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Research article

Historical and Epidemiological study of malaria cases of the "Refugee Hospital" in Veria in the context of Anti-Malaria Battle in Greece (1926–1940)

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ABSTRACT

Objectives: This Historical Epidemiological study aims to evaluate malaria in Greek refugees during the 1926–1940 period in the region of Imathia, Central Macedonia, Greece, in the context of the Anti-Malaria Battle in Greece.
Materials and methods: The archives of the Refugee Hospital of Veria, Imathia were examined (March 5, 1926 to October 27, 1940); this is a report of previously unpublished primary material comprising 15,921 cases, of whom 8,408 patients were hospitalized due to malaria. Multivariate logistic regression analysis was performed to identify independent risk factors for hospitalization due to malaria; adjusted odds ratios (ORs) and 95% Confidence Intervals (CIs) were estimated.
Results: Residence in lower elevation (adjusted OR = 0.95, 95% CI: 0.92–0.97, per increments of elevation), refugee status (from Bulgaria/Balkans, Caucasus, Constantinople and Thrace, Pontus and inland of Turkey), female gender, and younger age (adjusted OR per 10-year increase = 0.88, 95% CI: 0.86–0.90) correlated independently with hospitalization due to malaria.
Conclusions: Malaria was the leading cause of admission to the hospital in the region of Imathia during the studied period. The association with elevation reflects the aggravating role of marshes before the drainage of Lake Giannitsa.

1. Introduction

The word "malaria" originates from the Italian words mala (bad) and aria (air) (Kardamatis, 1932). It was used by the Italians to describe the causes of intermittent fevers (Kardamatis, 1908) resulting from exposure to marshes (Livadas and Sfagos, 1940), the weather conditions in Greece, as well as soil and hydrological factors, favor the formation of marshes with stagnant waters (Griffing et al., 2014). Malaria is a mosquito-borne infectious disease caused by parasitic single-celled microorganisms belonging to the *Plasmodium* group, discovered in Algeria, on 6 November 1880, by Charles Louis Alphonse Laveran (1845–1922) (Laveran, 1884; Gardikas, 2018). *Plasmodium vivax* (the cause of benign tertian fever), *Plasmodium ovale* (the cause of benign tertian fever - Ovale group), *Plasmodium malariae* (the cause of quartan fever) and *Plasmodium falciparum* (the cause of malignant tertian fever) are responsible for malaria. In 1902, Ronald Ross received the Nobel Prize for his research that showed the role of the female *Anopheles* in the dissemination of malaria (Dardavesis, 2001). The disease is transferred by mosquitoes and according to the Centers for Disease Control and Prevention (CDC) has an incubation period 7–30 days.

Malaria was endemic in Europe, primarily in Bulgaria, Italy, Romania, Russia, Spain, Ukraine, and in non-European English and French colonies

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Figure 1. The insignia of the Greek Anti-Malaria League.

during the Interwar period. On the initiative of Italian hygienist and epidemiologist Alberto Lutrario (1861–1937) the Malaria Commission to control the disease was founded in 1924 and the First International Congress of Malaria was held in Rome on October 4, 1925 (Gachelin and Opinel, 2011; Gordon, 1978). Malaria was also a major public health issue in the Ottoman Empire; malaria and tuberculosis were also serious challenges during the Turkish War of Independence (1919–1922). Therefore, after the proclamation of the Turkish Republic in 1923, programs were developed to combat malaria and since 1926 Turkey had been providing free diagnosis and treatment for malaria by the Ministry of Health structures (Kratz and Bridges, 1956; Piyal et al., 2013; Özbilgin et al., 2011).

In Greece, before the beginning of the Anti-Malaria Battle (1905) the absence of an organized public health system was crucial. The State was largely ignorant about the treatment of infectious diseases and therefore there was no pertinent legislation. During the Panhellenic Medical Congress of 1901, infectious diseases were thoroughly discussed and a session was especially dedicated to malaria. A similar meeting took place in 1903 at the Panhellenic Medical Congress where a law was proposed on the importation and circulation of quinine exclusively by the State. However, the proposals were not implemented. As a result, in 1905 the Anti-Malaria Battle officially began.

