

Brief Report

Global warming impact on the expansion of fundamental niche of *Cryptococcus gattii* VGI in EuropeMassimo Cogliati *

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Abstract

In the present study, we analysed how geographical distribution of the fungal pathogen *Cryptococcus gattii* VGI in Europe and Mediterranean area has evolved in the last four decades based on the climatic changes, and we tried to predict the scenario for the next decade. Niche modelling by Maxent analysis showed that recent climate changes have significantly affected the distribution of the fungus revealing a gradual expansion of the fundamental niche from 1980 to 2009 followed by an impressive increase in the last decade (2010–2019) during which the environmental surface suitable for the fungal survival was more than doubled. In the next decade, our model predicted an increase in the area of distribution of *C. gattii* VGI from the coasts of the Mediterranean basin towards the more internal sub-continental areas. On the basis of these predictions, an increase of cases of cryptococcosis due to *C. gattii* VGI is expected in the next decade and a constant monitoring of the epidemiology of this fungal pathogen represents a crucial strategy to detect the onset of future outbreaks.

Introduction

Environmental fungi able to infect humans represent a serious health problem. A growing number of fungal species associated with human diseases are emerging due to the increase in the number of susceptible hosts such as immunocompromised patients (Denham *et al.*, 2019; Friedman and Schwartz, 2019). *Aspergillus*, *Candida*, *Cryptococcus*, *Fusarium*, *Mucor*, *Rhizopus*, *Histoplasma*, *Coccidioides*, *Blastomyces*, *Scedosporium*, *Sporothrix*, are just some example of fungal genera including fungi

able to cause life-threatening disseminated diseases with a high mortality rate (de S Araújo *et al.*, 2017). To know how these fungi are distributed in the environment, which bioclimatic conditions enable their growth and the geographical area where these conditions are present is crucial to prevent contact between fungi and susceptible hosts. Furthermore, global warming trend represents a potential opportunity for environmental fungal pathogens to colonize new geographical areas expanding their distribution area (Gorris *et al.*, 2019; Hofer, 2019; Rickerts, 2019; Casadevall *et al.*, 2021). Niche modelling tools, which are able to infer the fundamental niche of a species on the basis of actual occurrence data, may identify the high-risk areas of contact with the fungus and may predict the future scenarios based on climatic changes (Phillips *et al.*, 2006; Escobar and Craft, 2016).

The basidiomycetous yeasts belonging to *Cryptococcus gattii* species complex (Kwon-Chung *et al.*, 2017) are emerging fungal pathogens that recently have captured the public health attention due to an unexpected outbreak that occurred in British Columbia (Canada) which then expanded along the Northwestern Pacific Coast of the United States (Kidd *et al.*, 2004; Byrnes and Marr, 2011). These fungi, together with those belonging to *C. neoformans* species complex, are the etiological agents of cryptococcosis, a disseminated fungal disease often causing fatal meningitis primarily in immunocompromised hosts (Kwon-Chung *et al.*, 2014). The yeasts live as saprophyte in the environment where those belonging to *C. neoformans* species complex were isolated from soil, trees, water, arthropods, bird excreta and mammal faeces, whereas those belonging to *C. gattii* species complex primarily from soil and trees (Cogliati, 2013). Usually, they reproduce asexually by budding and production of blastospores, but under optimal conditions, sexual reproduction may occur by the production of filaments, basidia and basidiospores (Velagapudi *et al.*, 2009). Small blastospores and basidiospores are released in the air and can infect humans and animals throughout respiratory airways. Pulmonary and meningeal involvements are the most common clinical signs with a high mortality rate when diagnosis and treatment are delayed (Maziarz and Perfect, 2016).

