

## Review

---

by **Prof. Dr. Rositsa Ivanova Kurdova-Mincheva PhD, Member of the Scientific Jury**

(**Order No.512 / 16.12.2019**)

**Scientific specialty** PARASITOLOGY AND HELMINOLOGY

**Institution:** National Center for Infectious and Parasitic Diseases, Sofia

**on the dissertation work** for the Doctor of Science Doctor of Philosophy) (in Scientific and Technological Sciences

**on the topic:** "Characteristics of imports and assessment of the possibility of malaria recovery in Bulgaria in the face of global climate change"

**Author:** **Dr. Iskren Tzvetkov Kaftandjiev,**

**Doctoral student:** self-study at NCSPD-Sofia

**Field of higher education:** 4. Sciences, mathematics and informatics, professional field 4.3. Biological Sciences

**Specialty:** Parasitology and helminthology

**Scientific adviser:** Assoc. Prof. Rumen Harizanov, MD, PhD, NCIPD-Sofia

I declare that there is no conflict of interest between me and the author of the dissertation within the meaning of para. 1, items H and 5 of the DR of ZRARB.

### **Analysis of the applicant's career profile**

Dr. Iskren Tzvetkov Kaftandjiev was born on 14.06.1962 in Sofia. After completing his medical education at the Medical Academy - Sofia in 1990, he initially worked as an intern at the Children's ward of the Municipal Hospital in Srednogorie until 1991. From 1991 to 1993 he was a resident at the National Center for Diabetic Children at the Scientific Institute of Pediatrics at the Medical Academy - Sofia and from 2007 until now he has been a resident at the Parasitology and Tropical Medicine Department at the National Center for Infectious and Parasitic Diseases (NCSPB) - Sofia. In 2012 he acquired the medical specialty Medical Parasitology. Dr. I. Kaftandjiev has 25 articles, 9 of which are in foreign publications with an impact factor and participation in one monograph "Clinical Parasitology and Tropical Medicine". He has participated in posters and papers in 52 regional and national and 3 international scientific forums. He speaks English and Russian languages both written and spoken.

Dr. I. Kaftandjiev participates in a number of courses for continuing medical training in medical parasitology and tropical medicine at the NCSPD-Sofia, as well as in an international "Introductory course in R statistics", which in combination with his practical work in the Department contribute to its construction as a qualified specialist.

### **Relevance of the topic developed in the dissertation**

Malaria continues to be one of the leading diseases globally, characterized by high morbidity and mortality. According to the World Health Organization (WHO) estimate, in 2018, there were 228 million cases worldwide, 405,000 of which were fatal, 67% (272,000) of those under the age of 5 (WMR, WHO, 2019).

WHO declared local malaria transmission in the WHO European Region eliminated in 2015 ([http://www.euro.who.int/\\_file/0003/307272/Facsheet-malaria-elimination.pdf](http://www.euro.who.int/_file/0003/307272/Facsheet-malaria-elimination.pdf)), But attention to this the parasitosis should not weaken because there is a risk of resumption of transmission in malaria-free territories for a number of reasons:

- In many WHO European regions, including Bulgaria, high levels of malaria susceptibility are maintained, meaning that there is a significant distribution and density of biological carriers - Anopheles mosquitoes that could carry malaria transmission if there is an accessible source the infection;
- The vulnerability of our territories to malaria is increasing due to the high import of malaria cases from endemic countries. About 8,000 imported cases of malaria are reported annually in the European Union WHO region. And the ongoing migration to Europe of refugees and migrants from endemic areas increases the risk of malaria recovery.
- Examples from the recent past when, in the 1990s, local transmission of malaria was resumed in 10 large-scale epidemics in the European Region with Azerbaijan, Turkey and Tajikistan clearly demonstrate how this potential risk in countries with malaria eliminated real.
- Climate change and global warming can also lead to changes in the basic biological and environmental characteristics of local malaria vectors that favor malaria transmission.

To prevent the recovery of local transmission in countries with malaria eliminated, the WHO recommends maintaining a high level of alertness and effective epidemiological and entomological surveillance.

Bulgaria was certified by the WHO as a malaria-free country in 1965, however, there is a potential risk of local malaria transmission occurring, necessitating monitoring of malaria vulnerability and susceptibility throughout the country, especially in conditions of global warming.

All this defines the given work as meaningful and relevant, which can serve as a scientific basis for the development of future surveillance measures and management decisions to prevent the return of malaria in our country.

### **General characteristics of the thesis**

In the dissertation the classical structure, including the following chapters, is observed:

Introduction - 3 pages,

Literary review - 20 pages,

Goals and objectives - 2 pages,

Materials and methods - 20 pages,

Results from own research - 103 pages,

Analysis and Discussion of Results - 26 pages,

Conclusions - 2 pages,

Declaration of originality. Contributions - 2 pages,

Publications, reports and communications in connection with the dissertation - 3 pages,

Summary - 3 pages,

Appendix - 5 pages and

Bibliography - 14 pages

The dissertation work is well balanced, with the greatest attention being given to two sections - Results and Discussion. The rich display of the text with appropriately selected and informative figures (86 pieces) and tables (43 pieces) that well represent the results obtained and the stated ones should be emphasized. The work is written on 203 standard pages in good Bulgarian language.

