MEDICAL UNIVERSITY OF SOFIA
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Topic:

ASSESSMENT OF HEALTH TECHNOLOGIES AND APPLICATION OF APPROACH TO MALARIA DISEASE IN BULGARIA

DISSERTATION ABSTRACT FOR ACQUISITION OF
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The dissertation work has been approved and directed for defense by the departmental council of the "Assessment of Health Technologies" Department at the Faculty of Public Health "Prof. Dr. Tsekomir Vodenicharov, PhD", Medical University - Sofia.

The dissertation contains 151 pages and is illustrated with 30 tables and 27 figures. 1 appendix is presented to it. The bibliographic reference contains 252 sources, of which 39 are in Cyrillic, 8 are in Greek and 205 are in Latin.

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Defense materials are available at the secretariat of the Dean's Office of the Faculty of Public Health "Prof. Dr. Tsekomir Vodenicharov, PhD, UMBAL "Tsaritsa Joanna - ISUL: EAD, 8 Byalo More St., Sofia. The numbering of the tables, figures and graphs does not correspond to that in the dissertation.

Abbreviations used

GDP – Gross Domestic Product

GMAP - Global Malaria Action Plan

DDT - dichlorodiphenyltrichloroethane

EC – European Commission

EU - European Union

LMPHM - Law on Medicinal Products in Human Medicine

BDA - Bulgarin Drug Agency

MP - Medicinal Product

MH - Ministry of Health

ICD - International Classification of Diseases

NHIF - National Health Insurance Fund

NCPRMP - National Council on Prices and Reimbursement of Medicinal Products

ARF – Acute Renal Failure

HTA – Health Technology Assessment

OTC - Drugs without a prescription

PDL - Positive Drug List

MAH - Marketing authorisation holder

RHI – Regional Health Inspection

USA - United States of America

WHO - World Health Organization

SOP - Standard Operating Procedure

MEF - MEFLOQUINE

CHL - CHLOROQUINE

P - PROGUANIL

DOX - DOXYCYCLINE

SP - SULFADOXINE + PYRIMETHAMINE

MAL - MALARONE (ATOVAQUONE + PROGUANIL)

SPC - Summary of Product Characteristics

DP - Direct Payments

„Malaria has long been a devastating and life-threatening global epidemic disease in human history.“

Prof. Tu Youyou - 2015 Nobel Laureate in Physiology or Medicine, awarded "for her discoveries concerning a new therapy against malaria"

Introduction

Malaria is one of the most common infectious diseases, known since ancient times. It is the most significant tropical disease causing high mortality. In one form or another, it infected and affected our ancestors long before the origin of modern man. During our recent evolution, the influence of the malaria parasite has probably been greater than that of any other infectious agent. The dissertation reviews the current burden of malaria worldwide and discusses current approaches and health technologies for its treatment and management.

Only by following or attempting to analyze malaria through its evolution and history can we understand its character and so be better prepared for our future management of this ancient disease. Malaria is a very old disease and references to it almost certainly being present in antiquity can be found in many extant epistolary sources: a Chinese document dated to 2700 BC, the clay tablets (cuneiform writing) from Mesopotamia from 2000 BC, Egyptian papyri from 1570 BC and Hindu texts from as early as the 6th century BC. All of these are believed to be the first written evidence that describes symptoms specific to malaria.

According to the official position of the Ministry of Health in Bulgaria, based on data from the World Health Organization (WHO), malaria is the infectious disease that is defined as the most widespread in terms of the number of infected worldwide. **It is a serious health problem in more than 100 countries, the territory of which is inhabited by about 2.4 billion people (this represents 40% of the population of the earth).** According to WHO estimates, in 2021 more than 247 million people were infected with malaria and 568,000 died as a result. In 2019, nearly 4 out of 5 deaths were of children under the age of 5. Malaria mortality halved between 2000 and 2015 from 30.1 per 100,000 population at risk to 15.0 per 100,000; it continued to decline thereafter, reaching 14.0 per 100,000 in 2019. In 2020, however, the death rate increased to around 15.1 per 100,000 of the population at risk, before falling slightly to 14.8 in 2021

"After the significant reduction of malaria in the middle of the last century, in almost all countries of the European region of the World Health Organization, at the end of the 20th century, a new upsurge of this parasitosis began. Processes of outbreaks of epidemics are also observed in a number of countries of Central Asia, the Caucasus and in neighboring Turkey. New cases imported into Europe from malaria-endemic regions and countries are also increasing. For the period 1998-2007, there were 125,330 reported cases, of which 561 were fatal. During the same period, 421,470 indigenous cases of malaria were officially registered in the WHO European Region.”

The disease is currently believed to be a threat to about 3.2 billion people in nearly 100 countries and territories worldwide. In order to limit the spread of the above-mentioned parasitosis, the WHO developed and adopted a "Global Malaria Programme", which was updated in 2021, and according to which by 2030 malaria in the endemic countries of the

European Region should be eliminated, as well as not allow the restoration of its local transmission in the countries where it was liquidated. The program consists of three main pillars, which are actively being worked on:

• Ensuring access to malaria prevention, diagnosis and treatment as part of universal health coverage for citizens.

• Accelerating efforts to eliminate and achieve “malaria-free zone”*.

• Making malaria surveillance a key priority for action by governments.

* Malaria-free zone – Countries/zones that have achieved at least 3 consecutive years of zero local cases are eligible to apply for a WHO certificate of malaria-free status.

Malaria cases imported from endemic countries are constantly being diagnosed in Bulgaria. For the period 1966-2008, their number amounted to 2934 people, of which 15 ended fatally. The geographical location of Bulgaria on the Balkan Peninsula, its proximity to the Mediterranean Sea, Asia and Africa and the global warming of the climate, along with the intensive migration of refugees to our country, provide real conditions and opportunities for the transfer and risk of local spread of some endemic tropical and other parasitic diseases. The prospect of parasitic diseases disappearing with a better standard of living and lifestyle of the population is theoretical and currently unrealistic.

Along with local parasitic diseases, some of which are highly prevalent (eg enterobiosis, giardiasis, echinococcosis, trichinellosis), the relative proportion of imported parasitoses is increasing (eg malaria, leishmaniasis, intestinal parasitoses). Currently, they represent a problem for us in two main directions: clinical and therapeutic consequences for the sick and asymptomatic parasite carriers and epidemiological consequences for the population of the country.

For the period 1998 - 2017, we have relatively few patients in our country, their number amounts to 226 Bulgarian and foreign citizens, and 3 of the cases of infection ended fatally.

Chapter I: Aim, objectives and methodology

Aim

The aim of the dissertation is to analyze the modern treatment of malaria and to apply the approach for evaluating health technologies for this disease in Bulgaria.

The objects of research are the patients with malaria in Bulgaria and the organization of the health system for the treatment of the disease in our country.

Tasks

To achieve the set goal, the following tasks are set:

1. To trace the historical development of scientific and practical knowledge about the treatment of malaria and to summarize and analyze the various pharmacotherapeutic options for the disease malaria;
2. To carry out a comparative analysis of the different countries at risk of contracting malaria and to analyze the severity of the studied health problem in Bulgaria and to build a "patient's path";
3. To carry out a specific pharmacoeconomic analysis of the value of the prevention and treatment of malaria in Bulgaria;
4. To make proposals to improve the process of providing drugs for the treatment of malaria in Bulgaria;
5. To evaluate the cost-effectiveness of the use of chemoprophylaxis through a decision tree and a Markov model;
6. To analyze the repositioning of medicinal products for the treatment of malaria, based on currently ongoing clinical trials.

Methodology

The following methods were used in the dissertation:

- Historical method of collecting information and data on the scientific and practical development in the treatment of malaria;
- Documentary research method of the Bulgarian and Greek legal framework related to the treatment of infectious diseases;
- Comparative-legal analysis - the legal framework related to health information was studied, mainly in two countries, the Republic of Bulgaria and the Republic of Greece;

- Method of comparative analysis in the study of the different countries at risk of contracting malaria;
- Pharmacoeconomic method for calculating the cost of malaria prevention and treatment in Bulgaria;
- Statistical method for processing the collected data with software - Microsoft Excel, specialized modeling program TreeAge Pro 64-bit and manually according to selected criteria.

Chapter II: Analysis of the results of the conducted survey

The most important thing for any disease is its prevention. Since during a potential malaria season (for Bulgaria it is from April to October), it is normal to pay attention to the danger of imported tropical parasitic diseases (in the case of malaria) that pose a risk of local transmission, this is the main activity to prevent the spread of the disease. After 1965, only cases imported from endemic countries, as a result of the movement of people, were observed and there is information in our country. In 2021, 9 cases of imported malaria caused by P. falciparum and P. vivax were officially registered in Bulgaria, of which 7 were Bulgarian citizens and 2 were foreign citizens. In the case of two of the Bulgarian citizens, the outcome was fatal.

As described in the world scientific literature, malaria prophylaxis can be carried out depending on the patient's risk of transmission through several different time-tested methods.

For those going to malarious countries, the personal physician should recommend chemoprophylaxis with drugs before, during the stay and after returning to Bulgaria. The table on the spread of malaria, the risk of infection, resistance and recommendations for chemoprophylaxis is published on the website of the National Center of Infections and Prasitic Disease, by the Department of "Parasitology and Tropical Medicine".

In 2015, the WHO made and published in all official languages of the organization a special classification of the risk of malaria. In addition to it, various types of preventive measures for prophylaxis are indicated.

	Risk of malaria	Type of preventive measures
Type A	Very low risk	Precautions against mosquito bites.
Type B	Risk of non-falciparum malaria	Protection against mosquito bites plus chemoprophylaxis with chloroquine or doxycycline or atovaquone - proguanil or mefloquine (choice according to drug resistance data, reported side effects.
Type C	Risk of P. falciparum malaria	Protection against mosquito bites plus chemoprophylaxis with atovaquone – proguanil or doxycycline or mefloquine (choice according to the data.

Table 1 Malaria risk classification and type of preventive measures

a/ Alternatively, for travelers in rural areas with a low risk of malaria, precautions for mosquito bites can be combined with the possibility of emergency treatment (stand-by emergency treatment - SBET).

b/ In some areas with multidrug resistance, chemoprophylaxis with mefloquine is no longer recommended. These areas currently include Cambodia, the Southeast region of Myanmar and Thailand.

More information on countries with endemic malaria can be found in (Table 5) in the dissertation on page 66.

In our country, there are officially approved recommendations for chemoprophylaxis of the Ministry of Health and the National Center for Infectious and Parasitic Diseases.

More information on the chemoprophylaxis scheme in endemic malaria areas can be found in (Table 6) in the dissertation on page 67.

Prevention of malaria with medicinal products and repellents

The table presents the calculation of each prophylactic course described in the chemoprophylaxis scheme. Calculations are made for a patient with a weight 80 kg.

More information on the calculation of each prophylactic course described in the chemoprophylaxis scheme can be found in (Table 7) in the dissertation on page 68.

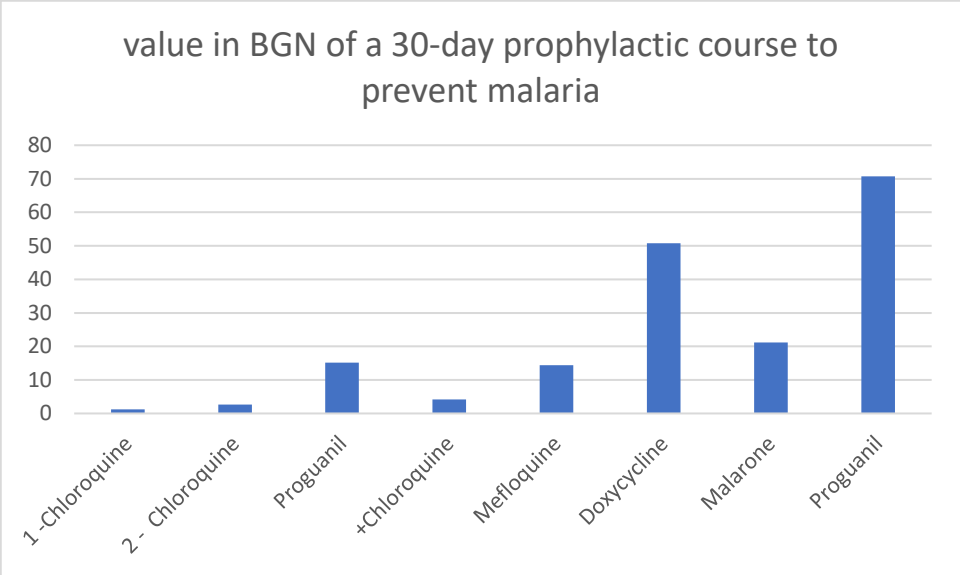


Figure 1 Calculation in BGN of a 30-day prophylactic course to prevent malaria

Other options for prevention are:

- Protection of the organism through repellent:

  Price of repellent Clamax (Clamax©) 50 ml – BGN 7.70.

  Price of repellent Autan (Autan©) BGN 15 – BGN 15.00.

  1. One pack of repellent is approximately enough for 5-10 days to treat open areas of the skin.

  2. Greater security is achieved by using denser/thicker clothes and treating them with a repellent in this case is enough for 3-5 days.

- Protection through nets placed on the windows:

For the protection of a 2-room, 1-kitchen apartment with mosquito nets, there must be at least one net per window sash and the front door.

Average window sash size:
height 1.50 m x width 0.70 m = 1.05 m^2

Average front door size:
height 2.0 m x width 0.8 m = 1.6 m^2

The total area is equal to 1.05 m^2 x 3 window wings + 1.6 m^2 entrance door = 4.75 m^2

1. The price of an anti-repellent net with magnets or a net attached with double-adhesive tape with a square footage between 1 and 2 m^2 is BGN 10 per square meter.

2. The price of a roller blind or a monetary one through a movable frame between 1 - 2 m^2 is BGN 100 per square meter.

- Protection of the sleeping bed by placing a safety net:

Protection by placing a net/canopy on the bed - bedroom with dimensions 1.6 m x 2.0 m - BGN 60.
Other methods of protection:

- Mosquitoes like air temperature to be around 16˚C and high humidity (around 80-90%). Therefore, most of the mosquitoes inhabit the shady shores of lakes, swamps, wet basements, wet meadows, etc. At an air temperature of more than 28˚C, mosquitoes stop flying. For this, it is good to stay in open and sunny places away from water bodies.
- The strong odors of essential oils repel mosquitoes, as do B vitamins. Many essential oils (lemon and eucalyptus, lavender, cinnamon, thyme, citronella, tea tree, and geraniol) can be rubbed into the skin or placed in diffusers or evaporators. The cost of one diffuser is approximately BGN 50, and if it works 24 hours, for the essential oil that would be used for a room of 20 m^2, the applicable rate would be BGN 2-5, depending on the quality of the oil.
- There are also biocides for vaporization using a vaporizer, the price of which is about BGN 10. Vaporization using smoldering candles is also possible. The consumption rate of liquid or laminated tablets is within 0.3 to - 0.5 BGN per day for a room with an area of 20 m^2. Smoldering products have a higher value and cover a shorter period of time. A smoldering spiral repels mosquitoes within 3 to 6 hours and the value varies from 0.5 to 0.7 BGN.

