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TROPICAL, TRAVEL AND EMERGING INFECTIONS (LH CHEN AND F NORMAN, SECTION EDITORS)

Updates on Malaria Epidemiology and Prevention Strategies

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Abstract

Purpose of Review The objective of this review was to provide an update on recent malaria epidemiology, both globally and in non-endemic areas, to identify the current distribution and repercussions of genetically diverse Plasmodium species and summarize recently implemented intervention and prevention tools.

Recent Findings Notable changes in malaria epidemiology have occurred in recent years, with an increase in the number of total cases and deaths globally during 2020–2021, in part attributed to the COVID-19 pandemic. The emergence of artemisinin-resistant species in new areas and the expanding distribution of parasites harbouring deletions of the pfhrp2/3 genes have been concerning. New strategies to curb the burden of this infection, such as vaccination, have been implemented in certain endemic areas and their performance is currently being evaluated.

Summary Inadequate control of malaria in endemic regions may have an effect on imported malaria and measures to prevent re-establishment of transmission in malaria-free areas are essential. Enhanced surveillance and investigation of Plasmodium spp. genetic variations will contribute to the successful diagnosis and treatment of malaria in future. Novel strategies for an integrated One Health approach to malaria control should also be strengthened.

Keywords *Plasmodium* spp. · Malaria · COVID-19 · Artemisinin resistance · *Pfhrp*2/3 gene deletion

Introduction

Recent World Health Organization (WHO) data provide insight into the evolving epidemiology of malaria globally. According to the World Malaria Report 2022, the number of total malaria cases increased again in 2021 (to 247 million), although case incidence remained stable following an increase from the preceding year [1••]. Similarly, deaths due to malaria increased in 2020 with respect to 2019, but then declined slightly in 2021. The excess in cases and deaths in these years have been attributed mainly to the disruption to prevention and control strategies attributed to the COVID-19 pandemic.

The epidemiology of imported malaria is also changing. Mirroring the decrease in population movements worldwide during the pandemic due to travel restrictions, the incidence of travel-related infections also decreased [2]. Despite this, several reports during the pandemic years alerted to a possible increase in severe malaria among persons returning from endemic areas and the possible causes are under investigation [3]. Travel is expected to gradually return to pre-pandemic levels so the possible spread of *Plasmodium* spp. following importation into non-endemic areas should continue to be monitored given the reports of competent *Anopheles* spp. expansion into new geographical areas, the appearance of autochthonous malaria cases in regions where malaria never occurred or which had interrupted malaria transmission, and the reporting of several cases of malaria following nosocomial transmission [4].

Genetic variability of *Plasmodium* species worldwide, including the emergence of artemisinin (ART) partially resistant species in new areas and the expanding distribution

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of parasites harbouring deletions of the *pfhrp*2/3 genes which may complicate diagnosis, is a cause for concern. Other factors impacting malaria epidemiology, not only direct human-related elements, should also be considered, such as the effect of climate change on the distribution of arthropod-borne diseases. Malaria may be emerging in temperate regions due to the increase in mobile populations, the deficiencies in public health systems and increased environmental temperatures [5, 6•].

All these interlinking factors contribute to the complexity of malaria dynamics and a profound knowledge of these interplaying aspects is necessary to maintain prevention strategies which may effectively tackle the worldwide malaria burden. The objective of this review was to provide an update on recent malaria epidemiology, both globally and in non-endemic areas, to identify the current distribution and repercussions of genetically diverse *Plasmodium* species and to focus on recent intervention and prevention tools such as vaccine development and implementation and possible benefits of other strategies such as mass drug administration (MDA) [7].

Epidemiology

Global Malaria Epidemiology

The number of total malaria cases globally increased in 2021 (from 245 million in 2020 to 247 million in 2021), with most of the increase occurring in Africa. However, case incidence remained stable from 2020 to 2021 (59 cases per 1000 population at risk) following an increase from 2019 (57 cases/1000 population) [1••]. The increase in 2020 was associated with disruption to prevention and control strategies attributed to the COVID-19 pandemic. Similarly, deaths due to malaria increased in 2020 with respect to 2019 by 10%, but then declined to 619,000 in 2021 [1••]. According to data from the Global Fund's malaria programme, at the start of the pandemic use of insecticide-treated bed nets decreased in certain areas, although home delivery of nets to avoid crowding managed to increase the number of nets distributed overall. However, the number of people with suspected malaria tested decreased by around 4%, with a consequent decline in treatment [8]. Overall, an estimated 63,000 malaria deaths between 2019 and 2021 were attributed to interruption of malaria control strategies in some areas due to COVID-19 [1••].

