

ARTICLE



## The changing risk patterns of *Plasmodium vivax* malaria in Greece due to climate change

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### ABSTRACT

It has great importance to study the potential effects of climate change on *Plasmodium vivax* malaria in Greece because the country can be the origin of the spread of vivax malaria to the northern areas. The potential lengths of the transmission seasons of *Plasmodium vivax* malaria were forecasted for 2041–2060 and 2061–2080 and were combined. The potential ranges were predicted by Climate Envelope Modelling Method. The models show moderate areal increase and altitudinal shift in the malaria-endemic areas in Greece in the future. The length of the transmission season is predicted to increase by 1 to 2 months, mainly in the mid-elevation regions and the Aegean Archipelago. The combined factors also predict the decrease of vivax malaria-free area in Greece. It can be concluded that rather the elongation of the transmission season will lead to an increase of the malaria risk in Greece than the increase in the suitability values.

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Resurgence; risk; bioclimatic variables; transmission; *Plasmodium vivax*

## Introduction

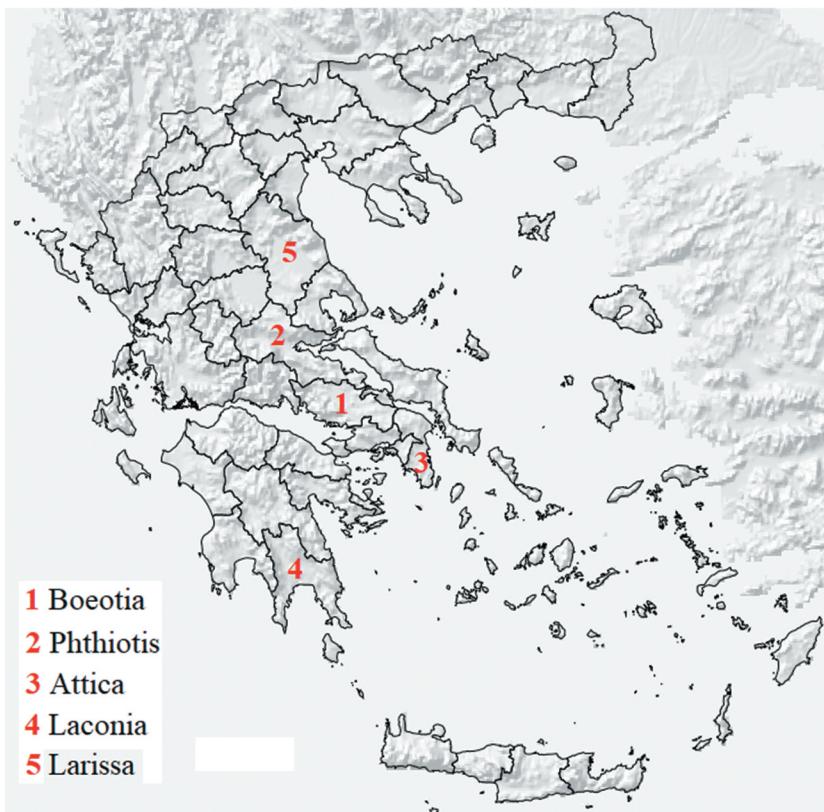
Malaria is endemic in over 100 countries of the world (World Malaria Report 2019). The most affected areas are sub-Saharan Africa and Southeast Asia and 70% of the annual cases are concentrated in only 11 countries of these two regions. It means that almost half the earth population – more than 3 billion people – live in malaria-endemic areas. About 228 million malaria cases were reported worldwide in 2018 and it is estimated that almost 405. 000 people died from malaria in this year. In 2018, children aged under 5 years accounted for 67% (272 000) of all malaria deaths (World Malaria Report 2019). The *Plasmodium vivax* Grassi & Feletti, 1890 caused vivax or *P. vivax* malaria is one of the five important human malaria parasites (the others are *Plasmodium falciparum* Welch, 1897, *Plasmodium ovale* Stephens, 1922, *Plasmodium malariae* Feletti & Grassi, 1889 and *Plasmodium knowlesi* Sinton and Mulligan, 1932). It is endemic mainly in Asia, Latin America, and in some parts of Africa, but it also can be found in Southeast Europe (World Health Organization 2015). It threatens 40% of the population of the Earth and causes annually about 132–391 million clinically observed infections (Price et al. 2007). Although the *P. falciparum* caused malaria is the main cause of global mortality due to malaria, *P. vivax* accounts for the major proportion of malaria cases in Asia and South America (Vogel 2013). It is plausible that *P. vivax* originally was endemic in Africa (Culleton and Carter 2012) and may be transmitted from macaques (Escalant et al. 2005). This malaria form was endemic in the major part of the Old Continent for centuries (Hutchinson and Lindsay 2006), including such temperate climate areas like the British Isles in the Middle Ages (Pinello, 2008). Malaria also has a long, at least 2500 years of history in the Peloponnese Peninsula

(Kousoulis et al. 2013). In Laconia, the first report of malaria is dated back to the 4–5th century BC, the era of Pericles (Carter 2003; Kousoulis et al. 2013). It is speculated that malaria originated in India and appeared in ancient Greece in the classic period (Carter 2003), where it caused the decline of several ancient Hellenic city-state populations (Carter 2003).

Before the 1970s, the malaria infection rate was high in the lowland regions of Greece (Barber and Rice 1935; Livadas and Sphangos 1941; Livadas 1958; Gardikas 2008). The most notable endemic regions were in Thessaly, in the central part of Macedonia, but minor historical malaria foci were also in Thrace (Larissa, Magnesia and Trikala), in Eastern Macedonia (Serres), in Epirus (Arta, Preveza and Thesprotia), in Western Greece (Acarnania and Aetolia), in Central Greece (Athens, Boeotia, East Attica and Phthiotis) and in the Peloponnese Peninsula (Corinthia, Elis, Laconia and Messenia; Sudre et al. 2013). Comparing the 20<sup>th</sup>-century occurrences of *P. vivax* malaria to the ancient situation, it can be stated, that its basic prevalence patterns did not change in the last two and half thousand years (Danis et al. 2011; Kousoulis et al. 2013; Tseroni et al. 2015). The last pulse of the anti-malaria campaigns started in 1946 in Greece (Vine 1948) and led to the eradication of malaria in 1974 in the country (Bruce-Chwatt et al. 1975). As in several other countries of the World, the agent of the mosquito control was DDT (Hadjinicolaou and Betzios 1973). Surprisingly, Martini and Teubner (1933) realized very early that the general change in housing for man and domestic stock also played an important factor in the eradication of malaria. This hypothesis was confirmed by Finnish authors who found that the former indoor microclimate conditions played an important role in the maintenance of malaria transmission in Finland (Huldén et al. 2008). It negatively affected both the mosquito and parasite populations when the households, the land use and the economy altered markedly between the 13<sup>th</sup> and the 19<sup>th</sup> centuries resulting in the notable decrease of the virulence of *P. vivax* malaria in Europe (Pinello, 2008). In the present times, *P. vivax* malaria mainly endemic in the southeast coastal lowland regions of Greece (Figure 1).

Socioeconomic and behaviour factors can strongly influence the local prevalence and mortality of malaria (Castilla and Sawyer 1993). It explains the observation that the prolonged financial crisis of the Greece economy also facilitates the resurgence of malaria (Bonovas and Nikolopoulos 2012). As a result of immigration and the related imported cases from the Middle East, endemic malaria appeared again in Greece in the turn of the 20<sup>th</sup> and 21<sup>st</sup> centuries (Sabatinelli et al. 2001). Immigration still causes an epidemiological hazard in Greece, because most of the present-day immigrants also came from such areas like Afghanistan, Bangladesh, India, Iran and Pakistan, where both *P. falciparum* and *P. vivax* malaria forms are endemic (Guerra et al. 2006). Tseroni et al. (2015) concluded that the outbreak of the *P. vivax* malaria cases in 2013–2014 in Evrotas, Laconia could be the consequence of the free contact between the competent vector *Anopheles sacharovi* Favre, 1903 and immigrants from the above described *P. vivax*-endemic countries. This circumstance could prevent the total eradication of malaria (Tseroni et al. 2015). On the other hand, climate change elongates the season length of malaria vectors in Southeast Europe (Trájer and Hammer 2018) and increases the possibility of pathogen development and the probability of *Plasmodium* transmission to humans (Kampen et al. 2002). Due to these causes, malaria could become a re-emerging disease in Greece and in other parts of South Europe (Andriopoulos et al. 2013; Danis et al. 2013). However, South Europe is not the only area in the continent, where *P. vivax* malaria could become endemic again. Model predictions show that due to the elongation of the season of the competent vectors due to climate change, the risk of malaria also increases in Central European countries like Hungary (Trájer and Hammer, 2018). Autochthonous *P. vivax* malaria transmission has been continuously observed in Greece in the last decades (Danis et al. 2011; Vakali et al. 2012). Autochthonous malaria cases were observed in the east coastal areas (e.g. in East Attica district), in central Greece (e.g. in Boeotia district) and Northern Greece (Evros Province; Kampen et al. 2002, 2003).

Climate changes have a strong influence on malaria distribution patterns. Sallares (2006) found that the post-Pleistocene changes in the environment were in strong coincidence with the spread of



**Figure 1.** The most important *Plasmodium vivax* malaria risk regions (in prefectoral region level) in Greece in 2011–2013.

malaria in Europe. The re-emergence of malaria is a worldwide observed and predicted phenomenon (e.g. Hay et al. 2002a; Linard et al. 2009; Gao et al. 2012). The future spread of *P. vivax* malaria is very plausible in the temperate zones (Petersen et al. 2013). In South Korea (Republic of Korea) the re-emergence of *P. vivax* malaria in 1993 plausibly was strongly linked to the warming climate and the consequent elongation of the transmission period in the Korean Peninsula (Park 2011). Temperature plays a very important role in the determination of the incidence of malaria. Kim et al. (2012) found that a 1°C increase in temperature was associated with a 17.7% increase in *P. vivax* malaria incidence after a three-week lag. According to Martens et al. (1999), the estimates of additional people at risk in 2080 range from 100 to 200 million for *P. vivax* that means a cardinal increase. Although the future climate suitability of malaria in a region is an important factor, a study also drew the attention to the fact that the biting willingness of the potential local vectors can notably alter the magnitude of the transmission risk in such temperate regions like the British Isles (Lindsay et al. 2010). Similar low biting willingness values of Anopheline vectors were reported from Hungary (Trájer 2018).