The Anti-Malaria Battle in Greece is divided into three periods: 1905–1930, with the support of the Greek Anti-Malaria League; between 1930-1945, with the support of the School of Hygiene and the Rockefeller Foundation; and 1945–1960, with the contribution of the Hygiene Center of Athens, the School of Hygiene, and the UNRRA (United Nations Relief and Rehabilitation Administration).

On February 18, 1905, inspired by the Italian League that had been founded by Angelo Celli (1857–1914) (Evans, 1989; Celli, 1933) and frustrated by the state's indifference towards malaria (Mandyla et al., 2011), Konstantinos Savvas (1861–1929), Professor of Hygiene and Microbiology at the School of Medicine at the National Kapodistrian University of Athens, and the pediatrician Ioannis Kardamatis (1859–1942) founded the Greek Anti-Malaria League (Michaleas et al., 2020). Its members were professors of medicine and pharmacy, deputies, journalists, pharmacists, doctors, bankers, clergymen, civil servants, and businessmen. The statute was approved by Royal Decree on April 4, 1905, and the League came under the patronage of King George I of Greece (1845–1913) (Kardamatis, 1928). The insignia of the League depicts the victory of Hercules at the Lerna marsh (Figure 1).

This study focuses on hospitalization due to one of the most common infectious diseases, namely malaria, in Greek refugees that, following the Treaties of Neuilly (1919) and Lausanne (1923) arrived from various places, including Thrace, Pontus, the hinterland of Turkey, Bulgaria/Balkans and the Caucasus, during one of the most important and difficult periods for the history of Europe and Turkey, just after the Greco-Turkish War (1922) and the Turkish War of Independence (1919–1923).

This study aims to evaluate malaria in Greek refugees during 1926–1940 in the region of Imathia, Central Macedonia, Greece, in the context of the Anti-Malaria Battle in Greece.

2. Materials and methods

Our data was collected between April 2014 and December 2014 at the archives of the General Hospital of Veria. The research was approved by the Hellenic Data Protection Authority (21.11.2013, Ref. ΓΝ/ΕΞ/5965-2, Permit Number 1235) and the 3rd Health District of Macedonia (09.01.2014, Reference Number Δ3β/297). Moreover, the details of the study were reviewed and approved by the relevant institutional review board committee (22.01.2014, Reference Number 472). The unpublished archival material contains 15,921 patients who were admitted to the Refugee Hospital from 5.3.1926 to 27.10.1940. Information about gender, age, place of residence, place of origin, cause, description, length

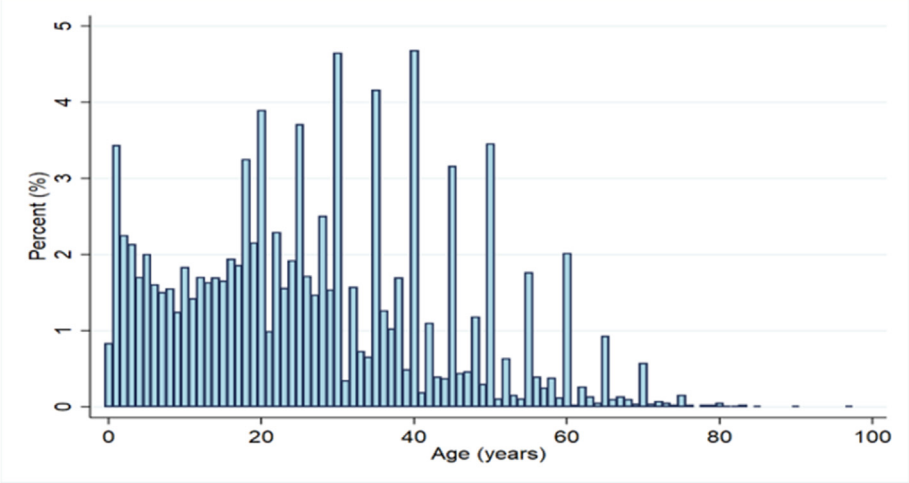


Figure 2. Histogram presenting the distribution of age of hospitalized cases due to malaria in the Refugee Hospital in Veria.

