Year: 2020

Rising temperature and its impact on receptivity to malaria transmission in Europe: A systematic review

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Abstract: BACKGROUND Malaria is one of the most life-threatening vector-borne diseases globally. Recent autochthonous cases registered in several European countries have raised awareness regarding the threat of malaria reintroduction to Europe. An increasing number of imported malaria cases today occur due to international travel and migrant flows from malaria-endemic countries. The cumulative factors of the presence of competent vectors, favourable climatic conditions and evidence of increasing temperatures might lead to the re-emergence of malaria in countries where the infection was previously eliminated. METHODS We performed a systematic literature review following PRISMA guidelines. We searched for original articles focusing on rising temperature and the receptivity to malaria transmission in Europe. We evaluated the quality of the selected studies using a standardised tool. RESULTS The search resulted in 1'999 articles of possible relevance and after screening we included 10 original research papers in the quantitative analysis for the systematic review. With further increasing temperatures studies predicted a northward spread of the occurrence of Anopheles mosquitoes and an extension of seasonality, enabling malaria transmission for annual periods up to 6 months in the years 2051-2080. Highest vector stability and receptivity were predicted in Southern and South-Eastern European areas. Anopheles atroparvus, the main potential malaria vector in Europe, might play an important role under changing conditions favouring malaria transmission. CONCLUSION The receptivity of Europe for malaria transmission will increase as a result of rising temperature unless socioeconomic factors remain favourable and appropriate public health measures are implemented. Our systematic review serves as an evidence base for future preventive measures.

DOI: https://doi.org/10.1016/j.tmaid.2020.101815

Originally published at:
Fischer, Lena; Gültekin, Nejla; Kaelin, Marisa B; Fehr, Jan; Schlagenhauf, Patricia (2020). Rising temperature and its impact on receptivity to malaria transmission in Europe: A systematic review. Travel Medicine and Infectious Disease, 36:101815.

DOI: https://doi.org/10.1016/j.tmaid.2020.101815

Travel Medicine and Infectious Disease 36 (2020) 101815

Contents lists available at ScienceDirect

Travel Medicine and Infectious Disease

journal homepage: www.elsevier.com/locate/tmaid

Rising temperature and its impact on receptivity to malaria transmission in Europe: A systematic review

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ARTICLE INFO

Keywords:
1.9 climate change
Global warming
Rising temperature
Malaria
Anopheles
Plasmodium
Europe
Incubation
Breeding

ABSTRACT

Background: Malaria is one of the most life-threatening vector-borne diseases globally. Recent autochthonous cases registered in several European countries have raised awareness regarding the threat of malaria reintroduction to Europe. An increasing number of imported malaria cases today occur due to international travel and migrant flows from malaria-endemic countries. The cumulative factors of the presence of competent vectors, favourable climatic conditions and evidence of increasing temperatures might lead to the re-emergence of malaria in countries where the infection was previously eliminated.

Methods: We performed a systematic literature review following PRISMA guidelines. We searched for original articles focusing on rising temperature and the receptivity to malaria transmission in Europe. We evaluated the quality of the selected studies using a standardised tool.

Results: The search resulted in 1′999 articles of possible relevance and after screening we included 10 original research papers in the quantitative analysis for the systematic review. With further increasing temperatures studies predicted a northward spread of the occurrence of *Anopheles* mosquitoes and an extension of seasonality, enabling malaria transmission for annual periods up to 6 months in the years 2051–2080. Highest vector stability and receptivity were predicted in Southern and South-Eastern European areas. *Anopheles atroparvus*, the main potential malaria vector in Europe, might play an important role under changing conditions favouring malaria transmission.

Conclusion: The receptivity of Europe for malaria transmission will increase as a result of rising temperature unless socioeconomic factors remain favourable and appropriate public health measures are implemented. Our systematic review serves as an evidence base for future preventive measures.

1. Introduction

Malaria is one of the most life-threatening vector-borne diseases and is affecting nearly half of the people worldwide [1]. Malaria is caused by *Plasmodia* parasites that are spread to humans through the bites of infected female *Anopheles* mosquitos. Five parasite species cause malaria in humans whereas *P. falciparum* and *P. vivax* pose the highest thread. *Anopheles* are mainly found in tropical and subtropical areas of the world. In 2018 some 228 million cases of malaria were estimated, mainly in sub-Saharan Africa with about 405′000 deaths, mostly in children under 5 years of age [2]. In Europe, malaria was endemic until its elimination in the 1970s, with Macedonia being the last endemic area in 1974 [3]. Many factors led to the decline of malaria, including land use and agricultural change, socioeconomic improvements and intervention efforts [4]. However, recent autochthonous cases registered in several European countries have raised awareness regarding the threat of malaria reintroduction to Europe. An increasing number of imported

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https://doi.org/10.1016/j.tmaid.2020.101815
Received 14 April 2020; Received in revised form 24 June 2020; Accepted 25 June 2020

Abbreviation

An	Anopheles
CLMcom-CCLM4-8-17	Climate Limited-area Modelling Community Model
EWS	Early Warning Systems
GCM	General Circulation Models
GIS	Geographic Information System
HadCM3	Hadley Centre Coupled Model, version 3
IPCC	Intergovernmental Panel on Climate Change
KNMI-RACMO22E	Royal Netherlands Meteorological Institute Regional Atmospheric Climate Model
R_0	Basic Reproduction Rate
RCM	Regional Climate Model
RCP	Representative Concentration Pathway
REMO	Regional Model
SRES	Special Report on Emissions Scenarios
UKCIP02	Climate Change Scenarios for the United Kingdom
VSI	Vector Stability Index
WettReg	Weather Condition-based Regionalization Method
WHO	World Health Organization

malaria cases are now registered due to international travel and migrant flows from malaria-endemic countries [5,6]. Together with the presence of competent vectors, favourable climatic conditions and evidence of a changing climate this may lead to the re-emergence of malaria in countries where this disease was previously eliminated. Locally transmitted cases have been reported in Germany [7], the Netherlands [8], Spain [9], France [10], Italy [11], Greece [12], and the UK [13]. The dominant *Anopheles* vector species in Europe are currently *An. Atroparvus*, *An. Labranchiae*, *An. Messeae*, *An. Sacharovi*, *An. Sergentii*, and *An. Superpictus* [14]. The main cause for autochthonous malaria in Europe is the human parasite *P. vivax* with *P. falciparum* occurring only sporadically [15].