### **Review of dissertation work and evaluation of the results**

**Literature review.** It deals with the specific topic of the dissertation and includes analysis of 215 sources, 71 of which are in Cyrillic and 144 in Latin. The presented material demonstrates that the thesis is well-informed about the problem, both globally and nationally, as well as its potential to adequately analyze the numerous data and facts, breaking it through current WHO perceptions.

On the basis of the literary analysis, the dissertation well fits the concept of the study, which is in accordance with the latest views and recommendations of WHO, defines the subject and object of the study in a motivated way and logically formulates the purpose and tasks of the dissertation.

**Purpose and tasks.** The aim of the thesis is "to evaluate the potential for malaria recovery in Bulgaria and the clinical and epidemiological consequences of imports in the face of global climate change."

The tasks reflect the main directions in the development of Dr. I. Kftandzhiev and specify the planned research.

**Materials and methods.** The study covered all officially registered malaria patients for the period 2000-2015. The impressive volume of data processed and analyzed from various sources is impressive: the official reporting documentation of the Regional health inspections (RII), epidemiological survey cards, accounting and reporting documentation of the National Cabinet of Parasitic and Tropical Diseases at the NCSPD, medical records, official data of the National Institute of Meteorology and Hydrology at the BAS for the average monthly multi-annual air temperatures 2000-2012 and the National Statistical Institute, as well as the Fifth Climate Change Assessment Report of 2013 of the International Commission on Climate Change. Appropriate modern epidemiological, analytical and statistical methods have been applied, including alternative and variational statistical analysis, test for normal distribution of the sample data, non-parametric statistical analysis, as well as spatial analysis of cases of malaria imported into the country through two software programs - SaTScan and FleXScan Software. GIS - based design of a medico-geographical map of Bulgaria, including the data from the spatial analysis of cases of imported malaria, and mathematical modeling of malaria transmission using the models of Ross-Macdonald and S.D. Moshkovsky. Statistical processing of the data justifies the results and conclusions to be objective.

### **Evaluation of results, their analysis and interpretation**

The implementation of a program to prevent the recovery of local transmission after the elimination of malaria in Bulgaria in 1965 requires a periodic assessment of susceptibility and vulnerability. The clinical and epidemiological characteristics of imported malaria cases embedded in the dissertation are an important component in the assessment of vulnerability.

As a result of a comprehensive study, Dr. I. Kftandzhiev made a modern clinical and epidemiological characteristic of imported malaria in Bulgaria for a 16-year period (2000-2015), thus updating the information on the vulnerability on the territory of the country.

An undisputed dignity of the work is the epidemiological analysis of malaria imported in Bulgaria, characterizing the vulnerability, which establishes that cases of imported malaria are registered annually in Bulgaria, totaling 175 for the period - with predominant *Plasmodium falciparum* (70.29%), predominantly from Sub-Saharan Africa, followed by *P. vivax* (22.29%) mainly from Asia. The dissertation correctly concludes that these data are an indicator of a moderate level of vulnerability in the territory, but recognizes that cases of imported malaria have been registered in a large part of the territory of the country - 17 districts, with the majority of cases in the districts of Sofia, Burgas, Varna and Plovdiv.

Important for the epidemiological surveillance of malaria and for the prioritization of preventive measures are data on the changed profile of persons with imported malaria compared to the period 1965-1999, when malaria was mainly imported from foreign nationals legally resident in the country, and now - more often than Bulgarian citizens. Migrants are predominant among foreign nationals, with a high frequency of them entering illegally and presenting a real risk, as sources of occurrence of local cases, which increases the vulnerability on the territory of Bulgaria. A serious risk of epidemiological consequences - locally acquired cases as a result of imports - is evidenced by the registration data of 62% of cases in our country during the potential malaria transmission period (April - October).

The clinical consequences of malaria imports - complications (16.6%), incl. deaths (6.67% - 25%) are serious and particularly worrying. The author correctly refers to the analysis of the causes and clarifies that they are mainly related to delayed diagnosis and etiological treatment showing insufficient clinical focus on malaria in contingents arriving from endemic areas, as well as with other oversight gaps. The author rightly points out that one of the reasons is the lack of awareness of malaria and its prevention of persons residing in endemic areas.

After establishing a statistically significant increase in average monthly temperatures in 19 districts of the country compared to the period 1916-1975, Dr. I. Kafandjiev focused his attention on determining the duration of sporogony in the vector under changing climatic conditions. As a result of the huge amount of work he has done, he found statistically significant reductions in the time required for sporogonia in all three malaria plasmodia (*P. vivax*, *P. falciparum* and *P. malariae*) in most of the country and accelerated the possible rates of infection. These data clearly indicate an increase in susceptibility to malaria. This would cause more malaria transmission and affect more populations in the event of an epidemic.