It is important that patients who come from areas with active malaria monitor their condition and, if symptomatic, notify their GP that they are coming from such an area, in order to assess whether and what steps to take and what tests are needed are made. Depending on the condition and severity of the symptoms, the patient's journey starts from the general practitioner or the emergency department. The incubation period varies depending on the causative agent from 7 to 50 days. The general practitioner or the specialist in emergency medicine can judge by running a blood count and hemoglobin, as well as the biochemical indicators ALT, AST and GGT, that it is an acute parasitic infection. In case of doubt, the patient can be referred to the specialized infectious disease hospital or department for additional examination, where there are rapid tests, as well as a specialist who can diagnose the disease by microscopic determination of blood. The following symptoms may be present in a patient infected with the malaria parasite - see (Figure 2)

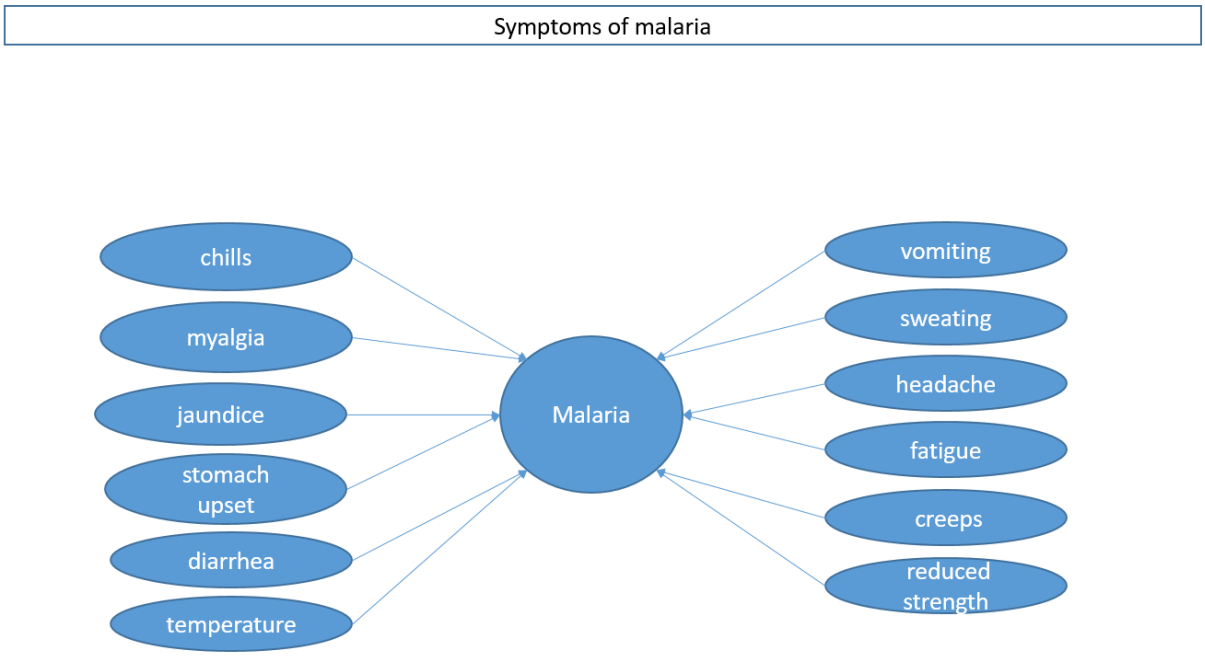


Figure 2 Symptoms of a patient infected with the malaria parasite

A joint health insurance model operates in Bulgaria. This means that a monthly health insurance contribution is paid and, if necessary, the rights granted by the National Health Insurance Fund (NHIF) to the insured person can be used. In order to use medical assistance under the National Health Insurance Fund, the patient must have continuous health insurance rights – all health contributions must have been paid for the last 60 months. If this condition is not met, the health insurance contributions have not been paid or there are missed ones, it is necessary to pay them, after which, from the date of payment, full insurance rights are obtained.

If the patient does not have health insurance, examinations and tests are paid at prices that are announced in the price list of the relevant medical institution. According to the Law on Health Insurance in Bulgaria, for every visit to a doctor, dentist, laboratory or for treatment in a hospital, citizens with health insurance pay a user fee, which remains at their expense. Children are exempt from paying a user fee for out-of-hospital, in-hospital and dental care, but they pay the so-called fee for taking biological material in a laboratory.

For an easier understanding of the possibilities provided by the Bulgarian health system, a "patient's path" has been compiled, which schematically provides information on what steps a person who may potentially be infected with malaria plasmodium goes through.

More information on the pattern of patient movement in the health system after arrival from a malaria-active area can be found in (Figure 11) of the dissertation on page 72. After confirmation of the diagnosis, treatment begins as described in the pharmacotherapeutic treatment guide under clinical pathway No. 99 (A and B). The figure below shows the main steps in the treatment of patients with malaria.

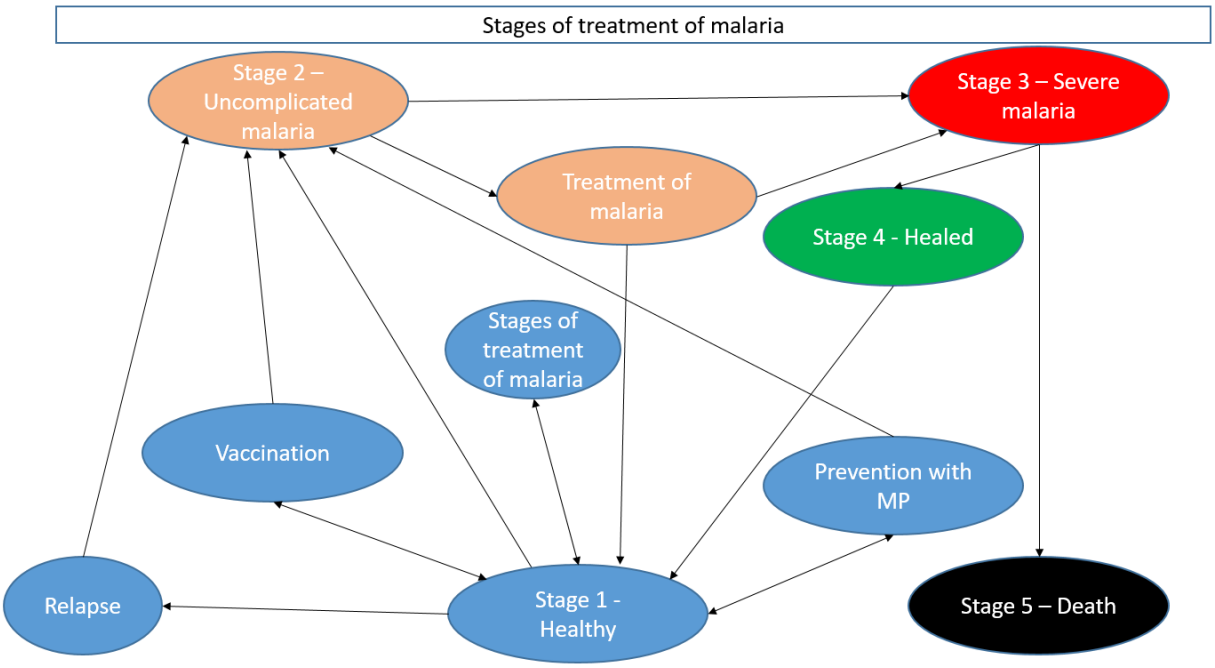


Figure 3 Stages in the treatment pathway of the malaria patient

More information on the treatment algorithm for uncomplicated tropical malaria versus the pharmacotherapy guideline can be found in (Figure 8) of the dissertation on page 73.

More information on the treatment algorithm for complicated forms of tropical malaria versus the pharmacotherapy guideline can be found in (Figure 9) of the dissertation on page 74.

In (Table 2) is shown a calculation of the value of one therapeutic course of treatment of uncomplicated caused by P. malariae according to the recommendations of the pharmacotherapeutic guide. The amount of the administered medicinal substance was calculated on the basis of a person with a weight 80 kilograms. Depending on the patient's weight, practice requires the use of a smaller or larger dose, since the tablets are film-coated, i.e. indivisible. A smaller dose reduces the therapeutic effect, and a larger one can increase side effects, so it is necessary to monitor them carefully and if necessary, reduce the dose.

Treatment algorithm for uncomplicated forms of Plasmodium malariae					
Medical product product (generic name)	Scheme for adults dosage for adults with a weight of 80 kg			цена в лева	
	dosage method in mg	Single dose in mg	Dose for 1 course of treatment in mg	per single dose	price of 1 course of treatment
Chloroquine phosphate tabl. 250 mg (150 mg base)	The total course dose for adults is 25 mg/kg body weight. for a 3-day course (10 – 10 – 5 mg/kg body weight daily)	800/800/400	2000	0.84/084/0.42	2.104

Table 2 Treatment algorithm for uncomplicated forms with Plasmodium malariae according to the pharmacotherapeutic guide

On (Figure 4) a calculation of different types of medicinal products, as independent therapy, is made. Some of these medicinal products are combined and contain two medicinal

substances to enhance the healing effect and reduce resistance. The calculation of each therapeutic dose is based on 80 kg. body weight of the patient for one therapeutic course of treatment, as for all medicinal products the course is different.

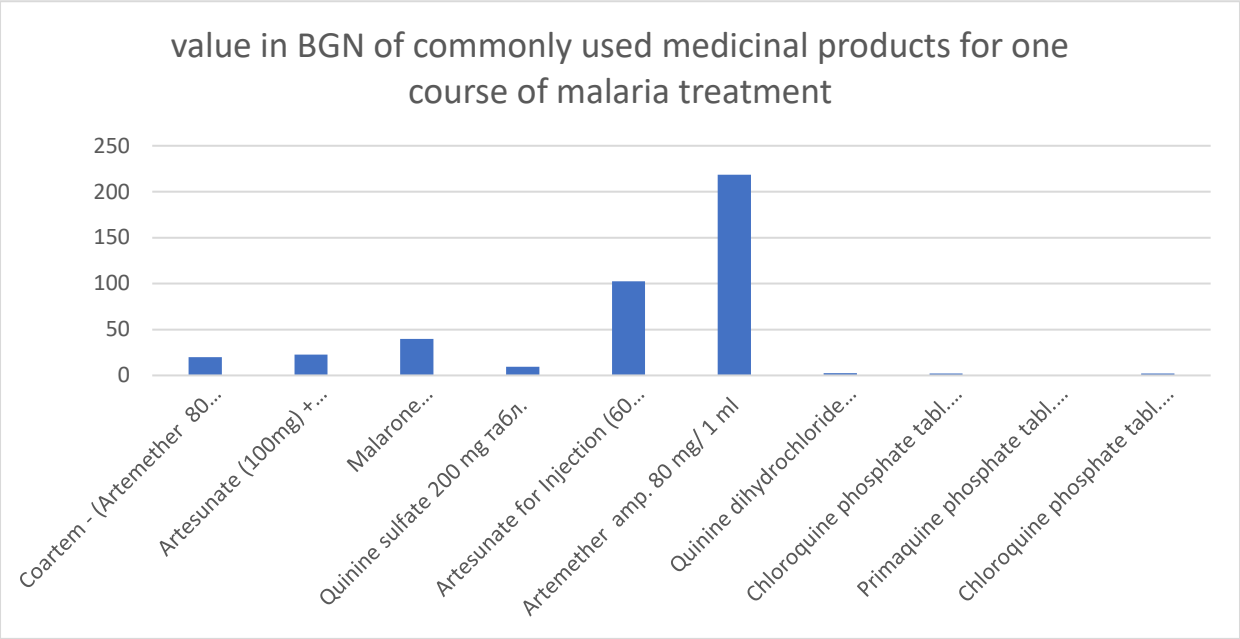


Figure 4 Value in BGN of self-used medicinal products for one course of malaria treatment

In our country, diagnosis and treatment of malaria disease is carried out according to the requirements of clinical pathway No. 99 "Diagnosis and treatment of infectious and parasitic diseases transmitted by the bite of arthropods" and includes the following coded activities:

1.3.1. Basic Diagnostic Procedures: 58500-00, 90909-00, 55113-00, 55036-00, 11709-00, 11700-00, 92182-08, 92182-01, 92182-02, 91937-07, 91937-00, 91937-00 02, 91937-03, 91910-04, 91910-34, 91910-33, 91907-03, 91919-09, 91922-00, 91922-01, 91922-02, 91922-03, 91922-04, 919 91922-06, 91923-10, 91903-02, 91903-03, 11012-00.

1.3.2. Main therapeutic procedures: 13706-02, 13706-03, 92061-00, 92062-00, 92063-00, 92064-00, 13706-05, 96199-07, 96199-02, 96197-02, 96199-09, 96200- 09, 96197-09."

58500-00 Chest X-ray

90909-00 Radiography elsewhere

55113-00 M-mode and real-time two-dimensional cardiac ultrasound

55036-00 Abdominal ultrasound

11709-00 Ambulatory continuous Holter electrocardiographic recording

11700-00 Other electrocardiography [ECG]

92182-01 Microbiological/microscopic examination of nervous system specimen and/or CSF for culture

92182-02 Microbiological/microscopic examination of nervous system and/or CSF specimen for culture and sensitivity

91937-00 Microbiological/microscopic examination of blood for bacterial smear

91937-02 Microbiological/microscopic examination of blood for culture and sensitivity

91937-03 Microscopic examination of blood for parasitology

91910-04 Blood count - at least eight or more of the following indicators:

hemoglobin, erythrocytes, leukocytes, hematocrit, platelets, MCV, MCH, MCHC

91907-03 Microscopic examination of spleen and/or bone marrow sample for parasitology

91919-09 Microscopic examination of a sample of the lower digestive tract and/or feces for parasitology

11012-00 Electromyography (EMG)

91923-10 Research on Chlamydia

91903-02 Serological test for Borellia (Lyme disease)

91903-03 Serological test for Rickettsia conorii (Marseille fever)

91922-06 Serological examination of antibodies against hepatitis C virus

91910-33 Sodium and Potassium

According to the currently effective National Framework Agreement, the cost of the clinical pathway paid by the NHIF for malaria treatment is BGN 993. As a result of the calculations of the medicinal products used, the price of the CP is mainly used to cover the costs of hospitalization and diagnostic procedures. (Figure 5) shows the value of each therapy described in the NCPRMP pharmacotherapeutic guide.

It is possible to perform additional procedures in case of a more severe course of the disease, related to the expression of the following symptoms and conditions:

- Coma (cerebral malaria)
- Seizures
- Acute anemia – clinical pathway No. 244.1 Diagnosis and treatment of hemorrhagic diatheses. anemias. for persons over 18 years of age
- Acute renal failure - clinical pathway No. 87.1 Diagnosis and treatment of acute renal failure in persons over 18 years of age
- Hypoglycemia
- Metabolic acidosis
- Acute pulmonary edema
- Acute circulatory collapse, shock, algid malaria
- Coagulopathy
- Hyperpyrexia
- Hyperparasitemia
- Malarian hemoglobinuria
- Aspiration pneumonia - clinical pathway No. 39 Diagnosis and treatment of bronchopneumonia and bronchiolitis in persons over 18 years of age - BGN 1,300.

A clinically healthy patient is defined as a patient who has had a triple negative malaria parasite test result.

Contemporary characteristics of imported malaria in Bulgaria for the 10-year period 2010-2020 - results of an in-house documentary study.

The study covered 110 cases of imported malaria in the country registered in the period 2010-2020. The forecast for the increase in average temperatures of the earth's surface according

to the five scenarios of the Sixth Assessment Report on climate change (according to IPPC: Climate change, 2022) was used). A survey was made for the presence of the carriers of the disease - the female mosquitoes of the Anopheles species, carried out in August 2003-2004. Also, the ratio between the different subspecies of this genus in the discovered mosquitoes was determined. Data from the Report of a study conducted for the period 2015-2019 on mosquito larvae of the Anopheles species in the Varna Region were used. A figure with the dynamics and current epidemiological characteristics of imported malaria in Bulgaria for a 10-year period (2011-2020) is presented.

More information on the distribution of the incidence of imported malaria by area can be found in (Figure 14) in the dissertation on page 78.

In the regions of Sofia, Plovdiv, Haskovo, Burgas, Varna and Pleven, 102 patients were registered /92.73% of the cases in our country/. We could explain this fact by the fact that these are regional centers of the country, which have a larger population and are important transport hubs in the field of air, sea and road transport, as well as having a well-organized hospital system. The city of Haskovo is an exception here, but it is quite possible that this is due to the proximity of the city to the Republic of Turkey, where the local population often travels to buy food and other goods due to the prolonged inflation in our neighboring country Turkey in the last decade, the passage on an international transport corridor and a difficult-to-control migrant wave.

The projected increase in average temperatures on the earth's surface according to the five scenarios of the Sixth Assessment Report on climate change (according to IPPC: Climate change, 2022) is presented. The scenarios are called Shared Socioeconomic Pathways (SSPs) in Bulgarian - Shared Socio-economic Pathways. A total of 5 scenarios SSP1-1.9, SSP1-2.6, SSP1-4.5, SSP1-7.0 and SSP1-8.5 were developed. According to these scenarios, the temperature of the earth's surface will continue to rise, which is visible in (Table 3).