In contrast to the continental European areas, the Peloponnese Peninsula has several potent malaria vectors. Recently, *P. vivax* malaria exist in larger numbers from May to September/October in villages of the Evrotas delta area of Lakonia district (Danis et al. 2011; Sudre et al. 2013). The Evrotas is one of the major rivers of the Peloponnese Peninsula. This river empties into the Laconian Gulf that partly has been aggraded by the sediment of the river in the last two millennia creating a swampy alluvial plain. This environment is favourable for *Anopheles superpictus* Grassi, 1899 which is the dominant vector of *P. vivax* in the Balkan Peninsula (Kasap et al. 1987; Sinka 2013). In Greece, *An. sacharovi*, *An. superpictus* and *Anopheles maculipennis* s.s. Meigen, 1818 are

also the potential vectors of *P. vivax* malaria (Vakali et al. 2012). Before the mass usage of DDT, *An. sacharovi* breed in high densities in all coastal areas of Greece (Patsoula et al. 2007). It is plausible that this Anopheline mosquito could be again the dominant or a very important vector of *P. vivax* malaria in Greece (Alten et al. 2007).

## Aims

Relatively few efforts were made to model future malaria risk patterns in Greece. For example, in their spatial predictive model, Pergantas et al. (2017) found that the *P. vivax* malaria transmission risk in Greece is high. They also found that some habitats like the seaside marshes, the lakeside and the rice fields represent potential malaria hotspots in Greece, although the future potential changes of the malaria occurrence were not modelled. In this study, it was aimed to model the future potential distribution and the annual transmission season length of *P. vivax* malaria for the periods 2041–2060 and 2061–2080.

## Materials and methods

### The workflow of the study

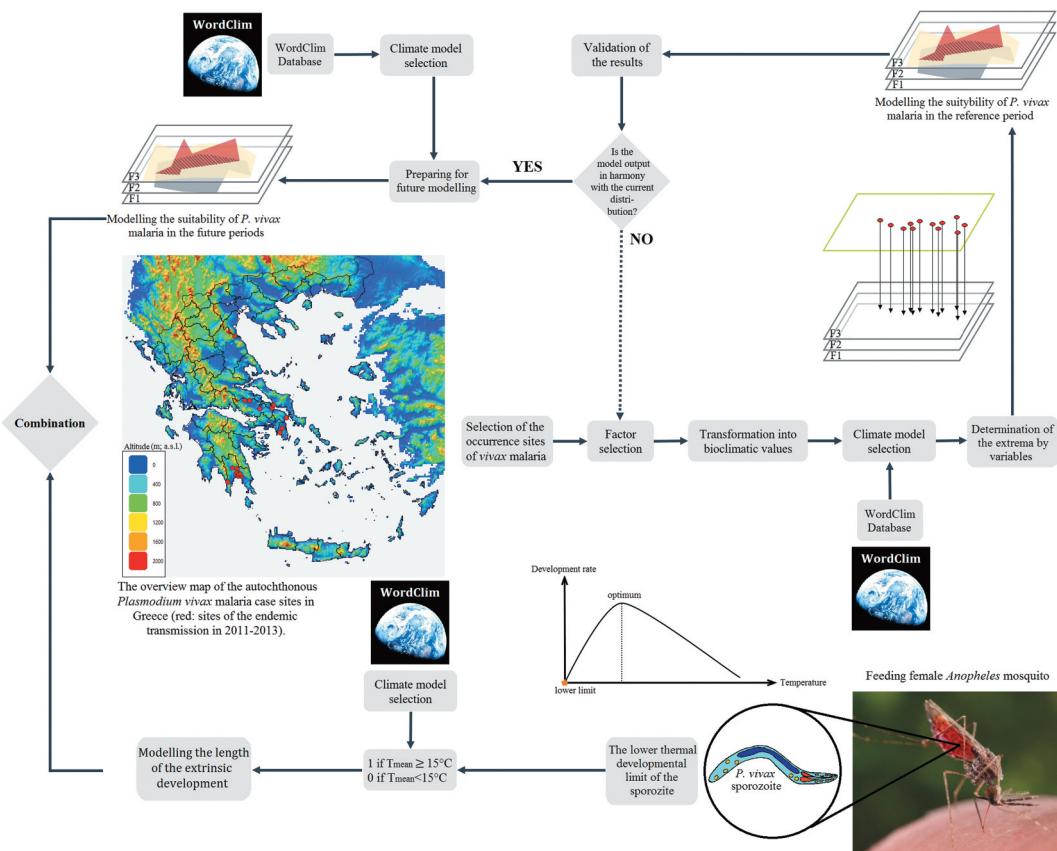
The risk of vector-borne diseases principally depends on two main factor groups: 1) distribution (spatial) and 2) temporal factors. Although very complex malaria models are available (e.g. Mandal et al. 2011), the parametrization of these models is generally problematic due to the lack of the knowledge of such individual parameters like the exact environmental factors-dependent ontogeny (by development stages) of the mosquito vectors, the hard to parametrize influences of the human factors, etc. It is also problematic that most of the malaria models were performed to predict the changing incidence patterns of the falciparum malaria and not for *vivax* malaria. Due to these facts, the modelling of the changing risk of *vivax* malaria was performed by the following steps:

- (1) the potential distribution of *P. vivax* malaria was modelled for 2041–2060 and 2061–2080 based on the four representative concentration pathway scenarios of the fifth assessment report of the Intergovernmental Panel on Climate Change (IPCC5 predictions) (model A, suitability model);
- (2) the potential length of the transmission season of *vivax* malaria was modelled based on the known 15°C lower threshold of the development of the parasite (Patz and Olson 2006), and finally (model B, season length model);
- (3) the two (the spatial and the temporal-like) factors were combined (model C, combined risk model).

Model A is indirectly related to the climatic requirements of the complete vector chain, including the climatic demands of the Anopheline vectors and the extrinsic development phase of *P. vivax* in the mosquito. Model B directly considers the lower thermal limit of the development of the sporozoites. Because model C is the combination of model A and B, it is related to the climatic requirements of the complete *P. vivax* malaria transmission. The models were validated by the comparison of the modelled maximum values and the observed occurrences of *P. vivax* malaria. Figure 2 shows the workflow of the study.

### Climate data and climatic factors

As the reference period, the years between 1970–2000 was selected. The average monthly temperature and bioclimatic data of this period were gained from the WordClim database (Hijmans et al. 2005) Version 2. The forecasted future climatic data were gained from WordClim database Version



**Figure 2.** The visual representation of the workflow of the study.

1.4. Two future time intervals were involved in the study: the periods of 2041–2060 and 2061–2080. These consecutive periods could have been treated together, but due to the non-linear nature of climate change-induced environmental trends, it seemed appropriate to treat them separately in the modelling. Future conditions were based on the downscaled global climate model (GCM) data of the IPPC's Fifth Assessment Report-based Coupled Model Intercomparison Project 5 results (CMIP5). Projections were made for four representative concentration pathways (RCPs, greenhouse gas concentration trajectories): rcp2.6, 4.5, 6.0 and 8.5. The simulation environment of the used projections was the Community Climate System Model 4 (CCSM4), which is a coupled atmospheric, oceanic, land surface and sea-ice-based complex climate model (Kay et al. 2015; Hurrel et al. 2013). The used spatial resolutions were 2.5 arc-minutes in each model. For modelling the future suitability patterns of *P. vivax* malaria, not the simple climatic values, but the so-called bioclimatic values were used. The use of bioclimatic variables instead of simple climatic values is an accepted method in ecological (niche) modelling (Ramírez Villegas and Bueno Cabrera 2009). To model the present and the future length of the transmission season of *P. vivax*, the downscaled monthly mean temperature values were used.

### Epidemiological data

The geographic distribution of re-emerging malaria was based on the occurrence of malaria cases in Greece 2011–2013, based on the report of Tseroni et al. (2015) and Danis et al. (2011). Only the locally acquired cases were involved in the study. In this period, autochthonous *P. vivax*

malaria cases were observed in Thessaly (Larissa), Central Greece (Euboea, Boeotia, Attica) and the south part of the Peloponnese Peninsula (Laconia). The sites of locally acquired cases in Greece formed the spatial units of the analyses. The number of the units (= the locally acquired *P. vivax* malaria cases in Greece) were as follows: 2009 ( $n = 7$ ), 2010 ( $n = 4$ ), 2011 ( $n = 42$ ), 2012 ( $n = 20$ ), 2013 ( $n = 3$ ). The localities of the cases were determined, and the points were georeferenced.

### **Model identification and factor selection**

#### **Modelling the suitability patterns (model A)**

Climate envelope or niche modelling is a widely used method to display the potential effects of climate change on the distribution of living organisms (Heikkinen et al. 2006). One of the problematic points of these modelling technique group is the validation because due to the basic nature of the modelling purpose, the predictable events have not yet occurred (Araújo et al. 2005). In the case of re-emerging malaria forms in Europe, it is somewhat a mitigating circumstance that the modelled ranges for the reference period(s) can be compared to the pre-eradication distribution patterns, however, in many cases, this is known only with approximately accuracy (Pearson et al. 2006). A common element of ecological niche models that the basement of modelling is the searching for the distribution limiting extrema related to each selected variable.

However, the use of both the upper and the lower extrema is not mandatory and depends on the area that was the base of the modelling (see below the selection criteria related to Greece).