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Cryptococcus gattii species complex can be distinguished in two serotypes, B and C, and in five main molecular types by different molecular techniques: VGI, VGII, VGIII, VGIV and VGV (Meyer *et al.*, 2009; Farrer *et al.*, 2019). Although the most susceptible hosts to cryptococcosis are immunocompromised hosts, some genotypes belonging to molecular types VGI and VGII are able to infect also immunocompetent hosts behaving as primary pathogens (Chen *et al.*, 2014; Diaz, 2020). This is the case of the outbreak occurring in the Northwestern Pacific Coast of North America where a high prevalence of immunocompetent hosts was observed among patients infected with VGII strains (Phillips *et al.*, 2015). VGII is also the prevalent *C. gattii* molecular type in Brazil where some outbreaks have been detected among immunocompetent people (Vilas-Bôas *et al.*, 2020). On the other hand, VGI is the most prevalent molecular type of *C. gattii* species complex worldwide with the highest prevalence in Australia where it is the cause of the majority of cryptococcosis cases. The presence of VGI was also reported from Asia, Americas and Europe (Cogliati, 2013). In Europe and Mediterranean area, VGI isolates were identified among both clinical and environmental isolates from Italy, Greece, Portugal, Spain and the Netherlands accounting for about 4% of the total *C. neoformans* and *C. gattii* species complex isolates which have been genotyped (Andreou *et al.*, 2019; Baró *et al.*, 1998; Chowdhary *et al.*, 2012; Cogliati, 2013; Cogliati *et al.*, 2016; Colom *et al.*, 2005; Colom *et al.*, 2012; Gerontiti *et al.*, 2017; Hagen *et al.*, 2012; Iatta *et al.*, 2012; Maestrale *et al.*, 2015; Mahmoud, 1999; Montagna *et al.*, 1997; Montagna *et al.*, 2018; Morera *et al.*, 2011; Mseddi *et al.*, 2011; Passera *et al.*, 2020; Romeo *et al.*, 2012; Solla *et al.*, 2008; Tortorano *et al.*, 1997; Trovato *et al.*, 2019; Velegraki *et al.*, 2001). Furthermore, genotyping and phylogenetic analysis of the European VGI isolates showed the presence of a genotypic cluster endemic in the continent confirming that bioclimatic conditions of Europe are suitable for the survival of this fungus (Hagen *et al.*, 2012; Cogliati *et al.*, 2019). In a recent niche modelling study, the bioclimatic conditions existing in Europe and the whole Mediterranean area were analysed and correlated to the presence of *C. gattii* VGI in the environment. The results showed that the geographical areas, compatible with the survival of the fungus, are characterized by a temperate hot climate with warm winters, and dry and hot summers, confirming the endemicity of the pathogen (Cogliati *et al.*, 2017). A further study identified where the potential risk of contact with the fungus is higher and revealed that more than 137 million people are potentially involved (Alaniz *et al.*, 2020). In the last decades, cases of cryptococcosis due to *C. gattii* VGI in Europe have increased compared to the almost absence of cases reported in the

past, with half of the cases occurred in immunocompetent hosts (Andreou *et al.*, 2019; Hagen *et al.*, 2012; Iatta *et al.*, 2012; McCormick-Smith *et al.*, 2015; Passera *et al.*, 2020). Considering the above epidemiological picture, it is fundamental to carefully monitor both the occurrence of new clinical cases and the environmental distribution of the fungus to promptly detect the onset of possible outbreaks.

In the present study, we analysed how geographical distribution of *C. gattii* VGI in Europe and the Mediterranean area has evolved in the last four decades based on the climatic changes and we tried to predict the scenario for the next decade.

Results and discussion

Cryptococcus gattii VGI occurrence sites and climatic data

Georeferenced occurrence points concerning environmental isolation of *C. gattii* VGI in Europe and the Mediterranean area were obtained from the database of the website SCrEEN Project (Survey of Cryptococcosis through an European Epidemiological Network, <https://sites.google.com/view/screenprojectcryptococcus/database>). The database includes information about the place of isolation, geographical coordinates, type of samples, number of samples, number of positive samples and molecular identification. The database of Screen Project network is the most accurate and completely available for the geographical area here investigated. It includes all the *C. gattii* and *C. neoformans* species complex isolates recovered from the environment so far in the European and Mediterranean area, and it is the result of the efforts of several researchers participating in the network (Cogliati *et al.*, 2016). Twenty-two occurrence points were found for VGI isolates and were included in the present study. The isolates were from Italy, Greece, Spain, Portugal, Netherlands, Egypt and Tunisia, and were isolated from plant material, soil, water and animals (Supplementary Material, Table S1). *Cryptococcus gattii* VGI isolates were not recovered from surveys carried out in France, Germany, Croatia, Denmark, Belgium, Austria, Malta, Cyprus, Turkey, Libya and Israel. Non-random samplings from more than 400 sites were performed both in urban and rural areas and reported in detail in the Screen Project database. However, data are lacking from Great Britain, Scandinavian region, Eastern Europe, Morocco and Algeria.