Trends in Imported Malaria

A meta-analysis of national statistics on imported malaria from 40 non-endemic countries covering data on more than 50,000 individual cases over a 10-year period, performed in pre-pandemic years, identified several favoured routes for importation, with the West Africa region accounting for 56% of all cases [9]. France and the UK were the top receiving countries with an average 4000 malaria cases reported annually. Malaria surveillance data from the USA for 2018 also found a majority of imported cases were acquired in Africa (85%, out of over 1800 cases), and most of these were from West Africa (70% of those acquired in Africa) [10]. *Plasmodium falciparum* accounted for the majority of imported infections overall.

During the 2020–2021 period, as expected, registered cases of imported malaria were lower than for pre-pandemic years, although initial data were not homogeneous and detailed evidence was generally based on small series. The number of imported cases of malaria were higher in 2021 compared to 2020, coinciding with the easing of COVID-related travel restrictions. The European Centre for Disease Prevention and Control (ECDC), registered 2432 confirmed annual malaria cases in the European Union in 2020, and 4780 in 2021, following a peak of 8462 in 2019 (although this figure included over 1700 cases reported from the UK) [11]. Top reporting countries in 2020 and 2021 were France, Germany, Spain and Belgium (see Fig. 1 and Table 1).

As travel increases again, the number of imported malaria cases are rising. Of concern, several recent publications have highlighted an increase in severe malaria cases [3, 4, 12]. A report on malaria among personnel in the French Armed Forces noted an increase in severe cases in 2020 which was not attributed to an increased incidence in the cohort or decreased compliance with chemoprophylaxis [12]. A report from a Spanish national collaborative network also noted a significant increase in cases of severe malaria during 2020–2021 [3]. Another publication on imported *P. falciparum* found that parasitemia, rates of hyperparasitemia and severe malaria were significantly higher following relaxation of COVID-19 restrictions [4]. Although currently under investigation, some of the possible causes identified included delays between disease onset and diagnosis, due to fear of SARS-CoV-2 transmission in overcrowded hospital services, misdiagnosis of febrile illness as COVID-19 (cases of *Plasmodium* spp. and SARS-CoV-2 coinfection have been reported, complicating diagnosis further) and overburdening of laboratories during the pandemic [12–14].

Autochthonous Transmission in Non-Endemic Areas

Introduction or reintroduction and autochthonous transmission of *Plasmodium* spp. in certain geographical areas may alter disease dynamics.

In recent years, several cases of introduced malaria (mosquito-borne transmission from an imported case), airport malaria (due to an imported infected mosquito) and iatrogenic transmission have been noted in non-endemic areas [15, 16]. In the latter cases, parasite whole-genome

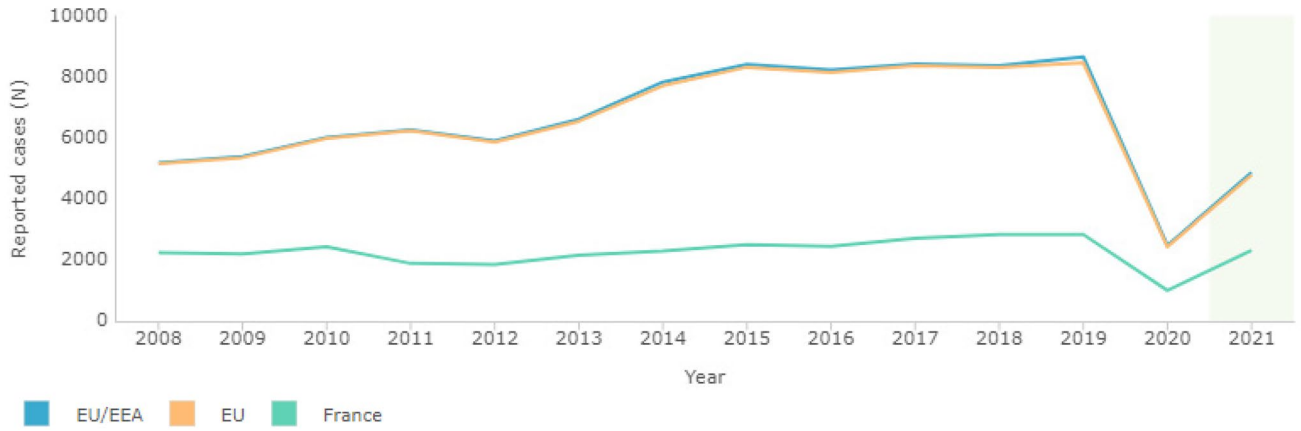

Fig. 1 ECDC. Surveillance Atlas of Infectious Diseases. Yearly reported confirmed cases of imported malaria [11]