The risk of malaria spreading depends on the receptivity and vulnerability in a given area. The WHO defines *receptivity* as a degree to which an ecosystem in a given area at a given time allows for the transmission of *Plasmodium spp.* From a human to another human through a vector mosquito [16]. The concept encompasses the vectorial capacity of the mosquito, susceptibility of the human population to malaria infection and the strength of the health system, including malaria interventions. Receptivity depends on vector susceptibility to particular species of *Plasmodium* and is influenced by ecological and climatic factors. *Vulnerability* of an area is defined as the frequency of influx of infected individuals or groups and/or infective *Anopheles* mosquitoes and is also referred as the “importation risk” [16]. Since local malaria transmission in Europe is only possible after introduction of a *Plasmodium* infected individual or mosquito, this systematic review refers to receptivity of Europe for malaria transmission only.

Climatic conditions, such as temperature, rainfall patterns and humidity affect the life cycle and survival of parasites and vectors and therefore highly determine the receptivity for transmission of malaria and other vector-borne diseases [4]. This is of special concern since the world’s climate is changing. The Intergovernmental Panel on Climate Change (IPCC) defines climate change as long-term change in the state of the climate that can be identified by changes in the mean or the variability of its properties that persists for an extended period, typically decades or longer [17]. Climate change impacts environmental factors including rise in temperature, precipitation, sea level, ocean acidification and extreme weather events (heat weaves, floods, windstorms). This systematic review focuses on the impact of rising temperature due to climate change. The IPCC stated that human activities have already caused approximately 1.0 °C of global warming since pre-industrial period and warming is likely to reach 1.5 °C between 2030 and 2052 if it continues to increase at the current rate [17]. The IPCC special report from 2018 provides multiple lines of evidence that this rapid global warming has major impacts on organisms and ecosystems, as well as on human systems and well-being and further emphasises that the risk for vector-borne diseases, such as malaria, are projected to increase with a high degree of confidence [17]. Global warming can increase vectorial capacity of malaria mosquitos through the reduction of the *Plasmodium* extrinsic incubation period, the extension of the mosquito breeding period and an increase in adult population density [18,19]. The aim of this systematic review is therefore, to assess the impact of rising temperature on the receptivity to malaria transmission in Europe and to provide an evidence base for the critical appraisal of the current state of knowledge on which health care guidelines and prevention efforts rely.

2. Methods

2.1. Literature extraction

The literature searches for this study were conducted following PRISMA guidelines, providing a set of items for reporting in systematic reviews and meta-analyses [20]. We searched for peer-reviewed articles published before October 21, 2019 in the electronic databases Embase, Medline, Cochrane Library and Scopus. Besides, we identified additional articles through other sources (reference list of identified papers, official reports from Ministries of Health and other surveillance reports, institutional reports from their website).

We used the following search terms in title, abstract and keywords (for full search methods see Appendix 1):

Associated keywords: ‘climate change’ or climat* or ‘global warming’ or seasonality.

2.2. Associated keywords: temperature

Associated keywords: malaria or *Anopheles* or *‘Plasmodium falciparum’* or *‘Plasmodium vivax’* or *‘Plasmodium malariae’* or *‘Plasmodium ovale’* or ‘Plasmodium *knowlesi*’ or ‘annual parasite index’ (API) or ‘annual parasite incidence’.

The three concepts have been combined through Boolean operator AND to a search set (n = 1′999) and animal studies have been removed (n = 274) (Fig. 1). After duplicate removal in total 1′040 studies have been screened for eligibility. Articles in English, French and German were reviewed.

2.3. Screening, inclusion and exclusion criteria

Eligibility criteria were original articles focused on rising temperature associated with climate change and transmission of malaria. This systematic review was restricted to malaria in Europe. Europe was defined according to the United Nations geoscheme for Europe, created by the United Nations Statistics Division (for countries see Appendix 2) [21].

We used the following inclusion criteria for selecting studies (in order of importance):

1. Studies must include current and future *spatial or temporal distribution of Anopheles mosquitos, malaria transmission, incidence or annual parasite index (API)* or the *impact on malaria by temperature.*
2. Studies using the climate variable *temperature* to analyse a (quantitative) trend of climate data and are relevant for the study of malaria.

3 Studies on *Europe.*
4 Articles in *English, French or German.*

Two authors (LF, PS) first independently screened titles, abstracts and keywords of relevant articles and then read full text articles to evaluate them according to our inclusion criteria. We also searched