Data concerning temperatures and precipitations that occurred in Europe and Mediterranean area from 1980 to 2019 were obtained from two different sources. The first source of dataset is WorldClim website (<https://www>.

worldclim.org/data/monthlywth.html) from where raster layers containing monthly data of maximum temperature, minimum temperature and mean precipitation were downloaded from 1980 to 2019. Rasters were then grouped in four periods of time (1980–1989, 1990–1999, 2000–2010 and 2011–2019) and new rasters containing the mean value for each decade were calculated using the function ‘raster calculator’ of the software QGIS v3.10 (<https://www.qgis.org>). The same software was also used to define and crop the geographical area of interest for the analysis and to convert the final file to a file in ASCII format.

The second source of dataset is E-OBS data from Copernicus (https://surfobs.climate.copernicus.eu/dataaccess/access_eobs_chunks.php) from where it is possible to download raster layers containing the mean values of mean temperature, maximum temperature, minimum temperature and mean precipitation of three intervals of time: 1980–1994, 1995–2010 and 2011–2019. These rasters were cropped in the geographical area of interest and converted to ASCII format using QGIS software. Since data from Copernicus do not cover all the area of interest for the study, they were used to confirm the result obtained using the WorldClim data. The geographical area of each raster considered for the analysis was included in the following coordinates: 10° West, 42° East, 28° North and 71° North. The area includes the whole European continent, part of Northern Africa and Middle Eastern countries. Both datasets from WorldClim and Copernicus sources are the most accurate climatic data available for the geographical region here investigated.

Fundamental niche of C. gattii VGI during 2010–2019 decade

Analysis of data was performed by Maxent v3.3.3 software (https://biodiversityinformatics.amnh.org/open_source/maxent) which is able to infer a distribution map of a species calculating the probability of presence of that species in each of the cells of the raster layers. The resulting distribution map corresponds to the area in the layer, which has similar bioclimatic conditions to support the presence of the species with a certain probability. The model is then tested using a random set of occurrence points verifying a statistical difference from a random distribution model. The reference parameter is the value of the area under the curve (AUC) obtained calculating the percentage of omission rate increasing the fraction of the predicted area. AUC values around 0.5 indicate that the model is not valid, whereas values that tend to 1 indicate a valid model. The software is also able to calculate the contribution of each variable present in the layers to infer the final distribution map using jackknife analysis. Three features types, based on the number of occurrence points, were used during the analysis: linear (value = 0.423), quadratic

(value = 0.423) and hinge (value = 0.5). The convergence of the algorithm was fixed at maximum of 500 iterations.

The first analysis was performed to predict a distribution model for *C. gattii* VGI based on the occurrence data and the bioclimatic conditions observed in Europe in the last decade (2010–2019) in which most of the positive samples occurred. All monthly raster layers (36 layers) from WorldClim were used in the analysis and the variables that contributed more than 80% to the model were selected for the following analyses.

The analysis results produced a distribution model with an AUC value of 0.973 (Supplementary Material, Fig. S1), and showed that the most relevant variables contributing to the model were the minimum temperature in February and November, the maximum temperature in July and December and the precipitations in May, November and December. The seven variables contributed for more than 80% of the model (Supplementary Material, Table S2). Optimal conditions for the survival of the fungus were predicted in the geographical areas where the rainfalls mean in May, November and December were less than 50, 100 and 50 mm respectively, the mean of minimum temperatures in February and November were more than 5°C and 10°C respectively and the mean of maximum temperatures in July and December were less than 33°C and more than 10°C respectively.