		2021-2040		2041-2060		2061-2100	
	A script	Best prediction	Most likely range	Best prediction	Most likely range	Best prediction	Most likely range
Global warming levels	SSP1-1.9	1.5	*1.2-1.7*	1.6	*1.2-2.0*	1.4	*1.0-1.8*
	SSP1-2.6	1.5	*1.2-1.8*	1.7	*1.3-2.2*	1.8	*1.3-2.4*
	SSP1-4.5	1.5	*1.2-1.8*	2	*1.6-2.5*	2.7	*2.1-3-5*
	SSP1-7.0	1.5	*1.2-1.8*	2.1	*1.7-2.6*	3.6	*2.8-4.6*
	SSP1-8.5	1.6	*1.3-1.9*	2.4	*1.9-3.0*	4.4	*3.3-5.7*

Table 3 Shows a forecast increase in average surface temperatures according to the five scenarios of the Sixth Assessment Report on Climate Change (IPPC: Climate change, 2022)

According to the most pessimistic scenario of the Sixth Report SSP1-8.5, by the end of the century average monthly temperatures will rise by 4.40C, which will inevitably lead to an extension of the current potential malaria season (April-October) and this increase would also help to carry out more turnovers of infection during the malarial active period.

Several studies were covered in the period 2003-2004, which showed the presence of 3 carriers of the malaria disease - the female mosquitoes of the genus Anopheles in the territory of

the Republic of Bulgaria, described in (Table 4). The analysis shows that the malaria transmission vector exists and there is a potential opportunity for malaria to return to our country.

a type of mosquito / a year	Anopheles maculipennis, Meigen	Anopheles sacharovi, Favre	Anopheles claviger, Meigen
2003	98.0%	1.4%	0.6%
2004	92.5%	3.3%	4.3%

Table 4 Proportion of Anopheles mosquitoes released in the period April - August 2003-2004.

A scientific study conducted for the period 2015-2019 of Anopheles mosquito larvae in the Varna region (Table 5) shows a tendency to preserve the absolute share of biotopes inhabited by Anopheles mosquitoes in 2019 compared to 2018. Anopheles larvae were found in 3 biotopes, which is 2.75% of all checked, in the municipalities of Devnya, Aksakovo and Avren against 3 biotopes or 2.97% for 2018. The analysis shows that there is a permanent settlement of Anopheles mosquitoes in 3 (three) biotopes, i.e. there is a predisposition for the return of malaria in Bulgaria.

A year	**Number of checked biotopes**	**Biotopes with Anopheles %**
2015	86	6.98
2016	52	9.62
2017	117	3.42
2018	101	2.97
2019	109	2.75

Table 5 Number of inspected biotopes by year and species of Anopheles mosquito larvae, in the Varna region for the period 2015-2019.

Imported malaria according to the type of causative agent

(Figure 5) and (Figure 6) below show the distribution of the various causative agents of diagnosed and treated patients in Bulgaria. This mainly shows from which malaria active areas the patients arrive. P. falciparum - found throughout Africa, P. vivax - found mainly in Asia and South America, P. malarie - found in South America, Asia and Africa, P. ovale - the second most common strain in Africa. Most of the patients are infected with P. falciparum and P. ovale, which is due to the fact that those infected more travel to Africa for vacation and work. Patients diagnosed with P. falciparum have a significantly more severe disease and higher mortality than P. vivax, P. ovale and P. malariae, which have a milder disease and a global mortality of about 10%.

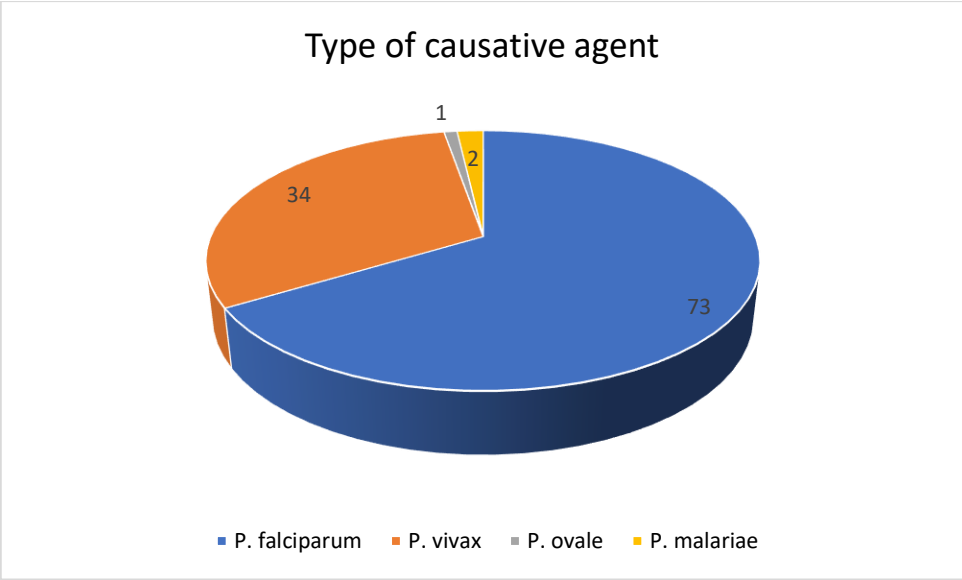


Figure 5 Imported malaria according to the type of causative agent for the period 2011 - 2020.

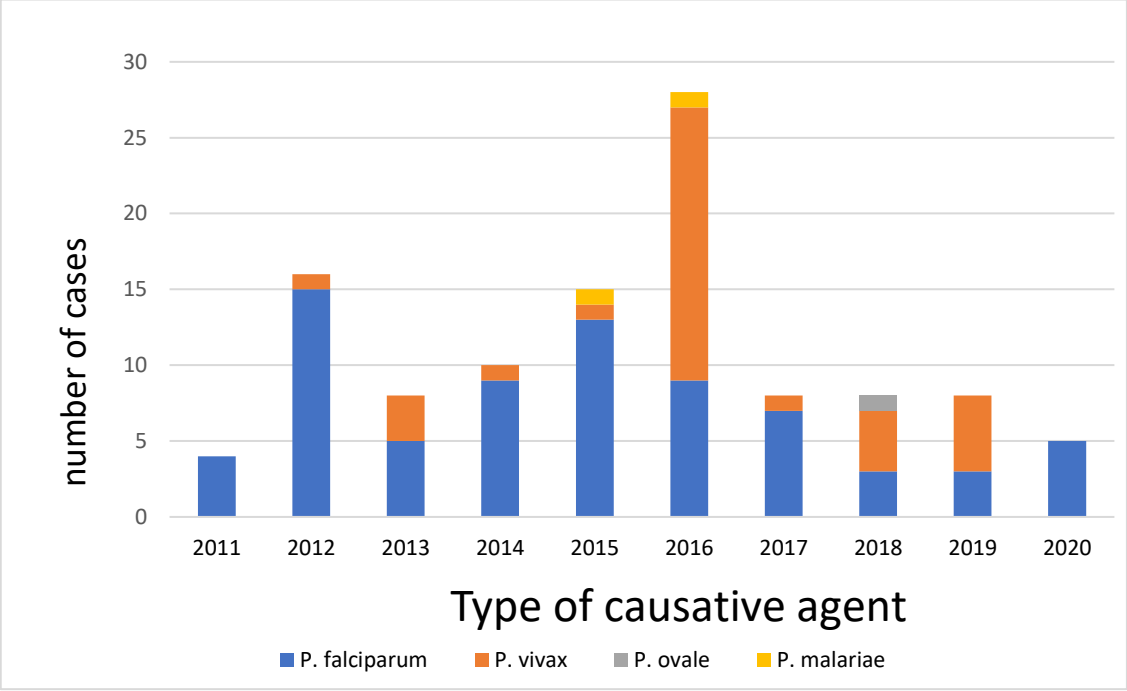


Figure 6 Imported malaria according to the type of causative agent for the period 2011-2020 by years

Mortality from imported malaria in the country

A total of 3 deaths were recorded in the reputed 10-year period shown in (Figure 9). The fatality rate varied from 3.57% (in 2016) to 12.5% (in 2013), with the average value of this indicator for the period being 2.72%. The high mortality rate of 12.5% is mainly due to the small number of patients, a total of 8 cases in 2013 and in all three cases the patients were infected with P. falciparum. The main causes of mortality are due to late diagnosis. It is most often delayed help sought, self-medication without consulting a doctor and delayed or inappropriate therapy, which can hardly be replaced promptly due to the complicated procedure for ordering unregistered drugs for the treatment of malaria in Bulgaria. As a result, the patients developed complications related to the central nervous system (coma and pre-coma) and also manifestations of, most often, chronic renal failure.

More information on imported malaria mortality in the country can be found in (Figure 17) in the dissertation on page 81.

Method of treating patients

During the study period, we have many hospitalized patients (104 people) and outpatients (6 people), which is presented in (Figure 7). Under the circumstances, hospitalization should have resulted in a lower mortality rate for the analyzed period due to intensive treatment and daily monitoring of the patients' condition, but nevertheless there were 3 deaths, the most likely reason, as mentioned, being late diagnosis , unavailability of appropriate medicinal products for the treatment of malaria disease and the inability to replace them in a timely manner, untimely dialysis therapy, lack of sufficient amount of blood for transfusion, as well as infection with the most deadly plasmodium P. falciparum.

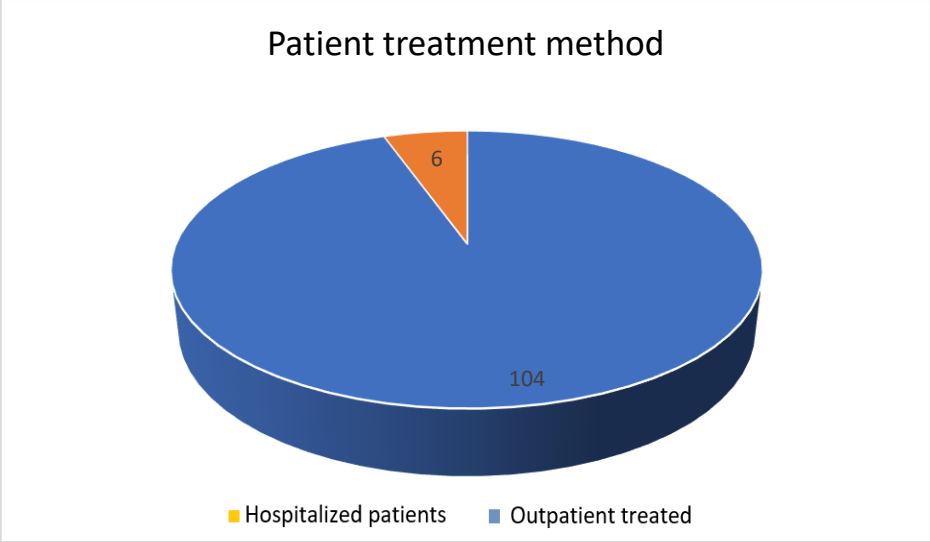


Figure 7 Mortality in absolute value from imported malaria for the period 2011–2020.

Distribution of imported malaria cases by gender

Distribution of cases of imported malaria by gender for the study period shows a statistically significant difference, see (Figure 8). According to general world statistics, the incidence of malaria affects both men and women equally, but in our case it is a matter of patients who became infected during their professional duties in endemic countries, mostly as employees of the sea and air transport, where men predominate, as well as emigrants from malaria-active areas, who are mainly men. There is evidence from malaria-active areas where the male-female ratio is different, and one explanation is that pregnant women are more likely to get the disease, but it is also thought that longer exposure during the hours when mosquitoes are most active also leads to greater morbidity, but the fluctuation is no more than 15% in favor of women.

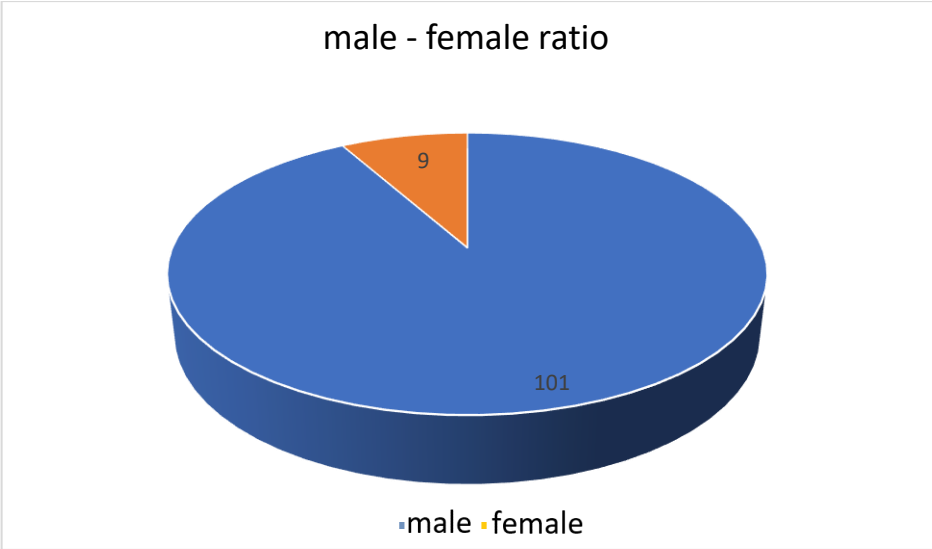


Figure 8 Distribution of imported malaria cases by sex

Legal framework, modern strategies for the prevention and treatment of malaria and provision of medicinal products in Bulgaria

The geographical location of the Republic of Bulgaria on the Balkan Peninsula, its proximity to the Mediterranean Sea, Asia and Africa, and the global warming of the climate, along with the intensive migration of refugees to the country, provide us with real conditions and opportunities for the transmission and risk of local spread of some endemic diseases tropical and other parasitic diseases. The prospect of parasitic diseases disappearing with a better living standard and household culture of the population is theoretical and unrealistic.

Currently, this group of diseases represents a problem for us in two main directions: clinical and therapeutic consequences for sick and asymptomatic parasite carriers and epidemiological consequences for the population of the country**.**

The purpose of the study is to objectively show the seriousness of the problem - malaria, by briefly discussing the available information on prevention, chemoprophylaxis and treatment, by showing the problems in the legislation of the Republic of Bulgaria.

A review of the regulatory framework was carried out, literature data on diagnostics, international recommendations for the prevention and treatment of malaria were collected. Different types of approved drug therapies were analyzed. An algorithm for therapeutic behavior in the prevention and treatment of malaria in the Republic of Bulgaria is presented. The information on medicinal products that are imported by authorized importing companies, at the expense of the budget of the medical facilities, which have concluded a contract with the NHIF for the admission of patients on these clinical pathways in accordance with the requirements of Ordinance No. 10/MH of 17.11.2011 and the conditions and procedure for treatment with unauthorized use of medicinal products in the Republic of Bulgaria (promulgated SG No. 95 of 2.12.2011).

The information in Ordinance No. 17 of July 30, 2008, which defines the conditions and procedure for conducting diagnostics, prevention and control of imported parasitic diseases, coming from regions endemic for parasitic diseases, with the aim of preventing the importation and spread of these diseases on the territory of the Republic of Bulgaria and those on reporting, registration and reporting with Ordinance No. 21/18.07.2005 (promulgated SG No. 62/ 29.07.2005).

To derive additional up-to-date information, the latest WHO Annual World Malaria Report (2015-2022) has been reviewed and analysed.

The results show that the reviewed legislative framework of health information in the Republic of Bulgaria for conducting chemoprophylaxis, recommendations for protecting travelers in malaria-active areas and treatment of malaria has a number of imperfections. In our country, in reality, in 95% of cases, it is not possible to carry out chemoprophylaxis by the ordinary citizen, because the medicines for its carrying out are not available in the pharmacy network on the territory of the state and there is no legal framework for their ordering and delivery. The availability of life-saving medicinal products for the treatment of malaria is not guaranteed, and there is no support for the hypothesis that this can happen in the short term due to the complexity of the procedure and the availability of the medicinal products from different suppliers. It is necessary for the state to maintain a reserve, which should be provided to the relevant medical institution if needed. Practice has shown that such a stock of drugs is absolutely necessary, and at this stage this is the only solution for the immediate supply of medical facilities in Sofia and the country with drugs for the emergency treatment of hospitalized cases with the above-mentioned parasitic diseases, including malaria.

Prevention, chemoprophylaxis and protection recommendations

Malaria prevention includes the following measures:

- in relation to the source of infection - early diagnosis and treatment of the sick and carriers and dispensary monitoring;
- in relation to vectors: control of larvae (larvicidal treatment and stocking of reservoirs with the fish gambusia), hydromelioration measures for drying and draining swamps and stagnant reservoirs, extermination of mosquitoes and others;
- individual prevention - protection against mosquito bites (use of repellents, insecticidal spray, high-frequency vibrators; netting of windows and doors, etc.); conducting chemoprophylaxis with medicinal preparations. Chemoprophylaxis should be carried out according to WHO recommendations.

When traveling abroad in malaria-active areas, it is necessary to visit the GP and/or parasitologist to obtain instructions on how to prevent malaria. It is necessary to obtain and take the recommended preparations for chemoprophylaxis and a personal dose in case of emergency.