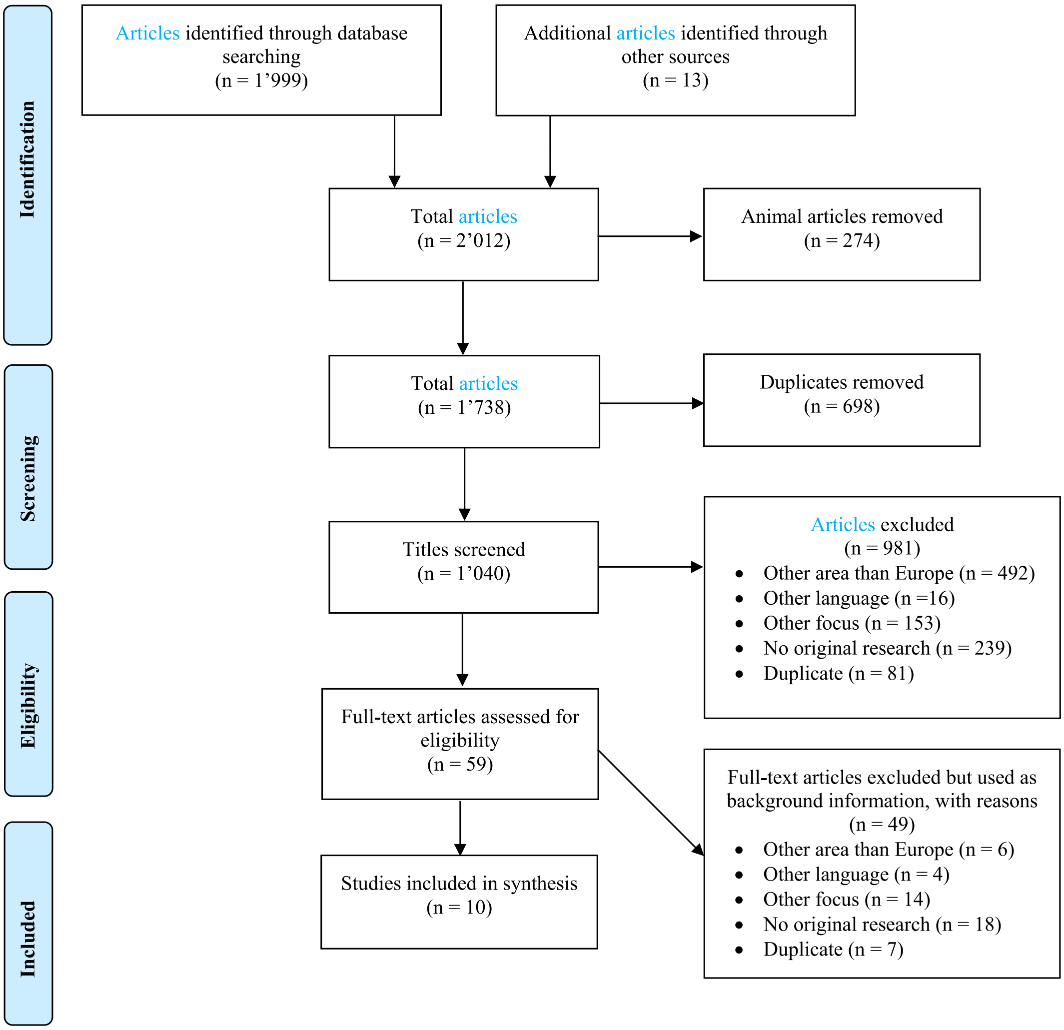

Fig. 1. PRISMA flow diagram.

websites of interest (WHO, ECDC, IPCC). In addition to the articles extracted from the electronic databases, we added 13 articles identified through other sources (Fig. 1).

The selected papers were systematically reviewed and thematically analysed. We excluded non-original research such as opinion pieces and viewpoints or articles referring to geographical areas other than Europe. The selected studies were read in more detail by one author (LF), who also hand-searched reference lists to ensure that no relevant articles are missing in this systematic review. An independent selection among the full-text articles assessed for eligibility was made by two authors (LF, PS) that discussed their choices and consequently agreed upon a final selection. Articles were further excluded for one of the following reasons: area other than Europe, other language, other focus, no original research or duplicate. Finally, a total number of 10 articles were included in the findings table of this systematic review. For documenting the research process a study flow diagram as recommended by the PRISMA statement was performed (Fig. 1). To ensure the quality of the included studies an assessment of the relevance and credibility was performed for each study individually, following a questionnaire from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Academy of Managed Care Pharmacy (AMCP) and National Pharmaceutical Council (NPC) Good Practice Task Force Report (Table 1) [22].

2.4. Data extraction

References were imported from the electronic databases and managed with the bibliographic software Zotero. For data management a summary of key findings of full-text articles retrieved and identified for qualitative synthesis was listed in a customised Microsoft Excel spread sheet. We used a uniform tool to extract data from eligible papers and recorded data on the journal, title, author, year, place, time period, method, vector species, response type, temperature, key findings, and additional comments. From a total of 10 articles that were included in the final selection, 8 used the occurrence of the *Anopheles* vector and two the malaria infection as marker of risk (Table 1). We summarized the models used as climate models including climate scenarios (Box 1 and 2) and the vector models (Box 3) found in the articles.

3. Results

We identified 1′999 articles in the electronic database searches, added 13 through other sources and after removal of duplicates and animal studies we screened 1′040 articles. We found 59 studies on malaria in Europe to access for eligibility and eventually included 10 articles in the final selection as shown in the PRISMA diagram (Fig. 1).

3.1. Modelling trends

We found two approaches for predicting the impact of rising temperature on receptivity to malaria transmission that can be distinguished. First, empirical correlative approaches that use statistical models of relationships between *Anopheles* mosquitoes and/or malaria

Table 1

Summary of published studies that assessed the effect of rising temperature on malaria receptivity in Europe.