Table 1. Terms describing manifestations of malaria cases in our sample, 1926–1940.

General	
Malignant malaria	Fatal malignant malaria
Post malarial malignant anemia	Persistent malaria
Persistent malignant malaria	Chronic malaria
Persistent chronic malaria	Exacerbation of chronic malaria
Malaria with uremia	
Malaria involving the urinary system	
Hemoglobinuria	Hemoglobinuric fever with jaundice
Hemoglobinuria in remission	Slight hemoglobinuria
Malignant malaria (generating uremia)	"Hemoglobinuric malignancy"
Malignant hemoglobinuria	Hemoglobinuric fever
Severe hemoglobinuria	Malaria with dysuria
Swamp nephritis	
Malaria – related fever	
Malignant swamp fever	Malignant fever
Malaria involving CNS	
Malignant malaria with seizures	Childhood malaria, type with seizures
Cerebral malaria	Chronic malaria, type with seizures
Malaria – related cachexia	
Malignant fever and swamp cachexia	Swamp cachexia
Types of visceral malaria	
Gastric malaria	Intestinal malaria
Visceral malaria	Biliary malaria
Persistent malaria with "gastrism"	
Malaria – related anemia	
Malaria with swamp anemia	Chronic malaria with malignant anemia
Acute malaria	
Acute malaria	Acute malignant malaria
Skin malaria	
Skin malaria	

and date of hospitalization, and self-reported religion was abstracted from the archive records for all hospitalized patients. Records were entered into a pre-coded database, so that analysis could follow. Regarding place of residence for hospitalized patients, the elevation of each settlement was individually sought and registered in Google maps.

Descriptive statistics were calculated regarding malaria cases. Multivariate logistic regression analysis was performed to identify independent risk factors for hospitalization due to malaria; adjusted odds ratios (ORs) and 95% Confidence Intervals (CIs) were estimated. Specifically, risk factors examined were altitude (incremental variable: 0–49, 50–99, 100–149, ≥150 m), place of origin (Greece set as reference category, Aegean Coastal Turkey, Bulgaria/Balkans, Caucasus, Constantinople and Thrace, Pontus, and Inland of Turkey), age (increment by 10 years), and gender (women as reference category). Statistical analysis was conducted with STATA/SE version 13 (Stata Corp., College Station, TX, USA). The map designed was made with GSIS 3.6 and the elevation of each settlement was calculated using Google Earth.

3. Results

At the Refugee Hospital of Veria, 52.8% (8,408 persons) were hospitalized due to malaria (from 5.3.1926 to 27.10.1940); women accounted for 51.0% (n = 4,287) of the patients. Age ranged from infants to 98 years old (Figure 2); it should also be noted that 35.2% of malaria-treated patients ranged from 0 to 18 years of age and the mean age was 26.7 years (SD = 17.1). The vast majority (99.0%, n = 8,324) were Orthodox Christians.

Table 1 presents the various terms describing manifestations of malaria cases in our sample, 1926–1940. Various terms were noted, presented malaria in general, malaria involving the urinary system, malaria-related fever, involvement of CNS, cachexia, anemia, types of visceral malaria, as well as acute malaria cases. The hospital had to deal with numerous cases of malaria daily with a capacity of only 45 beds. The chart (Figure 3) presents the average number of hospitalized cases per day separately for each month during the study period. The total hospitalizations are shown in red color and those of malaria are depicted in green. Seeing the graph as a whole, we found that the two lines follow the same pattern, namely the total number of incidents was actually determined by the flow of malaria incidents. Peaks were observed in late summer/early autumn, coinciding with the corresponding peaks of malaria incidents (August 1928, September 1932, August 1933, September 1936, and September 1940).