On return from abroad a visit to the general practitioner is again necessary, and it is also well to inform him that the patient has returned from a tropical country.

Malaria is characterized by fever attacks - a feeling of coldness, accompanied by a rise in temperature, followed by profuse sweating. These attacks are repeated at certain intervals of time, depending on the type of malaria plasmodium - every day, every other day or every other day. At the beginning of the disease, after the attack passes and until the next one occurs, the patient feels well. Very soon the general condition worsens, consciousness is confused, the liver and spleen are enlarged. One of the most serious complications leading to death is malarial coma.

More information on the life cycle of malaria can be found in (Figure 20) in the dissertation on page 85.

In (Table 6) are presented the medicinal products for chemoprophylaxis described in the scheme for chemoprophylaxis, as well as the status of their authorization for use in the Republic of Bulgaria, described in the pharmacotherapeutic manual.

MP for chemoprophylaxis in Bulgaria
Chloroquine phosphate[1]
Mefloquine (Lariam)[2]
Doxycycline (Vibramycin)[1]
Malarone (Atovaquone + Proguanil)[2]
Paludrine (Proguanil)[2] + Chloroquine[1]

Table 6 List of medicinal products for malaria chemoprophylaxis in the Republic of Bulgaria
Legend: Green 1 – registered in the country, Red 2 – not registered in the country

Treatment of malaria

The treatment is mainly carried out according to: Pharmaco-therapeutic manual specialty "medical parasitology" - Algorithm for therapeutic behavior: clinical pathway No. 99 (A and B) includes a group of life-threatening transmissible parasitoses - malaria and leishmaniasis.

In (Table 7) are provided the medicinal products for treatment described in the pharmaco-therapeutic manual for the treatment of malaria, as well as the status of their authorization for use in the Republic of Bulgaria.

MP for the treatment of malaria in Bulgaria
Coartem - Artemether/ Lumefantrine[2]
Malarone-Atovaquone/ Proguanil[2]
Chloroquine phosphate[1]
Doxycycline[1]
Quinine dihydrochloride/sulfate[2]
Primaquine phosphate[2]
Artesunate + Mefloquine[2]
Artemether[2]
Artesunate[2]

Table 7 List of medicinal products for the treatment of malaria in the Republic of Bulgaria
Legend: Green 1 - registered in the country, Red 2 - not registered in the country

Discussion

The provision of drugs for the prevention and treatment of malaria in Bulgaria is very complicated. In reality, the prevention of malaria cannot be carried out by the ordinary citizen, since the medicines for its realization are not available in the pharmacy network and there is no legal framework for their ordering and delivery from other countries.

The insufficient clinical-epidemiological focus of medical specialists on this disease and the increasingly common resistance of the malaria causative agent to the main chemotherapeutics lead to severe consequences for the patients and create a risk of the appearance of local malaria in the country. The increased migration of the population, the limited information about Bulgarian citizens who leave or return from malaria-endemic countries, the underestimation of the danger

of importation and spread of the disease also contribute to this. Practice has shown that it is necessary to have a medicinal reserve for such products, and this is perhaps the only solution for the immediate supply of medical facilities in Sofia and the country with medicines for the emergency treatment of hospitalized cases and the subsequent outpatient treatment of malaria, as well as for other parasitic diseases. It is necessary to centralize the information related to the prevention, instructions and methods for prevention, registration, chemoprophylaxis and treatment of malaria in Bulgaria in one place, i.e. creation of a single specialized portal with up-to-date information on prevention, prevention and treatment of malaria and other parasitic diseases.

Pharmacotherapy of malaria in modern times and in the present 21st century

Malaria is one of the most common infectious diseases today, but it has been known to mankind since ancient times. Scientists consider it the most significant tropical disease, causing high mortality, especially among children.

Globally, there were about 247 million cases of malaria in 2021, mainly distributed in 84 malaria-endemic countries (including the territory of French Guiana), which was an increase from the previous year's 245 million cases in 2020. Most of this increase in incidence came from countries geographically located in the WHO African Region. In 2015, the baseline year of launch of the Global Technical Strategy for Malaria 2016–2030, estimated cases at the time to be 230 million.

Globally, however, malaria deaths declined steadily over the period 2000–2019 from 897,000 in 2000, 577,000 in 2015 and to 568,000 in 2019. A year later (2020) saw a 10% increase compared to 2019, to approximately 625,000. Estimated deaths decreased slightly in 2021 to 619,000. Between 2019 and 2021, there were 63,000 more deaths attributable to of disruption of essential malaria care and therapy during the COVID-19 pandemic. The percentage of fatal outcomes from the disease in children under the age of 5 decreased from 87% in 2000 to 76% in 2015. Since then, there has been no change in this observed indicator.

Globally, malaria deaths (calculated per 100,000 population at risk) have halved from about 30 in 2000 to 15 in 2015; after that, it continued to decline, but at a slower pace, dropping to 14 in 2019. In 2020, the death rate unfortunately increased again to reach 15.1, before slightly decreasing to 14.8 in 2021.

According to the official statistics of the National Center for Disease Control and Prevention, 9 cases of malaria were registered in the Republic of Bulgaria in 2021, all of which were imported from abroad.

The geographical location of our country, located on the Balkan Peninsula, our proximity to the Mediterranean Sea, Asia and Africa and the global warming of the climate, together with the intensive migration of refugees to the region, provide real conditions and opportunities for the transmission and risk of local spread of some endemic tropical and other parasitic diseases. The prospect of parasitic diseases disappearing with a better standard of living and living culture of the population is theoretical and currently unrealistic to discuss.

Currently, the group of tropical diseases represents a problem for us in two main directions: clinical and therapeutic consequences for sick and asymptomatic parasite carriers and epidemiological consequences for the population of the country.

The purpose of the study is to collect, summarize and analyze officially published information on the diagnosis and treatment of malaria in the Republic of Bulgaria in the current 21st century. Through a documentary and comparative analysis of official recommendations and guidelines, including as part of the national legislation regarding the diagnosis and pharmacotherapy of malaria in the Republic of Bulgaria. A historical method of searching for information was also applied in published scientific articles, the two most significant in terms of their therapeutic effectiveness products used in the New Age were identified.

Malaria diagnosis – modern aspects

By Ordinance No. 17 of July 30, 2008 of the Minister of Health, the conditions and procedure for conducting diagnostics, prevention and control of imported parasitic diseases coming from regions endemic for parasitic diseases are determined, with the aim of preventing the importation and spread of these diseases to the territory of the Republic of Bulgaria.

The specific parasitological laboratory methods of research are of great importance for proving the parasites in the host's body, but the following more important non-parasitological studies are also of no less importance for guiding the diagnosis of "parasitosis":

- Hematological: Complete blood count and differential count: Anemia, leukopenia with relative monocytosis, lymphocytosis, accelerated ESR is observed in malaria.

- Blood biochemistry: Bilirubin increased, liver (ASAT, ALAT and GGT) transaminases increased, urea and creatinine increased more in acute renal failure in complicated malaria (P. falciparum and P. malariae).

- Biopsy material: malarial parasites in bone marrow.

Malaria Antigen Rapid Test Pf/Pv (Whole Blood) is a rapid test for the qualitative detection of the presence of P.falciparum-specific HRP-II antigens and/or P.vivax LDH antigens found in P.vivax(Pv) also used in practice. The test uses a colloidal gold conjugate to selectively detect Pf-specific HRP-II antigens and Pv-LDH antigens in whole blood.

Amplification of parasite DNA by PCR is a specific method and can detect low concentrations of parasites, but it is time-consuming and requires specialized equipment.

Treatment of malaria in historical terms

The bringing of quinine bark to Europe in the 17th century.

The history of the use of Cinchona bark is a mixture of facts and legends, first collected by the researcher S. Baldi in 1663-1669 and subsequently studied by many other authors. There is historical evidence of the first documented use of this medicinal plant by the Spanish in Peru around 1630.

Although the bark is not included in the Inca pharmacopoeia, it appears to have been widely used by the Andean population to combat bouts of fever (resulting from malaria). The

drug became known, among other names, as Peruvian bark (Cortex peruanus) or Jesuit powder, as it was imported into Europe from Latin America by the monks of the Order of Loyola.

The use of quinine tree bark in the 17th century.

In the second half of the 17th century, the bark began to be used increasingly to treat fever – and in particular intermittent fever, which 200 years later was shown to be caused by malarial parasites. During this period, the efficacy of the various parts of the tree, as well as the role of growing conditions in their action based on the unknown "active principle", was unknown - or only suspected.

An early example of an effective anti-malarial recipe can be found in the book Schedula Romana, published in 1649, which is believed to have been developed by the Spanish Cardinal Juan de Lugo, and there are described and reported experiments that he probably performed . Recommended dosages were used, which were probably established by trial and error, and it is reasonable to assume that de Lugo relied on the results obtained using various recipes suggested by Roman apothecaries. Briefly, the book describes that two drachms (7.5 to 9 g) of selected bark (no details specified) were to be ground into a very fine powder (a special mill was set up in Rome) and poured into hot strong wine. This mixture had to be applied every day (sometimes several times a day). A summary calculation based on the probable quinine content of the red bark leads to the conclusion that the doses used in 1650 were in the range of those used after the isolation of quinine, i.e. between 0.75 and 1.5 g as a daily dose.

The early modern market was flooded with barks from the quinine tree of varying efficacy, as well as ineffective and even poisonous barks from other trees, such as prickly periwinkle. The quinine tree was not known to Europeans, at least until it was described by real botanists around 1730, so fakes could easily be sold instead of the original product. In addition, the search for cheaper alternatives to quinine wood has contributed to market confusion. From the beginning, both the Jesuits and the Spanish crown tried to control the quality of the drugs shipped and sold in Europe. It is worth noting that the real "good" starting material (red and bitter bark) and a reproducible method for extracting its active principle were not established and published until the late 1830s. This goes some way to explaining the wide variation in the reported efficacy of the bark in the treatment of malaria. Knowledge of this has been gained empirically mostly by merchants and apothecaries. The scientific reasons for the differences between the barks and individual parts of the tree were not identified until 1842, when a full systematic study of their quinine content was made by Bouchard.

A curious historical fact is how was the proper dose of quinine first determined? The dosage used in 1820 and in later published studies appears to have been adapted from the amount of bark powder previously used for intermittent fevers. Depending on the origin of the bark, the quinine content is in the range of 1–4% dry extract. For example, in the court of Louis XIV, the so-called "pre-quinine" physicians routinely used 1.5–2 ounces of bark each day for a minimum of six days, in powder, extract, or pill form. This is on the order of 1–2 g of quinine per day. A rough calculation, based on more precise recipes for preparing decoctions of bark powder for cod, suggests daily doses equivalent to about 1 g of quinine, divided into several doses. Such a calculation is obviously subject to considerable uncertainty, particularly with respect to the

concentration of quinine in the original material. This suggests, however, that the daily doses used after 1820 were simply adaptations from a century and a half of bark powder use.

Synthesis and characterization of quinine in the 19th and 20th centuries

In light of the growing number of positive medical reports accumulated by the early 19th century, few doubted that Cinchona bark was a "good" remedy for intermittent fevers. After 1800, the refinement of acid-base extraction procedures for the active ingredients of medicinal plants yielded a number of purified molecules of medical and pharmaceutical interest. The treatment of several diseases, previously based on the use of crude plant extracts, can now be investigated on a more quantitative basis. As a result, there has been an explosion of clinical trials with new molecules. After the purification of quinine and other alkaloids from Cinchona in 1820, it was immediately tested on patients. Numerous medical observations and case reports from around the world soon after indicated that quinine was specific for "malarial" (intermittent) fevers. The treatment of fever with quinine thus contributed greatly to the nosography of malaria by distinguishing between fevers responsive to the extracts and those unresponsive.

However, quinine alkaloids are not the only drugs actively tested as antimalarials. After Paul Ehrlich discovered that certain dyes stained microorganisms, methylene blue began to be used as an antimalarial agent. A brief contemporary report on a controlled comparison of methylene blue with quinine concluded that the former was more effective, yet interest in methylene blue continues today. Its introduction led to chemical substitutions of the original aromatic core and the identification of a number of other molecules active against malaria (most of which were not tested until the 1930s – see text below).

In addition to the above, since arsenic and arsenic derivatives have also long been used as antimalarials, organic arsenic derivatives (Atoxyl and Salvarsan) developed to treat syphilis have been tested in malaria patients. However, the studies were poorly controlled and small-scale, and none of the compounds proved effective enough to displace quinine and its alkaloids from their dominant position in the treatment of malaria.

Malaria treatment in the 21st century

Malaria is a protozoan disease caused by Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale and Plasmodium malaria. The most severe forms are caused by P. falciparum. It develops after bites by an infected female Anopheles mosquito. Clinically, malaria proceeds with cyclical fever attacks (in 48 hours in P. vivax, P. ovale and P. falciparum, and in 72 hours in P. malariae), development of hypochromic anemia and hepatosplenomegaly. With the different antimalarial agents, the different phases of the development of the plasmodia are differentially affected.

With standard prophylaxis, primary destruction of tissue schizonts is achieved, which leads to prevention of the development of the erythrocyte phase, while clinical prophylaxis aims at destruction of the developed erythrocytes and suppression of clinical symptoms. Radical treatment leads to relapse-free recovery.

When malaria is proven, the treatment is mainly carried out according to the approved by the Ministry of Health and published on the website of the National Council On Prices And Reimbursement of Medicinal Products - Pharmacotherapeutic guide in the specialty "medical

parasitology" and in particular according to the "Algorithm for therapeutic behavior" specified there.

The group of life-threatening transmissible parasitoses - malaria and leishmaniasis - is included in clinical pathway No. 99 (A and B), on which medical facilities work with the National Health Insurance Fund

Algorithm of therapeutic behavior in diagnosed malaria:

1. In uncomplicated forms of tropical malaria (P. falciparum), oral medicinal products are administered according to the established WHO standards, as follows: Resochin tab. (INN: Chloroquine 250 mg) - used for resistant strains (204), Lumartem (INN: Artemether-lumefantrine 40/240 mg) - for treatment of uncomplicated cases of malaria, Artesunate + Mefloquine 25/50 mg tab. - for the treatment of uncomplicated cases of malaria, Atovaquone-Proguanil 250/100 mg tab. - for the treatment of drug-resistant P. falciparum, Quinine sulfate 200 mg - for the treatment of P. falciparum resistant to Chloroquine.

2. In cases of complicated tropical (P. falciparum) malaria, the following medicinal products are administered according to the established WHO standards, as follows: Artesunate for Injection (60 mg/ powder + 1 ml of 5% sodium bicarbonate) - indicated for the treatment of severe malaria, Artemether amp. 80 mg/ 1 ml for the treatment of severe and complicated malaria caused by areas where there is multidrug resistance and the treatment of uncomplicated malaria in situations where there is widespread multidrug resistance to P.falciparum. Quinine dihydrochloride Injection 600 mg/ 2 ml - for the treatment of acute attacks of malaria, including attacks due to resistance to chloroquine or multi-resistant strains of Plasmodium falciparum. Quinine is used parenterally in cerebral, severe or complicated malaria, or when vomiting allows the retention of an orally administered drug.

3. For malaria caused by P. vivax, the following drugs are administered: Resochin tab. (INN: Chloroquine 250 mg),

Primaquine phosphate tab. 15 and 7.5 mg - Used for anti-relapse treatment, after the completion of the treatment course with Chloroquine.

4. For malaria caused by P. vivax, the following drugs are administered: Resochin tab. (INN: Chloroquine 250 mg, Primaquine phosphate - no anti-relapse treatment with Primaquine phosphate is applied.

More information on the most common complications in malaria patients can be found in (Table 21) in the dissertation on page 92.

Therapeutic behavior regarding the complications of malaria:

• Coma (cerebral malaria) - Maintain airway, exclude other possible causes of coma, such as hypoglycemia and bacterial meningoencephalitis. Avoid the use of corticosteroids, heparin and catecholamines.

• Convulsions - Maintain airway; Diazepam - intravenous or intrathecal, or intramuscular Paraldehyde.

• Acute anemia – Blood transfusion and administration of erythropoietin

• Acute renal failure - Maintenance of water-salt balance. Dialysis, if needed.

• Hypoglycemia - Blood sugar monitoring; a glucose bolus is administered (followed by an infusion of 5 or 10% glucose solution.

