the plains and coastal marshes in all areas of the continent. Southern Europe is comprised of mountainous peninsulas, separated by stretches of sea that make up the Mediterranean. In each of these, mountain ranges divide plains, where water from rainfall tended to collect and frequently stagnate, forming marshes on its way to the sea. Coastal marshlands also existed all around the North Sea basin while there are numerous river valleys and flood plains in Central and Northwest Europe. European climatic conditions, particularly the extreme seasonality of temperate climate, presented a substantial challenge for *Plasmodium* species during their gradual spread across the continent, although the distribution of *P. vivax* in Europe until the twentieth century extended as north as Southern Finland [6]. Optimal temperature ranges for parasite development within the mosquito are 16–33 and 18–33°C for *P. vivax* and *P. falciparum,* respectively [7]. Evidently, European winter temperatures were not conducive to parasite development. Temperate *Plasmodium* strains circumvented this problem by employing biological mechanisms to ensure survival and maintain transmission during the winter. *P. vivax* relies primarily on dormancy in the human liver in the form of hypnozoites, whereas *P. malariae* on prolonged incubation and persistent low-level parasitemia for years or even decades. An additional opportunity for continued parasite survival and transmission was the overwintering of female mosquitoes indoors, in the warmth of animal shelters and human dwellings.

2. Introduction, rise and decline of malaria in Europe

It is most likely that malaria (caused by *P. vivax, P. malariae* and *P. falciparum*) was introduced into the area around the Mediterranean and thence to the rest of Europe during the Neolithic period (4000–3000 BC). *P. falciparum's* histidine-rich protein 2 was detected in Egyptian mummies from 3200 BC confirming its presence in the outskirts of the Mediterranean world in the fourth millennium BC, suggesting the known contact between Egypt and Greece in the Early Bronze Age as one possible route of its introduction to Europe. Another possibility is that all three species of *Plasmodium* made the crossing within human hosts, as populations of Neolithic farmers migrated to Europe from the Near East, the wetlands and plains of today's Israel, Palestine, Syria and Jordan, where agriculture is believed to have developed [8].

Attempts to trace the history of malaria in ancient Greece before the fifth century BC are plagued by shortage of evidence and confounded by difficulties in its interpretation. There is an interesting passage in Homer's Iliad in which Achilles hurrying to avenge Patroclus' death is compared to the bright star that rises in late July (Sirius) and heralds the arrival of fever (greek "πυρετός") for wretched mortals. Although impossible to prove that this is an early reference

to malaria, the association with the harvest calls to mind the name "aestivo-autumnal fever" frequently used for *P. falciparum* malaria by doctors many centuries later. However, the clearest references from historic sources that can be attributed to malaria are those to fevers with tertian and quartan periodicities. Hippocrates in the fifth and fourth centuries BC and Celsus in the early first century AD described two types of tertian fever (tertian and semitertian) with symptoms corresponding to vivax and falciparum malaria respectively and a quartan fever corresponding to infection by *P. malariae*. The association with swamps was also common knowledge since the time of Hippocrates' treatise "Airs, Waters, Places" although the connection with mosquitoes was not made, possibly because of the existence of regions where there was no malaria although mosquitoes were abundant. *P. vivax* was always the most important species in the area, as its life cycle characteristics and adaptations were well suited for transmission in the seasonal climate of the Mediterranean, but malaria due to *P. falciparum* and `*P. malariae* occurred as well, unlike *P. ovale* which is absent from the Mediterranean region. Vivax malaria appeared in spring and early summer, followed by falciparum malaria, which peaked in late summer and autumn. Periodic epidemics were also observed in areas of endemicity. Malaria was well known at the time of the Roman Empire. The Pontine Marshes, a 30 km^2 marshland area to the southeast of Rome in central Italy, was a haven for the disease for almost two millennia. The word "malaria" itself, meaning "bad air" (mal'aria) is Italian in origin and reflects the miasmatic theory on the nature of the disease. Julius Caesar, who had suffered from quartan fever himself when he was young, had ambitious plans to drain the Pontine Marshes and claim the land for agriculture, a feat that was finally accomplished by Mussolini, on the eve of World War II. Eminent Byzantine physicians, such as Oribasius and Paul of Aegina, provide information on fevers during the Middle Ages in the Eastern Roman Empire (Byzantium) [9].

P. vivax and *P. malariae* gradually made their way to the north-west and the north of the continent, probably through France and Spain. Little is known about the first centuries of the first millennium AD, but there can be no doubt that malaria was present in northwest Europe from the middle Ages until the nineteenth century. During the medieval climatic optimum, near the end of the twelfth century, increased temperatures and associated rise in sea level probably favored the spread of malaria northward. The coastal flood plains and marshlands in the Iberian Peninsula, France, England, the Netherlands, North Germany, Denmark, Scandinavia and Russia were most affected. A significant vector for coastal areas was the zoophilic *An. atroparvus*, a widely distributed species. Once established on the coast, malaria strains could move inland along river valleys, floodplains and swamps, possibly transmitted by inland mosquito species, such as *An. messeae*. Assessment of disease incidence and mortality from historical records is difficult. Nevertheless, evidence that malaria was the likely cause of fever in European coastal marshes can be gathered from accounts of disease symptoms, such as intermittent fevers (tertian and quartan), anemia and splenomegaly and by its seasonal pattern. Such descriptions exist in Anglo-Saxon medical texts dating back to the ninth century and can be found in accounts from north Germany, Denmark and the Netherlands. *P. malariae* is believed to have been endemic along the river banks of the Rhine, Rhone and Danube, along the eastern and southeastern English coast, and in the Netherlands and as far north as Sweden and Finland in the thirteenth century [10]. It appears that falciparum malaria was

rarely encountered in northwest Europe and when it did, it was probably imported from the south and could not really take root, as its causative agent, *P. falciparum* did not survive within the human host for more than a year and was poorly adapted to local mosquito species.