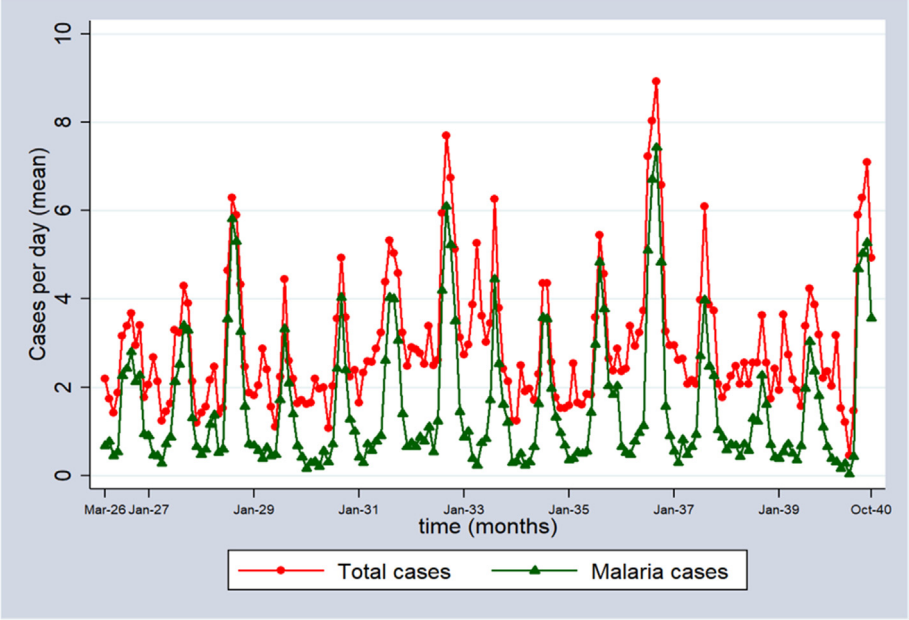
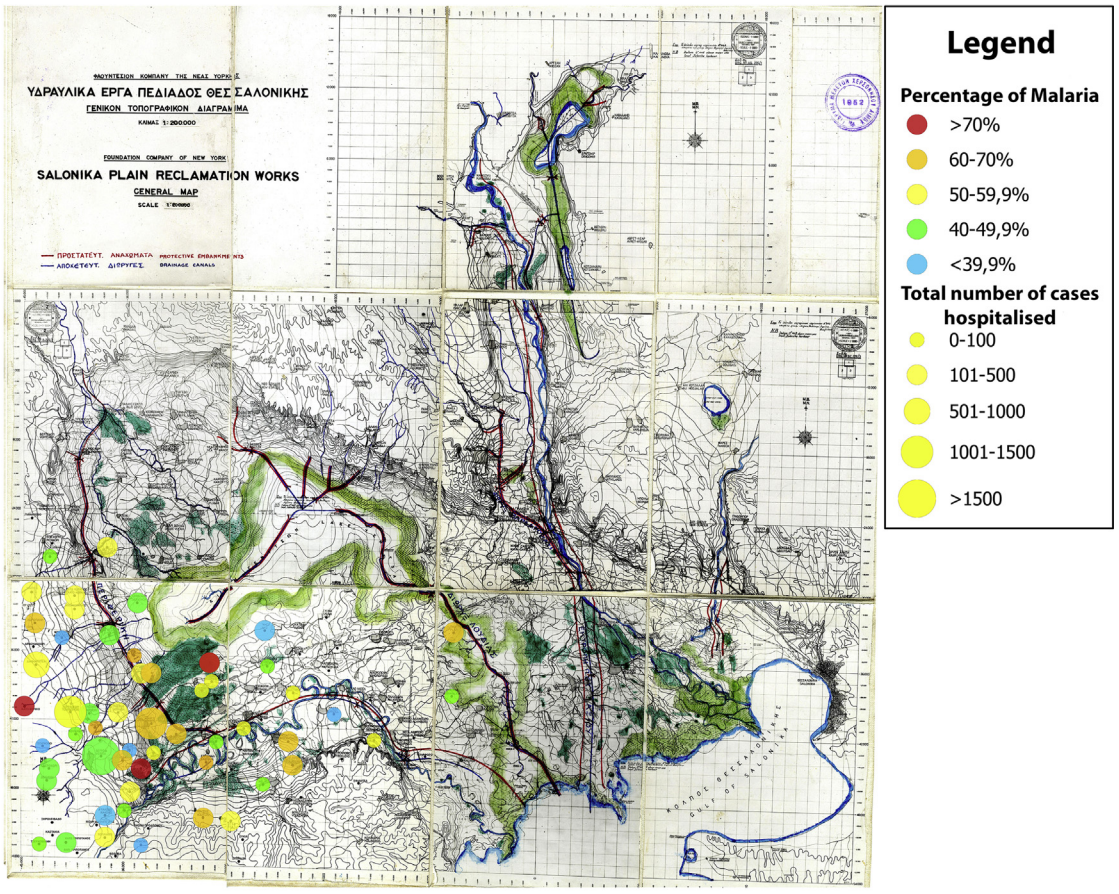