• Metabolic acidosis – treatment of hypoglycemia, hypovolemia, Gram-negative septicemia. Administration of physiological solution by infusion.
• Acute pulmonary edema – Prevent excessive rehydration. Appointment of oxygen. Application of Furesemid. Venesection and bloodletting.
• Acute circulatory collapse, shock, algid malaria – Rule out Gram-negative septicemia and draw blood for culture, administer parenteral antibiotics, and correct hemodynamic disturbances.
• Coagulopathy - Transfusion of whole blood or blood clotting factors - 10 mg Vit K - intravenously.
• Hyperpyrexia - administration of Paracetamol. Cooling with wet compresses, blowing with a fan.
• Hyperparasitaemia - Administration of parenteral antimalarial therapy. Administration of exchange transfusion.
• Malarial hemoglobinuria - Continuation of antimalarial treatment, if necessary - hemotransfusion.
• Aspiration pneumonia - Changing the patient's position, prescribing parenteral antibiotics, prescribing oxygen and breathing exercises (physiotherapy).

Criteria	***Time period***
Interruption of febrile seizures	*from 24 to 48 hours after starting treatment*
Reduction of parasitemia (number of parasites in µl of blood)	*up to 24 hours after starting the treatment and complete absence of malaria plasmodia at the end of the therapeutic course*
Impact of complications	*up to 48-72 hours after the start of treatment - coming out of coma (in case of cerebral malaria), normalization of kidney function (in cases of acute renal failure), spontaneous breathing (in cases of pulmonary edema or acute respiratory failure)*
Normalization of blood parameters (mainly Complete Blood Count)	*at the end of the therapeutic course*
Clinical recovery of the patient.	*at the end of the therapeutic course*
Triple negative for malaria parasites.	*at the end of the therapeutic course*

Table 8 Criteria for evaluating the efficacy of applied therapy in malaria

In (Table 9) below, a comparative analysis is made between the WHO Model List of Essential (Essential) Medicines for the Treatment of Malaria - 22nd List published in 2021, medicinal products for the treatment of malaria described in the Pharmacotherapeutic the guide for the treatment of this disease in our country, as well as whether the relevant drugs have a license for use in the Republic of Bulgaria.

Model list of essential drugs for the treatment of malaria World Health Organization - 22nd list, 2021.	Medicinal products for the treatment of malaria described in the 2019 pharmacotherapeutic guide.	Authorization for the use of the medicinal product for the treatment of malaria in the Republic of Bulgaria
Amodiaquine	No	No
Artemether	Yes	No
Artemether + Lumefantrine	Yes	No
Artesunate	Yes	No
Artesunate + Amodiaquine	No	No

Artesunate + Mefloquine	Yes	No
Artesunate + Pyronaridine tetraphosphate	No	No
Chloroquine	Yes	Yes
Dihydroartemisinin + Piperaquine phosphate	No	No
Doxycycline	No	Yes
Mefloquine	No	No
Primaquine	Yes	No
Quinine	Yes	No
Sulfadoxine + Pyrimethamine	No	No
He	Atovaquone-Proguanil	No

Table 9 Comparative analysis of the characteristics of the different drugs available on the WHO Model List of Essential (Essential) Medicines for the Treatment of Malaria

Discussion

Well-trained, qualified professionals who can recognize malaria plasmodia in a drop of blood by microscopic examination are not well trained to perform such a test and may misinterpret the results, which in turn delays the timely establishment of a correct diagnosis. There is a need for postgraduate continuing education for specialists to recall the important distinguishing features in recognizing the rarer tropical diseases.

In our country, treatment recommendations are carried out according to the Pharmacotherapeutic Guide for the specialty "medical parasitology", which is not adapted according to the latest published (22nd list, 2021) Sample list of the main drugs of the World Health Organization and the products indicated in it for the treatment of malaria.

In Bulgaria, there is only one registered drug, authorized for use and indicated for the treatment of malaria, which is included in the pharmacotherapeutic guide published on the website of the National Council on Prices And Reimbursement of Medicinal Products, compared to 9 products listed and specified there.

The provision of drugs for the treatment of malaria in Bulgaria is very complicated. In reality, in 90% of cases, it is not possible to be carried out by the ordinary citizen, since the medicines for its implementation are available in registered in the Republic of Bulgaria. Practice has shown that it is necessary to have a medicinal reserve of such products and this is perhaps the only solution for immediately supplying medical facilities in Sofia and the country with medicines for emergency treatment of hospitalized cases with malaria and other parasitic diseases. It is necessary to centralize the information related to indications, diagnosis by various methods and techniques, treatment algorithm, available medicinal products for the treatment of malaria in the Republic of Belarus in one place, for example by creating a single specialized portal (by analogy with the existing one for COVID- 19).

The Pharmacotherapeutic Guide needs to be updated to the latest WHO Model Essential Medicines List as it contains a list of recommended essential medicines, listing the most effective, safe and cost-effective medicines for priority conditions. Recommended products should be selected based on current and anticipated future public health importance and their potential for safe and cost-effective treatment. Experience with malaria shows that a manual can also be made to assist clinical laboratory, parasitology and microbiology specialists, describing both the popular instrumental methods of the recent past and the latest advances in science, through various

innovative established in the world practice tests that are applied in malaria active areas and have proven their effectiveness.

Comparative analysis of the official published information on the prevention, prophylaxis, recommendations for protection, diagnosis and treatment of the malaria disease - between the countries: Republic of Greece and Republic of Bulgaria

Diagnosis of the disease

R. Greece - A special Guide of the National Public Health Organization (NPHO) has been published. Malaria is historically the most common cause of fever in travelers coming from endemic countries.

More information on the countries that the Greek authorities consider endemic for malaria can be found in (Table 17) in the dissertation on page 95.

In any case of clinically suspected malaria, an immediate laboratory test for malaria is recommended, in particular microscopic examination of a peripheral blood smear (reference method) or a rapid diagnostic test at the nearest diagnostic laboratory.

It is important to emphasize that the clinical picture of malaria is not specific and the disease can present with symptoms of viral association. Malaria patients from endemic countries (eg Pakistan, Afghanistan, Bangladesh, India, sub-Saharan Africa) may have very mild symptoms due to partial immunity (eg decimal febrile movement and headache) or may not even show clinical symptoms (eg no fever) but have only compatible laboratory findings (anemia and/or thrombocytopenia) or splenomegaly. On the other hand, people without immunity usually have a fever with chills. A common laboratory finding is thrombocytopenia (either anemia or indicators of hemolysis).

The incubation time of malaria varies depending on the type of plasmodia. For P. vivax malaria specifically, the incubation period is usually 12-18 days, but can be much longer (up to 6-12 months in some cases). In addition, patients with P. vivax or P. ovale malaria frequently experience relapses (up to > 5 years). Vigilance for suspicious cases should therefore remain throughout the year and regardless of the patient's length of stay in Greece and the time of year.

Immediately, any patient with malaria should be evaluated for clinical and laboratory findings to determine whether it is simple/uncomplicated or severe/complicated malaria, as treatment is different. Immediate medical assessment of the severity and severity of the disease and timely administration of appropriate treatment are critical to the patient's prognosis.

The purpose of the conducted study is to objectively show the seriousness of the problem - malaria, by briefly discussing the available information on prevention, chemoprophylaxis, protection recommendations and procedures for arrivals from malaria-active areas, dynamics of transmission, diagnosis and treatment, showing the similarities and the differences in the Republic of Bulgaria and the Republic of Greece.

A review of the regulatory framework was carried out, literature data on diagnostics, international recommendations for the prevention and treatment of malaria were collected. Different types of drug therapies were analyzed. An algorithm for therapeutic behavior in the prevention and treatment of malaria in the Republic of Bulgaria and the Republic of Greece is presented. In the Republic of Bulgaria, information is summarized on medicinal products that are imported by authorized importing companies at the expense of the budget of the medical institutions, which have concluded a contract with the NHIF for the admission of patients on these clinical pathways in accordance with the requirements of Ordinance No. 10/MH of 17.11.2011 , the terms and conditions for treatment with unauthorized use of medicinal products in the

Republic of Bulgaria (State Gazette, No. 95 of 2.12.2011). In the Republic of Greece, a review of Law 4512/2018 (SG 5/A` 17.1.2018) and the procedure related to it responsible for the import and distribution of approved medicines (in the EU and third countries) that are not sold in Greece and apply to approved indications and are intended exclusively for individual use. The attending physician can, through the unified electronic prior authorization system, electronically request drugs from abroad that are not in circulation in Greece, for the needs of a specific patient. Through the system, electronic management and consideration of requests for reimbursement of medicines by the Ministry of Health of Greece is carried out. In this case, the National Medicines Organization (Εθνικός Οργασίας Φαρμάκων - EOF) allows the movement of the product/s in Greece as long as the conditions are met.

To derive additional up-to-date information, the latest WHO Annual World Malaria Report (2015-2022) has been reviewed and analysed.

The results of the study show that the legislative regulations of health information in the Republic of Bulgaria and the Republic of Greece for the implementation of chemoprophylaxis, recommendations for protection, procedures for arrivals from malaria-active areas and treatment of the disease malaria have similarities, but also differences. The similarity comes mainly from following WHO procedures, and the differences are due to differences in local legislation, prevention, treatment methods and means of informing the population. In the Republic of Bulgaria, in reality, in 95% of cases, it is not possible to carry out chemoprophylaxis by the ordinary citizen, since the medicines for its carrying out are available in the pharmacy network and there is no legal framework for their ordering and delivery. In the Republic of Greece, there are enough registered products for conducting chemoprophylaxis. In Bulgaria, the lack of life-saving medicinal products for the treatment of malaria is not guaranteed to happen in a short time due to the complexity of the procedure and the availability of the medicinal products in different suppliers. It is necessary for the state to maintain a reserve, which, if necessary, will be provided to the relevant medical institution. Practice has shown that such a drug reserve is absolutely necessary, and at this stage this is the only solution for immediately supplying medical institutions in Sofia and the country with drugs for the emergency treatment of hospitalized cases with the above-mentioned parasitic diseases, including malaria. In Greece, there are enough registered products to carry out malaria treatment. There is also an electronic system for ordering medicinal products for the treatment of malaria by filling in a form from the attending physician, which greatly facilitates the procurement process.

Republic of Bulgaria - By Ordinance No. 17 of July 30, 2008, the conditions and procedures for conducting diagnostics, prevention and control of imported parasitic diseases coming from regions endemic for parasitic diseases are determined, with the aim of preventing the importation and spread of these diseases the territory of the Republic of Bulgaria.

The specific parasitological laboratory methods of research are of great importance for proving the parasites in the host's body, but the following more important and non-parasitological studies are of no less importance for guiding the diagnosis of parasitosis:

- Hematologic: Complete blood count and differential count: Anemia, leukopenia with relative monocytosis, lymphocytosis, accelerated ESR is seen in malaria.
- Blood biochemistry: Bilirubin increased, liver (ASAT, ALAT and GGT) transaminases increased, urea and creatinine increased more in acute renal failure in complicated malaria (P. falciparum and P. malariae).
- Biopsy material: malarial parasites in bone marrow.

Microscopy is considered the "gold standard" for malaria diagnosis. Rapid and accurate diagnosis of malaria is essential to reduce morbidity and mortality. The most reliable and standard method used to detect malaria infections is microscopic examination

of Giemsa-stained thick and thin blood smears and examined by a highly trained microscopist. However, the lack of qualified specialists in medical facilities in the affected areas often leads to misinterpretation of the results. The ideal blood sample for testing is obtained by pricking a finger or pinna, as the density of developed trophozoites or schizonts is greater in blood from this capillary-rich area. Blood obtained by venipuncture collected in heparin- or sequestrin-coated (EDTA)-coated tubes with anticoagulant is acceptable if used soon after collection to prevent alteration of white blood cell (WBC) morphology and malaria parasites. Both thick and thin blood films should be prepared.

Amplification of parasite DNA by PCR is a specific method and can detect low concentrations of parasites, but it is time-consuming and requires specialized equipment.

Prevention, chemoprophylaxis and protection recommendations

R. Greece - Malaria is the most frequently "imported" disease by travelers. International travel is constantly increasing as more and more people travel for business, social, humanitarian or recreational purposes. The high-risk destinations are Sub-Saharan Africa, especially West Africa, followed by Oceania, Southeast Asia, Central and South America. The number of travelers to these countries exceeds 125 million annually. Of these, 50% are travelers visiting relatives and friends, with whom the increasing number of imported malaria cases in developed countries is mainly associated.

Tropical and subtropical countries where malaria is endemic are increasingly popular destinations for Greek travelers as well. Greater transmission of malaria in travelers occurs in sub-Saharan Africa. According to studies, 5-49% of travelers to these areas develop antibodies against malaria. The risk of infection increases with length of stay and is greater when travelers visit rural areas. This risk is 10-20 times the risk for travelers in Asia and 30-40 times the risk for travelers in South America. The majority of travelers are infected with strains of P. falciparum and P. vivax. Less than 5% of cases are due to P. ovale, P. malariae and P. knowlesi strains resistant to antimalarials. In most parts of Africa and especially in sub-Saharan Africa, South America, the Indian subcontinent, S.A. chloroquine-resistant P.falciparum is endemic to Asia and Oceania. Areas with chloroquine-susceptible P. falciparum are some countries in Central and South America, North Africa, Asia and the Middle East. The only areas with known Plasmodium resistance to mefloquine are the border region between Thailand and Myanmar and between Thailand and Cambodia. With regard to doxycycline and the combination of atovaquone/proguanil, Plasmodium resistance has not been reported to date.

No single precaution alone provides complete protection. Each measure contributes to prevention and all together provide maximum protection.

The mosquitoes that carry malaria bite mainly from sunset to sunrise. For this reason, travelers are advised to:

- To prefer clothes with long sleeves and long pants.
- At night to sleep in rooms with mosquito nets or mosquito nets on the windows and doors.
- To use insecticides (tablets, fuming spirals or sprays) to spray the rooms before sleep.

- Do not move, even for short periods of time, without being covered in insect repellent. The most effective insect repellents are those that contain DEET (N,N-diethyl-meta-toluamide) in a concentration of 30-50%.
- Don't sleep outside without a tent.

Prophylaxis with antimalarial agents (chemoprophylaxis) according to:
- The country and region of destination
- The time at which the journey will take place
- The duration of the trip
- The individual characteristics of the traveler

antimalarials (chloroquine, or mefloquine, or atovaquone/proguanil, or doxycycline, or primaquine) are recommended. Depending on the drug recommended, the starting time and duration of chemoprophylaxis varies. What every physician should know is that any fever in a traveler returning from a malaria-endemic country, up to 12 months after his return, should raise the suspicion of malaria, and that any case of suspected malaria should be treated as urgent. Most cases of malaria complications and deaths are due to delays in diagnosis and treatment.

`R. Bulgaria - Malaria prevention includes the following measures:
- according to the source of infection - early diagnosis and treatment of the sick and carriers and dispensary monitoring;
- in relation to vectors: control of larvae (larvicidal treatment and stocking of reservoirs with the fish gambusia), hydromelioration measures for drying and draining swamps and stagnant reservoirs, extermination of mosquitoes and others;
- individual prevention - protection from mosquito bites (use of repellents, insecticidal spray, high-frequency vibrators; netting of windows and doors, etc.); conducting chemoprophylaxis with medicinal preparations.

When traveling abroad - to visit the general practitioner or parasitologist to receive instructions on how to prevent malaria; obtaining and taking with you the recommended preparations for chemoprophylaxis and for a personal dose in case of emergency.

When returning from abroad, to visit the general practitioner again and to inform that the patient has returned from a tropical country; for any temperature condition up to three years after the return to immediately seek medical help.

In (Table 10) are provided the medicinal products for chemoprophylaxis described in the manuals for chemoprophylaxis in the respective country, as well as the status of their authorization for use in the Republic of Greece and the Republic of Bulgaria.

MP for chemoprophylaxis in Greece	MP for chemoprophylaxis in Bulgaria
Chloroquine phosphate[1]	Chloroquine phosphate[1]
Meflocin (Mefloquine)[1]	Mefloquine (Lariam)[2]
Doxoxycycline (Doxycycline)[1]	Doxycycline (Vibramycin)[1]
Malarone (Atovaquone + Proguanil)[1]	Malarone (Atovaquone + Proguanil)[2]
Ripacin (Primaquine)[2]	*
Paguanil (Proguanil)[2]	*
*	Paludrine (Proguanil)[2] + Chloroquine[1]

Table 10 List of medicinal products for chemoprevention of malaria in the Republic of Greece and the Republic of Bulgaria
*Legend: Green 1 – registered in the country, Red 2 – not registered in the country, * not described in the chemoprophylaxis manual*

Malaria treatment (according to national recommendations in both countries)

Republic of Greece - There are several documents that describe the treatment of malaria: Parasitology Textbooks and Manuals, Working Papers: Malaria - Algorithm for Initial Assessment and Treatment of Adults in Greece, Guidelines for the Treatment of Malaria in Greece - Updated: January 2020, "Standby" Emergency Treatment: (SBET) – describing treatment regimens for travelers.