Malaria reached the height of its endemicity in northwest and north Europe in the Early Modern Age (late fifteenth and early sixteenth centuries), mainly due to high population densities in coastal areas and a variety of human interventions, like the construction of embankments, floodgates, canals and harbors. Surprisingly, the increase in disease frequency occurred despite a general drop in temperature, which began halfway into the sixteenth century, lasted for 150–200 years and was so pronounced that it was termed the Little Ice Age. The area of malaria distribution was the greatest it had ever been at the end of the nineteenth and the beginning of the twentieth centuries. At that time, malaria was highly prevalent in southern Europe while its northernmost limit ran along the 64° N parallel from central England to southern Norway, central Sweden and Finland and Northern European Russia.

The disappearance of malaria from Europe progressed from northwest to southeast and was the result of various contributing factors, including environmental changes, ecological and social developments, introduction of effective treatment and concerted human control efforts. One of the most important factors in lowering the prevalence of malaria is considered to have been the habitat separation of humans from cattle [6]. Malaria transmission in Europe has always been predominantly unstable, due to environmental, climatic and vector biology factors including strong zoophilic behavior. In such an epidemiological setting, it was relatively easy for human interventions to tip the fragile human-parasite balance against the parasite, leading to disease elimination.

The drainage, reclamation of swampland and improvements in water management in the fields drastically reduced the availability of mosquito breeding sites resulting in reduced mosquito populations in many areas. Agricultural innovations led to better human overall health and an increase in animal populations. Animals were fed during the winter and kept in stables, byres and pigsties. These animal shelters and their occupants proved much more attractive for the main vector of malaria in most of Europe, the zoophilic *An. atroparvus*, diverting mosquitoes from the nearby human dwellings. Improvements in house construction and living standards played a significant role as well. Buildings where human living quarters and animal shelters were found together progressively disappeared. This human-domestic animal habitat separation played a major role in the decrease of malaria transmission. Finally, the extensive use of cinchona bark brought to Europe in the 1600s and the introduction of quinine in the 1820s further moderated disease transmission.

Nevertheless, in the beginning of the twentieth century, malaria still plagued a significant part of Europe, particularly the south. At the end of the nineteenth century, malaria was affecting approximately 10% of the Italian population, with annual cases in the range of two million and about 15,000–20,000 deaths per year [11]. The situation was somewhat worse in Greece. During his visit in 1906, Ronald Ross was surprised to discover that 65% of the children in the particularly malarious area around lake Copais in Voiotia were suffering from the disease [12]. The Greek-Turkish War in Asia Minor in 1922 and the tragic events that led to a backwave of 1,300,000 Greek refugees were followed by an increase in the outbreaks and the death toll of malaria in the late 1920s. A communication from Greece to the WHO reported that, in

the 1930s, *P. falciparum, P. vivax* and *P. malariae* all occurred in the country; the annual attack rate was estimated at 15–30% of the total population, and the mortality rate was 73.7 deaths per 100,000 inhabitants. Treatment required approximately 30 tons of quinine each year [13]. In 1924, the League of Nations established the Malaria Commission to conduct research and strategize the control of malaria. The socioeconomic devastation and mass displacements caused by World War II interrupted the implementation of national elimination programs and destroyed environmental engineering works that had reduced transmission, setting back malaria control efforts. Control interventions, drug therapy and insecticide spraying resumed successfully in the late 1940s, and the World Health Organization certified the achievement of malaria eradication in Hungary in 1963, followed by Spain in 1964, Bulgaria in 1965, Poland and Romania in 1967, the Netherlands and Italy in 1970, Yugoslavia and mainland Portugal in 1973. In 1975, the last focus of indigenous malaria reported from Macedonia in Greece had been extinguished and Europe was malaria free for the first time in history.