Figure 3. Line chart presenting the mean number of hospitalized cases per day (total cases: red line; malaria cases: green line).

a



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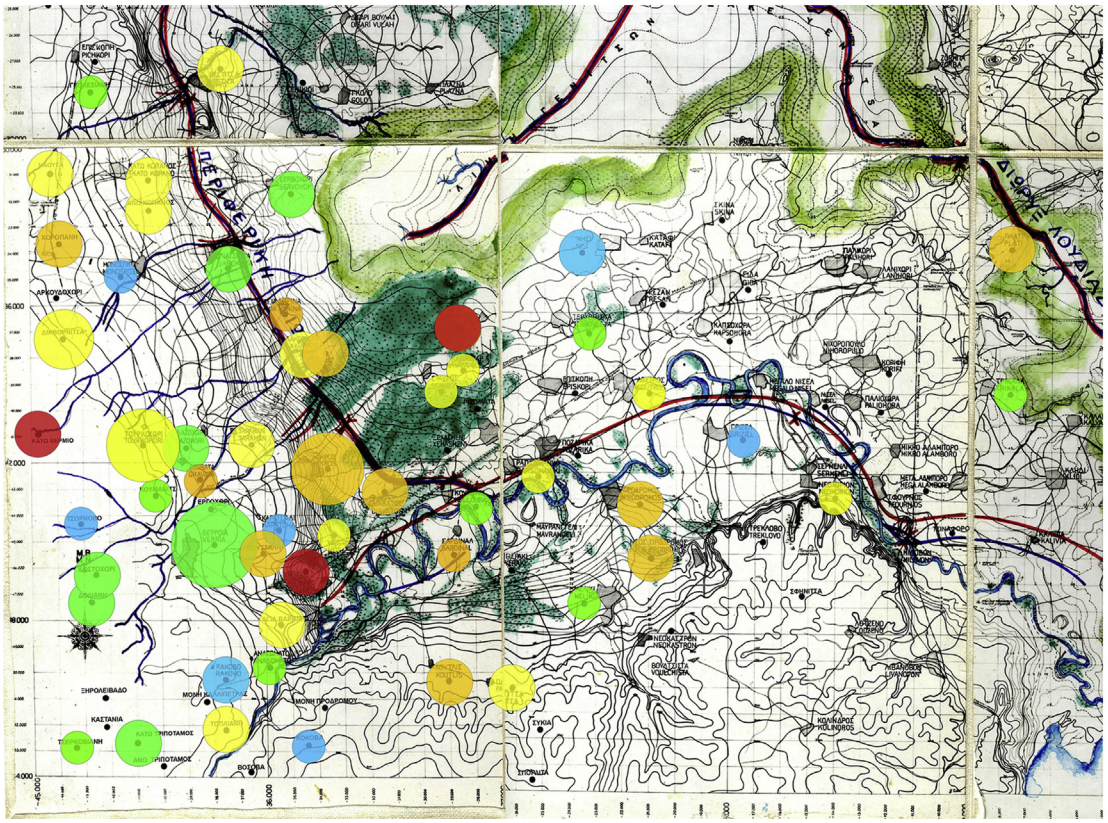