Author	Place	Time period	Method	Vector species	Response type investigated	Key findings	Quality of the study[a]
Hertig 2019 [23]	Europe and the Mediterranean area	1985–2005, 2040–2060, 2080-2100	Mathematical model: Boosted Regression Trees using regional climate model simulations (KNMI-RACMO22E and CLMcom-CCLM4-8-17, under RCP4.5 and RCP8.5 scenarios)	*An. Atroparvus, An. Labranchiae, An. Messeae, An. Sacharovi, An. Sergentii, An. Superpictus*	Vector abundance (distribution maps from literature) and transmission stability (vector stability index (VSI))	Projected northward spread of *Anopheles* vector occurrences. Highest vector stability increases are predicted for Southern and South-Eastern European areas.	Sufficient: Relevance 4/4 Credibility 10/11
Trájer and Hammer 2018 [24]	Central and Eastern Europe and the North Balkan	1961–1990, 2011–2040, 2041–2070	Mathematical model: based on regional climate model (REMO, under A1B scenario) and Hungarian mosquito data	*An. Maculipennis*	Vector abundance (mosquito sampling)	*An. Maculipennis* larva season is predicted to increase by 1–2 months in Central and Eastern Europe and the North Balkan between 2041 and 2070, while April and October showed the most notable changes.	Sufficient: Relevance 4/4 Credibility 8/11
Ivanescu et al., 2016 [29]	Romania	1961–2014, 2030	Mathematical model: based on extrapolation of temperature evolution and diagnosed malaria cases	*An. Atroparvus, An. Labranchiae, An. Messeae, An. Sacharovi, An. Sergentii, An. Superpictus*	malaria cases	There will be a slight increase of temperatures to an average of 24C° in 2030, which may ensure a favourable climate for the development of *Anopheles* and is therefore increasing the risk of malaria re-emergence in Romania.	Sufficient: Relevance 4/4 Credibility 9/11
Holy et al., 2011 [26]	Germany	1961–1990, 1991–2007, 1991–2020, 2021–2050, 2051–2080	Mathematical model: based on temperature measurements and regional climate models (REMO or WettReg, under B1 or A1B scenario)	*An.atroparvus*	transmission risk (basic reproduction rate (R_0))	Both climate modelling approaches resulted in prolonged seasonal transmission gates in the future, enabling *P. vivax* malaria transmissions up to 6 months in Germany in the period 2051–2080 (REMO, scenario A1B).	Sufficient: Relevance 4/4 Credibility 8/11
Lindsay et al., 2010 [25]	UK	1961–1990, 2015 and 2030	Mathematical model: based on general circulation model (HADCM3, under UKCIP02 scenario for the UK) Statistical model: using logistic regression	*An. Atroparvus*	transmission risk (basic reproduction rate (R_0)) and areas of environmental suitability for malaria transmission	Although the current and future climate in the UK is favourable for the transmission of vivax malaria, the future risk of locally transmitted malaria is considered low because of low vector biting rates and the low probability of vectors feeding on a malaria-infected person.	Sufficient: Relevance 4/4 Credibility 10/11
Zhao et al., 2016 [4]	Europe	1900–2009	Statistical model: using correlations	NA	malaria cases	Socioeconomic improvements such as wealth, life expectancy and urbanization were strongly correlated with decline of malaria in Europe, whereas climatic and land use changes showed weaker relationships.	Sufficient: Relevance 4/4 Credibility 10/11
Benali et al., 2014 [28]	Portugal	2001–2010	Statistical model: using simple linear correlations and multivariate models based on mosquito sampling and satellite-derived temperature data	*An. Atroparvus*	Vector abundance (mosquito sampling, vector density) and areas of environmental suitability (larval habitat suitability)	Present environmental conditions are suitable for vector development at high densities and the spatial and temporal patterns closely resemble the ones registered in the past endemic period.	Sufficient: Relevance 4/4 Credibility 9/11
Sainz-Elipe et al., 2010 [27]	Spain	1961–1986, 2005 and 2006	Statistical model: using climate diagrams, ecological characteristics and mosquito sampling	*An. Atroparvus*	transmission risk (Gradient Model Risk (GMR) index)	Temperature increase favoured a widening of the potential transmission window in an historically endemic area in Spain, starting two months before, in May, and lasting until September in the case of *P. falciparum* and until October in case of *P. vivax*, respectively.	Sufficient: Relevance 4/4 Credibility 9/11
	France	2005					Sufficient:

(*continued on next page*)

Table 1 (*continued*)

Author	Place	Time period	Method	Vector species	Response type investigated	Key findings	Quality of the study[a]
Ponçon et al., 2007 [30]			Statistical model: linear correlations based on mosquito sampling	*An. Algeriensis, An. Atroparvus, An. Hyrcanus, An. Melanoon*	Vector abundance (mosquito sampling)	*An. Hyrcanus* is currently the main potential malaria vector in the Camargue, France, and its population increased in a pattern related to summer temperatures and the condition of rice fields in the area.	Relevance 4/4 Credibility 8/11
Kuhn et al., 2002 [18]	Europe	1927–2001	Statistical model: Multivariate logistic regression models using climate surfaces and remotely sensed land cover fitted to reported vector presence and absence	*An. Atroparvus, An. Labranchiae, An. Messeae, An. Sacharovi, An. Superpictus*	Vector abundance (mosquito data from literature)	Risk maps of different *Anopheles* species: *An. Atroparvus* was most common and widely distributed. The distribution of European malaria vectors has frequently been linked with irrigated crop land (such as rice fields) and marshes as well as rising temperature.	Sufficient: Relevance 4/4 Credibility 9/11

Note: Relevance questions refer to the usefulness of the modelling study to inform the particular health care decision and are finally assessed as Sufficient or Insufficient. The credibility is captured with questions in the following seven domains, Validation, Design, Data, Analysis, Reporting, Interpretation, and Conflict of interest and overall credibility of the modelling study and is judged as Sufficient or Insufficient. The questionnaire consists of 15 questions related to the relevance and credibility of a modelling study and each question is answered with Yes/No/Can't Answer.

[a] Assessed using a questionnaire to assess the relevance and credibility of a modelling study following an International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Academy of Managed Care Pharmacy (AMCP) and National Pharmaceutical Council (NPC) Good Practice Task Force Report [22].

distribution and rising temperature. Second, process-based mathematical models that aim to simulate epidemiological processes between environmental conditions and vectorial performance estimated independently of current distributions. From the 10 articles included in the quantitative analysis of this systematic review, five studies used statistical models to conclude their results, four used projecting mathematical models and one used both methods (Table 1).

The six papers that were found using correlative statistical modelling approaches were based on empirically observed data on *Anopheles* mosquitoes and/or current/historical malaria distribution as well as climate data. Climate data, including temperature, was found to be either satellite-derived (1) or obtained from national weather stations (4). The five identified papers that used predictive mathematical models included historical and current data while allowing to make projections for the future. In our analyses five different climate models were identified and an overview of the models used can be found in Box 1. The models were either general circulation models (GCM) or regional climate models (RCM) and used different climate scenarios to make projections for future malaria transmission in Europe (Box 2). In addition, four different vector models have been identified that have been used as a measure for the risk prediction of possible transmission and spread of malaria. A summary of the identified malaria vector models can be found in Box 3.