The author correctly considers that it is important to determine which territories in the country are more risky in terms of future malaria imports. Through a spatial analysis of Poisson cases, he comes to the conclusion that in the coming years, in several clusters - Plovdiv, Pernik, Sofia, Vratsa, Pleven, Turnovo, Sliven, Burgas and Varna, malaria imports are likely to occur, which is valuable information on health structures and their focus on maintaining alertness, diagnostic and therapeutic preparedness and high levels of epidemiological surveillance for malaria in these territories.

The mathematical models of malaria transmission applied by Dr. I. Kafandjiev provide an opportunity for scientifically substantiated study, analysis and planning of effective measures for the control and elimination of malaria locally and globally, as well as with a high probability of predicting possible damage, which can also cause the disease when sending contingents to malaria endemic areas.

### **Assessment of conclusions and contributions**

The author formulates 8 conclusions, which are derived from the concrete results of the study and emphasize the relevance of the studies and their theoretical and applied importance.

I accept contributions from the PhD student's self-assessment and I think that they reflect objectively his or her real achievements.

I appreciate the following contributions as more significant and original:

1. A spatial epidemiological analysis method for evaluating the risk of malaria reintroduction in Bulgaria has been approved and applied; to identify the riskiest territories. This method could also serve as a model for other vector-borne diseases.
2. By comparative analysis of climate change in the country, some major elements of malaria transmission, such as the time required for sporadic malaria plasmodia in vectors, and the possible number of revolutions of malaria infection, have been updated and a prognostic algorithm for the development of the epidemic process has been developed. possible malaria recovery in the country or sending contingents in malaria-endemic areas.

Some contributions of a scientifically applied nature deserve special attention, such as:

1. A modern epidemiological characterization of the imported malaria in Bulgaria for a 16-year period (2000-2015) and noso-geographical mapping of the cases has been made and the information on the vulnerability on the territory of the country has been updated.
2. Characterization of the clinical consequences of malaria imports in Bulgaria has been performed in recent years and the main causes of complications have been clarified - delayed diagnosis and etiologic treatment showing insufficient clinical focus on malaria in contingents arriving from endemic regions and gaps in surveillance of malaria.
3. The main groups of persons presenting potential risk as possible sources of local malaria recovery as an epidemiological consequence of imports have been identified. The contingent of Asian malaria with Tertiary malaria was identified as riskiest.
4. There have been gaps in the awareness of malaria of persons residing in endemic areas, which is the reason for the late seeking medical help, and from there - for the development of complications and deaths.
5. A version of a card for epidemiological study of a case and outbreak of malaria has been developed, the application of which in practice would improve the epidemiological surveillance of the disease.
6. The up-to-date epidemiological characteristics of imported malaria in Bulgaria and of the potential malaria season, as well as data on the impact of global warming on possible changes in susceptibility, can serve as a scientific basis for the development of future surveillance measures and management decisions.

I believe that the results of this study should be brought to the attention of the responsible factors in healthcare, because they demonstrate the seriousness of the problem of malaria and the gaps in epidemiological surveillance in our country. The malpractice epidemiological

study card drawn up by the dissertation must be submitted to the Ministry of Health for replacement of the existing one, according to the regulations.

### **Reflection of the candidate's scientific results in literature**

The abstract is written on 71 pages and includes a summary in English. Its content is in line with the thesis in the thesis.

Four publications related to the topic of the dissertation were presented - 2 in Bulgarian journals and 2 in foreign ones with IF 1,083 and 1,439. In two works, Dr. I. Kaftandjiev is the first author to testify to his active role in their planning, development and design of publications. He has participated in 4 national scientific forums and one international one, which is documented with abstracts.

### **Critical notes**

The dissertation is precisely designed and I have no significant remarks. Upon final completion, the author took into account all the notes and suggestions made during the internal defense.

### **Conclusion**

The reviewed dissertation treats important health and social and representative for Bulgaria question concerning the import of malaria and an assessment of the possibility of its recovery in the country in the conditions of global climate change. The work has clearly formulated concepts, goals and objectives, has been developed competently, under the expert guidance of the scientific advisor, taking into account the latest achievements in the world literature in this field and applying modern research methods. Scientific results are well analyzed, argued, documented and illustrated. The dissertation work is valuable not only in scientific-theoretical aspect, but it can also be applied in practice for improving the epidemiological surveillance of malaria introduced in our country.

Publication activity in connection with the thesis is sufficient for this scientific degree.

The dissertation work fully complies with the scientific criteria in the ZRASRB and the Rules of the NCSPD for the ONS "Doctor". This gives me reason to vote strongly for the award of the Doctorate degree in the scientific specialty Parasitology and helminthology to Dr. Iskren Tzvetkov Kafandjiev.

Prepared the review:



12/27/2019

Sofia

Prof. Dr. Rositsa Kurdova-Mincheva, Ph.D.