Fundamental niche of C. gattii VGI inferred for three past decades from 1980 to 2009

The second step was to infer a distribution model for each of the three previous decades (1980–1989, 1990–1999 and 2000–2009) using the main layers identified in the previous analysis and projecting the optimal bioclimatic conditions for the species calculated for 2010–2019 decade.

Then, the four distribution models were compared to calculate the increase of the probability of species presence that occurred over time. The increase between consecutive decades was calculated using the function ‘raster calculator’ of QGIS software by subtracting one predicted map raster for a decade to that of the previous decade. The result generated a new raster map containing the values of the probability increases for each cell and, therefore, allowed us to visualize the geographical areas where an increase has occurred.

The maps showing the evolution of *C. gattii* VGI fundamental niche over four decades, from 1980 to 2019, are reported in Fig. 1. Fundamental niche maps of *C. gattii* VGI were very similar in the two less recent decades (1980–1989 and 1990–1999) where the predicted geographical areas suitable for fungal survival were identified in Southern Portugal, Southern coasts of Spain and

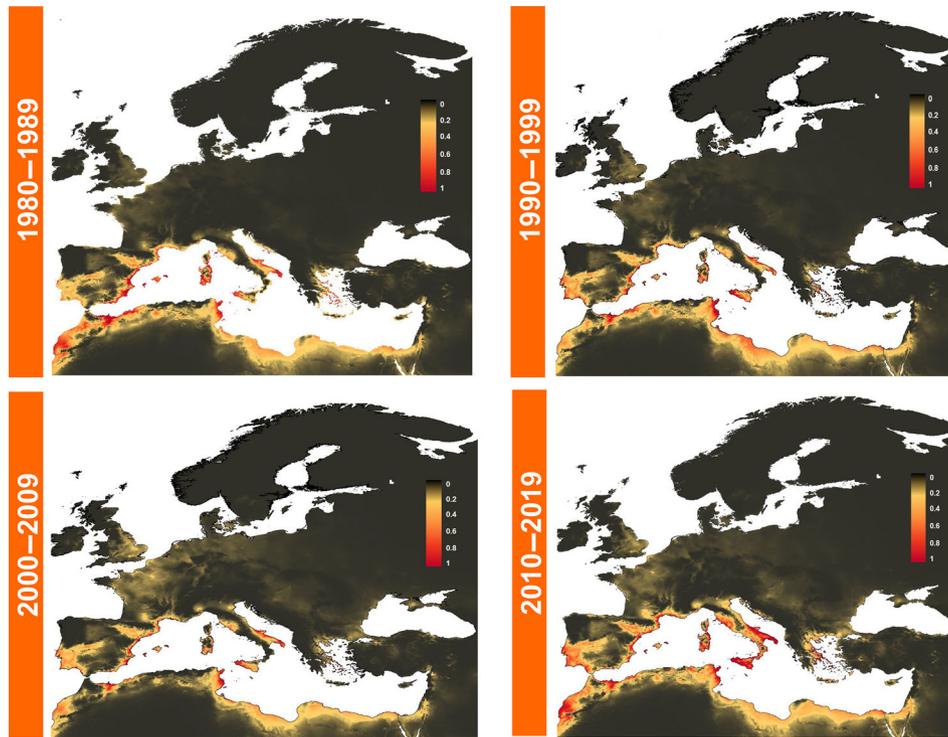


Fig. 1. Maps of species distribution inferred by Maxent v.3.3.3.3. Bioclimatic optimal conditions used to draw the distribution map of *Cryptococcus gattii* VGI in the 2010–2019 decade have been projected on the bioclimatic conditions existing in the past three decades to infer new distribution maps. Colour gradients represent the different probability of presence for the fungus in a specific geographical area.