For this aim, the following further preparatory steps were conducted:

- (1) suitable climatic parameters were selected;
- (2) the sites of endemic *P. vivax* malaria cases were identified in the period 2011–2013, based on literary data;
- (3) the bioclimatic values of each site were determined based on the reference period's georeferenced climate data;
- (4) the lower and upper extrema were determined considering each site;
- (5) the gained extrema were used in suitability modelling.

Modelling results were displayed using Quantum GIS 3.4.4 (QGIS project 2019) with GrassGis7.4.1 software (Neteler and Mitasova 2013). The Lambert Azimuthal Equal Area (EPSG:3035) was used as projection system.

It was important to make a careful selection between the variables considering the geographical position of the studied country in the reflection of the worldwide distribution of *P. vivax* malaria. It is known that *P. vivax* malaria presently is endemic from East Africa, Southeast Asia, the Hindustani Peninsula, China, the Caucasus (Guerra et al. 2010). It means that certain climatic limiting values must be discredited from modelling because the climatic factors behind the endemic case in Greece represent only a regional spectrum of the limits of *P. vivax* malaria occurrence. The selection of the climatic values was performed through the general considerations: Greece represents one of the northernmost occurrences of endemic *P. vivax* malaria in Europe that indicates that only the lower temperature limits can be used as distribution limiting values in general. It is supported by the fact that the topography of Greece is various and although the climate of the country is mainly hot and warm-summer Mediterranean (Csa and Csb); but and humid subtropical (Cfa) and humid continental (DSb) areas also occur in the mountainous areas of the country. Because Greece can be found in the coolest regions of the world (see the maps of Battle et al. 2019 and compare with the climatic maps of; Peel et al. 2007), where the endemic transmission of *P. vivax* occurs in the present times, both the upper and lower values of the minimum temperature of the coldest month can be important, so both values were included in the analysis. Greece receives a relatively high annual precipitation sum, compared to other *P. vivax* malaria-endemic areas of the



Earth, like East Africa and the Hindustan Peninsula. This fact implicates that in general, the upper limit of the precipitation values can be used as distribution limiting factors.

The above-described selection of the limiting factors is important because climatic scenarios predict the general warming of Greece and the decrease of the annual precipitation sum which trends can be observed even in the present times as the plausible causes of the increasingly frequent wildland forest fires (Dimitrakopoulos et al. 2011). It means that in the future such as high seasonal and monthly temperatures and low precipitation sums will occur (Giannakopoulos et al. 2011) which is not characteristic to the present-day country. However, the distribution-limiting climatic factors were based on the ‘present’ (reference periods) climate characters of the country. If we could apply the higher limits of the temperature factors (in general) and the lower limits of the precipitation sum factors, we could underestimate the environmental capacity of *P. vivax* malaria to the hotter and warmer environments.

The limits of the climatic variables used in modelling were as follows: the lower limit of the annual mean temperature ( $\text{bio1}_{\min}$ ), the lower limit of the max temperature of the warmest month ( $\text{bio5}_{\min}$ ), the lower and upper minimum temperature of the coldest month ( $\text{bio6}_{\min}, \text{bio6}_{\max}$ ), the upper limit of the annual temperature range ( $\text{bio7}_{\max} = \text{bio5}_{\max} - \text{bio6}_{\max}$ ), the lower limit of the mean temperature of the wettest quarter ( $\text{bio8}_{\min}$ ), the lower limit of the mean temperature of the driest quarter ( $\text{bio9}_{\min}$ ), the lower limit of the mean temperature of the warmest quarter ( $\text{bio10}_{\min}$ ), the upper limit of the mean temperature of the coldest quarter ( $\text{bio11}_{\min}$ ), annual precipitation ( $\text{bio12}_{\max}$ ), the upper limit of the precipitation of the wettest month ( $\text{bio13}_{\max}$ ), the upper limit of the precipitation of the driest month ( $\text{bio14}_{\max}$ ), the upper limit of the precipitation seasonality (coefficient of variation;  $\text{bio15}_{\max}$ ), the upper limit of the precipitation of the wettest quarter ( $\text{bio16}_{\max}$ ), the upper limit of the precipitation of the driest quarter ( $\text{bio17}_{\max}$ ), the upper limit of the precipitation of the warmest quarter ( $\text{bio18}_{\max}$ ) and the upper limit of the precipitation of the coldest quarter ( $\text{bio19}_{\max}$ ). **Table 1** shows the values of the used extrema.

For modelling of the potential distribution areas of species, the selected 17 extrema of the climatic factors were used. A distribution function is found within the extrema, which shows the distribution of the maximum for the given factor, however, in the proposed approach, the distribution of the internal interval is neglected and the appearance of the species is characterized by true or false (0; 1) values. The formulas described below were based on the method and mathematical representation logic of Trájer and Sebestyén (2019).

Using the above-described bioclimatic factors, the distribution function of *P. vivax* malaria can be written in the following form:

$$A = A_{\text{bio}T} \cap A_{\text{bio}P} \quad (1)$$

where  $A$  shows the potential distribution area of *P. vivax* malaria which contains the remaining areas after taking into consideration the bioclimatic temperature and precipitation limitations;  $A_{\text{bio}T}$  is the temperature-type bioclimatic factors-determined area of *P. vivax* malaria and  $A_{\text{bio}P}$  is the precipitation-type bioclimatic factors-determined area of *P. vivax* malaria.

**Table 1.** The used climatic distribution limiting extrema.

Temperature-type variable	limit	Precipitation-type variable	limit
$\text{bio1}_{\min}$	15.0°C	$\text{bio12}_{\max}$	913 mm
$\text{bio5}_{\min}$	27.2°C	$\text{bio13}_{\max}$	186 mm
$\text{bio6}_{\min}$	1.5°C	$\text{bio14}_{\max}$	22 mm
$\text{bio6}_{\max}$	8.7°C	$\text{bio15}_{\max}$	87 mm
$\text{bio7}_{\max}$	29.2°C	$\text{bio16}_{\max}$	546 mm
$\text{bio8}_{\min}$	9.7°C	$\text{bio17}_{\max}$	69 mm
$\text{bio9}_{\min}$	24.2°C	$\text{bio18}_{\max}$	69 mm
$\text{bio10}_{\min}$	24.9°C	$\text{bio19}_{\max}$	353 mm
$\text{bio11}_{\min}$	5.5°C		

The function arguments must satisfy the following conditions in the case of the temperature-type bioclimatic factors:

$$1(bio1) = \begin{cases} 0 & \text{if } bio1 < bio1_{limit,min} \\ 1 & \text{if } bio1 \geq bio1_{limit,min} \end{cases} \quad (2)$$

$$1(bio5) = \begin{cases} 0 & \text{if } bio5 < bio5_{limit,min} \\ 1 & \text{if } bio5 \geq bio5_{limit,min} \end{cases} \quad (3)$$

$$1(bio6) = \begin{cases} 0 & \text{if } bio6_{limit,max} < bio6 < bio6_{limit,min} \\ 1 & \text{if } bio6_{limit,max} \geq bio6 \geq bio6_{limit,min} \end{cases} \quad (4)$$

$$1(bio7) = \begin{cases} 0 & \text{if } bio7 < bio7_{limit,min} \\ 1 & \text{if } bio7 \geq bio7_{limit,min} \end{cases} \quad (5)$$

$$1(bio8) = \begin{cases} 0 & \text{if } bio8 < bio8_{limit,min} \\ 1 & \text{if } bio8 \geq bio8_{limit,min} \end{cases} \quad (6)$$

$$1(bio9) = \begin{cases} 0 & \text{if } bio9 < bio9_{limit,min} \\ 1 & \text{if } bio9 \geq bio9_{limit,min} \end{cases} \quad (7)$$

$$1(bio10) = \begin{cases} 0 & \text{if } bio10 < bio10_{limit,min} \\ 1 & \text{if } bio10 \geq bio10_{limit,min} \end{cases} \quad (8)$$

$$1(bio11) = \begin{cases} 0 & \text{if } bio11 < bio11_{limit,min} \\ 1 & \text{if } bio11 \geq bio11_{limit,min} \end{cases} \quad (9)$$

Where  $A(bio1; bio5; bio6; bio7; bio8; bio9; bio10; bio11)$  shows the potential temperature-type bioclimatic factors-based distribution area of *P. vivax* malaria, which contains the remaining areas after taking into consideration the temperature limitations.

The potential areas determined by the temperature-type bioclimatic factors can be determined according to the following mathematical formalism:

$$A(bio1; bio5; bio6; bio7; bio8; bio9; bio10, bio11) = bio1 \cap bio5 \cap bio6 \cap bio7 \cap bio8 \cap bio9 \cap bio10 \cap bio11 \quad (10)$$

The function arguments must satisfy the following conditions in the case of the precipitation-type bioclimatic factors:

$$1(bio12max) = \begin{cases} 0 & \text{if } bio12_{limit,max} \leq bio12 \\ 1 & \text{if } bio12_{limit,max} > bio12 \end{cases} \quad (11)$$

$$1(bio13max) = \begin{cases} 0 & \text{if } bio13_{limit,max} \leq bio13 \\ 1 & \text{if } bio13_{limit,max} > bio13 \end{cases} \quad (12)$$

$$1(bio14max) = \begin{cases} 0 & \text{if } bio14_{limit,max} \leq bio14 \\ 1 & \text{if } bio14_{limit,max} > bio14 \end{cases} \quad (13)$$



$$1(bio15max) = \begin{cases} 0 & \text{if } bio15_{limit.max} \leq bio15 \\ 1 & \text{if } bio15_{limit.max} > bio15 \end{cases} \quad (14)$$

$$1(bio16max) = \begin{cases} 0 & \text{if } bio16_{limit.max} \leq bio16 \\ 1 & \text{if } bio16_{limit.max} > bio16 \end{cases} \quad (15)$$

$$1(bio17max) = \begin{cases} 0 & \text{if } bio17_{limit.max} \leq bio17 \\ 1 & \text{if } bio17_{limit.max} > bio17 \end{cases} \quad (16)$$

$$1(bio18max) = \begin{cases} 0 & \text{if } bio18_{limit.max} \leq bio18 \\ 1 & \text{if } bio18_{limit.max} > bio18 \end{cases} \quad (17)$$

$$1(bio19max) = \begin{cases} 0 & \text{if } bio19_{limit.max} \leq bio19 \\ 1 & \text{if } bio19_{limit.max} > bio19 \end{cases} \quad (18)$$

The potential areas determined by the precipitation-type bioclimatic factors can be determined according to the following mathematical formalism:

$$\begin{aligned} A(bio12; bio13; bio14; bio15; bio16; bio17; bio18, bio19) \\ = bio12 \cap bio13 \cap bio14 \cap bio15 \cap bio16 \cap bio17 \cap bio18 \cap bio19 \end{aligned} \quad (19)$$

Where  $A(bio12; bio13; bio14; bio15; bio16; bio17; bio18; bio19)$  shows the potential precipitation-type bioclimatic factors-based distribution area of *P. vivax* malaria, which contains the remaining areas after taking into consideration the precipitation limitations.