and phylogenomic analyses may aid investigation of nosocomial malaria transmission, as demonstrated in a recent retrospective case report [17]. Importation of *P. falciparum* artemisinin-resistant lineages have already been reported in returning travellers highlighting further the relevance of clinical and genotypic surveillance of imported infections which may spread locally if host, environmental and vectorial conditions are favourable [18].

The potential role in transmission dynamics of submicroscopic malaria in recently arrived migrants should also be considered. Several studies have detected submicroscopic malaria in migrants using PCR (polymerase chain reaction), with prevalences of up to 14% in asymptomatic migrants from Sub-Saharan Africa [19]. The more widespread use of molecular techniques to detect *Plasmodium* spp. infections in various settings has contributed to the detection of many infections not diagnosed by conventional microscopy. Although, by definition, these correspond to low-density infections, the potential for transmission exists [20].

Various species of *Anopheles* mosquitoes, such as *A. atroparvus*, inhabit temperate regions of the world and though these may be refractory to African strains of *P. falciparum*, transmission of other *Plasmodium* species such as *P. vivax* may be possible [21, 22]. If other competent *Anopheles* species are introduced and become established in novel geographical areas due to climate changes, the risk of local transmission may be increased. Spread of insecticide-resistant species such as *Anopheles stephensi* in the African region may also challenge control efforts and initiatives have been launched to halt the further spread of this vector which may thrive in urban environments [23].

Table 1 ECDC. Yearly reported confirmed cases of imported malaria in the European Union and top reporting countries, 2019–2021 (adapted from [11])

	2019	2020	2021
EU	8462*	2432	4780
France	2839	1007	2322
Germany	999	366	605
Belgium	417	241	365
Italy	811	181	443
Spain	783	210	430

*Data for UK included until 2019

Plasmodium spp. Genetic Variability

The cornerstone of malaria control is effective and rapid diagnosis and access to appropriate and highly effective treatment. The World Health Organization (WHO) recommends that before treating a patient with malaria symptoms, the presence of the parasite must be confirmed by an appropriate diagnostic method (microscopy or rapid diagnostic test, RDT). Both microscopy and RDT diagnosis should be supported by a quality assurance programme [23]. This avoids clinical or presumptive diagnosis and therefore unnecessary treatment. However, there are currently two major problems in dealing with malaria cases: (a) false-negative RDT results and (b) the growing and worrying presence of antimalarial resistance, both for prevention and treatment.

RDTs and the Presence of False Negatives Due to Deletion in *pfhrp2* and *pfhrp3* Genes

The use, variety and quality of malaria rapid diagnostic tests (RDTs) have increased significantly during the last 10 years and they are currently the preferred field diagnostic test for malaria [24]. The majority of RDTs are based on detecting HRP2 (histidine-rich protein 2), a specific *P. falciparum* protein encoded by the *pfhrp2* gene [25]. Testing using RDTs is a method with high sensitivity and specificity for the diagnosis of malaria; however, its performance has been threatened by the detection of parasites lacking the

pfhrp2 and *pfhrp3* genes [26]. Initially detected in Peru, the presence of deletions in both genes is currently widespread throughout the world, also being detected in Sub-Saharan Africa and Asia [27–29]. The presence of these mutations in Africa has a particularly critical role as the high prevalence of *P. falciparum* malaria in this continent increases the potential consequences of these deletions for malaria control and public health.

A deletion prevalence of 5% for these genes has been defined by the WHO as the minimum prevalence for changing the type of RDT used, as a prevalence higher than 5% could threaten the effectiveness of the test and affect public health guidelines for malaria control [29]. The increasing presence of parasites with deletions is complicating the diagnosis of *P. falciparum* not only in endemic areas, but also in non-endemic countries where migrant patients or travellers with malaria are seen. For this reason, a second confirmatory diagnostic test may be necessary when RDTs are negative. The use of exon 2 of *pfhrp2* and *pfhrp3* to detect deletions (non-amplification of exon 2 being associated with false-negative RDTs) could be performed by semi-nested PCR [30].