Republic of Bulgaria: The treatment is mainly carried out according to: Pharmaco-therapeutic manual specialty "medical parasitology" - Algorithm for therapeutic behavior: clinical pathway No. 99 (A and B) includes a group of life-threatening transmissible parasitoses - malaria and leishmaniasis.

In (Table 11), the medicinal products for chemoprophylaxis described in the manual for chemoprophylaxis are provided, as well as the status of their authorization for use in the Republic of Greece and the Republic of Bulgaria.

MP for the treatment of malaria in Greece	MP for the treatment of malaria in Bulgaria
Coartem - Artemether/ Lumefantrine[2]	Coartem - Artemether/ Lumefantrine[2]
Dihydro- artemisin- piperaquine[1]	*
Malarone-Atovaquone/ Proguanil[1]	Malarone-Atovaquone/ Proguanil[2]
Chloroquine phosphate[1]	Chloroquine phosphate[1]
Mefloquine[1]	*
Clindamycin[1]	*
Doxycycline[1]	Doxycycline[1]
Quinine dihydrochloride/sulfate[2]	Quinine dihydrochloride/sulfate[2]
Primaquine phosphate[2]	Primaquine phosphate[2]
*	Artesunate + Mefloquine[2]
*	Artemether[2]
*	Artesunate[2]
Plaquenil Hydroxychloroquine[1]*	*

Table 11 List of medicinal products for the treatment of malaria in the Republic of Greece and in the Republic of Bulgaria
*Legend: Green 1 - registered in the country, Red 2 - not registered in the country, * not described in the Pharmacotherapeutic Guide*

Discussion

In the Republic of Bulgaria, recommendations for prevention, statistics, treatment and all other procedures are scattered in many places, for example: National Center for Infectious and Parasitic Diseases, Ministry of Health, Ministry of Foreign Affairs, National Council on Prices and Reimbursement of Medicinal Products, National Center for Public Health and Analyses, numerous hospitals and RHIs with different actuality and completeness of information, etc.

In the Republic of Greece, information is centralized, various methods of recommendations for prevention, treatment, statistics and analysis are located on their page - the National Organization for Public Health (EODY), as well as materials for training medical

specialists with up-to-date information. The methods of analysis in the Republic of Greece and the Republic of Bulgaria are similar, but in Bulgaria there is not enough availability of the necessary laboratory materials in the country and enough trained personnel in places. Also, there is a lack of a single portal where travelers can familiarize themselves with the statistics, brochures about adults and children with malaria prevention methods and behaviors for travelers to malaria-active areas and electronically accessible malaria registration forms.

In conclusion, we should note that in the Republic of Bulgaria and the Republic of Greece there is a potential risk of a resumption of the local occurrence of malaria. This is determined by the presence of two components - susceptibility and vulnerability of these two territories. Vulnerability is currently moderately likely and is determined by how many imported cases from malaria-endemic areas there are in the two countries separately and together. However, it is directly related to a number of factors - migration processes, social and cultural ties, etc., which may change in the future, and therefore vulnerability is subject to constant monitoring. To limit the consequences of the import and prevent malaria in Bulgaria and Greece, as for Bulgaria, a high level of malaria surveillance must be maintained, as well as the availability of established diagnostic methods and consumables with relevant trained specialists in places, as well as the availability of sufficient medicinal products in sufficient availability for timely implementation of chemoprophylaxis and treatment of malaria. It is necessary to centralize information related to prevention, instructions and methods for prevention, registration, chemoprevention and treatment of malaria in the Republic of Bulgaria in one place - preparation of a single specialized portal with up-to-date information on prevention, prevention and treatment of malaria and other parasitic diseases.

Estimating the cost-effectiveness of chemoprophylaxis use using a decision tree and Markov model

To estimate the cost-effectiveness of chemoprophylaxis, two economic models were used: a decision tree and a Markov model. Both models were prepared with a specialized modeling program TreeAge Pro 64-bit. The chosen analysis is of the cost-effectiveness type, in which the final results are measured in the form of costs to the payer (NHIF) and health benefits in the form of life years added (LY). In this analysis, incremental values for costs and health benefits are calculated, from which a value for the incremental cost-effectiveness ratio (ICER=BGN/LY) is generated. The analysis was carried out at a pre-set cost efficiency threshold of BGN 60,636/LY (3 times GDP per capita for 2021).

Since there are different types of chemopreventive regimens, it was necessary to choose one regimen to use as an example in the modeling. Malarone (atovaquone + proguanil hydrochloride) was chosen as a popular option for which there is a significant amount of published data. Efficacy data for this chemopreventive regimen were extracted from the publication by Sukwa et al. (1999).

Decision tree

The decision tree traces the path of a patient at risk of malaria, with final results generated based on the probability of the modeled patient events occurring.

In (Figure 22) in the dissertation on page 104 the structure of the model is presented. A modeling period of 1 year is assumed, as annual probabilities of event occurrence as well as annual values for health benefits and costs are used. Depending on the strategy chosen, the patient

enters the model with a probability of disease of 37% (for the no-prophylaxis arm) and 2% (for the prophylaxis arm). These values were derived by literature reference.

Upon entering the "healthy" state, the patient exits the model with a final outcome of BGN 0 for treatment and 1 added year of life, since no treatment cost was generated and the patient survives.

Upon entering the "sick" state, the patient has three subsequent options: recovered, relapse, and death. The probability of death was calculated on the basis of a database of malaria mortality in the period 2011-2020 from Bulgaria (2.70%) in (Table 21) in the dissertation on page 105. The probability of recurrence is based on expert opinion and is according to the real clinical practice in Bulgaria (25%).

Leaving the model in a recovered state, the patient accumulates treatment costs (CP No. 99 "Diagnosis and treatment of infectious and parasitic diseases transmitted by the bite of arthropods" worth BGN 1,072.56) and health benefits of 1 additional year of life. At relapse, patients are again likely to die (2.70%) or recover. An equal probability of death is assumed, regardless of whether it is a primary infection or a relapse.

In the case of recovery and death after a relapse, 2 CP#99s are reported, since re-hospitalization is required for the relapsed disease. Recovered patients get +1 added life year as health benefits and deceased get 0 added life years as health benefits.

Leaving the model in the state of death after illness (without having entered the state of relapse), the patient accumulates a one-time expenditure for CP #99 worth BGN 1072.56 and 0 added years of life.

More information on the decision tree structure used to model the pathway of a patient at risk of malaria can be found in (Figure 22) in the dissertation on page 104.

Data for 2011-2020		
Total malaria patients, no	**Total deaths, no**	**Percentage of deaths from malaria, %**
111	**3**	**2,70%**

Table 12 Average annual probability of death from malaria (data from Bulgaria for the period 2011-2020)

The results of the cost-effectiveness analysis are presented in (Table 13). According to the analysis, the "with prophylaxis" strategy leads to an average cost of BGN 26.81 compared to BGN 496.06 for the "without prophylaxis" strategy (difference of BGN 469.25). Mean health benefit values were 1.00 life-years added for the "with prophylaxis" strategy versus 0.99 life-years added for the "no-prophylaxis" strategy. On the basis of these values, it can be summarized that the "with prevention" strategy would lead to an average value for the saved cost for the NHIF payer of BGN 469.25 and added health benefits for the patient of 0.01 years of life. According to the cost-effectiveness analysis conducted using a decision tree model, the "with prevention" strategy was found to be dominant over the "no prevention" strategy (cost savings at higher values of health benefits).

Strategy	Cost average, BGN.	Average for health benefits, LY	ICER, BGN LY
With prevention	26,81	1,00	**"With prevention" is a dominant strategy**
No prophylaxis	496,06	0,99	
Difference	**-469,25**	**0,01**	

Table 13 Results of the performed analysis (decision tree)

Markov model

To assess a longer time horizon, a Markov model was used to model the possible health states of patients at risk of malaria. The time horizon used is 60 years. In (Figure 23) in the dissertation on page 107, the structure of the model is presented in detail, which includes 5 health states and two possible strategies: "with prophylaxis" and "without prophylaxis".

The health conditions included in the model are:

- Healthy
- Sick with malaria
- Relapsing malaria
- Had malaria (cured)
- Death

In (Figure 24) from the dissertation on page 108, a simplified structure of the model by health states and the possible transitions between them is presented. Death and 'malaria passed (cured)' are absorbing health states and patients entering them remain in that health state until the end of the modeled period. The model takes a simplistic approach in which it is assumed that a patient contracting malaria would not be exposed to the same initial risk of contracting the disease. For this reason, the model considers that a patient who has passed through a disease state ('sick with malaria' and/or 'relapsing malaria'), when leaving the model in the state 'passed through malaria (cured)', remains in that state until the end of the modeled time horizon.

More information about the Markov model: a detailed image and structure of the Markov model by health states can be found in (Figure 23) and (Figure 24) in the dissertation on pages 107 and 108, respectively.

All patients enter the model in a “healthy” state, being at risk of disease. Depending on which arm the modeled patient was in, he would have a probability of disease of 37% (for the arm without prophylaxis) or 2% (for the arm with prophylaxis). These values are derived by literature reference.

Upon entering the 'malaria-affected' state, the modeled patient could either recover and transition to the 'malaria past (cured)' state, relapse and transition to the 'relapsing malaria' state, or die and transition to the "death".

The model takes into account a one-time cost of hospitalization in case of malaria, as well as in case of recurrence of the disease. The cost is consistent with actual clinical practice in Bulgaria and is worth BGN 1,072.56 (the price of CP No. 99 Diagnosis and treatment of infectious and parasitic diseases transmitted by arthropod bites").

Health benefits in the model are counted as life-years added, and each year in a state other than “death” is counted as one life-year added.

It is assumed that the probability of death from malaria is the same regardless of whether it is a primary infection or a relapse. The annual probability of death in patients suffering from malaria was calculated on the basis of a database from Bulgaria for the period 2011-2020 and has a value of 2.70%.

Data for 2011-2020		
Total malaria patients, number	**Total deaths, number**	**Malaria death rate,%**
111	**3**	**2,70%**

Table 14 Average annual probability of death from malaria (data from Bulgaria for the period 2011-2020)

The probability of relapse is based on expert opinion and is consistent with actual clinical practice in Bulgaria (25%).

The results of the cost-effectiveness analysis are presented in (Table 15). According to the analysis, the "with prophylaxis" strategy leads to an average cost per patient for the entire modeled time horizon of BGN 940.14 compared to BGN 1340.70. for the "no prophylaxis" strategy (a difference of -400.56 BGN). The mean health benefit values were 59.19 added life years for the "with prevention" strategy versus 58.11 added life years for the "no prevention" strategy. Based on these values, it can be summarized that the "with prevention" strategy would lead to an average cost savings for the NHIF payer of BGN 400.56 and added health benefits for the patient of 1.08 years of life. According to the cost-effectiveness analysis conducted using a Markov model, the "with prevention" strategy was found to be dominant over "without prevention" (cost savings at higher values of health benefits).

Strategy	Average value for spend, BGN	Average for health benefits, LY	ICER, BGN/LY
With prophylaxis (malaron)	940,14	59,19	**"With prevention" is a dominant strategy**
No prophylaxis	1340,70	58,11	
Difference	**-400,56**	**1,08**	

Table 15 Results of the analysis (Markov model)

Sensitivity analysis

In order to assess the robustness of the results, a sensitivity analysis was performed comparing the "with prophylaxis" and "without prophylaxis" strategies. In probabilistic sensitivity analysis, each parameter under evaluation is assigned a parametric distribution—normal for costs and beta for probabilities. The parameters vary: price of CP #99, probability of death and probability of illness (for each evaluated arm). The chosen interval in which to vary the parameters is ±20%. The analysis uses a syringe set threshold of favorable cost efficiency of BGN 60,636 (3 times GDP per capita according to NSI data for 2021).

A one-way sensitivity analysis was not performed because, according to ISPOR recommendations, the graphic representation of ICUR with a negative value ("with prophylaxis" dominates) should be avoided and therefore a one-way sensitivity analysis (tornado diagram) was not performed.

(Table 16) presents the results of the Monte Carlo simulation with 1000 iterations. The summarized (average) simulation results are presented in (Table 25) in the dissertation on page 110 in Monte Carlo simulation: comparison between "with prophylaxis" and "without prophylaxis".

In (Figure 25) of the dissertation on page 110, the results of the analysis are presented graphically, with each point representing one iteration. In 100% of the iterations, the "with prevention" strategy was cost-effective (above the threshold for favorable cost-effectiveness of BGN 60,636). This is interpreted as a 100% probability of cost effectiveness of the strategy "with prevention" compared to "without prevention" in (Figure 26) of page 112 of the dissertation. .

Based on these results, it can be concluded that the probabilistic sensitivity analysis confirms the results of the main analysis and thus validates their robustness.

More information on Monte Carlo simulation: a comparison between "with prophylaxis" and "without prophylaxis" can be found in (Table 24) in the dissertation on page 111.

Strategy	Expenses, BGN	Δ expenses, BGN.	LY	Δ LY	ICER, BGN/ LY
With prophylaxis	935,75	-	59,19	-	-
Without prophylaxis	1351,31	-415,56	58,10	1,09	**"With prophylaxis" dominant**

Table 16 Probabilistic sensitivity analysis: summary results

Compassionate treatment. Regulatory framework in Bulgaria. The role of medical staff in access to compassionate use medicines

According to the recently adopted European regulation, patients with severe and life-threatening diseases for which there are no suitable authorized or reimbursed drugs can gain access to the so-called compassionate treatment with an unlicensed product for which the clinical trial has been completed but is not yet approved for sale or is still in the testing phase. In Bulgaria, compassionate treatment is regulated by the changes to the Law on Medicinal Products in Human Medicine and changes to Ordinance No. 10 adopted in October 2018. This gives patients access to treatment that can be life-saving or life-prolonging. This treatment is organized and financed by the pharmaceutical companies and is carried out only if there is sufficient data on efficacy and safety. Patients can be informed by their attending physician about compassionate use programs in Bulgaria that are suitable for their condition. For this purpose, the Medicines Executive Agency publishes on its website information on the activities of treatment with medicinal products for compassionate use, for which it has a positive opinion.

Many new drugs and medical devices have been developed in recent years. Marketing authorization and reimbursement for new therapies often takes time, and the wait is exhausting, and in some cases, impossible for patients. Previously, clinical trials were the only way to access new drugs in development. However, not all patients meet the inclusion criteria, especially patients with life-threatening, long-term, severely disabling and rare diseases. Those patients for

whom there are no suitable authorized or reimbursed drugs and who do not meet the criteria for participation in a clinical trial can access treatment with unlicensed products within programs approved by the regulatory authorities in the respective countries. These programs are called by different names in different states: early access, special access, managed access program, compassionate use, compassionate access, patient-named access, provisional use authorization, cohort access, prior approval access. In Bulgaria, all regulatory documents use the term "compassionate use"; newspaper and magazine publications also use the term "charitable use".

Very often in these programs, the pharmaceutical companies provide the medication at their own expense, at no cost to the patients. When clinical trials are in phase 3 and nearing completion, or when marketing authorization is under consideration, pharmaceutical companies can open compassionate use programs. In certain indications, for example oncology, programs can also be started at an earlier stage of development, for example when the drug is in phase 2 clinical trials. Historically, in the US, compassionate use began in the late 1970s with the provision of investigational drugs to certain patients, and in 1987, the FDA introduced compassionate use regulation and a formal program was established in response to the request of HIV patients /AIDS to drugs under development outside of clinical trials. In the 1990s, while phase 3 clinical trials were underway, Glaxo-Wellcome did a compassionate use program and provided its AIDS drug Retrovir (Ziduvidine) for free to 22,000 patients. Genzyme Corporation runs three large-scale international compassionate use programs and provides Cerezyme (imiglucerase) for the life-saving treatment of hundreds of severely affected patients with Gaucher disease.

In 1992, "Temporary Authorization for Use (ATU)" was adopted in France, and in 1994 in Great Britain "Guidance on use and supply of "Specials", which regulations regulate compassionate use in these countries. It was not until 2004 that the European Union (EU) introduced the compassionate use of medicines as an exception with Regulation 726/2004. The European Medicines Agency (EMA) provides regulations and recommendations, according to which each member state has developed its own rules and regulations. Currently, 18 EU Member States have well-defined national regulations and procedures for the compassionate use of medicines.