According to Eq.1, the union of the temperature and precipitation-type bioclimatic factors-determined areas produces the potential distribution of *P. vivax* malaria. The modelled number of the satisfied factors in each point was converted into percentage (%) values. Hereinafter, these values were held as the habitat-suitability factors of *P. vivax* malaria. The satisfied 17 factor number means the 100%, the 0 satisfied factor represents the 0% suitability value.

It should be noted that the above-presented method was not aimed to model the local *P. vivax* malaria patterns because the local risk of malaria could only be predicted by the involvement of several biotic and abiotic factors. On the other hand, because the presented model was based on 2.5 arc-minutes (~5 km) spatial resolution georeferenced models, it can be held as a large-scale model study of *P. vivax* malaria risk patterns. Naturally, in the local level, such factors like the type of vegetation, the distribution of the mosquito breeding places could modify the large-scale predictions and determine the realized local occurrence of malaria. Altitude, which is also an important factor, immanently was the part of the presented models, because the altitudinal patterns make one of the bases of climate models.

### ***The number of the months when the extrinsic development is possible (model B)***

There is a distribution function within the extrema, which shows the distribution maximum for the given factor, but in the proposed approach the distribution of the internal interval is neglected, the appearance of malaria is characterized by true or false (0; 1) values according to the Boolean algebra.

Using climatic factors, deterministic unit step functions can be written in the following form:

$$1(P) = \begin{cases} 0 & \text{if } P \leq P_{limit.min} \\ 1 & \text{if } P_{limit.min} \leq P \end{cases} \quad (20)$$

$$1(T) = \begin{cases} 0 & \text{if } T \leq T_{limit.min} \\ 1 & \text{if } T_{limit.min} \leq T \end{cases} \quad (21)$$

Where  $T$  represents the georeferenced climate model data of the monthly average temperature ( $^{\circ}\text{C}$ ), the  $T_{\text{limit},\text{min}}$  is the lower limitation factor (extremum) of the extrinsic development of *P. falciparum* parasites in  $^{\circ}\text{C}$ ;  $P$  is the georeferenced climate model data of the monthly precipitation and  $P_{\text{limit},\text{min}}$  shows the precipitation minimum extrema of falciparum malaria occurrence in mm. As can be seen, the limitation factor values are climate model-independent. The  $T_{\text{limit},\text{min}}$  of the extrinsic (sporogonic) cycle of *P. vivax* parasites are  $15^{\circ}\text{C}$  according to Patz and Olson (2006). The annual minimum rainfall ( $P_{\text{limit},\text{min}}$ ) required to support mosquito breeding is  $>80$  mm (Blanford et al. 2013).

The temperature and precipitation climate models are available in a monthly resolution. Although the precipitation limit has annual nature, it can be used as an annual limiting factor. The areas excluded by the limiting factors must be summed, and the intersection of the potential area designated by the three factors gives the aggregated distribution area, formally:

$$A(T_{\text{min}}; P) = T_{\text{min}} - \sum_{i=1}^{12} 0(T_{\text{min}}) \cap P - 0(P) \quad (22)$$

Where  $A(T_{\text{min}}; P)$  show the potential distribution area of the given species, which contains the remaining areas after taking into consideration the temperature and precipitation limitations.

Modelling results were displayed using GIS (Quantum GIS 3.4.4 with GRASS GIS 7.4.1 software). The Lambert Azimuthal Equal Area (EPSG: 3035) was used as a projection system. After, the individual presence-absence maps were summarized and displayed in a heat-map model. To quantify the depicted model results, a sampling grid was selected which is identical to the grid of Figure 1 and contains each of the areas of Greece. The modelled suitability values and the length of the modelled transmission seasons were sampled.

### ***The combined (risk) factor (model C)***

The modelled suitability values of malaria represent the spatial aspect of the malaria risk. In contrast, the modelled transmission season length values can be held as a kind of temporal nature factor of the risk of malaria. Although in an indirect sense, the length of the transmission season should contribute to the determination of the range of malaria, the combination of the two factors could provide a more sensible factor in the modelling of the risk of *P. vivax* malaria. Multiplying the two factors is the most adequate method of the combination of the two primary factors. The combination of two or more suitability models to reduce uncertainty is an accepted method in suitability modelling. For example, it was used by Capinha et al. (2009) who aimed to model the distribution of *Anopheles atroparvus* van Thiel 1927 that was the competent vector of malaria in Portugal in the historical times. Although this process requires the normalization of the factors before the multiplication. The formula of the combined factor is the following:

$$F_c = \frac{D_s}{17} \times \frac{L_{TS}}{12} \quad (23)$$

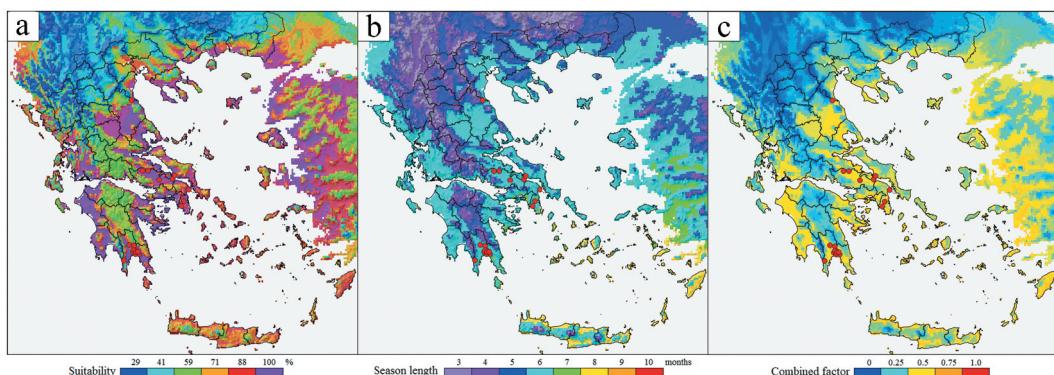
Where  $F_c$  is the combined factor (% x month or without dimension; range: 0 to 1);  $D_s$  represents the modelled bioclimatic factors-based suitability of *P. vivax* malaria according to Eqs. 1–5 (in %);  $L_{TS}$  is the modelled length of the *P. vivax* transmission season (in months) according to Eq. 5. In the denominators: 17 is the number of the used factors in the modelling of the bioclimatic factors-based suitability values, 12 is the number of the months of the year related to the modelling of the potential transmission season length values.



## Results

### Reference period's patterns and the quality assessment of the models

In the reference period, maximal suitability values for *P. vivax* malaria are predicted in Thessaly, including the middle and south parts of Larissa, the southeast regions of Karditsa and the lowland areas of Magnesia. Also, maximal suitability values are modelled in the wide east and west coastal areas of Central Greece, including Athens, East and West Attica, Euboea, Boeotia, Piraeus and Phthiotis. Maximal values predicted in Western Greece (both in the lowlands of Aetolia and Acarnania) and in the narrow coastal areas of East Macedonia and Thrace. In Macedonia, Thessaloniki, in Thrace, Kavala predicted to be the most influenced regions by *P. vivax* malaria in the reference period. In the northwest coastal region, only the seaboard of Arta in Epirus seems to be suitable for malaria. Some parts of the Ionian Islands show higher suitability values, but the most part of the islands are not modelled to be suitable for *P. vivax* malaria. The modelled suitability values are greater in the Aegean Islands than in the Cyclades. Crete does not seem to be an endangered area for *P. vivax* malaria. The model predicts maximum suitability values in the lowland regions of the Peloponnese Peninsula, including the lowlands including almost the entire area of Argolis, Elis, Messenia and the major parts of Argolis and Laconia. The islands of the Eastern Aegean area seem to be most influenced by *P. vivax* malaria in the northern parts and the modelled suitability values are the highest in Lesbos. The results indicate that large areas of Greece are characterized by the 'anophelism without malaria' situation in the present times. It seems that *P. vivax* malaria nowhere could occur in the reference period where the potential length of the transmission season is less than 6–7 months (the transmission season length threshold of *vivax* malaria) and the modelled suitability of *P. vivax* malaria is less than 82% (the bioclimatic factors-based suitability threshold of *vivax* malaria). The potential length of the transmission season of *P. vivax* malaria could be 7–8 months in the south Aegean Islands and Crete, but in the present times, malaria does not occur in these islands (for the possible explanation see the related text of the Discussion). Expressed in a combined factor, this means that malaria occurs at places where the combined factor reaches the 0.44 value, the combined factor threshold of *vivax* malaria. In each model, the autochthonous *P. vivax* malaria case sites in Greece (2011–2013) fall in the highest suitability values of the different models which validate the adequacy of the models. It equals to the ranges of 88–100% in *model A*, more than 5 months in *model B* and 0.25< in the case of the *combined model* (Figure 3).



**Figure 3.** The potential suitability values (a), the length of the transmission season (b) and the patterns of the combined factor (c) *Plasmodium vivax* malaria in 1970–2000 in Greece. Red points show the autochthonous *Plasmodium vivax* malaria case sites in Greece in 2011–2013.