Resistance to Antimalarial Drugs

The emergence of drug resistance, particularly among *P. falciparum* parasites, the most prevalent species in the world, has been a major contributor to the global burden of malaria in the past 30 years [31]. Resistance has played a critical role in the recent doubling of malaria-related child deaths in Eastern and Southern Africa [32].

Resistance to Sulfadoxine/Pyrimethamine (SP)

The SP combination was withdrawn as a treatment for malaria years ago due to high resistance. Nowadays, although it is not useful as a treatment option in Africa, it is routinely administered as intermittent preventive treatment (IPT) for malaria, particularly to pregnant women (IPTp) and infants (IPTi, now called Perennial Malaria Chemoprophylaxis) [23].

Resistance to SP has been associated with a single nucleotide polymorphism (SNP) in two different genes, dihydrofolate reductase (*pfdhfr*) and dihydropteroate synthase (*pfdhps*), which encode for the enzymes PfDHFR and PfDHPS respectively, both of which are important in the folate synthesis pathway [33]. Three haplotypes with combinations of SNPs related to SP resistance have been described: partially resistant (quadruple mutant: *pfdhfr* 51I59R/108N + *pfdhps* 437G), IRNG haplotype; fully resistant (quintuple mutant: *pfdhfr* 51I/59R/108N + *pfdhps* 437G/540E), IRNGE haplotype; and super resistant (sextuple mutant: *pfdhfr* 51I/59R/108N + *pfdhps* 437G/540E/581G), IRNGEG haplotype [34, 35].

Artemisinin Combination Therapies (ACTs)

ACTs are the treatment of choice for uncomplicated malaria worldwide. The combination of an artemisinin derivative and an associated treatment with a longer half-life achieves a complete cure of the patient in the majority of cases. However, the recent gains in global malaria control as a result of ACT use are threatened by the emergence of artemisinin resistance in Southeast Asia (SEA) and the spread to other geographical areas [36]. Failure rates associated with specific ACT combinations have led to some provinces changing their first-line therapy to artesunate-pyronaridine combinations (another WHO recommended ACT for uncomplicated malaria) [1••]. Low-level ART resistance has been identified in Africa to date [37]. Ongoing worldwide surveillance is necessary due to the potential public health impact such resistance could have, especially in children under 5 years of age and pregnant women from Africa, as well as in non-immune travellers [37].

ART resistance in the SEA region has been linked to SNPs in the Kelch propeller domain on chromosome 13 (*pfk13*). Markers, validated by WHO, which have been associated with resistance to ART, are F446I, N458Y, M476I, Y493H, R539T, I543T, P553L, R561H, P574L and C580Y [37]. Only mutations C580Y, Y493H, R539T, I543T and N458Y have been detected in parasites with the slow-clearance phenotypic trait [37, 38]. These mutations can be detected by nested PCR, sequencing and sequence analysis using appropriate software [39].

Given the number of malaria-infected migrants and travellers arriving to non-endemic countries, epidemiological surveillance of these infections would be necessary to check for slow clearance, the first step in detecting resistance, or actual resistance. Molecular studies of parasites to determine their genetic profile by PCR and sequencing may be useful to understand the parasite's behaviour in relation to the treatment used. Experts have raised concerns that a three-day treatment may be insufficient to achieve cure and that patients should be followed-up closely beyond the 3-day treatment period [40].

Prevention Strategies

Malaria prevention includes several strategies such as vector control, preventive chemotherapies, mass drug administration (MDA), vaccines and more recently, the use of monoclonal antibodies.

Preventive Chemotherapy

In the past, preventive chemotherapy in moderate to high transmission areas was usually linked to other health interactions;

intermittent preventive treatment of malaria in pregnancy (IPTp) was delivered through antenatal clinics and perennial malaria chemoprophylaxis (PMC), together with expanded immunization programmes (EPI) [23]. A shift towards decentralisation is taking place, seasonal malaria chemoprevention (SMC), recommended for under 5s in areas of moderate to high seasonal transmission, is benefitting from a door to door community-based approach to obtain high coverage [41]. The most recent guidelines are more flexible regarding age of administration and number of cycles required as well as adding several new recommendations [23]. PMC has been expanded to children up to 24 months of age [42]. When the needs of the population at higher risk, under 5s, are covered, intermittent preventive treatment of malaria in school-aged children (IPTsc) can be considered. The latter targets children between 5 and 15 years old, and can be delivered through schools [43]. Finally, post-discharge malaria chemoprevention (PDMC) consists of administering full courses of antimalarials at predetermined intervals to children admitted with severe anaemia in endemic settings to reduce re-admission and mortality, a community-based delivery system is often preferred [44].