The most compassionate use programs are in oncology, neurology, and genetic diseases.

In Bulgaria, compassionate use programs are conducted after coordination with the Bulgarian Drug Agency (BDA). The change enters into force in October 2019, after the promulgation of the Ordinance amending and supplementing Ordinance No. 10 of 2011 on the conditions and procedures for treatment with medicinal products not authorized for use in the Republic of Bulgaria, as well as the conditions and procedures for inclusion, changes, exclusion and supply of medicinal products from the list under Art. 266a, para. 2 of the Law on Medicinal Products in Human Medicine.

The purpose of the conducted study is to present the legal framework in Bulgaria and to present to the medical specialists another opportunity for patients with serious diseases to access new treatment options. Also inform healthcare professionals how their patients can apply for and be enrolled in compassionate use programs. Last but not least, we would like to point out the main differences between compassionate use programs and clinical trials.

A review of the available regulatory framework in Bulgarian legislation governing the organization, coordination and implementation of compassionate use programs was carried out. Outline the role of medical staff in the process of obtaining medicines for compassionate use. By using a documentary method, a parallel is drawn between clinical trials and compassionate use programs and the main differences between the two processes are indicated.

In Bulgaria, the terms and conditions for the treatment of a group of patients with a medicinal product for compassionate use are regulated by the Law on Medicinal Products in Human Medicine in force from 13.04.2007 (amended on 10.2018) and Ordinance 10 from 17.10.2011 on the terms and conditions for treatment with medicinal products not authorized for use in the Republic of Bulgaria, medicinal products applied outside the conditions of the authorization for use, and medicinal products for compassionate use, as well as the terms and conditions for inclusion, changes, exclusion and delivery of medicinal products from the list under Art. . 266A, para. 2 of the law on medicinal products in human medicine (2019 amendments).

Regulation 10 Section IV sets out the terms and conditions for the treatment of patients under compassionate use programs.

The place where patients can be treated under compassionate use programs is regulated in Article 19, para. 2, and the way to store and manage the drugs is legally placed under the responsibility of the hospital pharmacist.

Article 20 defines who is eligible to apply for a compassionate use program. According to Regulation 10, the program applicant (the so-called "responsible person") submits an application form with accompanying documents to the Bulgarian Drug Agency (BDA). Within 14 days from the date of submission of the documentation, BDA examines the submitted documents. In case of incomplete documentation, BDA may request additional information. Once the program is agreed, the BDA notifies the EMA indicating whether an opinion from the Committee for Medicinal Products for Human Use (CHMP) is required on the compassionate use conditions, publishes the compassionate use program on its website, maintains an updated list of data on those included in the program patients, medical facilities and attending physicians, documents the received reports of adverse drug reactions from patients and sends them to the "EudraVigilance" database.

At this time, only two Compassionate Use programs are posted on the BDA page. There is no word on whether these programs are still open or have ended.

More information on compassionate use programs in Bulgaria can be found in (Table 27) in the dissertation on page 115.

Obligations of the responsible person: The responsible person is the applicant for a use permit under Art. 6 of Regulation (EC) 726/2004 for the relevant medicinal product; or the manufacturer of the medicinal product or the sponsor of an approved clinical trial. The responsible person has the following obligations:

- conducts the Compassionate Use Program as agreed by BDA
- provide the attending physician with the protocol and all necessary documents that are provided to patients
- notifies the BDA on the initiation of the compassionate use program, upon inclusion/exclusion of a patient in it, upon early termination or suspension
- provides the medicinal product free of charge

- provide the attending physician and the BDA with any new safety-related information that may change the benefit/risk ratio; submits received reports of suspected adverse drug reactions to the " EudraVigilance" database, submits an annual safety report to BDA
- presents to the BDA and to the attending physician the opinions accepted by the CHMP according to Art. 83, paragraph 4 of Regulation (EC) 726/2004 and findings from compassionate use programs that take place in another EU Member State or in another EEA State
- notifies the BDA of any change in the information under Art. 20, para. 3, 4 and 5 and to attach the relevant documents;
- keep all documentation for at least ten years after its completion or early termination
- takes out insurance covering the liability of the responsible person and the attending physician(s).

The role of the attending physician is specified in Ordinance 10, Art. 24 and 25 also define the role and duties of the attending physician in conducting compassionate use programs. The attending physician may inform a patient with the relevant disease of the possibility of being included in a program, and the patient must sign a written informed consent, which can be withdrawn at any time. The attending physician has the obligation to notify the responsible person of each included/excluded patient, is responsible for conducting the treatment, documents and communicates to the responsible person any suspicion of an adverse drug reaction related to the medicinal product.

Enrollment of new patients in a compassionate use program continues until the medicinal product is on the market; or the responsible person terminates the program early, of which BDA is notified. Patients already enrolled in a compassionate use program receive the program drug until reimbursement begins in the respective country so that patients' treatment is not interrupted.

Differences between compassionate use programs and clinical trials

Both clinical trials and compassionate use programs provide new drugs to seriously ill patients when they have exhausted all available treatment options. In essence, these are different processes. As compassionate use programs become more common in the global health care system, it is important for medical staff, patients and patient organizations to be aware of the differences between them.

The biggest difference is the reason. A clinical trial is conducted by a drug manufacturer seeking approval and registration for use. To get approval, the manufacturer must prove to regulatory authorities that the drug is safe to use and that it is at least as good, if not better, than existing drugs already in clinical practice. Clinical trials allow the manufacturer to test their drug in a controlled and regulated setting to gather the necessary safety and efficacy data.

The Compassionate Use Program has another purpose. Although the drug manufacturer may collect safety and efficacy data from patients and medical staff, these programs are not essentially done to obtain registration. They were created solely to deliver medicine to the seriously and critically ill. The drug manufacturer usually provides the drug through a compassionate use program because it is the patient's last hope.

However, programs have certain benefits and can offer a number of additional benefits to a pharmaceutical company, such as:

• Provides an opportunity to bridge the 'gap' between clinical trials and commercial offering

• Provides valuable information on usage prior to mass release into clinical practice

• May reveal subclasses of patients not represented in clinical trials

• May help identify patients who may be referred to a clinical trial

• Improves the company's reputation and avoids negative publicity

More information on the main differences between clinical trials and compassionate use drug programs can be found in (Table 27) in the dissertation on page 118.

In some cases, clinical trial participants may be transferred to open-label study phase or compassionate use programs. Transfer from a registration study program is appropriate when:

• Treatment, not data collection, is the primary goal.

• The pharmaceutical company wants to ensure continued access to treatment for patients who benefited from the treatment during a clinical trial or were in the placebo group.

• The pharmaceutical company wants an alternative to an open-label study.

• The pharmaceutical company is no longer willing to develop and commercialize the product, even though doctors and patients have found benefit from the treatment.

Discussion

The updated Law on Medicinal Products in Human Medicine (amendments of 10.2018) and Regulation 10 of 17.10.2011 on the conditions and procedures for treatment with medicinal products not authorized for use in the Republic of Bulgaria clearly indicate the ways of organizing programs and the responsibilities of all persons involved in the process. But despite the changes in the legislative framework, at the moment there are only two programs for compassionate use in the field of neurology approved in Bulgaria. Compassionate use can also be used for NEW malaria drugs, which would help significantly in a complicated form of malaria with proven good results during the clinical trial, such as low toxicity and little or no resistance.

Further education is needed among healthcare professionals about the options for patients with serious and life-threatening illnesses to access compassionate use programs. These programs can meet the needs of patients who are unable to obtain drugs through clinical trial or commercial channels and can be life-saving. Doctors, patients and patient organizations can pressure pharmaceutical companies to provide access to their drugs in development. Compassionate use programs should be considered as an integral part of any product strategy and as a possible extension of clinical trials.

Repositioning of medicinal products for the treatment of malaria

Repositioning can be defined as the re-search for new therapeutic options for the use of known drugs. It is a strategy to discover new indications of already authorized or tested drugs beyond their original indications. In recent years, pharmaceutical companies have increasingly adopted the drug repurposing strategy in their drug discovery and development programs, leading to the identification of new biological targets through innovation. This strategy is highly efficient and innovative, time-saving, cost-effective and carries a lower risk of failure compared to traditional drug discovery methods. By maximizing the therapeutic value of existing drugs, their reuse increases the likelihood of success through these new health technologies. It serves as a valuable alternative to the long, expensive and resource-intensive process of finding new molecular entities through traditional or de novo drug discovery approaches.

Drug repurposing combines activity-based or experimental innovation methods with in silico-based or computational approaches to rationally develop or identify new uses for drug molecules. It uses existing drug safety data tested in humans and redirects their application based on valid target molecules. The strategy also focuses on drug polypharmacology to unlock new opportunities to logically design more effective therapeutics for undiscovered medical disorders through innovative health technologies. Drug repositioning also presents certain regulatory challenges that hinder its further use. The review outlines the remarkable role of drug repositioning in new drug discovery, methods for predicting the molecular targets of a drug molecule, the advantages the strategy offers to pharmaceutical industries, explaining how industry collaboration with academia can help discover more opportunities for repositioning. The focus of the review is to highlight the latest applications of drug repositioning in various disorders. The review also includes a comparison of old and new therapeutic uses of repurposed drugs, with an assessment of their novel mechanisms of action and pharmacological effects in the management of various disorders. Various limitations and challenges that repurposed drugs face during their development and regulatory phases are also highlighted.

Resistance of the malaria parasite to chloroquine is a serious and growing health problem in tropical countries. Another problem for malaria treatment is the clinically silent hepatic stage of Plasmodium infection, which occurs in a mammalian host and is the major bottleneck in the life cycle of the malaria parasite. Liver infection necessarily precedes the blood stage of infection, where the disease develops, providing an opportunity for targeted prophylaxis. Furthermore, in the case of relapsing Plasmodium species, the liver also represents a reservoir of dormant hypnozoites that can be reactivated weeks to years after illness. primary infection, posing an additional burden to global malaria eradication efforts. Therefore, targeting this stage of the parasite life cycle is an absolute requirement to achieve a radical cure of infection by recurrent Plasmodium parasite species. Currently, only two drugs, primaquine and tafenoquine, are approved for the elimination of hypnozoites in the treatment of malaria relapses. However, the use of these 8-aminoquinolines is hindered by their toxicity. In fact, these drugs are known to cause hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, a genetic disorder that is quite common in malaria-endemic areas. Therefore, the existing gap in prophylactic and therapeutic needs related to liver Plasmodium infection needs to be urgently filled. One possible approach to this challenge is to use the reusability of approved drugs from different therapeutic categories to bridge this gap. Given the increasing levels of resistance to existing therapy, new options for the treatment and prevention of malaria are needed.

Description of the performed experimental part:

Detailed analyzes were performed on the malaria clinical trials database available at *www.clinicaltrials.gov*. All clinical trials were reviewed, retrieved, analyzed and included in the study.

In our case of advanced search, the following criteria were applied:

• Type of study - "Interventional studies (Clinical trials)"

• Status - "Finished"

• Research phase - "2/3 and 3"

• Condition or disease – “Malaria; P. falciparum; P. vivax; P. malariae'

• Population – "Adult and Older Adult"

• Launch of the first survey - "May 2001"

• Initial completion of last survey - "14/06/2022"

From the criteria set in this way, we have 81 research results distributed with the following primary purpose.

Main aim of the study	Number of studies
Treatment	52
Prevention	23
Diagnostic	3
Others	1
There is no	2
Total	**81**

Table 17 Showing the number of surveys according to their main objective

Of these, 15 clinical trials (18.5%) test medicinal products without a malaria indication in the Summary of Product Characteristics (SmPC) and have the potential for repositioning (a total of 8 different therapies).

MP candidates for repositioning	Number of studies
Azithromycin	5
Cotrimoxazole	4
Paracetamol	1
Ivermectin	1
Ivermectin + Albendazole	1
Protease inhibitors (lopinavir, ritonavir, efavirenz, zidovudine, lamivudine)	1
Folic acid	1
Zinc supplementation	1
Total	**15**

Table 18 Shows the medicinal products candidates for repositioning for the disease malaria

In this case, 5 Azithromycin studies were selected and analyzed due to the fact that they are the most numerous and available in a large database.

Studies with Azithromycin were conducted in the period:

• Launch of the first study - "September 2003"

• Initial completion of last survey – "January 2013"

All participants in the two studies NCT00082576 and NCT00367653 were hospitalized, a total of 467 participants, after three consecutive daily blood smears that were negative for asexual P. falciparum parasitaemia were included in the studies of the following two arms Azithromycin/Chloroquine and Mefloquine. Study participants were evaluated weekly for 42 days, with the primary endpoint being polymerase chain reaction (PCR)-adjusted parasitological clearance rate.

Conclusions in adults with symptomatic uncomplicated falciparum malaria in Africa, the combination of azithromycin 1000 mg and chloroquine 600 mg once daily for three days resulted in a Day 28 PCR-corrected parasitological clearance of ≥98% and no greater -lower

than Mefloquine treatment. The combination of Azithromycin and Chloroquine is well tolerated.

The clinical trial NCT01136850 enrolled 2,793 participants. The purpose of the study is periodic preventive treatment during pregnancy has not been evaluated outside of Africa. Low birth weight (LBW, <2500 g) is common in Papua New Guinea (PNG) and contributing factors include malaria and reproductive tract infections. Patients were included in the following two arms: Chloroquine, Sulfadoxine, Pyrimethamine and Azithromycin, Sulfadoxine, Pyrimethamine.

The study concluded that the combination of Azithromycin, Sulfadoxine, Pyrimethamine is effective and safe in reducing low birth weight, probably acting through multiple mechanisms, including effects on malaria and sexually transmitted infections. The efficacy of this combination in the presence of resistant parasites and the contribution of Azithromycin to bacterial antibiotic resistance require further investigation. The ability of Azithromycin, Sulfadoxine, Pyrimethamine to improve pregnancy outcomes requires further evaluation.

Their extended duration and the large number of included patients determine the larger volume of data on the use of the medicinal product that is collected and processed. Further evaluation of key parameters such as long-term safety, improved efficacy or proof of a new indication can be performed by pooling and combining clinical trials in our case phase II-III. There are various regulatory and marketing strategies to extend the life cycle of medicinal products. Repositioning, for example, is an effective strategy for identifying new pharmacological or therapeutic indications for developed drug molecules. When a drug interacts with a common signaling pathway in the human body that is part of various pathological mechanisms, it can lead to the discovery of new therapeutic alternatives for existing conditions. With its antibiotic and additive effect in combination with other medicinal products, Aizthromycin shows potential for redirection in different areas – such as malaria. and others. The widespread use of this macrolide antibiotic has contributed to the successful development and approval of biosimilar medicinal products by drug regulators in the US and Europe. The purpose of this analysis is to explore the creation and current status of Azithromycin, to analyze the potential for reuse in different indications, and to examine the development and impact of generics of the antibiotic.

Repositioning enables more savings and shortens time to market. Research and Markets describes in its 2020 report on drug repurposing that the cost of developing and marketing a repurposed drug is estimated at USD 300 million, compared to USD 2-3 billion for a new drug.

Part of this cost reduction may stem from the use of in silico repurposing approaches that use highly sophisticated systems to recognize the drug-disease relationship. There are two main ways of doing this – one uses computerized molecular approaches, 'OMIC data' and predicts the interaction between chemical structure and drug targets. Others are real-world data (RWD) approaches, which use data collection methods focused on identifying an unknown and/or unexpected relationship between prescribing trends and patient outcomes. On the one hand, they can reduce preclinical development costs and eliminate the need for animal testing. On the other hand, savings may come from avoided costs due to unacceptable toxicity or failure to demonstrate clinical benefit during later phases.

During clinical trials, savings can be generated by skipping some of the development phases during the collection of information needed for regulatory approval. It is described that the average costs are as follows – Phase I at 3.4 million, Phase II at 8.6 million and Phase III at

21.4 million. These costs depend mainly on the number of subjects randomized, participating countries and sites, but the type of molecule studied is not a significant cost factor. That being said, greater savings can occur when a molecule proven to be safe and efficacious is repurposed near its previously authorized indication and only phase III trials are conducted.

The analysis of the data collected from the study shows that the mechanism of action of Azithromycin may affect an important step in the pathogenesis of malaria. For this reason, the molecule has the potential to be reused in a wide range of indications. This process opens up new treatment options for patients, shortens the time it takes to obtain marketing approval for medicinal products, and reduces costs for healthcare systems. Another tool for expanding access to biologic therapies is the development and authorization of biosimilars.