3. Malaria in Europe: current situation

Europe, in the most prevalent definition of the term, is distinct from the area currently designated "the WHO European Region" which comprises all countries of the European Union (EU), the Balkans, South Caucasus and Central Asia and the Russian Federation, Israel and Turkey (53 countries in all), some of which do not belong to Europe geographically. The European Centre for Disease Prevention and Control (ECDC) issues annual epidemiological reports on malaria in Europe based on data retrieved from the European Surveillance System (TESSy) that collects, analyzes and disseminates data on communicable diseases that generally originate from national surveillance systems. Malaria is a notifiable disease in the EU and its reporting is compulsory in 24 countries, voluntary in France and Belgium and "not specified" in the United Kingdom (UK). Active disease surveillance is in place only in the Czech Republic, Slovakia, the UK, and in high-risk areas in Greece. The latest available data on the number of malaria cases in EU and European Economic Area (EEA) countries reported to the ECDC are shown in **Table 1**. Nearly all malaria cases (99.9%) are currently imported by international travelers and immigrants [14, 15]. Of the 31 European countries reporting to the ECDC the highest number of confirmed cases in 2014 and 2015 were reported from France (n = 2299 and 2500) and the United Kingdom (n = 1510 and 1397, respectively) (**Table 1**). Imported malaria in these countries was mainly linked to travel to West Africa, particularly for the purpose of visiting friends and relatives residing in countries and European territories endemic for malaria, such as Mayotte and French Guiana [15]. The causative species depends on the area the parasite is imported from and the largest proportion is identified as *P. falciparum* [16]. Similarly, the incidence and species distribution in refugees and immigrants reflects the local epidemiology in their country of origin and along the migration route they followed. Notably, many immigrants prefer to remain unnoticed by the authorities until they reach the country they intend to request asylum from, and therefore a significant proportion of malaria cases in this population, possibly even half of them are thought to remain unreported [17]. Permanent foreign residents that have settled in European countries and regularly return to their malaria endemic country of origin

Countries	2011		2012		2013		2014		2015	
	Cases confirmed (reported)	Rate**	Cases confirmed (reported)	Rate	Cases confirmed (reported)	Rate	Cases confirmed (reported)	Rate	Cases confirmed (reported)	Rate
Austria	7	0.1	28	0.3	42	0.5	68	0.8	81	0.9
Belgium	184	1.7	206	1.9	253	2.3	235	2.1	276	2.5
Bulgaria	8	0.1	16	0.2	8	0.1	10	0.1	20	0.3
Croatia	—	—	23	0.5	0	0.0	6	0.1	7	0.2
Cyprus	6	0.7	1	0.1	3	0.3	8	0.9	3	0.4
Czech Republic	28	0.3	25	0.2	27	0.3	30	0.3	29	0.3
Denmark	—	—	—	—	—	—	—	—	—	—
Estonia	1	0.1	6	0.5	3	0.2	3	0.2	4	0.3
Finland	33	0.6	46	0.9	38	0.7	39	0.7	39	0.7
France	1891	—	1851	—	2165	—	2299	—	2500	—
Germany	0 (562)	0 (0.7)	0 (547)	0 (0.7)	0 (637)	0 (0.8)	—	—	0 (1063)	0
Greece	92	0.8	95	0.9	25	0.2	38	0.3	84	0.8
Hungary	10	0.1	5	0.1	5	0.1	15	0.2	12	0.1
Iceland	—	—	—	—	—	—	—	—	—	—
Ireland	61	1.3	65	1.4	71	1.5	79	1.7	82	1.8
Italy	—	—	—	—	—	—	—	—	—	—
Latvia	4	0.2	3	0.1	4	0.2	6	0.3	1	0.1
Liechtenstein	—	—	—	—	—	—	—	—	—	—
Lithuania	3	0.1	6	0.2	8	0.3	5	0.2	8	0.3
Luxembourg	3	0.6	7	1.3	4	0.7	3	0.5	1	0.2
Malta	1	0.2	2	0.5	5	1.2	3	0.7	7	1.6
Netherlands	253	1.5	194	1.2	162	1.0	276	1.6	340	2.0
Norway	30	0.6	37	0.7	72	1.4	120	2.3	94	1.8
Poland	14	0.0	21	0.1	36	0.1	19	0.0	29	0.1
Portugal	67	0.6	71	0.7	117	1.1	144	1.4	194	1.9
Romania	40	0.2	32	0.2	43	0.2	47	0.2	30	0.2
Slovakia	1	0.0	6	0.1	4	0.1	5	0.1	0	0.0
Slovenia	6	0.3	7	0.3	3	0.1	7	0.3	5	0.2
Spain	405	0.9	421	0.9	518	1.1	688	1.5	706	1.5
Sweden	95	1.0	85	0.9	119	1.2	354	3.7	250	2.6
United Kingdom	1677	2.7	1378	2.2	1501	2.3	1510	2.3	1397	2.2

Countries	2011		2012		2013		2014		2015	
	Cases confirmed (reported)	Rate**	Cases confirmed (reported)	Rate	Cases confirmed (reported)	Rate	Cases confirmed (reported)	Rate	Cases confirmed (reported)	Rate
EU/EEA	4920 (5482)	0.8 (1.0)	4637 (5184)	0.7 (0.9)	5236 (5873)	0.8 (1.0)	6017	1.0	6199	1.0

*ECDC = European Centre for Disease Prevention and Control.

**Rate denotes number of cases per 100,000 population. Reporting in France is voluntary and surveillance coverage is not nationwide.

Note: • 99.9 and 99.8% of cases for which travel information was provided were travel related in 2014 and 2015 respectively.

Source: [14, 15].