3.2. *Anopheles mosquitos are still present in Europe*

All studies included in this systematic review confirmed that *Anopheles* mosquitoes transmitting *Plasmodium vivax* are still present in European countries, although in lower densities compared to the pre-elimination period. *An. Atroparvus* was found to be the most widely distributed species in Europe (evaluated in 8 studies) that is capable of transmitting *P. vivax* malaria. Three studies evaluated *An. Labranchiae*, *An. Messeae*, *An. Sacharovi*, and *An. Superpictus* respectively, two studies *An. Sergentii* and one study *An. Maculipennis*, *An. Algeriensis*, *An. Hyrcanus*, and *An. Melanoon* respectively. Studies on environmental suitability for malaria (8 from 10 studies) further concluded that the present environmental conditions would be suitable for *Anopheles* mosquito development at high densities and the spatial and temporal patterns closely resemble those registered in the past in endemic regions [25,28].

We found two studies that generated risk maps of the competent *Anopheles* mosquito species currently present in Europe that can be used as a preliminary step towards predicting future scenarios for receptivity to malaria transmission [18,23]. Receptivity depends on vector susceptibility to particular *Plasmodium* species and was higher in *P. vivax* than in *P. falciparum*. The most widely distributed *Anopheles* vector belong to the *Anopheles maculipennis* complex that includes several species with different susceptibility to *Plasmodium* species due to different behavioural pattern and feeding preferences. The most common species, *An. Atroparvus*, was found to be widely distributed in Northern and Western Europe, Spain, Portugal, Italy, the Balkans, but not in North Scandinavia, the Alpine regions, and North Africa [18,23,25–29]. *An. Messeae* was identified as the second most common *Anopheles* mosquito and its presence has been mapped in Scandinavia and North-Western Europe, including the Baltic States and Russia [18,23]. *An. Labranchiae* was found to be the third most common species and restricted to Southern Europe, comprising Italy, the coastal regions of the Balkans, Eastern Spain and North Africa [18,23]. *An. Sacharovi* was present mainly in South-Eastern Europe, from Eastern Spain along the Alps to the Balkans, Turkey and the Black Sea [18,23]. The distribution of *An. Superpictus* was mapped similar but less extensive than that of *An. Sacharovi* and ranges from the Alps to the Balkans, Turkey and North Africa [18,23]. Besides that, one study stated that *An. Hyrcanus*, and not *An. Atroparvus*, was reported the main potential malaria vector in Southern France in 2005 [30].

Box 1
Climate models used in the publications selected in this review.

Name (Abbreviation)	Climate Model
KNMI regional atmospheric climate model (KNMI-RACMO22E)	Regional atmospheric climate model developed by the Royal Netherlands Meteorological Institute (KNMI) in the Netherlands. The model is based on the European community Earth-System Model (EC-EARTH) and uses the Representative Concentration Pathway (RCP) scenarios for future projections.
Climate Limited-area Modelling Community Model (CLMcom-CCLM4-8-17)	Regional climate model developed by the Climate Limited-area Modelling Community (CLM-Community) in Germany. The model is based on the Max Planck Institute Earth-System Model (MPI-ESM-LR) and uses the Representative Concentration Pathway (RCP) scenarios for future projections.
Regional Model (REMO)	Numerical regional climate model developed by the Max Planck Institute for Meteorology in Germany. The model is based on the global ECHAM climate model and uses the scenarios A1B, A1, B1 for future projections. REMO is used by about 15 institutes in Germany, France, Switzerland, Greece and China.
Weather Condition-based Regionalization Method (WettReg)	Statistical regional climate model developed by Climate & Environment Consulting Potsdam in Germany. The model is based on the global ECHAM climate model and uses the scenarios A1B, A1, B1 for future projections.
Hadley Centre global climate model (HadCM3)	Coupled atmosphere-ocean general circulation model (AOGCM) developed at the Hadley Centre in the United Kingdom. It was one of the major models used in the Intergovernmental Panel on Climate Change (IPCC) third Assessment Report in 2001.

3.3. *Northward spread of Anopheles mosquitos*

Five studies were found assessing the potential transmission of malaria in the future, of which all modelled increased *Anopheles* abundance for large parts of Europe under rising temperatures. However, distinct changes in the distribution of the dominant European malaria vectors were predicted. In general, we found that rising temperatures are expected to lead to a northward spread of *Anopheles* vector occurrence [23]. Most noticeable is the projected spread of *An. Atroparvus* and *An. Messeae* to the North until the end of the 21st century. Concurrently, *An. Messeae* is predicted to decline over the Western parts of Europe. *An. Labranchiae*, *An. Sacharovi* and *An. Superpictus* have been found to be expected to extend northwards, but with a lower probability of occurrence [23]. In contrast, we found that for some Mediterranean areas occurrence probabilities may decline. Most pronounced seems to be the reduction of *An. Superpictus*, *An. Sacharovi* and *An. Sergentii* over the Eastern Mediterranean area and North Africa under future climate conditions. Hertig assumed that these distribution changes are related to the general temperature increase and the strong temperature increase over North-Eastern Europe and the Mediterranean area in spring and autumn, but also to the predicted reduction in precipitation [23]. Moreover, we found a geographically northward decline in malaria transmission stability towards Scandinavia in the predictive modelling studies. The authors stated that the duration of the extrinsic incubation period in the mosquito could also in the future, be still temperature-limited over Northern Europe [23,25]. In addition, we found that the future risk of locally transmitted malaria is considered limited due to low biting rates and the low probability of vectors feeding on a malaria-infected person, as stated in a study on the UK by Lindsay et al. [25].