### **Future malaria suitability patterns**

For the period 2041–2060, the expansion of *P. vivax* malaria is predicted in Central Greece, Thessaly and in the Aegean Islands. Crete, which island in the reference period was modelled to be unsuitable for *P. vivax* malaria, could be suitable in 2041–2060. The situation is similar in the Cyclades and the East Aegean Islands, where the modelled future suitability values are higher than the reference periods. The model projects the notable regression of the malaria-free areas even in the mountainous areas of the Peloponnese Peninsula, including the mountain ranges of Achaea, Arcadia and Laconia. The model predicts, that for the period 2061–2080, larger, continuous malaria-free areas only will remain in the higher elevation areas of Achaea, Arcadia in the Peloponnese Peninsula. Also, a notable increase of the suitable regions can be seen comparing the reference period and the later future period in the case of West Greece, Thessaly, the coastal areas of Macedonia, the Aegean Islands and Crete. The models predict the most marked increases in the suitability of *P. vivax* malaria in the mountainous regions, the Aegean Islands and Crete. The order in the magnitude of the increasing suitability values is as follows: rcp2.6 < rcp.6.0 < rcp.4.5 < rcp.8.5 (Figure 4).

Comparing the future highest altitude values where the suitability reaches the maximum (100%) value to the identical altitudinal value of the reference period, it can be seen the models predict the clear upward altitudinal shift of *P. vivax* malaria in Greece in both future periods. The mean values of the modelled upward shift are 139 m in 2041–2060 and 214 m in 2061–2080 (Table 2).

### **Future patterns of the transmission season length**

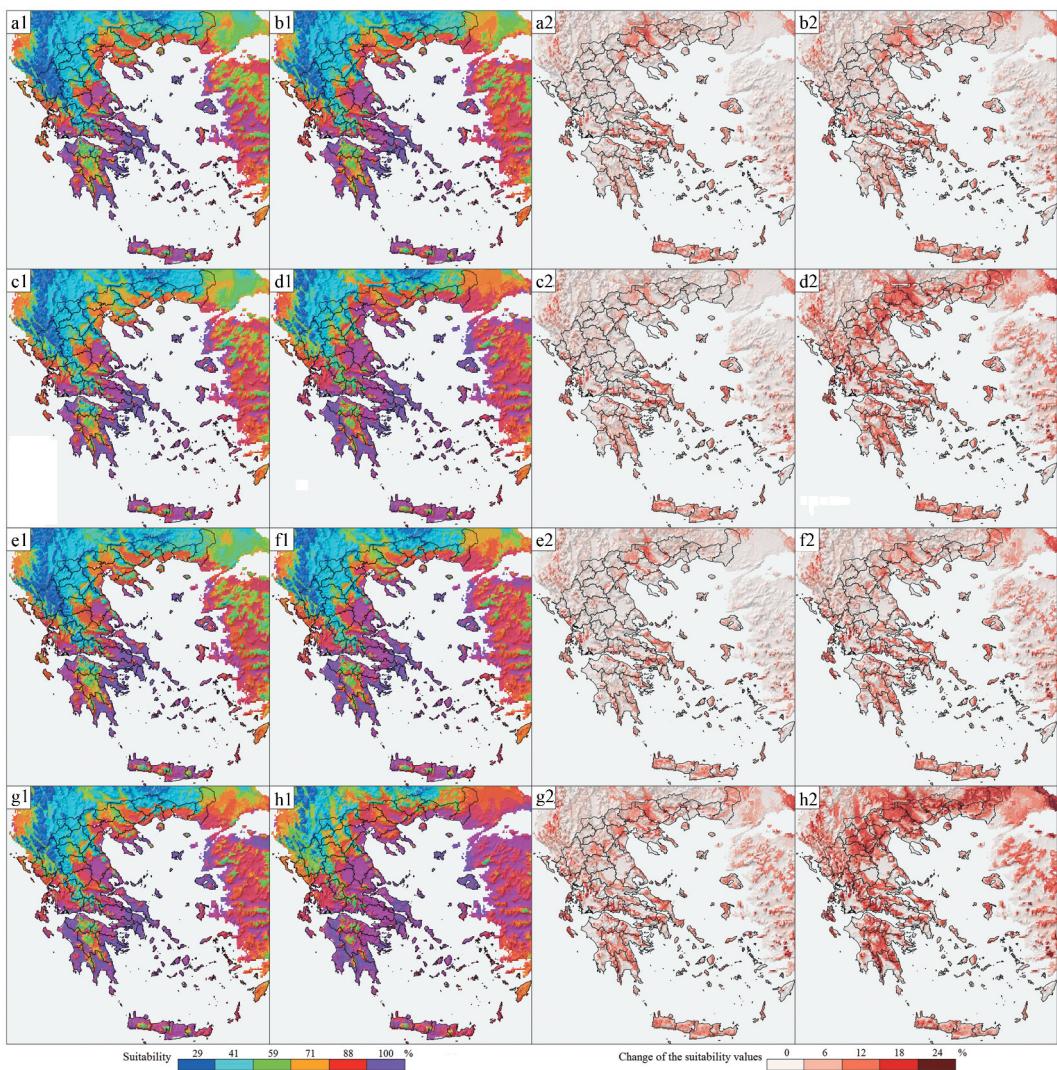
For 2041–2060 and especially to the period 2061–2080, in the southern continental lowlands of Greece, the length of the transmission season of *P. vivax* will reach the 8 months. In the coastal areas of the South Aegean Islands and Crete, the potential length of the transmission season will reach the 9–10 months in the second half of the 21<sup>st</sup> century. In general, the predicted elongation of the transmission season is 1–2 months in Greece depending on the period and the representative concentration pathway scenario. In West Macedonia, where the potential length of transmission season is only 3–5 months, it will reach the 6-months threshold value in the valley and foothill lands. The elongation of the transmission season shows less expressed heterogenic geographical patterns compared to the suitability values. The highest increases can be seen in the mountainous regions and the coastal lowlands (Figure 5).

### **Future patterns of the combined factor**

Although the combined factor shows the most notable changes in the Aegean Islands, the island of Crete and in the mid-elevation regions, the pan-peninsular increase of the combined factor is clear in each future prediction compared to the reference period. In the future, the malaria-suitable areas of the Peloponnese Peninsula, Aetolia, Attica and Thessaly will form a single great area. The minor distribution areas of Thrace and Thessaly also could be amalgamed. For 2061–2080, only the higher elevation areas of Northwest Greece (the ranges of the Pindus Mts.) could remain free of *P. vivax* malaria (Figure 6).

### **Quantification of the model results**

According to the sampled grid (it is identical to the grid of Figure 1), except for the rcp26 scenario-based model for the period 2041–2060, the predicted differences between the averaged suitability values of the reference and future periods show moderate increases. The maximum value is +10.7% in the case of the latest predicted period and the worst representative concentration pathway (rcp8.5) scenario. The change of the transmission season length is positive in each case and ranges between +0.7 to +1.5 months. The modelled mean change of the bioclimatic factors-based



**Figure 4.** The future potential suitability values for *Plasmodium vivax* malaria in Greece (2050 – A1: rcp2.6, B1: rcp4.5, C1: rcp6.0 and D1: rcp8.5; 2070 – E1: rcp2.6, F1: rcp4.5, G1: rcp6.0 and H1: rcp8.5) and the difference from the reference period's patterns (2050 – A2: rcp2.6, B2: rcp4.5, C2: rcp6.0 and D2: rcp8.5; 2070 – E2: rcp2.6, F2: rcp4.5, G2: rcp6.0 and H2: rcp8.5) according to the CCSM4 climate projections.

suitability values seems to be less notable than the predicted mean change of the transmission season. The magnitude of the change of combined factors are between the primary factors and the change is positive in each case (Table 3 Part A). The proportion of the above the threshold areas within the sampled grid also were calculated. As it was presented before, the determined thresholds of the distribution suitability, the length of the transmission (extrinsic incubation) season and combined factor were as follows: 82%, 6 months and 0.44. Based on these extrema, except for the rcp2.6-based scenarios, the range of *P. vivax* malaria will moderately increase in Greece for the second half of the 21<sup>st</sup> century. In the case of the season length and the combined values, each of the model predict increasing percentage values for both future periods. The modelled areal changes compared to the reference period values are the most expressive in the case of the season length values. In this case, the increase in the suitable regions for vivax malaria can reach the +44.2–64.6% change in the sampled grid for 2041–2060 and 2061–2080 (Table 3 Part B).

**Table 2.** The highest altitude where the modelled suitability value of *P. vivax* malaria reaches the 100% values and its changes compared to the reference period value.