In conclusion, Azithromycin is a promising molecule that retains its potential and is of interest for both repurposing and biosimilar development.

Inferences

The analysis of the data from the conducted studies give grounds for the following conclusions:

As a summary, the following results can be reached:

• Malaria affects all continents and many islands with a tropical and subtropical climate and a very important condition is also the presence of water bodies and marshy places

• The results show that at an altitude above 1600-2000 meters, the probability of infection decreases dramatically.

• Only two types of malaria causative agents P.vivax and P.falciparum are widespread.

• The following chemoprophylaxis drugs Mefloquine, Chloroquine, Proguanil, Doxycycline, Sulfadoxine – Pyrimethamine, Malarone (Atovaquone + Proguanil) and Artesunat are provided. Some of the preparations are registered in other countries or those registered in the Republic of Belarus are not kept in stock due to their small use.

• Malaria develops in countries with low economic development, countries with tropical climates and countries with poor health care.

• The main methods of protection against mosquito bites are the use of repellents and protective mosquito nets.

• All technologies, medical interventions, the entire national health policy should be evaluated according to the principles of HTA from the point of view of their ability to provide lasting results of a health, economic, social and ethical nature for citizens.

1. The detailed follow-up in the historical development and the analysis of the scientific and practical knowledge about the treatment of malaria showed the relevance of the problem in the past and the treatment methods that were empirical and quite ineffective due to the difficult dosing of non-standardized drugs used for the treatment of malaria.

2. With the exception of two medicinal products (Hydroxychloroquine and Amphotericin B), the country lacks registered life-saving medicinal products for the treatment of imported from tropical countries and other parasitic diseases such as malaria, leishmaniasis, filariasis, amebiasis, schistosomiasis and trypanosomiasis.

3. The registration of prophylactic products would reduce the possibility of malaria infection of Bulgarian citizens and the treatment in Bulgaria or abroad depending on their stay.

4. The severity of the investigated health problem in Bulgaria was analyzed and a "path of the patient" was built, in which the conclusion was reached that in many cases there is a delayed diagnosis and late initiation of therapy due to the poor training of general practitioners, the lack of of supportive education and the unavailability of medicinal products to start therapy immediately after diagnosis.

The constructed patient pathway diagram shows that a unified system of registration of patients leaving and arriving from malaria-active areas would greatly facilitate the early diagnosis of patients and the initiation of timely treatment would speed up the treatment process, reduce the likelihood of relapses, as well as and the reduction of deaths.

5. The specific pharmacoeconomic analysis carried out shows that the cost of treating a patient with medicinal products is quite low and the availability and maintenance of a centralized stock of unregistered medicinal products for the treatment of malaria and other parasitic diseases would not involve a significant financial resource, but would help for faster healing, fewer side effects and a lower probability of developing malaria, leishmaniasis, filariasis, amoebiasis, schistosomiasis and trypanosomiasis relapse.

6. The conducted study showed that a specialized drug reserve is absolutely necessary and at this stage this is the only solution for immediately supplying medical facilities in Sofia and the country with drugs for emergency treatment of hospitalized cases with the above mentioned parasitic diseases.

7. Up to now, the necessary medicines, after the relevant permission of the Ministry of Health and the Bulgarian Drug Agency , have been imported by authorized importing companies at the expense of the budget of the hospitals, which have a contract with the National Health Insurance Fund for the admission of patients on these clinical pathways in accordance with the requirements of Ordinance No. 10/MH from 17.11.2011 on the conditions and procedures for treatment with medicinal products not authorized for use in the Republic of Bulgaria. The national legal framework regulating the public drug supply process with unregistered medicinal products for the treatment of malaria includes a large number of normative acts of different rank - laws, regulations, etc., which creates conditions for their difficult implementation. The administrative system for the supply of unregistered medicinal products is built centrally, with a lack of balance in the distribution of powers between the responsible authorities. Frequent legislative changes in various normative acts and the lack of a clearly constructed strategy further complicate the process.

8. The results of the own studies confirmed two of the defined scientific hypotheses:

- that our country lags behind the European trends in the provision of unregistered medicinal products for the implementation of chemoprophylaxis, which is due to various legislative barriers and the second hypothesis was also confirmed, the same problem is observed in the treatment of patients suffering from the disease malaria, but in more to a small extent, since there is a procedure for ordering medicinal products here, which is quite cumbersome and complicated.

- that the lack of effective medicinal products for the treatment of malaria and the high resistance to already established products provide an opportunity for the development of innovative methods and new health technologies that can be used in repositioning. Its main benefits are the reduction of time for development of a new indication for a medicinal product, comprehensive information on already established bioavailability, pharmacokinetics, toxicity and expected side effects. A very important and essential point is the reduction of funds for the development of new molecules that would enter the market faster at a significantly lower cost for the patient.

Recommendations

The following recommendations can be noted:
Recommendations to the Council of Ministers.
The following recommendations should be taken into account as the main holders of legislative initiative:
1. Timely updating of the current legislation in terms of possibilities for prevention and timely treatment of malaria and implementation of all new legislative changes;
2. Inclusion in the National Health Strategy as a priority, stimulating the active participation of doctors specializing in parasitology and noting the problems related to the prevention and treatment of parasitic diseases, as well as the renewal of the regulatory framework according to the latest WHO recommendations in the annual reports on malaria disease.
3. A change in the legislation aimed at stimulating the consideration of the patient's point of view in his treatment.

Recommendations to the Ministry of Health
The Ministry of Health takes over the main organization involved in the medicinal supply process of unregistered medicinal products, which outlines the following recommendations:

1. The legal regulation of health information in Bulgaria for chemoprophylaxis is very incomplete. In fact, in 90% of cases, it is not possible to conduct it by the ordinary citizen, since the medicines for its conduct are available in the pharmacy network and there is no legal framework for their ordering and delivery
2. The lack of life-saving medicinal products for the treatment of malaria is not guaranteed to happen in a short time due to the complexity of the procedure and the availability of the medicinal products in different suppliers. The state needs to maintain a reserve that can be provided to the relevant medical facility if necessary.
3. Practice has shown that such a drug reserve is absolutely necessary and at this stage it is the only solution for immediately supplying the medical facilities in Sofia and the country with drugs for the emergency treatment of hospitalized cases with the aforementioned parasitic diseases.
4. It is recommended that the Ministry of Health, together with the leading specialists in parasitology, initiate a clarification of the legislation regarding the medicinal procurement process of non-authorized medicinal products for the prevention and treatment of malaria and other parasitic diseases, as well as launch a campaign for their promotion.
5. It is necessary to centralize information related to prevention, guidelines and methods for prevention, registration, chemoprophylaxis and treatment of malaria in the Republic of Belarus in one place - preparation of a single specialized portal.
6. Prioritizing the need to prepare registers of patients and their diseases. Among the many benefits of registries would be accessible information for the preparation of HTA, as well as the possibility of long-term follow-up of patients in order to prevent relapses of the disease malaria.
7. According to the cost-effectiveness analysis conducted using a decision tree model, the "with prevention" strategy is found to be dominant over the "no prevention" strategy (cost savings at higher health benefit values).
According to the cost-effectiveness analysis conducted using a Markov model, the "with

prevention" strategy was found to be dominant over "without prevention" (cost savings at higher values of health benefits).
8. Allocation of the necessary financial and material resources to ensure the implementation of anti-relapse diagnostics and prophylaxis for already cured patients.

Recommendations to the Medicines Executive Agency

1. Ensuring greater access to patients and patient organizations at the various stages of the treatment process.
2. Introduction of simplified administrative procedures.
3. Digitization of the processes related to the sale of applications and documents.
4. Informing patients and their representatives about the progress of science, with the aim of better compliance with subsequent therapy.

Recommendation to the NHIF

1. It is recommended that the NHIF start using the data from real clinical practice, collected through its own database, the NCIPD and NSI and perform analysis and evaluation and, if necessary, update the clinical pathways.

Recommendation to Medical Universities

1. It is recommended to all MUs to include and expand the horary of hours in the curricula of medical students, considering the normative and practical requirements in the implementation of prevention, diagnosis, treatment, as well as the imposition of practice for continuing education after graduation with topics on infectious diseases , tropical diseases, epidemiology and pharmacotherapy.

Referral to the media

1. It is recommended that the media act in a socially responsible manner. When commenting or covering cases of adverse drug reactions - to seek the opinion of prominent professionals in this field and to give the floor to all interested parties.

Contributions

Scientific – theoretical

❖ The main conceptual aspects of malaria treatment are systematized, emphasizing the organization and participants in the process.

❖ The regulatory framework in the field of diagnosis, prevention, prophylaxis and treatment of malaria in Bulgaria from the past to the present has been studied and analyzed in detail.

❖ With a retrospective analysis, the number of malaria patients in Bulgaria was estimated, and the trends in the development of the sector were followed in comparison with WHO recommendations for prevention, prophylaxis and treatment.

❖ The main barriers (legislative, administrative and strategic) to possible prevention and timely treatment of malaria in Bulgaria are defined.

❖ The main factors influencing the overall process are outlined, including: awareness of the population, prevention, diagnosis and treatment of malaria by doctors, the regulatory framework and the Ministry of Health in Bulgaria.

❖ The main conceptual aspects of the treatment are systematized, with an emphasis on the process of supplying the medical facilities with medicinal products for treatment not approved for use in the country and

❖ The main legislative barriers that prevent returning travelers from malarious areas from being proactively taken by an officer through a border questionnaire or an electronic system to take a detailed epidemiological history and before infection is suspected (unclear temperature status and evidence of anemia and hepatosplenomegaly) have been identified referred by the general practitioner to a laboratory performing parasitological tests.

❖ The main factors that influence the familiarity and willingness of travelers to check the information on the page of the Ministry of Foreign Affairs before traveling or in another place such as the RHI and a personal doctor in Bulgaria are presented

Scientific - applied

❖ Recommendations have been formulated for changes in the Bulgarian legislation to improve the quality of malaria treatment, etc. tropical other parasitosis and the reduction of the probability of recurrence.

❖ Recommendations were formulated for changes in the Bulgarian legislation, which would lead to the introduction of a methodology system for informing the departing and arriving malaria regions.

Conclusion

An assessment was made of the potential consequences not only for medicinal products for the treatment of malaria, but also for necessary laboratory tests and medical interventions, but also for preventive organizational measures and policies for reforming the health care system related to ensuring the constant availability of medicinal products for malaria treatment and monitoring of arrivals from malaria-active areas.

The main task of HTA is to provide decision-makers with a thorough and comprehensive assessment of the potential effects and outcomes on health status, the implications for medical practice, the health system, the economy and society. Valid conclusions in the HTA process enable an informed decision to be made whether to adopt or reject a technology, to accelerate or slow down its diffusion, and to take various measures to accelerate the development of existing practice and scale-up and in the appropriate direction to help of the patient.

In recent years, processes of introducing and harmonizing HTAand creating specialized agencies have been accelerated in the EU member states in order to guarantee transparency and efficiency in the process of evaluating new health technologies. Bulgaria is one of the first countries with a nationally competent, regulatory body and a legally introduced process for HTA, at this stage only for medicinal products. As described, this tool uses many complex criteria that should be taken into account when evaluating and deciding to pay with public funds even for indications that are related to the prevention and treatment of small groups that need to be protected, diagnosed and/or treated for malaria. Evaluation and access to innovative technologies, including off-label drug therapies for malaria treatment, should be outside the debate about political priorities, but lead to the expansion of the resource capacity of the health system and respond to public attitudes.

The development of medicine and the growing variety of medicinal products for the prevention and treatment of malaria and tropical diseases require a constant reassessment of the importance of different types of treatment and their implementation in legislation and real practice using HTA. This reassessment should also lead to a review and improvement of the prevention and treatment of malaria patients and a reduction of the damage and recurrence of the disease in the long term of their health.

In addition to the shortcomings, omissions and expectations of the experts listed in the study, it should be noted that for Bulgaria the main problem is the lack of solid and systematically built and maintained clinical, epidemiological and economic data and evidence, which by themselves are a prerequisite for making informed and adequate decisions for access to innovative health technologies borrowed from the World Health Organization. Filling this gap is an important and fundamental point in supporting rational inferences in the assessment of health technologies, their validity for medical practice. Expectedly, a strong push in this direction will be given by the introduction of electronic health care and the system of registers.

Also such an important part is the constant development and improvement of the legislation and its implementation. For the process to be effective, the main building block – people – must be properly selected, trained and managed.

Effective leaders of the new age must respect the opinions and understand the values of their "followers", the professionals involved in HTA activities at every level in the health system and environment, as well as the HTA consuming and receiving parties. ready to believe and follow

the principles of a new era in health care even in the treatment of rare diseases such as malaria. This is the way for the health sector and the specialists working in it to carry out their work, motivated and willing to give their best. This will inevitably have a positive impact on the results and commitment of the teams dealing with HTA, and hence on the results at the regional level in the HTA field as a whole, and success is the business card with which HTA experts present themselves to the public.

Having a vision, a clear goal and direction is an important part of realizing a successful activity in the field of HTA. In order to achieve commitment from the professionals who work and are expected to drive the HTA processes, it is necessary that they feel excited about understanding the leadership's visions for the mission of health organizations and institutions.

The present development can be used as a reference point in the planning of the expert activities during the assessment to ensure the availability of unregistered medicinal products for the prophylaxis, prevention and treatment of malaria. It provides basic recommendations for making health policy decisions based on scientific methods.

The study confirms the need for an efficient system for the distribution of available resources, as well as for adequate decisions guaranteeing transparent, publicly accountable positions, the result of a careful evaluation of the clinical and economic evidence provided by competent experts, with a guaranteed absence of conflict of interest and in accordance with societal values and priorities where possible. To realize these goals, it is necessary for the delegates to carry out HTA activities, representatives of the Ministry of Health together with the representatives from the NHIF, NCIPD, NCPRMP and BDA, together with members of the subcommittees, to introduce HTA processes, accompanied by a review and re-standardization of the subsidized indications, especially for the hard-to-reach, but in our case, not expensive technologies in this development.

Last but not least, the legal framework currently does not recognize the importance of the patient for HTA. A review of current legislation and regulations is needed to ensure indexation of the burden of patient participation. Good practices taken from countries that have already walked the path of patient participation in HTA show that legislative changes are the first necessary step to lay a solid foundation and illuminate the patient's path to better treatment, a better quality of life with a given disease and acceptable coping with the difficulties of existing despite the adversities of illness.

List of publications related to the dissertation

1. Zlatanov A, Grigorov E, Belcheva V, Yanakieva A. Early historical evidence of malaria disease - Bulgarian Medical Journal, 14, 2020, №3, 35-39

2. Zlatanov A, Yanakieva A, Advancements in malaria pharmacotherapy in the modern period and the 21st century - "Annual for Hospital Pharmacy", volume IX, 2023, No. 1, 38-46

3. Zlatanov A, Yanakieva A, Mutafova I, Grigorov E. Up-to-date information on prevention, chemoprophylaxis, prevention recommendations, procedures for arrivals from malaria-active areas, dynamics of transmission, diagnosis and treatment of disease malaria, the similarities and differences in the Republic of Bulgaria and in the Republic of Greece.

Official note issued in confirmation that the report on the topic: "Official information on prevention, prophylaxis, recommendations for the prevention, diagnosis and treatment of the disease malaria - a comparative analysis between the Republic of Greece and the Republic of Bulgaria" has been accepted for publication in a collection of "Fourth International Conference Health Care - A Contribution To The Quality Of Life" June 9-10, 2023, organized by the Department of Health Care, Faculty of Public Health, together with UMBAL "Sveta Marina" - Varna and Faculty of Nursing Hamidie, to University of Health Sciences, Istanbul, Turkey.

4. Zlatanov A,Yanakieva A, Mutafova I. Legal framework, modern strategies for the prevention and treatment of malaria and problems related to the provision of medicinal products for the disease in Bulgaria - Collection of reports The sixth scientific conference of BNDOZ "Public health: challenges to the health system", organized by Medical University - Pleven, 26-27 May 2023, Section 6. Health Technology Assessment, Digital Health and Telemedicine, eHealth, pp. 434 – 439.

5. Zlatanov A, Grigorov E, Mutafova I. Compassionate use. regulatory framework in bulgaria. the role of medical personnel in access to compassionate use medicines - The 6th Scientific Conference of BNDOZ "Public Health: Challenges to the Health System", organized by Medical University - Pleven, May 26-27, 2023, Section 2. Health care , pp. 182 – 190.