MDA

Mass drug administration (MDA) consists of administering a full course of antimalarial drugs to the whole population at the same time and often at repeated intervals. MDA is recommended together with other malaria control strategies to reduce the burden of disease in areas with moderate to high transmission of *P falciparum*, including during emergency settings. Its use is also recommended to reduce transmission in areas with very low to low transmission of *P. falciparum* or *P. vivax* [7, 45].

Several reviews suggest that MDA has a limited impact on prevalence of disease in moderate to high transmission settings and a more important effect on both prevalence and incidence in low transmission settings. This impact is limited in time, lasting from 1 to 3 months, and the strategies should be tailored to the setting and used as part of the overall package of malaria prevention strategies. The need for further research to better ascertain the long term impact of MDA malaria campaigns has been identified [7, 46–48].

The effect on malaria prevalence in areas of moderate to high transmission seems to be greater in emergency settings when access to healthcare facilities is limited. During the recent Ebola epidemic in West Africa, MDA administration reduced malaria morbidity but moreover reduced the number of febrile cases presenting to a weakened health system and reducing the risk of nosocomial transmission of Ebola [49, 50].

Vaccines

Two malaria vaccines, RTS,S/AS01 and R21/MM, are currently available.

RTS,S/AS01 is a recombinant protein based on repeat T epitopes from an antigen on the surface of the *P. falciparum* sporozoite, S antigen, derived from the hepatitis B surface antigen (HBsAg) and AS01, a proprietary adjuvant [51–54].

In a phase III trial, the RTS,S/AS01 vaccine demonstrated vaccine-induced partial protection against clinical malaria in children between 5 to 17 months old receiving 3 doses plus a booster, with added benefit when a booster was administered at 20 months. Vaccine efficacy was 36% (95% CI 32–40) [55]. The effect of the vaccine wanes with time with a reduction in one of the trials for children ages 5 to 17 months who had received three doses of RTS,S/AS01 from 44% (95% CI 16–62) to zero efficacy at years 1 and 4 of follow-up [52].

Since 2019, a pilot vaccine implementation programme has been ongoing in areas of Ghana, Kenya and Malawi [56]. Based on the initial results from this initiative, RTS,S was approved by WHO in 2021 and recommended in the 2022 guidelines for children at risk in areas of moderate to high transmission of *P. falciparum* in Sub-Saharan Africa [23, 57, 58•].The implementation of RTS,S in these areas is underway. Similar to other malaria prevention strategy, RTS,S vaccine shows greater efficacy when combined with other interventions such as SMC [59].

The R21/MM vaccine is a virus-like particle based on the circumsporozoite from *P. falciparum* fused to the N terminus HBsAg and M-matrix as a proprietary adjuvant. In a phase II trial, with 3 doses, the vaccine efficacy was 74% (95% CI 63–82%) with low-dose adjuvant MM and 77% (95% CI 67–84%) when combined with high-dose adjuvant MM. The trial was implemented in addition to passive and active case detection, bednet use, SMC and indoor residual spraying [60]. However, there are limited data at this time on durability of protection and this vaccine has not been prequalified yet. Data comparing R21/MM and RTS,S/AS01 use are currently lacking.

There are other vaccines which are currently under investigation, such as a whole attenuated sporozoite vaccine PfSPZ [61], protein-based vaccines targeting other stages of the life cycle (Rh5, Pfs35, Pfs230) [62, 63], as well as DNA- and mRNA-based vaccines [64].

Monoclonal Antibodies

A novel approach to control malaria is the use of monoclonal antibodies (mAbs), and two are currently under development.

L9LS, a mAb targeting the circumsporozoite protein, achieved 88% protection against malaria infection in a small number of healthy individuals in a phase I trial following a single dose [65]. Phase II clinical trials are currently ongoing. CIS43LS is a mAb against *P. falciparum* sporozoites. In a phase II trial, this mAb showed a degree of protection against malaria infection after one dose of 88% (adjusted 95% CI 79–93) [66•].

