Imported malaria in Switzerland, (1990–2019): A retrospective analysis

Giannone, Bodo ; Hedrich, Nadja ; Schlagenhauf, Patricia

Abstract: BACKGROUND Malaria is a life-threatening, mosquito-borne parasitic disease, caused by Plasmodium spp. It is a major public health issue. Malaria in Switzerland is primarily "imported" by infected international travellers, migrants, and asylum-seekers. METHOD We investigated the epidemiology and characteristics of imported malaria in Switzerland in the period between 1990 and 2019 using data from the Swiss Federal Office of Public Health (BAG). We also obtained traveller statistics from the World Tourism Organization (UNWTO). RESULTS During the last thirty years a total of 8'439 malaria cases and 52 deaths were reported in Switzerland. The main origin of infection was West Africa, followed by Central Africa and East Africa. The profile of malaria in migrants in Switzerland has changed, reflecting variation in migrant flows. The estimated risk of malaria in travellers sank significantly over the time frame of the study (p < 0.001, 95% CI -0.076 to -0.043). CONCLUSIONS Travel medicine should focus on West Africa, the main source of malaria in Switzerland. Despite most cases and all but one death being caused by Plasmodium falciparum, Plasmodium vivax remains a threat for travellers and is associated with complex prevention and therapy regimens. Public health authorities need to pre-empt the need for malaria screening, prevention and treatment based on the profile of migrant waves from malaria endemic areas including Eritrea and Afghanistan arriving in Europe.

DOI: https://doi.org/10.1016/j.tmaid.2021.102251

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-213932
Journal Article
Published Version

The following work is licensed under a Creative Commons: Attribution 4.0 International (CC BY 4.0) License.

Originally published at:
Giannone, Bodo; Hedrich, Nadja; Schlagenhauf, Patricia (2021). Imported malaria in Switzerland, (1990–2019): A retrospective analysis. Travel Medicine and Infectious Disease, 45:102251.
DOI: https://doi.org/10.1016/j.tmaid.2021.102251
Imported malaria in Switzerland, (1990–2019): A retrospective analysis

Bodo Giannone a, Nadja Hedrich b, Patricia Schlagenhaus a,c,*

a Kantonsspital St.Gallen, Emergency Department, Switzerland
b University of Zürich, Epidemiology, Biostatistics and Prevention Institute, Switzerland
c MilMedBiol Competence Centre, Hirschengraben 84, 8001, Zürich, Switzerland

ABSTRACT

Background: Malaria is a life-threatening, mosquito-borne parasitic disease, caused by Plasmodium spp. It is a major public health issue. Malaria in Switzerland is primarily “imported” by infected international travellers, migrants, and asylum-seekers.

Method: We investigated the epidemiology and characteristics of imported malaria in Switzerland in the period between 1990 and 2019 using data from the Swiss Federal Office of Public Health (BAG). We also obtained traveller statistics from the World Tourism Organization (UNWTO).

Results: During the last thirty years a total of 8,439 malaria cases and 52 deaths were reported in Switzerland. The main origin of infection was West Africa, followed by Central Africa and East Africa. The profile of malaria in migrants in Switzerland has changed, reflecting variation in migrant flows. The estimated risk of malaria in travellers sank significantly over the time frame of the study (p < 0.001, 95% CI -0.076 to –0.043).

Conclusions: Travel medicine should focus on West Africa, the main source of malaria in Switzerland. Despite most cases and all but one death being caused by Plasmodium falciparum, Plasmodium vivax remains a threat for travellers and is associated with complex prevention and therapy regimens. Public health authorities need to pre-empt the need for malaria screening, prevention and treatment based on the profile of migrant waves from malaria endemic areas including Eritrea and Afghanistan arriving in Europe.

1. Introduction

Malaria is a major parasitic disease, caused by Plasmodium spp., and it constitutes a significant public health issue. In 2019, an estimated 229 million cases of malaria occurred worldwide, most occurring on the African continent (215 million, 94% of cases), followed by South-East Asia (6.3 million, 3% of cases), the Eastern Mediterranean Region (5 million), the Western Pacific Region (1.7 million), and the Americas (0.9 million). Europe has been malaria-free since 2015. In 2019, there were an estimated 409,000 deaths from malaria globally, with children under 5 years as the most vulnerable group, accounting for 67% of all malaria deaths worldwide [1].

Several different Plasmodium species cause malaria in humans. Plasmodium falciparum is the most prevalent malaria parasite, accounting for more than 99% of estimated malaria cases in Africa and 97% worldwide in 2019. The other major species, Plasmodium vivax, accounts for only 3% of malaria cases worldwide and 0.3% in Africa, but for 23.3% in the Eastern Mediterranean Region, 33.9% in the Western Pacific Region, 51.7% in South-East Asia, and 72.3% in the Americas [1].