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We noticed that the villages located around the marshes (like the one near Vergina) present high rates of malaria (Figure 4a, b). Logistic regression analysis confirmed this observation (Table 2); in particular, the increase by one category (increment) in the 0–49, 50–99, 100–149, ≥150 m classification was inversely associated with the likelihood of malaria admission (OR = 0.95, 95% CI: 0.92–0.97, $p < 0.001$). Regarding the place of origin, refugees from Bulgaria/Balkans, the Caucasus, Constantinople, Thrace, Pontus, and the hinterland of Turkey were more likely to be hospitalized due to malaria than the native population ($p < 0.001$ for all the aforementioned comparisons). Concerning age, the results of multivariate logistic regression analysis showed that older age correlated inversely with the odds of malaria admission, and in particular that a 10-year increase in age was associated with a reduction in malaria odds by 12% (OR = 0.88; $p < 0.001$). Finally, in relation to gender, it was noticed that women had a higher probability of hospitalization than men ($p < 0.001$).

In our archive material we noticed hospitalizations due to undesirable side effects of quinine, used to treat malaria (Table 3). We also noticed a peculiar case where a 20-year-old worker was been admitted to the hospital due to "suicide attempt by quinine tablet"; the worker was successfully discharged from the hospital the same day.

4. Discussion

Malaria has been the leading cause of hospitalization in our study material. The high rate of hospitalization was due not only to extensive uncultivated marsh areas (Kardamatis, 1924) but also to climatic conditions that helped the spread of mosquitoes. The fact that many refugees originated from contaminated or from marshy areas (Bozhkov, 1966), such as Amisos of Pontus, Caucasus, and Aydin, had taxed their health, especially since in Greece settled in infectious areas. For instance, Veria is located near both the Aliakmonas River and the Giannitsa Marsh Lake. The Greek jurist and politician Georgios Modis (1887–1975) recalls about the lake that it was an independent kingdom of waters, leeches and mosquitoes, while the Greek soldier at the Macedonian Front Grigoris Dimopoulos, wrote in his journal: "Serious smell, moisture, mold, mosquitoes and other bugs, real hell". The mosquitoes even pierced the thick clothes of the soldiers to suck blood, thus transmitting malaria. The soldiers were forced to burn greens, so that the smoke could kill the insects (Modis, 1967).

Our multivariate analysis highlighted that in relation to elevation, the areas far away from the marshes were less prone to malaria hospital admission. For the creation of new land plots for refugees, the American company "Foundation Company of New York" undertook the drainage of the lake. The works lasted from 1928 to 1937. Regarding the cases of malaria (Tzamalis, 1916), a considerable variety of manifestations was noted; the disease was referred to by various names such as malignant fever, swamp cachexia and acute malaria.

A seasonal pattern was documented in our analysis. The peaks in summer are expectable, as malaria is transmitted by mosquitoes that are abundant in the summer. However, it is worth observing a different pattern in winter months, when malaria cases were minimal while total morbidity appeared to be significant. Looking back on our records, we found that this impressive deviation was mainly due to the incidence of pneumonia and respiratory infections unrelated to malaria. Interestingly, there was a sharp decline in the height of the malaria peak between 1928 and 1929, as the winter of 1928–1929 was characterized by extreme cold (the lowest recorded temperatures over the last 100 years from now) for Macedonia, which may have affected the mosquito's life cycle and consequently the epidemiology of malaria in the region. Regarding the presence of malaria in the area after the drainage of Lake Giannitsa in 1937, we noticed that it continued to appear until the late 1940s. Further studies beyond that time interval should be performed to study the long-term, beneficial effect of the lake's drainage upon malaria incidence in the region.