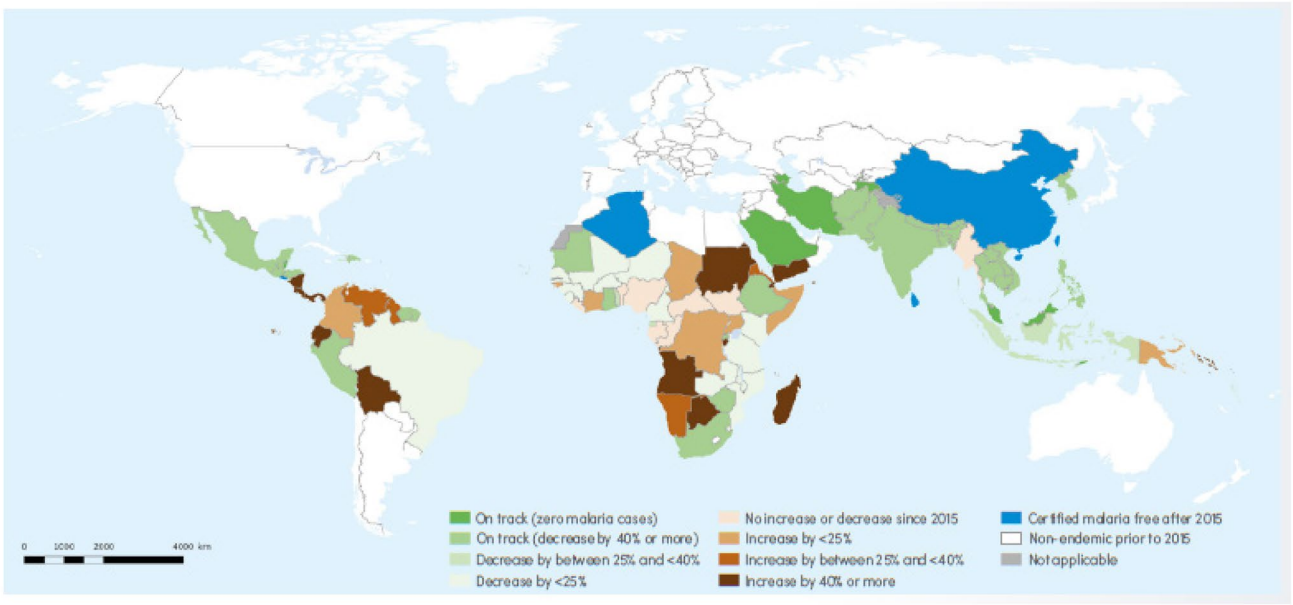

Fig. 2 World Health Organization. Map of malaria endemic countries showing progress towards the GTS (Global Technical Strategy 2016–2030) 2020 malaria case incidence milestone of at least 40% reduction from a 2015 baseline [1]

Further research on the use of mAbs against malaria is needed and should be performed in endemic areas and include at risk groups such as under 5s and pregnant women. The future role of mAbs for malaria prevention will depend on accessibility and the ultimate overall cost of implementation.

Future Perspective

An unexpected pandemic maimed the progress towards the global control of malaria but gradually prevention strategies are regaining impetus to build on the achievements of the last decades. There may be room for some optimism as several endemic countries have shown progress in achieving milestones set in the Global Technical Strategy 2016–2030 (see Fig. 2) [1••]. Control and elimination in endemic regions may have repercussions on the prevalence of imported malaria and measures to prevent re-establishment of transmission in malaria-free areas are also essential. Enhanced surveillance and research of *Plasmodium* spp. genetic variations will contribute to the successful diagnosis and treatment of malaria in future, both in endemic and non-endemic countries.

Although key factors contributing to prevention have been highlighted (vector control strategies, surveillance of *Plasmodium* spp. genetic variability, use of preventive chemotherapy, vaccines and monoclonal antibodies), control of disease will not be achieved if only one aspect is appraised in an isolated manner and in this sense, an integrated One Health approach to malaria control should be considered. Novel strategies such as using insecticide-treated livestock to eliminate zoophagic mosquitos are under investigation (partial zoophagic behavior contributes to maintenance of vector populations even though certain animals are not a natural reservoir for the parasite) [67]. Adaptation of technological advances and social networking to strengthen control may also have a role. Web-based mobile phone apps may reduce the burden of reporting RDT results in low-resource settings and assist with surveillance strategies [68]. Smartphone applications have been used for automated malaria screening of peripheral blood smear images making the process faster and less human dependent [69•]. For international travellers, telemedicine provided through a mobile application may also allow earlier diagnosis and prompt treatment of malaria [70]. A profound knowledge of all interlinking aspects of malaria epidemiology is necessary to maintain prevention strategies which may effectively tackle the worldwide malaria burden.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

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- • Of importance
- •• Of major importance

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