Even though malaria is not locally transmitted in Switzerland [2], it can be “imported” to non-endemic countries by infected international travellers, migrants [3–5], and asylum-seekers [6]. These individuals acquire malaria in an endemic country and arrive in Switzerland already infected. Ranked by proportional morbidity, malaria together with acute diarrhoea is the top diagnosis concerning significant, travel-associated infections in European travellers [7].

Although most malaria cases in Switzerland are imported, other ways to contract malaria in Switzerland exist, including induced malaria (“Transfusion-Malaria”) [8], introduced malaria (“Airport-Malaria”) [9, 10], and congenital malaria [11], but such cases are rare [3].

Various risk factors such as purpose of travel [7,12,13], region of travel [7,13], and age and sex of the traveller [14] have been identified that influence the individual risk of a traveller contracting malaria.

The objective of the study was to retrospectively review the epidemiology and characteristics of imported malaria in Switzerland between 1990 and 2019 with special attention to the risk factors (sex, region of exposure, reason for travel) and the geographical patterns of different Plasmodium species.

* Corresponding author.
E-mail address: patricia.schlagenhaus@uzh.ch (P. Schlagenhaus).

https://doi.org/10.1016/j.tmaid.2021.102251
Received 22 November 2021; Received in revised form 23 December 2021; Accepted 26 December 2021
Available online 29 December 2021
1477-8939/© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
2. Materials and methods

2.1. Malaria cases

Reporting cases of malaria to the Swiss Federal Office of Public Health (Bundesamt für Gesundheit, BAG) has been mandatory in Switzerland since 1974. Laboratories must declare a positive diagnostic result for \textit{Plasmodium} spp. The reporting form lists the initials of the patients, test methods, test materials, and results. The physician’s report form, which must be sent to the authorities within one week, supplies additional data with information on the patient, clinical findings, and exposition history. Detailed contents of the report form include patient initials, anonymous personal data (date of birth, sex, nationality, country and canton of residence), clinical findings (fever, date of manifestation, date of lab-sampling, outcome), parasitological findings (\textit{Plasmodium} species, parasitaemia), exposition history (area of exposure, duration of exposure, date of departure, pretravel consultation/chemoprophylaxis, congenital malaria, induced malaria, introduced malaria), and since 1994, also the travel risk category (tourist, VFR, business, immigration, other) [15]. The data are periodically analysed in shorter intervals, and published in the weekly bulletin of the Swiss Federal Office of Public Health [16].

The BAG shared data extracted from these anonymised report forms with us. We analysed confirmed malaria cases in Switzerland between 1990 and 2019. If several countries of travel were mentioned in the report form, the one which the reporting clinician considered the most probable source of infection was considered to be the country of acquisition. For better visualization, the countries were grouped into continents and the African continent was further categorized into regions according to the scheme for geographic sub regions used by the United Nations [17], according to which Turkey is counted as a part of Asia [17]. Co-infections containing one or more \textit{Plasmodium} spp. were identified and considered as “mixed” infections.

The database was checked for consistency and missing data. Thereafter, the database was locked and spreadsheets were extracted for analysis with the statistics software “R”. Data was first analysed using descriptive statistics and where appropriate a time-series was done. Statistical tests were considered significant if the p value was <0.05. The statistical analysis was supported by the Department of Biostatistics of the University of Zürich’s Epidemiology and Biostatistics Institute.

2.2. Returning travellers

The World Tourism Organization (UNWTO) provides data concerning outbound tourism for specific countries based on arrivals in destination countries. These data are obtained on the basis of data supplied by each of the destination countries and therefore correspond to arrivals in these countries. The information sources vary from country to country and consist of “arrivals of non-resident tourists at national borders”, ”arrivals of non-resident tourists in hotels and similar establishments”, and ”arrivals of non-resident tourists in all types of accommodation establishment” and are counted by nationality or by country of residence respectively [18]. If for a specific destination country several sources exist, we used the one with the highest number.

We analysed the UNWTO-data concerning outbound international travellers from Switzerland arriving in foreign countries starting from 1995, the first year where they are available for Switzerland. Since to our knowledge no validated differentiation of the total numbers of travellers in tourists, VFR and business travellers exists, we instead aggregated the BAG’s case-categories “Tourist”, “Visiting Friends and Relatives”, and “Business Travellers” as “Travellers”. We used the numbers of outbound international travellers from Switzerland in conjunction with the malaria cases in Switzerland to calculate an estimated risk of malaria in Switzerland for travellers.