Ebro's valley, the Southwestern coasts of France, South-eastern regions of Italy, Sicily and Sardinia, Aegean coasts of Greece, and most of the Mediterranean coasts of Northern Africa. The distribution area of the fungus, with a probability of presence >0.4 , expanded by only 7%. In the following decade (2000–2009), a slight expansion of the fundamental niche was observed towards France and Northern Europe, the Southeastern regions of Great Britain, as well as the Western coasts of the Black Sea. However, the total area of distribution did not increase. Finally, in the most recent decade (2010–2019), the area of suitability of the fungus further expanded including most of Spain, the whole Southern coast of France, Southern and Central Italy, Croatian coasts, Eastern Greece and Aegean Islands, and the Aegean coast of Turkey. Compared with the previous decade the area of distribution increased by about 127% (from 248 493 to 564 585 km²).

In term of probability of the presence of *C. gattii* VGI, Fig. 2 shows a high increase (+47% of the probability mean in the whole investigated area) in all the Mediterranean area in the last decade (2010–2019) compared with a low increase (+8%) observed in Eastern France, Northern Europe and Southeastern Great Britain, in the previous decade (2000–2009).

Fundamental niche expansion in the next decade

The final step of the analysis aimed to infer a new niche model to predict a distribution map of *C. gattii* VGI for the next decade (2020–2029). The main layers identified in the first analysis were selected for two decades, 2000–2009 and 2010–2019, and then subtracted each to the other to obtain new raster layers containing the increase of temperature and precipitation that occurred between the two decades. These increases were then added to the corresponding rasters of the 2010–2019 decade to obtain new rasters containing the predicted temperature and precipitation in the next decade (2020–2029). These latter rasters were then used by MaxEnt software to infer a new distribution model for the 2020–2029 decade projecting the optimal bioclimatic conditions for the species calculated for the 2010–2019 decade. A distribution map, showing the geographical areas where an increase in the probability of species presence between 2000–2009 and 2010–2019 decades occurred, was also generated calculating a new raster from the difference of the values present in 2000–2009 raster and 2010–2019 raster.

Prediction of the fundamental niche of *C. gattii* VGI in the next decade (2020–2029) showed an expansion towards Northern Spain, all Southern France regions,

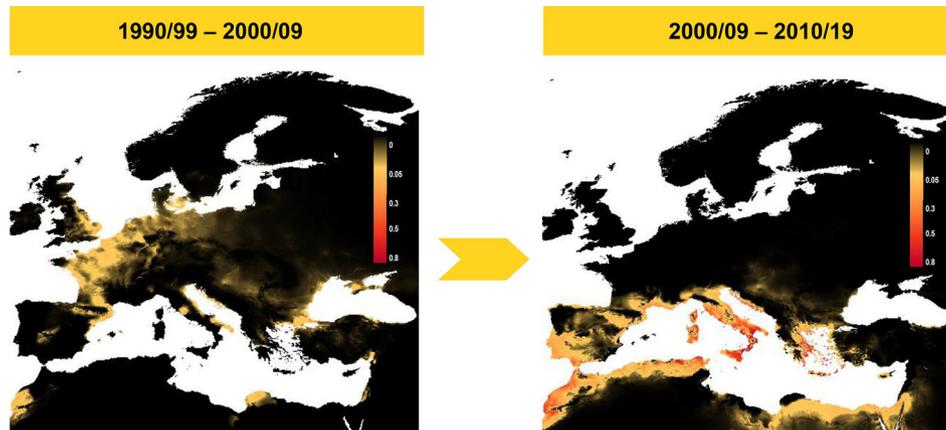


Fig. 2. Maps showing the geographical areas where an increase in the probability of the presence for *Cryptococcus gattii* VGI has been observed. Increment values are displayed with different colours. The two pictures show the high increase in all Mediterranean area occurred in the last decade (2010–2019, right panel) compared with the low increase of the previous decade (2000–2009, left panel).

Northern Italy, most of Croatian coasts, the whole Aegean area and Southern Israel with a further 40% increase of the total area of distribution compared with 2010–2019 decade (from 564 585 to 790 671 km²) (Fig. 3A-B).