Table 1. Malaria cases in the European Union (EU) and European economic area (EEA) reported to the ECDC* during 2011–2015: confirmed cases (reported cases) and rate per 100,000 population.

to visit friends and relatives (also known as VFRs) are currently the most significant high-risk population for malaria importation, for geographic and behavioral reasons. Specifically, they visit endemic areas frequently, often stay in rural areas with poor health infrastructure for longer periods than tourists do, do not usually seek pre-travel medical advice and have poor compliance with malaria chemoprophylaxis and protection measures. *P. falciparum* and much less so *P. ovale* and *P. malariae* are usually imported from sub-Saharan Africa, particularly West Africa, whereas *P. vivax* from Asia and areas of South America. *P. falciparum* is usually detected shortly after the patient's arrival, due to its prominent clinical presentation, whereas *P. vivax* and *P. malariae* might remain undetected for a significant amount of time. Obviously, the possibility that individuals infected with malaria may remain undetected for several months after arrival to Europe could be a significant risk factor for local transmission, particularly regarding *P. vivax* for which competent vectors are still widely distributed across the continent.

Europe has been considered malaria free since 1975, as was the rest of the WHO European Region at that time, except for Turkey. However, in the late 1980s and early 1990s, autochthonous malaria transmission chiefly due to *P. vivax* resumed in the Transcaucasian countries, the Central Asian republics and less so in the Russian Federation, most likely due to mass population movements, socio-economic challenges, agricultural and developmental schemes and the neglect of malaria prevention and control services. The Roll Back Malaria (RBM) Initiative in 1998 and the Tashkent declaration for "The move from malaria control to elimination" in 2005 [18] seem to have successfully reached their targets. According to WHO, the WHO European Region reported zero indigenous malaria cases in 2015, thus achieving its set goal of disease elimination [19]. As far as the European continent itself is concerned, since the late 1990s, sporadic autochthonous malaria cases occurred in several countries, caused by infection of local mosquitoes by travelers or immigrants from endemic regions. Locally transmitted malaria cases have been reported in Spain [20], Germany [21], the Netherlands [22], France [23], Italy [24] and Greece [25]. More recently, 5 cases were reported to the ECDC as locally acquired in 2014, 7 in 2015, 10 cases in 2016 and 17 in 2017 recorded from 8 different countries (**Table 2**). Epidemiology and modes of transmission included congenital transmission from mothers

infected in an endemic country, induced malaria following a transplant from a donor who had traveled to an endemic country, introduced malaria due to residence near imported cases and "suitcase malaria" [26–28]. Among the locally acquired cases in 2017 included a fatal case of falciparum malaria in a four-year-old diabetic girl in Italy. Epidemiological investigations identified hospitalization of this case along with two other patients infected with *P. falciparum*

Year	Total cases	Country (no. of cases)	Parasite species	Mode of transmission-epidemiology
2014	5	France (2)	Unspecified	Undocumented residents, travel to endemic region possible
		Spain (3)	*P. falciparum*	Congenital (mother originally from Equatorial Guinea)
			P. malariae	Induced (kidney transplant from traveler to Equatorial Guinea)
			P. vivax	Introduced (residence near imported case)
2015	7	Greece (6)	*P. vivax*	Mosquito-borne, autochthonous in receptive rural areas, presence of patients from endemic countries in the area
		Belgium (1)	*P. falciparum*	"Suitcase malaria"
		Netherlands (1)	*P. vivax*	Congenital (mother: an Eritrean refugee)
2016	10	Greece (6)	*P. vivax*	Mosquito-borne, introduced
		France (2)	Unspecified	Mosquito-borne, introduced or airport malaria
		Spain (1)	Unspecified	
		Lithuania (1)	Unspecified	
2017	17 (until 15/12/2017)	France (2)	*P. falciparum*	Mosquito-borne, in the area where *P. falciparum* malaria imported from Burkina Faso occurred
		Greece (7)	*P. vivax* (6)	Mosquito-borne, introduced
			P. falciparum (1)	Nosocomial, mosquito-borne or iatrogenic (not transfusion), patient recently hospitalized in ward where a patient was treated for *P. falciparum* malaria.
		Italy (5)	*P. falciparum* (1)	Mosquito-borne or nosocomial, fatal, 4 years old diagnosed with diabetes mellitus; two patients infected with *P. falciparum* were hospitalized in the same ward
			P. falciparum (4)	Mosquito-borne, patients originally from Africa
		UK (3)	*P. vivax*	Mosquito-borne, contracted in Northern Cyprus

Source: [26–28].

Table 2. Locally acquired malaria cases in Europe during 2014–2017.

in the same ward. Another case of potentially nosocomial *P. falciparum* transmission was reported from northwest Greece.

4. Risk of malaria re-emergence in Europe

The possibility of malaria re-emergence in Europe in the face of climatic and demographic changes was renewed in the 2000s partly aroused by reports of epidemics in neighboring Turkey and central Asia. The risk of malaria introduction in a given area, also known as its malariogenic potential, depends on three characteristics: receptivity, vector infectivity and vulnerability [29].