The main goals of the Anti-Malaria League in Greece were to raise awareness of the disease, its control and eradication, and the drainage of marshes (Vakalis, 2008). The League also distributed information leaflets about the origin, treatment, and prophylaxis of malaria throughout Greece (Dafoulis, 2008). The first act of the League was held in Oropos during the summer of 1905. Within a few days, 1,000 g of quinine were dispensed and Kardamatis was forced to seek the government's help to send additional grams (Tsiamis et al., 2013). The difficulty of importing quinine and shortage caused the adulteration of supply and the surge of its price in the domestic market (Savvas, 1928). Hence, on February 13, 1908, the State passed the Law 3252 (Official Government Gazette, 1908) concerning quinine's monopoly (Pomonis, 1925).

After 1924, the government had no longer control over the import of quinine. The circulated "new quinine" contained 0.1 g of substance per tablet, even though the notation on the box was 0.2 g. Due to the increased demand for quinine, the prime minister Eleftherios Venizelos (1864–1936) established the Law 4070/1929 which repealed the import duty of quinine and regulated its price which could not exceed the corresponding wholesale price in Athens allowing for a 30% profit; quinine was distributed free of charge to those who could not afford it. It is noteworthy that according to the local press of Veria in 1930, a quinine adulteration scandal appeared, resulting in the arrest of the Director of the Thessaloniki Chemical Laboratory. In 1931, Law 5043 defined the import, packaging, and sale of quinine and made the Ministry of Health responsible for the substance, preventing its illegal importation by private pharmaceutical manufactures.

The Refugee Settlement Commission had purchased 19,000 kg of quinine in tablets and 5 million cartridges and was selling them at a low price to the refugees (Krimpas, 1999–2000). The Director of the Health Service, Manthos Metalinos, reported that during the years 1925–1930, 10,000 cartridges were distributed to the Refugee Hospital of Veria free of charge (Metalinos, 1932). In May 1925, the Commission founded the Health Service of Macedonia-Thrace to combat malaria in Northern Greece (Dimissas, 1976). In 1928, malaria cost approximately 700 million drachmas per year to the State (Katsapis, 2007).

The Athens School of Hygiene was founded in 1929 (Law 4069) (Kontogiorgi, 2016) that included a dedicated Department of Malaria (Dardavesis, 2005). Meanwhile anti-malaria infirmaries and experimental malaria stations had been established throughout the country. In 1930, under Eleftherios Venizelos Premiership, the Anti-Malaria Commission became part of the Ministry of Health (Law 4555/1930) with an annual funding at an estimated 24 million drachmas. Intense reactions from the opposing party due to the excessive funding led to the abolition of the Commission. In response the Ministry of Health founded the Department of Anti-Malaria Battle and the country was split into four sectors, each headed by Malaria Inspectors (Kopanaris, 1933). In 1939, the Directorate of Anti-Malaria Battle divided Greece into six sectors with corresponding experimental anti-malaria stations and infirmaries. During the Athens Hygiene Exhibition in 1938, kiosks n. 23/24 included the Anti-Malaria Battle and the importance of quinine (Tsiamis et al., 2014).

Figure 4. The colored imprinted map combines the malaria rates and the number of admissions per village (a, b). The map shows the villages who had 21 incidents and more (>21). Villages with fewer incidents (<21) are imprinted with a black dot. For its creation it was necessary to register the patient admissions to the hospital from each village and isolate those who presented with malaria. The diameter of the circle is proportional to the number of the total patient admissions per village, while its color indicates the proportion of malaria hospitalization on the total admissions per village. More specifically, in red appear the incidents of malaria above 70%; in orange from 60 to 70%, in yellow from 50 to 59.9%, in green from 40 to 49.9%; in blue less than 39.9%. This figure is based on the map of Salonica plain reclamation works by the Foundation Company of New York; Institute for Balkan Studies (I.B.S.), Thessaloniki, Greece, reproduced with permission (a: the whole plain; b: zoon in Veria region).

Table 2. Results of multivariate logistic regression analysis examining factors independently associated with hospitalization due to malaria.