In addition, an increase of the probability of presence (+20%) was predicted in Southern Portugal, Northern Spain, the whole Italy, Croatian coasts, Greece, South-western Turkey, Southern Israel, and the Mediterranean coasts of Egypt, Libya, Algeria, and Morocco (Fig. 3C).

The same analyses described above were repeated using the E-OBS Copernicus data confirming the trend showed by WorldClim data).

Conclusions

The present study showed that recent climate changes have significantly affected the distribution of the fungal pathogen *C. gattii* VGI in Europe and the Mediterranean area. The analysis revealed a gradual expansion of the fundamental niche of the fungus from 1980 to 2009 and an impressive increase in the last decade (2010–2019) during which the environmental surface suitable for the fungal survival was more than doubled. This trend is in line with the climatic anomalies observed in Europe in the last decade with a decrease in mean precipitations, an increase of mean temperatures and extreme climatic events (Chan *et al.* 2020, Bastos *et al.* 2020). Global warming is also having a high impact on the ecosystems in Europe influencing animals and plants distribution and their life cycles. An increase of cases due to vector-borne diseases like Chikungunya, Zika, Dengue, West Nile and Malaria was observed during the last decade in Southern Europe confirming that climate changes are causing the expansion of the distribution of some species of mosquitoes (Brugueras *et al.*, 2020). Other studies showed that

warmer temperatures have favoured seed production of some plants and the proliferation of tick nymphs increasing the risk of tick-borne diseases (Bregnard *et al.*, 2020). Furthermore, association with temperature and precipitation data and the foodborne disease caused by *Campylobacter* suggested a change in the transmission route different from food, with future scenarios predicting a high increment of cases (Kuhn *et al.*, 2020).

Cryptococcus gattii VGI is strictly related to trees and decaying wood which act as a reservoir in nature, this means that a change in the distribution of some tree species, with whose it is known to be associated in the Mediterranean area, such as *Eucalyptus camaldulensis*, *Olea europaea*, *Ceratonia siliqua* and *Pinus halepensis*, could lead to the colonization of new geographical areas by the fungus (Cogliati *et al.*, 2016). A recent study carried out in Italy confirms that starting from 1992, olive tree cultivation areas increased in Northern Italy where climatic conditions have become suitable after recurrent winter droughts and local warming (Salvati *et al.*, 2013). Other authors report a study based on the analysis of biodiversity data recorded over a 40-year period in Europe concluding that vascular plants are more sensitive to temporal changes in taxonomic composition (turnover) in responses to global climatic changes leading to colonization by more tolerant and generalist species and/or invasive taxa (Pilotto *et al.*, 2020).

In the next decade, our model predicted an increase in the area of distribution of *C. gattii* VGI from the coasts of the Mediterranean basin towards the more internal sub-continental areas. However, the increase of the distribution area suitable for *C. gattii* VGI survival here predicted could be underestimated due to the ability of some alien species to increase their distributional range (non-stability hypothesis) in the colonized area (Broennimann *et al.*, 2007). This seems to be confirmed by the finding of this fungus in