Receptivity depends on the presence of a competent vector, and ecological and climatic conditions, conducive to vector survival and proliferation. Vectorial capacity is determined by mosquito population density, life span, feeding preferences and duration of parasite development (sporogony). Several *Anopheles* species capable of transmitting malaria are still abundant across Europe. The geographical distribution of the European dominant malaria vector species and their main bionomical characteristics are shown is **Figure 1** and **Table 3**, respectively. The most widely distributed belong to the *Anopheles maculipennis* Subgroup. Historically, *A. atroparvus* was the primary malaria vector in most of northern, western and central Europe [30]. It occurs along the coast of the Atlantic Ocean, from south Sweden to Portugal and Spain, around the Baltic Sea and variably in central Europe and the Balkans. Its distribution in Europe has contracted with the disappearance of coastal marshlands and increasing water pollution. *An. labranchiae* and *An. sacharovi* were the most important malaria vectors in southern Europe, the Balkans, Italy and Greece. *An. labranchiae* has been reported from Corsica, the coastal areas of Italy, Sardinia, Sicily, the Istrian Peninsula and the Dalmatian Coast of Croatia; it also occurs in North Africa. Once endemic in southern coastal Spain, *An. labranchiae* has since disappeared after abandonment of rice cultivation and desiccation of wetlands. *An. sacharovi* is encountered in Greece, the Balkans, south Russia, Turkey and the Middle East [6, 31, 32]. Other species considered malaria vectors of minor importance are also currently encountered in Europe. Some belong to the *An. maculipennis* Subgroup (*An. messeae, An. maculipennis s.s. An. melanoon*); others included *An. algeriensis, An. claviger, An. hyrcanus, An. plumbeus, An. superpictus*. The eradication campaigns of the twentieth century led to severe reduction of *Anopheles* numbers but failed to achieve complete eradication. Over time, in certain areas, *Anopheles* populations recovered to initial levels giving rise to the phenomenon known as "anophelism without malaria" which essentially signifies the presence of *Anopheles* mosquitoes in formerly malarious areas of Europe where malaria no longer occurs.

The climate of south European countries around the Mediterranean Sea, characterized by mild-wet winters and hot-dry summers, is suitable for malaria transmission, whereas in northern Europe ambient temperatures permit outdoor parasite development only during the summer. To the extent that climate change can be predicted with any degree of certainty, it is

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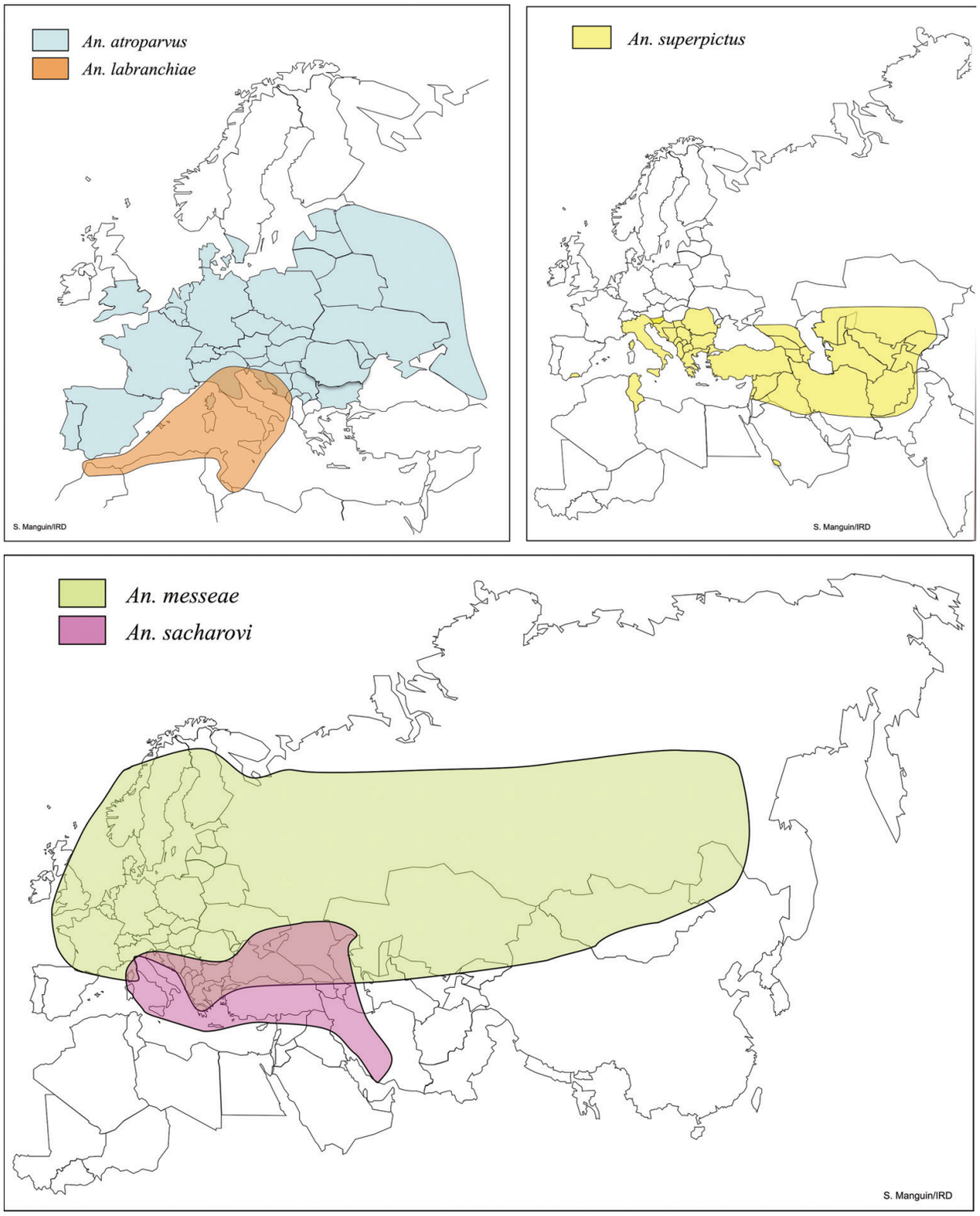

Figure 1. Geographical distribution of dominant malaria vector species in Europe. A: *An. atroparvus* (blue), *An. labranchiae* (orange), B: *An. superpictus* (yellow), C: *An. messeae* (green) and *An. sacharovi* (purple). Source: updated maps from Ref. [6].