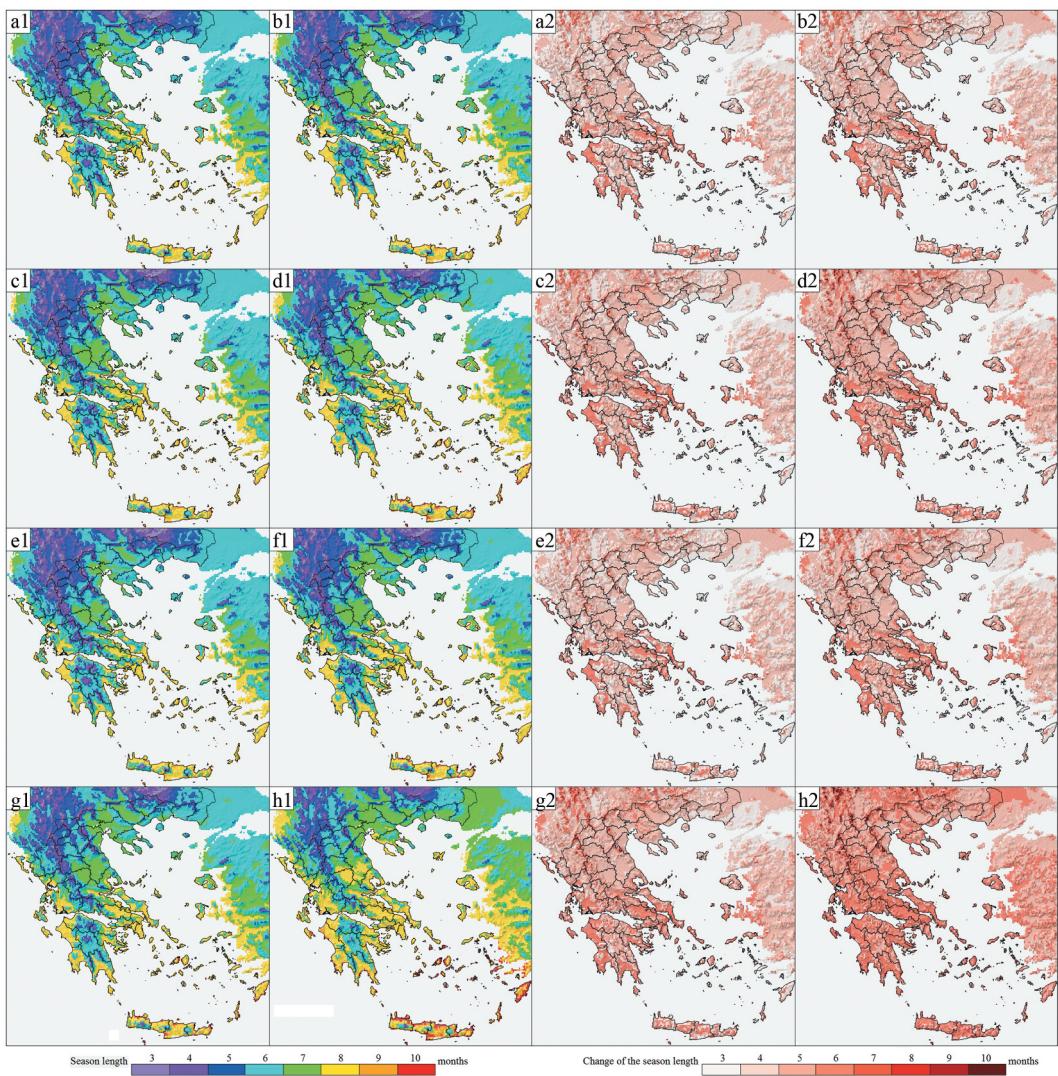
period	rcp	maximum altitude (m, a.s.l.)	change (m)	mean of the period (m, a.s.l.)
<b>1970–2000</b>	NA	636	0	636
<b>2041–2060</b>	rcp26	730	94	775
	rcp45	731	95	
	rcp60	736	100	
	rcp85	904	268	
<b>2061–2070</b>	rcp26	796	160	850
	rcp45	834	198	
	rcp60	820	184	
	rcp85	951	315	

The standard deviation heat map of the suitability values shows the highest variances in those coastal regions where the present risk of *P. vivax* malaria is the highest. There are no notable differences between the standard deviations of 2041–2060 and 2061–2080. The character of the standard deviation heat maps of the length of the transmission season is the opposite of the suitability maps because the highest standard deviation values can be seen in the higher elevations, not in the coastal and lowland regions. The standard deviation heat maps of the combined values show the highest values in those regions, where the models predict the spread of *P. vivax* malaria in the future (Figure 7).

## Discussion

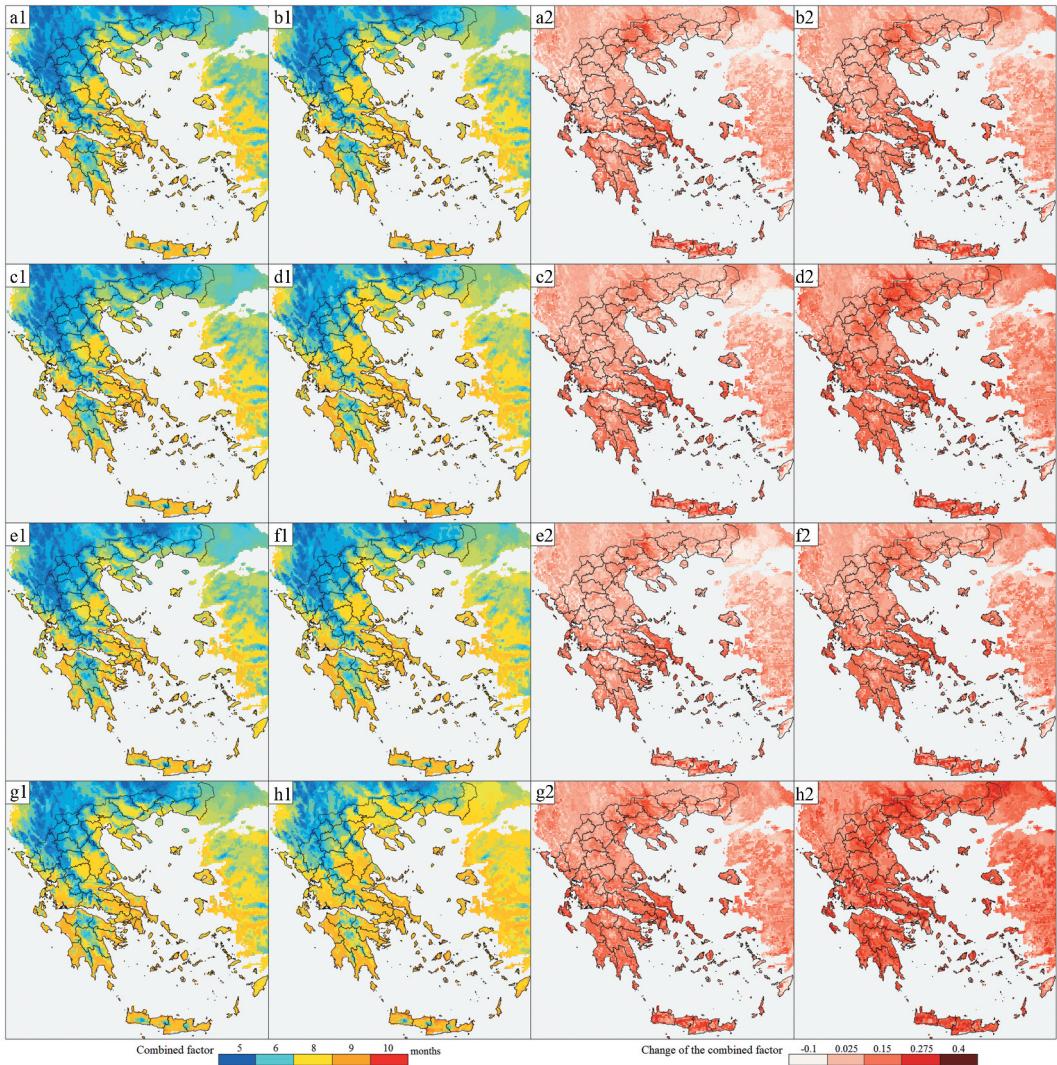
The modelled future suitability values – except for the model of the rcp26-based model of 2041–2060 – predict the moderate increase of the suitability values for *P. vivax* malaria predominantly in the mountainous areas and in the Aegean Islands which means the extension of the potentially malaria-endemic areas in Greece. Parallelly, the notable, 1 to 2 months increases of the transmission season are also predicted mainly in the mountainous areas. The combined factors show also a moderate increase in the risk of *P. vivax* malaria and the highest increases can be seen in the mid-elevation regions of Greece. These findings are in accordance with the projections that climate change can facilitate the resurgence of malaria in mid-mountainous areas (Hay et al. 2002b; Githcko 2009). The fact that the future increase of the suitability values is moderate is not a surprising outcome of this study, because most of the coastal lowland, the inland alluvial plain and the lower mountain foothill areas of Greece still belong to the maximum suitability areas. It confirms the findings of Pergantas et al. (2017) who concluded in their study that the ‘malaria transmission risk in Greece is potentially substantial’. The relationships between the modelled suitability, transmission season length values and the altitudinal patterns are clearly visible. It is known that there is a relationship between altitude and intensity of malaria transmission that is predominantly the consequence of the altitude-related atmospheric cooling trend, the lapse rate. The main effect of the lapse rate is the decrease in vector abundance, the reduction in the proportion of infective mosquitoes and the shortening of the transmission season (Bødker et al. 2003). However, in the seasonally or permanently rainfall deficient regions, the mountain valley can be more hostile for malaria mosquitoes than the lowlands. The increasing altitudinal gradient of precipitation due to the cloud interception of the mountainous areas is a general phenomenon (McJannet et al. 2007).

Since 17 variables were used in suitability modelling, it is important to discuss if the models were sensitive to the relatively high number of variables or not, because theoretically, the high quantity of variables could lead to poor model fit. It is important to note that the used basic climate envelope modelling method is based on the independent layers of the input environmental variables (Bede-Fazekas et al. 2014). The conception of climate envelope modelling method is to relate the observed distribution data of species one by one to the georeferenced data of climate factors to surmise



**Figure 5.** The future potential suitability values for *Plasmodium vivax* malaria in Greece (2050 – A1: rcp2.6, B1: rcp4.5, C1: rcp6.0 and D1: rcp8.5; 2070 – E1: rcp2.6, F1: rcp4.5, G1: rcp6.0 and H1: rcp8.5) and the difference from the reference period's patterns (2050 – A2: rcp2.6, B2: rcp4.5, C2: rcp6.0 and D2: rcp8.5; 2070 – E2: rcp2.6, F2: rcp4.5, G2: rcp6.0 and H2: rcp8.5) according to the CCSM4 climate projections.

models of climatic resilience (Shi et al. 2014). Another possibility is the utilization of neuronal network-based algorithms (e.g. Bede-Fazekas et al. 2015). An important disadvantage of this technique is that due to the black-box nature of the method, it can be difficult to acquire the individual distribution limiting thresholds by variables. This is a consequence of the methodological basis that artificial neural networks-based algorithms do not use task-specific rules. In a technical sense, it means that the found correlations between the input and output layers are stored in the weighted connections of the hidden layers of the artificial neurons (nodes) (Schmidhuber 2015). In contrast, Climate Envelope Modelling is based on determined climatic extremes (Braunisch et al. 2008). Because both the determination of the extremes during the preparation steps and the use of these upper and lower limits in the utilization of modelling is also done separately, it indicates that the high number of the input variables and multicollinearity could not result in parameter estimates to be imprecise.