3.4. *Lengthening of possible transmission season*

The results of our systematic review also show a lengthening of the possible malaria transmission season, which was investigated in four studies. We found one study that has already observed an expansion of the potential malaria transmission window in Spain in 2005, based on data corresponding to a 26-year-period [27]. The authors noted that the favourable transmission period was longer and started two months earlier, in May, and lasting until September in the case of *P. falciparum* and until October in case of *P. vivax*, respectively. In addition, we found three predictive modelling studies that suggest an extension of the potential malaria transmission season for regions other than Southern Europe and the Mediterranean area. Changes in the length of *Anopheles* larva season were expected for Central and Eastern Europe and the North Balkan region [24,29]. Based on the REMO climate model, Trájer and Hammer predicted that the season for *An. Maculipennis* larvae will increase by one or two months between 2041 and 2070, with April and October showing the most notable changes [24]. We also found an expected prolonged seasonal transmission in *An. Atroparvus* for Germany, enabling malaria transmissions due to *P. vivax* up to six months in the period 2051–2080 (REMO, scenario A1B) [26]. Moreover, we identified a widening of the potential malaria transmission window favoured by rising temperature for the UK, where the climate is predicted to be suitable for *P. vivax* malaria transmission for three to four months by 2030 [25].

3.5. *Expected risk areas in Europe*

In general, all predictive models showed that the areas of potential malaria transmission are increasing where rising temperature favours *Anopheles* occurrence and also significantly impacts the vectorial capacity. As a result, highest malaria transmission stability was found to be projected for Southern and South-Eastern European areas. The authors stated that a rise in global mean temperature by 2100 of about 4.8 °C compared with pre-industrial levels (RCP8.5 scenario) is predicted to lead to an increased vector stability especially in South and South-Eastern Europe [23]. An increased risk was predicted for the following areas: Spain, France, Italy, Greece, the Central and Eastern European countries Bulgaria, Romania, Macedonia, Serbia, Croatia, Hungary, Ukraine and Russia [23,24,27,29].

A further finding of our analysis is that socioeconomic factors will most likely play a large role in the determination of malaria risk in Europe [18]. Zhao et al. showed that the elimination of malaria in Europe was already in the past mainly related to socioeconomic improvements and only to a limited extent to climatic changes including temperature [4].

4. Discussion

In its most recent report, the IPCC stated that global warming of 1.5 °C–2 °C compared to pre-industrial levels is expected to have major impacts on vector-borne diseases such as malaria and that their risk is projected to increase with high confidence including potential shifts in their geographic range [17]. This, together with the fact that its former vectors are still distributed across the continent [14], has led us study the effects of rising temperature on the receptivity to malaria transmission in Europe, in order to assess the risk of malaria re-emergence in

Box 2
Climate scenarios used in the publications selected in this review.

Name (Abbreviation)	Climate Scenario	Comments
Representative Concentration Pathway (RCP)	Group of 4 individual scenarios developed by the IPCC in 2014 to supersede Special Report on Emissions Scenarios (SRES). RCP is a greenhouse gas concentration (not emissions) trajectory adopted by the IPCC for its fifth Assessment Report (AR5) in 2014.	The four RCPs (RCP2.6, RCP4.5, RCP6, and RCP8.5) are labelled after a possible range of radiative forcing values in the year 2100 (2.6, 4.5, 6.0, and 8.5 W/m^2, respectively). In the RCP8.5 scenario, the rise in global mean temperature by 2100 is about 4.8 °C compared with the pre-industrial state or 4 °C compared with 1986–2005. In the RCP4.5 middle scenario, the warming reaches 2.6 °C compared with the pre-industrial level. In the RCP2.6 scenario, however, the mean global temperature rise of the model remains below the 2 °C target.
Special Report on Emissions Scenarios (SRES)	Group of 40 scenarios developed by the IPCC in 2000. SRES scenarios quantify anthropogenic emissions of greenhouse gases (and some other pollutants), land-use and other factors for the 21st century by giving a wide range of possible alternatives, based on modelling (socioeconomical, biogeochemical) and research.	The A families are characterized by rapid economic development, while B scenarios represent environmental sustainability. A1 and B1 versions show population decrease after few decades and global solutions for the world challenges, whereas A2 and B2 scenarios indicate continuous population growth with local socioeconomic solutions. A1 scenario has three groups describing alternative directions of technological change in the energy system: fossil intensive (A1FI), non-fossil energy sources (A1T), or a balance across all sources (A1B). By the end of the 21st century, the highest concentration levels are reached in A1FI and A2; more “optimistic” future paths are resulted by B1 and A1T; and A1B is a medium scenario.
Medium-high climate change scenario for the UK (UKCIP02)	This scenario uses the Hadley Centre global climate model (HadCM3) for a medium-high climate change scenario (SRES A2), which is used to drive a regional version of the model.	

countries where the disease was previously eliminated.

The articles we identified focused on the vector species historically associated with the distribution of endemic malaria in Europe. They confirmed that several *Anopheles* species capable of transmitting *P. vivax* caused malaria are still present in Europe, leading to a phenomenon known as “*anophelism* without malaria”. The current and historically most widespread species *An. Atroparvus*, *An. Labranchiae* and *An. Sacharovi* are among the members of the subgroup *An. Maculipennis*. Malaria vectors of minor importance comprise other members of the subgroup *An. Maculipennis (An. Messeae, An. Maculipennis s.s., An. Melanoon)*, or refer to *An. Algeriensis*, *An. Claviger, An. Hyrcanus*, *An. Plumbeus*, *An. Superpictus*, and *An. Sergentii*. Moreover, *An atroparvus* was found to be the dominant malaria vector in large parts of Europe not only under past and present but also under future climate conditions [23]. An important role is assigned to this vector with regard to the change in potential transmission stability, based on expected increases in length of the transmission season and the extrinsic incubation period.