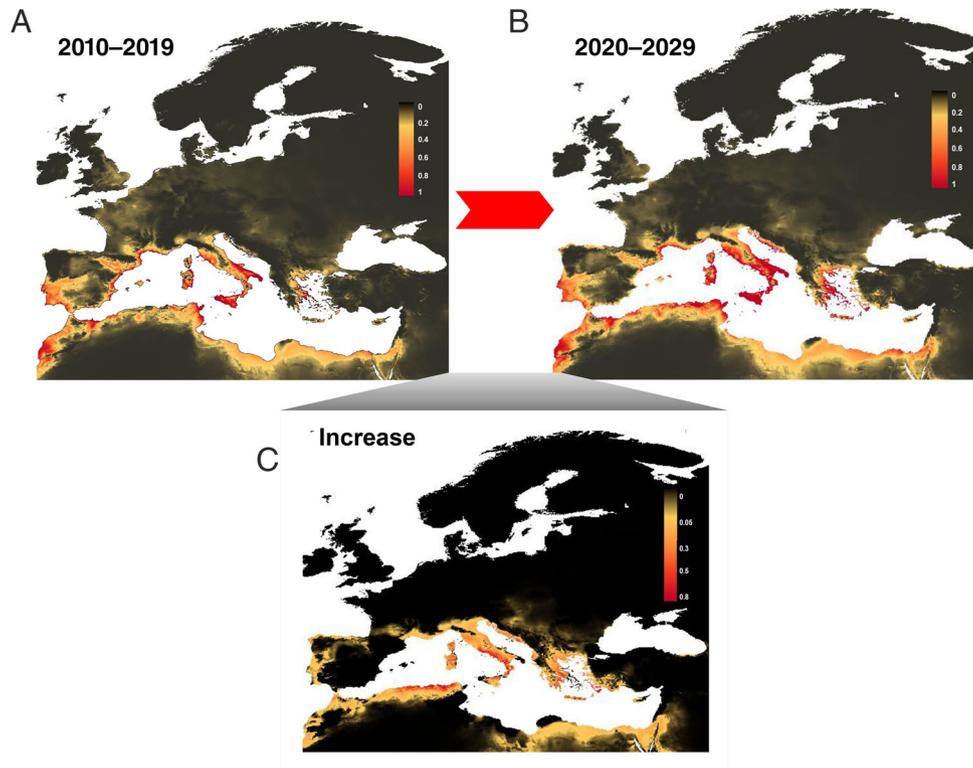


Fig. 3. Maps of species distribution predicting the expansion of fundamental niche for *Cryptococcus gattii* VGI in the next decade (B) compared with the present (A). The map at the lower side (C) shows the geographical areas where an increase in the probability of the presence of the fungus is expected.

Northern Europe outside the predicted area of our model (Chowdhary *et al.*, 2012). However, the high prediction level of our model is confirmed by the distribution of European autochthonous cases caused by *C. gattii* VGI, which were observed in Italy, Greece, Spain, France and Portugal, inside the predicted area of the fundamental niche (Cogliati *et al.*, 2019).

The present analysis is conditioned by the sampling method adopted, which, although extended over more than 400 locations in 18 countries, does not cover the whole geographical area investigated. On the other hand, randomized samplings over all European continent and the Mediterranean basin are difficult to realize due to both the wide extension and the political fragmentation of the territory. Therefore, the results here reported are likely underestimated. In addition, improvement of isolation methods using biomolecular techniques could increase the number of detectable positive samples giving new important insights on the distribution of this fungal pathogen. A further uncertainty linked to our model is the degree of extension of *C. gattii* VGI fundamental niche because it is based on changes in temperature and precipitations values recorded in the last 20 years. The trend of global warming in the next decade will deeply influence the area of distribution of the fungus.

The Mediterranean coasts are geographical areas with a high density of population and therefore an expansion of the distribution of *C. gattii* VGI, associated with an increase of its probability of presence in these areas, corresponds to an increase in the risk of contact with the fungus for more than 137 million persons (Alaniz *et al.*, 2020). On the basis of these predictions, an increase of cases of cryptococcosis due to *C. gattii* VGI is expected in the next decade and a constant monitoring of the epidemiology of this fungal pathogen represents a crucial strategy to detect the onset of future outbreaks. The SCrEEN Project network is moving in this direction promoting the development of a network of clinicians and researchers in the European and the whole Mediterranean area with the aim to record all clinical cases of cryptococcosis, as well as veterinary cases and environmental findings. The network also promotes the conservation and the genotyping of all collected isolates for phylogenesis and population genetics studies to elaborate distribution and prediction maps and to identify high-risk geographical areas. Finally, integration of clinical, veterinary and environmental data with climatic records will better elucidate how global warming is influencing the distribution of this life-threatening fungal pathogen.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1. Area under the curve (AUC) calculated for the distribution model applied to the analyses of the present study.

Table S1. Occurrence data concerning *Cryptococcus gattii* VGI environmental isolates recovered in Europe and the Mediterranean area.

Table S2. Percentage of contribution of the 36 variables used to infer the *Cryptococcus gattii* VGI distribution model