Variable	Category/Increment	Adjusted OR	95% Cl	p-value
Altitude	Incremental variable: 0–49, 50–99, 100–149, ≥150 m	0.95	0.92–0.97	<0.001
Place of origin	Greece	1.00	Ref.	
	Aegean Coastal Turkey	1.11	0.94–1.32	0.203
	Bulgaria/Balkans	1.82	1.58–2.10	<0.001
	Caucasus	1.55	1.40–1.71	<0.001
	Constantinople and Thrace	1.47	1.32–1.64	<0.001
	Pontus	1.69	1.52–1.87	<0.001
	Inland of Turkey	1.57	1.39–1.78	<0.001
Age	Increment by 10 years	0.88	0.86–0.90	<0.001
Gender	Woman	1.00	Ref.	
	Man	0.82	0.77–0.87	<0.001

CI: Confidence Interval; OR: odds ratio.

Table 3. Side effects of quinine in our study sample.

Side effect	Frequency (cases)
Hemoglobinuria after intake of quinine	2
Gluteal abscess after quinine injection – abscess drained	1
Abscesses due to quinine injection	2
Gangrene of right thigh after injection of quinine	1
Slight poisoning due to quinine	1

At that period, the most widespread malaria treatment was quinine. They considered it a safe medicine because it did not show any dangerous or toxic side-effects. In 1920, quinine was commercialized under the name *Athermoli* produced by the pharmacist Elias Katsogiannis from Thessaloniki, which he provided free of charge to those who had been afflicted (Simeonidou, 2011). In addition, the Italian company Bisleri exported to Greece the pharmaceutical product *Esanofle* and the Greek company Spes produced the well-known *Antithermoli* (Diamantopoulos and Marselos, 1993). At the beginning of the 20th century Dr. H. Philippe released the *Antidote-malaria* which contained quinine, adrenalin, iron, and extracts of cinchona bark, bile, and spleen (Philippe, 1922).

In our archive material we noticed hospitalizations due to undesirable side effects of the drug. Quinine could be administered intramuscularly but with serious side-effects: tissue necrosis that led to the hardening of the skin, abscess, tetanus, sciatica, convulsions, loss of consciousness and varicosities, while administered subcutaneously caused inflammation, tissue necrosis, and local injury. It was also prescribed in under the form of rectal suppositories, and tablets and capsules for oral administration.

At that era, the elimination of mosquitoes in their aquatic stage (larvae) was considered the most effective method to combat malaria at the local level. The drainage, the embankment, and the removal of water from residential areas resulted in the disappearance of the habitats where larvae grew. Other measures were also used: supply of the small fish *gambusia affinis* from Italy for the destruction of mosquito larvae –a measure that failed because the fish became prey to other, native fish (Livadas, 1936); applying oil to the surface of the water –a measure both poisonous and toxic, expensive, and malodorous; placing of metal screens at the entrances and windows of the houses (Gardikas, 2008).

Refugees and migrants always constitute vulnerable population groups, and their movements present a concern for the state. Tracing the interrelationships between history, refugee memory, and the geopolitical challenges presented by the movement of peoples necessitated by modernity, it should be noted that current refugee movements in Greece bear similarities and differences with those occurring during the Interwar period (Benelli et al., 2018). Greece was declared "malaria free" in 1974 after an intensive eradication program. According to the Hellenic Center for Disease Control and Prevention (H.C.D.C.P.) the current movement of refugee populations between 2015 and 2018 correlate with a slight uptick of malaria incidents. Epidemiological reports on malaria recorded 262 cases from January 2015 to September 2018 (an average of 85 cases per year).

5. Conclusion

Malaria was the leading cause of admission to the hospital in the region of Imathia during the studied period. The correlation with the elevation of the area reflects the aggravating role of the marshes in the area before the draining of lake Loudias by the Foundation Company of New York. The findings of this study confirm what the Prime Minister of Greece Eleftherios Venizelos underlined in his July 1928 speech in Thessaloniki, namely that malaria was one "social scourge" of the Interwar period.

Declarations

Author contribution statement

Spyros N. Michaleas, Theodoros N. Sergentanis, Neni Panourgia, Artemis K. Tsitsika, Theodora Psaltopoulou, Athanase D. Protogerou, Marianna Karamanou: Conceived and designed the analysis; Analyzed and interpreted the data; Contributed analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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