Species	Breeding habitats	Feeding	Resting habits	Overwintering	Susceptibility to *P. falciparum*
***An. atroparvus* van Thiel**	Fresh water, brackish and tolerates saltwater. Marshes, ditches, ground pools, river margins, streams, rock pools, rice fields, even used tyres, sun-exposed habitats.	Opportunistic feeder: mostly zoophilic, but anthropophilic too, Exophagic.	Exophilic	Hibernation of female incomplete (periodic feeding), gonotrophic disassociation (without oviposition)	Refractory to Asian and African *P. falciparum* but competent in supporting a European strain
***An. labranchiae* Falleroni**	Mainly freshwater habitats, occasionally brackish water and lagoons. Warmer environment than *An. atroparvus*. Sunlit rock holes, pits, ditches, drains, canals, slow flowing streams/ rivers, ground pools, ponds, lakes, rice fields.	Opportunistic: zoophilic, but anthropophilic too	Mostly exophilic	Hibernation of female incomplete (with occasional blood feeding without ovipositioning) and complete (without feeding and nongonoactive)	Refractory to tropical *P. falciparum* strains Historical evidence of natural infection with European strains Experimental evidence of infection with some strains of African *P. falciparum*
***An. messeae* Falleroni**	Shaded, clear, still or slow flowing fresh water, Lake margins, marshes, swamps, ditches.	Mostly zoophilic, exophagic	Endophilic	Hibernation of female with full diapause, do not feed during the winter	Refractory to tropical *P. falciparum* strains
***An. sacharovi* Favre**	Brackish and fresh still or flowing water. Sunlit sites with aquatic vegetation such as swamps, marshes, river margins, springs, seepages, pools, ditches, irrigation canals, small water collections.	Opportunistic feeder but mainly anthropophilic; exophagic and endophagic	Endophilic	Hibernation of female incomplete (periodic feeding), gonotrophic disassociation (without oviposition)	Essentially refractory to tropical P. falciparum strains (inconclusive experimental results) Historical evidence of natural infection with European strains
***An. superpictus* Grassi**	Brackish and fresh still or flowing water in full sunlit. Small pools in river beds, irrigation canals, storage tanks, rice fields, ditches, borrow pits.	Mostly zoophilic and exophagic	Mostly endophilic	No information	No information

Source: [6, 32].

Table 3. Bionomical characteristics of the European dominant malaria vector species.

expected to encompass changes in temperature, precipitation and the intensity and frequency of extreme weather phenomena. By the end of the twenty-first century, with continuing temperature increase, fewer cold and more frequent hot temperature extremes are projected to occur on daily and seasonal timescales, while heat waves are likely to last longer and occur more often. It is estimated that many regions will probably experience more frequent and intense extreme precipitation events [33]. Occurrence of higher temperatures for longer periods during the summer may increase chances for malaria transmission in certain previously inhospitable areas. Malaria endemicity however is not simply a matter of the right temperature. Climate change is but one element in a complex epidemiological setting and other components such as human activity are probably more important determinants.

Infectivity reflects the vector competence to replicate and transmit a particular *Plasmodium* species or strain. Replication is assessed by the presence of oocysts in the mosquito midgut and capability to transmit is determined by the presence of sporozoites in its salivary glands. European *Anopheles* exhibit variable sensitivity to *Plasmodium* strains from malaria endemic regions. Members of the *An. maculipennis* Subgroup have been found capable of developing *P. vivax* sporozoites following an infected blood meal, but competence is difficult to evaluate given the absence of reliable *P. vivax* gametocyte culture. On the whole, although there is substantial knowledge on the vectorial potential of numerous tropical and subtropical mosquito species, corresponding data on European indigenous species are scarce [34]. Earlier studies have shown European *An. atroparvus* and *An. labranchiae* populations to be refractory to infection by tropical strains of *P. falciparum*, although not universally [35–38]. *An. labranchiae* has been an important malaria vector in the central and western Mediterranean, where both *P. vivax* and *P. falciparum* occurred in the past, and there is historical data from the early twentieth century confirming the existence of naturally infected *Anopheles* in the area, however, without specifying the species. A recent experimental study reported that *An. maculipennis s.l.* from Corsica were successfully infected with the NF54 African strain of *P. falciparum*; furthermore, sporozoites were detected in the salivary glands of some mosquitoes, indicating they were capable of transmission, albeit with very low competence [32]. *An. labranchiae* is thought to have been involved in autochthonous transmission of vivax malaria in southern Italy and possibly in Corsica in 2011 and 2006, respectively [39, 23].