4.1. Impact on malaria by rising temperature

The distribution of European malaria vectors has already in the past frequently been linked with rising temperatures [18]. It has been speculated that rising temperatures associated with climate change may increase the frequency of the *Anopheles* mosquitos and its bite rates as well as shorten the extrinsic incubation period of the *Plasmodium* parasites leading to an increased vectorial capacity [18,19]. Moreover, temperature influences the development and survival rate of the mosquito and also of parasites within the mosquito. For *P. vivax* a minimum temperature of 14.5–15 °C is required to develop inside the mosquito, while *P. falciparum* requires 16–19 °C [31,32]. For both *Plasmodium* parasites the optimal temperature for transmission ranges up to 33 °C. However, a recent modelling study from Mordecai et al. [33] suggests an optimal malaria transmission already at 25 °C (6 °C lower than previous models), which makes many more areas vulnerable to possible transmission, also in Europe. This is consistent with one of our identified studies from Portugal, reporting favoured *Anopheles* abundance at temperatures between 19 and 25 °C [28].

Our assessment of the impact of rising temperature on the receptivity to malaria transmission in Europe showed that large areas of the continent could support malaria transmission today and could extend in the future. In general, potential malaria transmission in Europe is highly seasonal due to temperate climate conditions. Temperature suitability is usually much higher in Southern than in Northern European areas, where the vector development is probably constrained by lower temperatures in winter [18]. Southern Europe and the Mediterranean area, with mild and wet winters and hot and dry summers, was and still is suitable for malaria transmission. Also in the future under the RCP8.5 scenario, projecting a rise in global mean temperature by 2100 of about 4.8 °C compared with the pre-industrial state, large parts of Southern and South-Eastern European areas emerge as regions of high transmission stability [23]. This finding is consistent with previous studies that investigated the impact of climate change on potentially emerging vector-borne diseases in Europe [34,35]. However, extreme temperatures in summer especially in Southern countries may also constrain *Anopheles* development [28]. A transmission risk currently exists, lasting from May until September (*P. falciparum*) or October (*P. vivax*) and an extension of this season is expected in the future [24–27]. Therefore, if the climate becomes warmer, conditions for malaria transmission in Europe become more favourable and last for longer. Moreover, we found a general northward spread of the *Anopheles* mosquito occurrence in our analyses, which was already modelled in previous global modelling studies [23]. An assessment of possible future changes of malaria transmission using general circulation models (GCM) and different malaria impact models also showed that until the 2080s a northward shift of the malaria epidemic belt over Central and Northern Europe could occur [15].

4.2. Other driving forces

Despite the substantial number of imported malaria cases from travellers and migrant flows from endemic areas that could contribute to an increased infectious parasite reservoir and the documented presence

Box 3
Vector models used in the publications selected in this review.

Name (Abbreviation)	Vector Model
Vector Stability Index (VSI): $\mathrm{VSI} = \sum_{m=1}^{12} a_{i,m}^2 p_{i,m}^E / -\ln(p_{i,m})$ m month i vector (*Anopheles* species) a human-biting proportion p daily survival rate E length of extrinsic incubation period in days	Global index representing the potential malaria transmission stability. The spatial index includes the most important intrinsic properties of *Anopheles* mosquitos that interact with climate to determine the vectorial capacity [23].
Relative monthly larvae abundance value (A_{rm}): $A_{rm} = \frac{N_m}{N_a} \times 100$ N_m number of the total collected larvae according to a given month N_a total number of the collected larvae representing the entire period	Measure for mosquito larva season [24].
Basic Reproduction Rate (R_0): $R_0 = \frac{\mathrm{m}a^2bp^n}{-\ln(p)r}$ m relative frequency of mosquito a number of blood meals per human and day b ratio of mosquitos in which parasites can develop after ingestion of infected blood p daily survival probability of adult mosquitoes n duration (days) of parasite development in adult mosquitoes r recovery rate of malaria-infected people	Measure used for the risk prognosis of malaria disease spreading [25,26]: if $R_0 \geq 1$ risk of a malaria spread if $R_0 < 1$ no risk of a malaria spread
Gradient Model Risk Index (GMR index): $GMR = GDD \times \frac{R}{PET}, if \frac{R}{PET} > 0.2$ GDD growing degree-days R rainfall PET potential evapotranspiration	Measure applied to forecast the malaria transmission risk, e.g. along the year. if GMR $\geq$116 transmission risk exists (116 is the value required for the development of one *Plasmodium* generation) [27]

of *Anopheles* mosquitos [36–38], autochthonous malaria transmission has only rarely been observed in Europe since its elimination in the 1970s [13]. Recent studies have further stated that malaria transmission caused by imported infectious mosquitoes or travellers with parasitaemia does not occur on a large scale, even at Central European airports, and it is unlikely that such transmission could be sustained by native *Anopheles* mosquitoes [39]. The present situation of "*anophelism* without malaria" indicates that current socioeconomic and environmental conditions maintain the basic reproduction number (R_0) below 1, indicating no spreading of the disease [18].

It should be noted that a temperature increase does not necessarily mean a transmission risk increase if accompanied by a precipitation decrease. The role of precipitation in promoting malaria transmission is mainly through the availability of larval breeding sites [31]. Also in our analysis we found a decrease of malaria transmission stability to the South that was mainly related to the projected rainfall reductions and the resulting decline of vector occurrences due to the drought-induced inhibition of the aquatic life-cycle of the mosquitos [23]. Moreover, we found that changes in land use practices and draining of marshlands for cropping resulted in fewer mosquito breeding sites in the past [4,18], which is consistent with other studies [40–42]. Nevertheless, this limitation can, for example, be offset by artificial irrigation of agricultural landscapes as also reported in our identified studies [18,24,27,30]. Hence, areas with high *Anopheles* vector abundance tend to be related with ecosystems where irrigated agriculture periods coincide with the optimal temperature interval, generally spring and summer [27,28,30].

Furthermore, several authors have reported already in the past that socioeconomic changes such as the increase in Gross Domestic Product (GDP), life expectancy and urbanization were significantly correlated with the decline and elimination of malaria in Europe [4]. Rising temperature associated with climate change is only one component in a complex epidemiologic setting and other aspects such as human activities are therefore probably more important for the determination of malaria spreading as reported previously [43,44].