**Figure 6.** The future combined factor values for *Plasmodium vivax* malaria in Greece (2050 – A1: rcp2.6, B1: rcp4.5, C1: rcp6.0 and D1: rcp8.5; 2070 – E1: rcp2.6, F1: rcp4.5, G1: rcp6.0 and H1: rcp8.5) and the difference from the reference period's patterns (2050 – A2: rcp2.6, B2: rcp4.5, C2: rcp6.0 and D2: rcp8.5; 2070 – E2: rcp2.6, F2: rcp4.5, G2: rcp6.0 and H2: rcp8.5) according to the CCSM4 climate projections.

In this study, generally, the lower thermal limits were handled as a kind of northernmost distribution limiting factors of *P. vivax* malaria. However, it is true that *P. vivax* malaria was endemic as far north like Finland in the pre-industrial times (Petersen et al. 2013). Because malaria was eradicated from North, West and Central Europe by the middle of the 20th century (Piperaki 2018), it is not evident, that the remnant populations of *P. vivax* parasites in the Circum-Mediterranean area could inhabit again the cooler climate regions of Europe. The eradication of the northern ecotypes of *P. vivax* should result in the bottleneck of the parasite in Europe because the disease-causing *Plasmodium* parasites exist only in the human blood (Smith et al. 2014). It implies that it is not justified to consider the former range of recurrence malaria in Europe for present or future prediction purposes and the present-day lower thermal limits of the South European populations can be used to model the northern distribution borders of the parasite.



**Table 3.** Part A: The modelled averages and the changes of distribution suitability, transmission season length and the combined factor values of *P. vivax* malaria in the sampled grid; Part B: The proportions and the percentage changes of the above the threshold areas in the sampled grid sorted by the modelled risk factors (A: distribution suitability values above the threshold 82%, B: transmission season length values above the threshold 6 months, C: combined values above the threshold value 0.44).

**Part A**

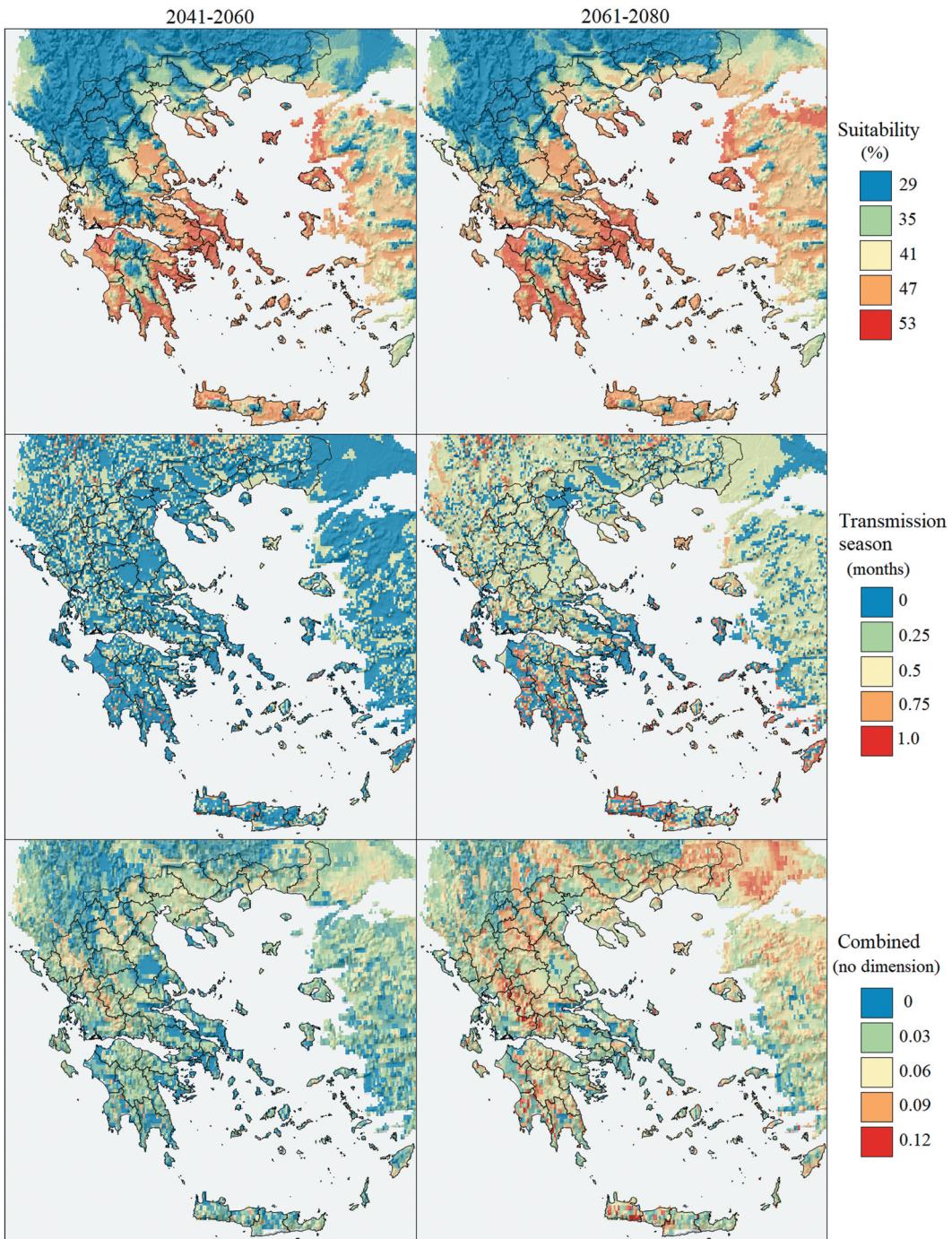
Model	Suitability values (%)		Season lengths (months)		Combined	
	Modelled	Difference	Modelled	Difference	Modelled	Difference
ref_1970-2000	70.3	NA	5.43	NA	0.33	NA
rcp26_2041-2060	70.4	0.1	6.2	0.7	0.38	0.05
rcp45_2041-2060	72.4	2.1	6.3	0.8	0.40	0.07
rcp60_2041-2060	70.7	0.4	6.3	0.8	0.39	0.06
rcp85_2041-2060	77.5	7.2	6.5	1.1	0.44	0.11
rcp26_2061-2080	69.6	-0.6	6.2	0.7	0.38	0.05
rcp45_2061-2080	74.3	4.0	6.4	1.0	0.41	0.08
rcp60_2061-2080	75.1	4.8	6.5	1.0	0.42	0.09
rcp85_2061-2080	81.0	10.7	7.0	1.5	0.48	0.15

**Part B**

model	% of above the threshold areas of <b>A</b> modelled		% of above the threshold areas of <b>B</b> modelled		% of above the threshold areas of <b>C</b> modelled	
	difference	difference	difference	difference	difference	difference
ref_1970-2000	35.0	NA	10.2	NA	36.2	NA
rcp26_2041-2060	34.7	-0.3	34.5	24.3	41.7	5.5
rcp45_2041-2060	39.6	4.6	38.3	28.1	46.7	10.5
rcp60_2041-2060	35.9	0.9	37.7	27.4	43.7	7.3
rcp85_2041-2060	50.5	15.5	44.2	34.0	56.3	20.1
rcp26_2061-2080	33.0	-2.0	33.1	22.9	40.4	4.3
rcp45_2061-2080	44.9	9.9	41.5	31.2	51.3	15.2
rcp60_2061-2080	45.8	10.8	42.9	32.7	52.4	16.2
rcp85_2061-2080	57.3	22.4	64.6	54.4	69.4	33.3

It is also worth discussing why not such primary climatic variables like the monthly mean temperatures and precipitation sums were directly used for modelling. In a technical sense, several bioclimatic variables are not only the simple derivatives of the primary temperature and precipitation-like climatic values. Such bioclimatic values like the ‘mean temperature of the wettest quarter’ were made by the addition of the climatic values of different months. For example, the wettest quarter of the year varies by climatic zones: it is the fourth quarter in such Mediterranean countries like Greece or Italy and the second in the temperate climate countries like Germany or Hungary. Bioclimatic indices are frequently used in ecological modelling studies (e.g. Attorre et al. 2007) because these factors are the good predictors of such biotic and abiotic factors like the vegetation type (Nakamura et al. 2007) and the edaphic conditions (Boira and Blanquer 1998). That is an extra value of bioclimatic variables that these values are in strong correlation with the Köppen-Geiger climatic classification system which basically reflects the biotic regimes of the climatic zones. Due to these advantages, the so-called ‘bioclimatic envelope modelling’ (Thuiller 2003) forms a separate methodological branch of Climate Envelope Modelling.