A species that has recently become the focus of increasing attention is *An. plumbeus* (Stephens 1828). It is widely distributed all over Europe (except in the far north regions), the Middle East and North Africa. *An. plumbeus* was originally known as a dendrolimnic species, encountered in forests and breeding almost exclusively in tree holes. Recent reports indicate that it has been adapting to human-made habitats, such as abandoned animal shelters, artificial water containers, septic tanks, sewage ditches, rainwater and liquid manure pits, and that it is becoming increasingly common in suburban and urban environments. It overwinters as an egg or larva, has a relatively long-life span (up to 2 months) and is an avid biter of reptiles, birds and mammals, while some populations have exhibited high anthropophily [30]. Experimental studies have shown it to be a competent vector for both *P. vivax* and *P. falciparum* [40–42]. Furthermore, it has been implicated in indigenous vivax and falciparum

malaria transmission in England and Germany, respectively [21, 43]. Its potential role as a vector under changing climatic conditions and availability of infected human reservoir can only be speculated at present.

Vulnerability depends on the introduction and maintenance of a human reservoir that can transmit the parasite gametocytes to the mosquito populations. A patient suffering from malaria becomes infective for mosquitoes upon the appearance of *Plasmodium* gametocytes in the peripheral blood. In *P. vivax* malaria, gametogenesis occurs early in the course of the infection, within 3 days from the onset of clinical disease, whereas in *P. falciparum* malaria gametocytes usually appear 10 days after blood invasion. Therefore, a patient with vivax malaria is usually infective to mosquitoes frequently even before presenting for medical assistance. The additional delays in diagnosis and treatment, which are common in non-endemic countries, allow more time for transmission of the parasite to the local *Anopheles* populations.

In the past few years, Europe has witnessed a dramatic increase in the number of refugees and migrants, which peaked in 2015, with 1,257,000 asylum applications, double that of the previous year, a trend that continued in 2016 and 2017 [44]. Recently, a substantial increase in the incidence of vivax malaria has been recorded in refugees seeking asylum in European countries. More specifically, from spring 2014 to summer 2015, 37 cases of vivax malaria were diagnosed in newly arrived Eritrean refugees in Germany. Notably, their treatment was complicated by relapses due to difficulties in procuring primaquine for hypnozoite eradication, as the drug was not licensed in Germany [45]. During the same time, 105 malaria cases were recorded in Eritrean refugees in Sweden, of which 84 were due to *P. vivax* [46]. It is speculated that the refugees contracted the disease either at home or somewhere along their route from Eritrea through Ethiopia and Sudan. Interestingly, a cluster of 15 vivax malaria cases in Eritrean refugees was observed in 2010 in Israel [47].

According to data from the European Agency for the Management of Operational Cooperation at the External Borders of the Member States of the European Union (Frontex), a truly explosive increase occurred in 2015 at the Eastern Mediterranean route with 885,386 migrants arriving in Europe through Turkey, compared to 50,830 the previous year. These originated mainly from Syria, followed by Afghanistan and Somalia, and landed on Greek Islands, primarily Lesbos [48].

At present, it is not feasible to make specific, valid predictions as to where malaria might re-emerge, based on existing data. This occurrence will probably be determined by numerous factors besides vector presence, abundance and susceptibility to infection, *inter alia* possible climatic changes in the future, human interventions and population movements among others, none of which can be predicted with any degree of certainty. Recent experience has shown that indigenous cases and outbreaks in Europe typically occur around immigrants or travelers from endemic areas. Neither the settlement location nor the duration of stay of the various migrant populations is predictable, particularly in view of the uncertainty of the current migration crisis. Notably, the potential repercussions of an infectious human reservoir build-up in a previously endemic area conducive to malaria transmission were illustrated by a malaria outbreak experienced in Greece in recent years. Since malaria eradication in Greece in 1974, cases were mostly imported, with a few sporadic reports of autochthonous transmission in 1991, 1999 and 2000 [49]. Since 2009,

however, locally acquired *P. vivax* malaria cases and clusters began to appear consistently almost every year, peaking in the 2011 outbreak, when 42 cases were reported from several foci around the country [50]. Five potential malaria vectors including *An. sacharovi* occur in Greece whereas the country's geomorphology and climate allow for temporary and permanent mosquito breeding sites. The period from May to October has been established as the most favorable for mosquito infectivity and transmission in the area. An important contributing factor for increased vulnerability and malaria occurrence was the presence of migrant farm workers from Pakistan and Afghanistan in the affected areas. Many of these resided in poor housing conditions, situated close to mosquito breeding sites. Moreover, if they fell ill they were often reluctant to utilize the freely available healthcare services, due to their frequently illegal status, thus increasing the chance of parasite transmission to local *Anopheles* populations [50]. *P. vivax* isolates from the affected areas were genotyped revealing a number of different strains [51]. Furthermore, there was indication of sustained transmission for two consecutive years at least in one focus; an observation that has truly unsettling implications in light of the current financial depression and immigration crisis the country is facing [51]. The Greek public health authorities initiated control efforts that focused on training of medical professionals to ensure early detection and treatment, vector control, surveillance, active case detection and public education. Finally, a mass drug administration program to immigrants living in the affected areas was also implemented [52]. The CDC has recently issued guidelines for the presumptive pre-departure treatment of asymptomatic malaria in refugees from sub-Saharan Africa [53]. Similar measures could be implemented for immigrants arriving in Europe from malaria endemic countries, which should include screening for malaria among the newly arrived to prevent clinical malaria in this population and curtail the possibility of transmission to local mosquitoes. An additional measure one should take into account when considering malaria prevalence in immigrants, is the existence of asymptomatic individuals with sub-microscopic *P. falciparum* parasitaemia, and the fact that asymptomatic carriers of *Plasmodium vivax* liver hypnozoites are impossible to detect with any of the currently available methods.