4.3. *Future implications*

With our systematic review we could determine the receptivity and identify risk areas of potential future malaria disease spreading for Europe due to rising temperature under climate change. Although the potential of malaria spreading is currently considered limited for Europe, mainly owning to socioeconomic conditions, strengthening of disease awareness and maintaining of robust public health care infrastructures for surveillance and vector control are of great importance, especially in the most vulnerable areas such as Southern Europe and the Mediterranean area. Monitoring drivers of malaria and other infectious diseases, such as changes in environmental and climatic conditions, can help predict the threat of malaria re-emergence, as shown in a recent study from Semenza et al. [40] on prototype early warning systems for vector-borne diseases in Europe. Targeted epidemiological surveillance, vector control activities and awareness raising among the general population and health care professionals, in particular in the areas projected environmentally suitable for malaria transmission as also recommended by the WHO [45]. Interestingly, these areas are often those that once supported malaria in the past [25,28]. Adapting existing surveillance practices in Europe will improve preparedness and facilitate public health responses to potentially emerging infectious diseases, including malaria, thereby helping to contain human and economic costs [46].

4.4. *Strengths and limitations*

A strength of our systematic review is the wide range of screened databases and Public Health agency documentation (WHO, ECDC, IPCC) as well as the adherence to the PRISMA guidelines and the quality assessment of the included studies. One possible limitation is that we have only included the aspect of temperature as a climate driver, although precipitation patterns and humidity also impact the life cycle of parasites and vectors. Moreover, most studies were based on mathematical models whose quality highly depends on the parameters used. A selection bias may be our inclusion of articles in English, French or German languages only.

5. Conclusion

Although malaria was officially eliminated in Europe in the 1970s, its former vectors are still distributed across the continent, leading to a phenomenon known as "*anophelism* without malaria". The current and future climate in large parts of Europe, in particular Southern and South-Eastern Europe, is predicted to be favourable for the receptivity to malaria transmission. As a result of rising temperature, the geographic occurrence of the *Anopheles* mosquito is expected to spread northwards and the possible season of malaria transmission to be extended. The risk of malaria transmission will therefore increase unless socioeconomic factors remain favourable and appropriate public health and anti-vector measures are implemented and maintained. Our systematic review assessed the impact of rising temperature on the receptivity of Europe for malaria transmission and provided a critical appraisal of transmission predictions. It will serve as an evidence base for future preventive measures.

Authors' contributions

LF and PS conceived the study plan and instigated the analysis. LF and PS did the literature review, the analysis and interpretation of the results. LF and PS drafted the paper. NG, MK, JF and PS provided significant input to drafts and revisions of the paper. All authors read and approved the final manuscript.

Funding

This project was supported by a collaborative research agreement of the Swiss Armed Forces and the University of Zurich Competence Centre MilMedBiol.

Declaration of competing interest

None of the authors report any conflicts of interests in this paper.

Appendix 1. Electronic database search strategy (last search on October 21, 2019)

1. Embase: ('climate change'/exp OR 'climate change':ti, ab OR climat*:ti, ab OR 'global warming':ti, ab OR seasonality:ti,ab) AND ('temperature'/exp OR temperature:ti,ab) AND ('malaria'/exp OR malaria:ti, ab OR anopheles:ti, ab OR 'plasmodium falciparum':ti, ab OR 'plasmodium vivax':ti, ab OR 'plasmodium malariae':ti, ab OR 'plasmodium ovale':ti, ab OR 'plasmodium knowlesi':ti, ab OR 'annual parasite index':ti, ab OR 'annual parasite incidence':ti,ab) NOT ([animals]/lim NOT [humans]/lim) → 485 retrieved hits
2. Medline: (exp Climate Change/or (climat* or global warming or seasonality).ti,ab.) AND (exp Temperature/or temperature.ti,ab.) AND (exp Malaria/or (malaria or anopheles or plasmodium falciparum or plasmodium vivax or plasmodium malariae or plasmodium ovale or plasmodium knowlesi or annual parasite index or annual parasite incidence).ti,ab.) NOT (Animals/not (Animals/and Humans/)) → 382 retrieved hits
3. Cochrane: (MeSH descriptor: [Climate Change] explode all trees OR ((climat* OR 'global warming' OR seasonality):ti,ab,kw)) AND (MeSH descriptor: [Temperature] explode all trees OR temperature: ti,ab,kw) AND (MeSH descriptor: [Malaria] explode all trees OR (malaria OR anopheles OR 'plasmodium falciparum' OR 'plasmodium vivax' OR 'plasmodium malariae' OR 'plasmodium ovale' OR 'plasmodium knowlesi' OR 'annual parasite index' OR 'annual parasite incidence'):ti,ab,kw) → 6 retrieved hits
4. Scopus: (TITLE-ABS-KEY("climate change" OR climat* OR "global warming" OR seasonality)) AND (TITLE-ABS-KEY(temperature)) AND (TITLE-ABS-KEY(malaria OR anopheles OR "plasmodium falciparum" OR "plasmodium vivax" OR "plasmodium malariae" OR "plasmodium ovale" OR "plasmodium knowlesi" OR "annual parasite index" OR "annual parasite incidence")) AND NOT ((animal* OR …) AND NOT (human* OR patient*)) → 852 retrieved hits

Appendix 2. European countries (according to United Nations geoscheme for Europe [21])

Åland Islands, Albania, Andorra, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Channel Islands, Croatia, Czechia, Denmark, Estonia, Faroe Islands, Finland, France, Germany, Gibraltar, Greece, Holy See, Hungary, Iceland, Ireland, Isle of Man, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Monaco, Montenegro, Netherlands, North Macedonia, Norway, Poland, Portugal, Republic of Moldova, Romania, Russian Federation, San Marino, Serbia, Slovakia, Slovenia, Spain, Svalbard and Jan Mayen Islands, Sweden, Switzerland, Ukraine, United Kingdom of Great Britain and Northern Ireland.

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