The difference between the present occurrence of autochthonous malaria in Greece and the extension of the modelled regions is a partial case of ‘anophelism without malaria’ if we consider the individual regions and not the whole country. Jetten and Takken (1994) showed that this phenomenon can be observed in many parts of Europe. On the other hand, Greece always was the field of malaria studies for European scholars due to the endemicity of the disease. In an early and pioneering study which was performed by Raymond Corbett Shannon in 1935 in Greece, the author tried to explain why malaria is absent from several parts of Europe, where the potential Anopheline mosquito vectors exist (Shannon 1935). In fact, each of the observed cases can be found within the maximally suitable areas, although the potential range of malaria is higher than it could be concluded from the geographical occurrence of the observed cases. Comparing the occurrence of the historical malaria foci before the eradication of malaria in 1974, it can be stated that the



**Figure 7.** The standard deviations of the four representative concentration pathways (rcps)-based models in each period and model types.

reference period model returned the historical areas of *P. vivax* malaria in Greece published by Sudre et al. (2013; Figure 2). For example, the model returned the large malaria-endemic area in the central part of Thessaly, that is identical to the Trikala and Larissa lowlands-formed central plain of the administrative region. The model also returned the former malaria foci of Thrace in Southeast



Evros, in the south (coastal part) of Xanthi and Kavala. In Eastern Macedonia, the malaria foci of South Serres also was predicted. In Epirus and Western Greece, each of the former malaria foci can be found in the reference model as individual foci. In Central Greece, the former endemic malaria foci in Phthiotis around the western edge of the Malian Gulf, the endemic area in Boeotia along the river basin of Cephissus, Lake Copais and Lake Yliki; as well as the former malaria foci in East Attica and Athens were returned correctly. The only former endemic foci that cannot be found clearly in the reference periods model is the endemic foci of Central Macedonia, however, the model also gave high values for this area, if not the maximum values. It should be noted, that in the future suitability maps, Central Macedonia belongs to the important malaria-endemic areas in Greece. In the Peloponnese Peninsula, the former endemic foci of Corinth, Elis, Laconia, Messenia can be found in the modelled reference periods map. It is also important to note that the observed malaria foci in the past did not affect the Aegean marine archipelago or Crete. This high degree of similarity between the observed historical and the modelled malaria foci confirm the validity of the model.

Because the distribution of *P. vivax* malaria was based on two reports (Danis et al. 2011; Tseroni et al. 2015) which cover a relatively short period (2011–2013), it is important to consider the problems of data availability and discuss whether this data is sufficient enough for accurate predictions or not. First, it is very important that different reports in Greece consistently present very similar endemic malaria areas apart from some sporadic cases (Danis et al. 2011; Tseroni et al. 2015). This even more obvious if we compare the geographical distribution of the used occurrence data with the prefectural regions with autochthonous introduced malaria cases in Greece, 1991–2010 (Vakali et al. 2012). These observations, along with the historical observations indicate the relative long-term stability of the potentially malaria-endemic areas in Greece. However, arriving at this topic, it should also be clarified that the pre-eradication and the modern distribution patterns cannot be compared directly with each other because the environmental and social factors affecting malaria transmission have changed significantly over time. This is precisely the circumstance that triggered the construction of the presented models. However, the natural topographic and climatic patterns changed less in the last centuries compared to the social factors, the man-induced changes of the vegetation cover and land use. Because this study was performed to model the large-scale potential risk patterns of *P. vivax* malaria and not the local occurrences, the use of the large-scale climatic patterns was justified. In this sense, the comparison of the former endemic patterns with the observed present endemic foci and the projected future ones may be instructive but cannot be used as a base of a direct comparison.

It is an important question of how the increasingly frequent severe drought periods influence the malaria seasons. It is known that that global warming could largely affect drought severity in Greece even the correct prediction of the severity and length of the future drought episodes is problematic (Vasiliades et al. 2009). For example, in Thessaly, climate change will result in a significant increase in drought impulses which is predicted to become evident even in the period 2020–2041–2060 (Loukas et al. 2007, 2008). It was showed that Thessaly is one of the largest and most vulnerable areas related to malaria risk in Greece. The potential effect of the increasing drought frequency on malaria endemicity is controversial and seems to depend on the area. It was proved in Senegal, that the changes in vector populations could lead to lower malaria transmission which resulted in the consequent decrease of the endemicity (Faye et al. 1995). A similar effect was observed in 2004–2005, Zambia, when due to extended drought, the transmission was nearly zero (Kent et al. 2007). In fact, where severe drought episodes occur repeatedly, malaria is unstable as it was observed e.g. in Sudan (Theander 1998). However, except Zambia, both Senegal and Sudan can be found in the Sahel belt of Africa where the annual evaporation is very high, and the annual sum of the precipitation shows highly fluctuating patterns by year-to-year. It is less plausible that in the higher latitude, drought could be as severe to cause the cessation of the endemicity of malaria. The effect of extreme drought on malaria or Anopheline vectors is less known in South Europe. In 2005, Osório et al. (2008) did not capture any *An. algeriensis* Theobald (1903) imagoes at none of the three collection points in Portugal. However, in 2006, in each site, the authors trapped the species.

Because the years 2004 and 2005 were characterized by extremely dry conditions and the year of 2006 was rainy, they concluded that the reduction of the abundance of this mosquito could be the consequence of the extremely dry conditions before 2006. Investigating the past effect of the meteorological conditions on the incidences of malaria in 1927–1934 in Hungary, Trájer and Hammer (2016) found that there was a medium-strong, significant correlation between the summer precipitation sums and the annual malaria incidences. It implies that severe summer droughts could reduce the annual incidence of malaria also in the temperate regions in Europe.

Where *P. vivax* malaria occurs, the modelled suitability values are approximate the maximum and, the length of the transmission season of *P. vivax* malaria is equal or more than six months. The Aegean Islands and Crete form an exception, while in the South Aegean Islands and Crete, the present suitability values less than the maximum, the potential length of the transmission season is more than six months, but presently, malaria does not occur. It is known that many parts of Greece are karst areas. The except of some active volcanic islands – Methana, Milos, Nisyros, Santorini and Yali (Siebert et al. 2011) – the islands of the Aegean Islands are mainly built up karstified limestones strata (Riedl and Papadopoulou-Vrynioti 2001). The poorly developed surface river network is characteristic for the karst areas (Ford and Williams 2013). Because due to tectonic causes and the post-glacial transgression resulted in the absolute and relative sinking of the Aegean landmasses (Lambeck 1996), the well-developed alluvial fans missing in general in the coastlines of the Aegean Islands. On the other hand, under the hot Mediterranean climatic conditions, many of the existing streams are only intermittent or ephemeral (Zaimis et al. 2010). The lack of delta marshes and the wetlands accompanying the river, a large population of mosquitoes cannot survive on the islands permanently.

The results presented in this paper have also important social and economic implications. As it was presented, the model outcomes-projected geographically heterogenic extension of the malaria-suitable areas and the increase of the elongation of the malaria season in Greece could lead to the increase of the exposure of the Greek population to acquire *P. vivax* malaria in the second half of the 21<sup>st</sup> century. Cervellati et al. (2017a) showed that higher exposure to malaria increases the incidence of civil violence. Resurging malaria with weather shocks like heat waves, droughts and drought-induced wildfires could trigger civil conflicts due to the loss of lives and the decrease of the economic performance (Cervellati et al. 2017b). Mitigation strategies can also have adverse effects. A 25–30% decrease in the annual rainfall and enhanced evapotranspiration are expected by the end of the 21st century in the Mediterranean Basin (Erol and Randhir 2012). The increasing aridity trends will require the increased use of irrigation in lowland agriculture which is an important additional risk in the resurgence of malaria (Ijumba and Lindsay 2001). It is also known that the building of hydropower plants and water reservoirs could disturb severely the freshwater ecosystems causing the increase of the proportion of mosquito habitats (Farkas-Iványi and Trájer 2015) and the relative abundance of malaria mosquitoes within the local mosquito faunae (Trájer et al. 2015).

Comparing the model results of this study to the findings of Kim et al. (2012) in South Korea, we can agree with the conclusions of the authors, that the effects of climate change on climatic variables will increase the range of populations at risk of *P. vivax* infection that is especially true in such warm temperate regions like Greece. Because the *vivax* malaria seems to be a relatively neglected disease compared to the *falciparum* malaria, it is not uncommon *P. vivax* malaria and *P. falciparum* malaria is pooled together when malaria incidence is calculated (e.g. Bai et al. 2013). It indicates that those models that were performed individually to model the future range or seasonality conditions of this disease may hold valuable information for the present or the future affected human societies. Lindsay and Thomas (2001) demonstrated in Great Britain, that in many parts of the country, the seasonal temperatures are warm enough for *P. vivax* malaria transmission and the extent of these areas will increase in the future. The outcomes of the present study provide similar conclusions for Greece. Writing about ongoing malaria in Greece, Medlock and Leach (2015) assumed, that due to the increase in the summer temperatures, the rate of development for *P. vivax* parasites



will be shortened, which effect will raise the chance for transmission. The findings of this study strongly support this hypothesis.

It should not be forgotten that Greece is an important holiday destination in Europe (Chaitip et al. 2010). It implies that not only about 10.8 million inhabitants of the country could be affected, but the tourists also are at the risk of acquiring vivax malaria. It is very plausible that climate change will compromise the sustainability of Mediterranean tourism (Perry 2006). One of the factors is the increased risk of malaria. Isolated malaria transmissions by local *Anopheles* mosquitoes were linked to the heatwave events in Europe several times in the last few decades. For example, the heatwave of July 2006 resulted in the appearance of locally transmitted, autochthonous *P. vivax* malaria cases in Corsica (Armengaud et al. 2006). The first autochthonous malaria case due to *P. vivax* since its mid-20<sup>th</sup> century eradication (1961) in Spain was observed in October 2010 (Peralta et al. 2011), after a hot summer. In an etiological sense, similar autochthonous malaria-transmissions with *P. falciparum* parasites were observed related to the heatwave in 1997 in Germany and Italy (Baldari et al. 1998; Krüger et al. 2001). These individual cases draw attention to the importance of the investigation of future changes in the risk of malaria in such Mediterranean countries like Greece.

## Conclusions

It can be concluded that most part of the land of Greece is in the ‘anophelism without malaria’ situation because wide areas of the country, where the model predicts the potentiality of the presence of *P. vivax* malaria, it does not appear in the present times or it has a low prevalence. It seems that the elongation of the transmission season holds the most notable potential to trigger the re-emergence of malaria in such parts of Greece where it occurred in the historical times before the eradication. The changing patterns of the combined factors also predict the increased risk and the extending potential range of *vivax* malaria in mainly in the mid-altitude regions of the country and the Aegean Islands. The models also predict the moderate altitudinal shift of *P. vivax* malaria in Greece.

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## Disclosure statement

The author declare that they have no conflict of interest.

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