There is no common malaria treatment policy currently adopted by all European countries. Treatment regimens are based on WHO recommendations and vary from country to country, occasionally even between centers within the same country. There is extensive heterogeneity in the management of imported falciparum malaria in Europe for which discussions toward a consensus for management standardization of malaria might be beneficial [54]. *P. falciparum* susceptibility to antimalarials is not assessed in the laboratory; rather it is extrapolated based on the geographical origin of the infecting strain, and national or WHO recommendations are followed accordingly [55, 56]. The issue of antimalarial drug resistance does not constitute an imminent threat for Europe. If any, it might constitute a threat to individual patient health, chiefly when imported *P. falciparum* is involved, but given that disease prevalence in Europe is extremely low (even taking immigrants into account), this issue currently has no public health relevance.

Regarding the susceptibility to insecticides of European putative and confirmed malaria vector species in countries where malaria is not endemic, data originates from small-scale studies and is limited [57, 58]. As of this date, there is no systematic report on the status of *Anopheles* susceptibility to insecticides in the European Region.

5. Concluding remarks

Increasing concern about emerging infectious diseases has rekindled scientific and public interest in malaria. Reminders of widespread malaria endemicity across Europe in the past, the continuing presence of known and emerging vectors and the reality of a substantial population influx—including potential parasite carriers—from endemic areas combined with projections of climate change have raised the question of a possible re-emergence of malaria foci in the continent. Taking geomorphological, climatic and entomological factors into account, the risk of malaria resurgence appears to differ in various parts of Europe. In the northwest, manmade environmental changes in housing and livestock farming has led to continuing loss of breeding sites for *An. atroparvus*, the major vector in the area. In the event of a temperature rise in the region, mosquito survival would increase and *Plasmodium* sporogony would be facilitated, but the scarcity of mosquito vectors and the tendency of relevant species to preferentially feed on animals create an epidemiological setting where there is practically no considerable threat of renewed autochthonous transmission. *An. plumbeus*, with its reported adaptability to urban habitats and increased anthropophily could assume a more epidemiologically significant role as a vector in the future. Even so, however, provided that healthcare retains its current high standards, timely treatment of patients would prevent the buildup of an infectious human reservoir, thus preventing establishment of the parasite in the local mosquito populations. An influx of human gametocyte carriers could result in limited local transmission around untreated patients, which would be spatially and temporally restricted, provided of course that local healthcare services are aware of the risk and effective in early case detection and treatment.

Regarding Southern Europe, there can be no doubt that current climatic conditions are favorable for malaria transmission in selected areas, where competent mosquito vectors like *An. labranchiae* and *An. sacharovi* are also present in epidemiologically significant densities. The recent occurrence of sporadic autochthonous cases and minor outbreaks has demonstrated that previously endemic malaria parasite species, principally *P. vivax,* are still theoretically transmissible in the area. A future temperature rise might expand vector distribution and abundance, increasing the risk for malaria transmission in the long run, but such a change is unlikely to develop overnight. However, two variables that could unpredictably influence vulnerability south of Europe are changing rapidly, that is, population movement and economic hardship. It was only 20 years ago that Turkey and central Asia experienced epidemic malaria resurgence from small residual reservoirs, demonstrating the catalytic impact mass population displacement and socioeconomic upheaval could have on malaria epidemiology in vulnerable areas. Europe is currently witnessing an unprecedented influx of immigrants from malaria endemic areas, many of which are asymptomatic carriers of dormant *Plasmodium* forms. It is believed that the highly organized and efficient European healthcare services can avert malaria re-establishment through prompt diagnosis and treatment, provided that they maintain their current high operational standards. However, nowadays malaria is being imported into Europe through areas severely affected by economic recession, which is putting an increasing strain on available health resources for natives and migrants alike. Therefore, although the resurgence of malaria in Europe is currently unlikely, it is crucially important to improve, maintain and financially support disease awareness, diagnostic expertise, clinical competence, sustained surveillance and vector control to ensure that malaria is not allowed a foothold in the European continent.

Finally, it would be remiss not to mention that malaria history has repeatedly demonstrated the precariousness of malaria control. To quote Bruce-Chwatt and de Zulueta [59] "… *any deterioration of organized services by a major catastrophe or war may bring back to Europe a series of communicable diseases among which malaria would not be the last*." Indeed "…*the simple truth is that there will be no safety from any infectious disease as long as vast reservoirs of pathogens remain in parts of our shrinking world in which the Atlantic and the Pacific Oceans are figuratively demoted to the status of intercontinental rivers."*

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