Since the UNWTO-data are not complete, some countries are missing completely and for some other countries data does not exist for all years,

Table 1

| Year     | Total (N) | Male (SD) | Female (SD) | Sex | Missing |
|----------|-----------|-----------|-------------|-----|---------|
| 1990–1994 | 34.0 (14.7) | 503 (33.9%) | 957 (64.5%) | Yes | 24 (1.6%) |
| 1995–1999 | 34.0 (14.7) | 503 (33.9%) | 957 (64.5%) | Yes | 24 (1.6%) |
| 2000–2004 | 34.0 (14.7) | 503 (33.9%) | 957 (64.5%) | Yes | 24 (1.6%) |
| 2005–2009 | 34.0 (14.7) | 503 (33.9%) | 957 (64.5%) | Yes | 24 (1.6%) |
| 2010–2014 | 34.0 (14.7) | 503 (33.9%) | 957 (64.5%) | Yes | 24 (1.6%) |
| 2015–2019 | 34.0 (14.7) | 503 (33.9%) | 957 (64.5%) | Yes | 24 (1.6%) |
to calculate the risk we matched the UNWTO- and BAG-database to include only malaria data for countries and years for which the number of travellers was available, and to include only numbers of travellers for countries and years in which malaria cases were recorded. After matching the UNWTO- and BAG-databases we were able to include a total of 2,134 malaria cases into the database to calculate the risk of contracting malaria.

Considering the absence of a control group, and no clear exposure variable, we chose a regression to further investigate the risk for travellers contracting malaria. Since the outcome, malaria cases per 100,000 travellers, is continuous, a linear regression was the preferred analysis method for the dataset, with the explanatory variables being region of travel and year. Since only one case of malaria was identified in the travellers to Europe this group was chosen as the reference group. Unfortunately, the number of travellers to Europe was about 20 times higher than the second largest group and about two magnitudes higher than the number of travellers to the regions with the most malaria cases, and some countries had very small numbers of travellers, resulting in some outliers. Quantile-quantile plots were used to determine normal distribution of the data. Due in part to the outliers, a very right skewed density was visualised, suggesting the need to log transform the outcome. The logarithm transformed risks showed a near to normal distribution and were therefore used in the linear regression model.

2.3. Ethical approval and ethical conduct of the study

We have investigated the necessity of ethical clearance with the local bureau of the Swiss Ethics Committees on research involving humans (Kantonale Ethikkommission Zürich). Their conclusion was that ethical clearance is not necessary for this study.

3. Results

3.1. General overview

During the thirty years between 1990 and 2019 a total of 8,439 malaria cases were registered in Switzerland, of which 5,280 (62.6%) occurred in males and 3,179 (36.4%) in females (Table 1). The mean age was 34.4 years with a standard deviation of 15.7. Median was 33 years with a minimum of 0 years and a maximum of 91 years. The percentage of missing data ranged between 11.6% for Plasmodium species to 28.9% for "reason for travel". Major inconsistencies were identified in the data concerning atypical transmission of malaria.

In the beginning of the study’s time frame between 1990 and 1994 the typical patient importing malaria to Switzerland was young (mean age 18.9 years) and female (53.3%). Since then, older people (mean age 36.7 years) and males (56.4%) have been more affected. From 1996 onwards, the age distribution has become more even between males and females (Fig. 1). The proportion of male imported malaria cases has increased steadily from 31.6% in 1996 to 55.0% in 2019, while the proportion of female cases has decreased from 68.4% in 1996 to 45.0% in 2019 (Fig. 2).

| Region of Exposure | Plasmodium species | P. falciparum | P. vivax | P. ovale | P. malariae | Unknown/other | Total |
|--------------------|--------------------|--------------|----------|----------|-------------|--------------|-------|
| Europe             | 6 (0.1%)           | 3 (0.1%)     | 1 (0.1%) | 0 (0%)   | 0 (0%)      | 0 (0%)       | 10 (0.1%) |
| North Africa       | 10 (0.2%)          | 12 (0.8%)    | 4 (1.3%) | 0 (0%)   | 0 (0%)      | 0 (0%)       | 26 (0.3%) |
| East Africa        | 760 (14.9%)        | 504 (32.4%)  | 62 (19.7%)| 48 (15.4%)| 31 (10.4%)  | 41 (13.8%)   | 1,486 (17.6%)|
| Central Africa     | 1,387 (27.0%)      | 837 (17.5%)  | 62 (14.3%)| 48 (10.9%)| 31 (6.8%)   | 41 (9.0%)    | 2,100 (9.8%)|
| Southern Africa    | 2,013 (43.5%)      | 970 (23.6%)  | 137 (3.4%)| 101 (25.1%)| 57 (14.4%)  | 18 (4.4%)    | 3,110 (13.0%)|
| Africa (N/S)       | 44 (0.9%)          | 8 (0.2%)     | 1 (0.2%) | 0 (0%)   | 0 (0%)      | 0 (0%)       | 57 (0.7%)  |
| Americas           | 39 (0.8%)          | 116 (29.7%)  | 5 (1.6%) | 4 (1.2%) | 8 (2.1%)    | 13 (3.3%)    | 194 (2.3%) |
| Asia               | 134 (2.6%)         | 306 (67.5%)  | 13 (2.8%)| 6 (1.2%) | 14 (2.9%)   | 14 (3.0%)    | 493 (5.8%) |
| Oceania            | 4 (0.1%)           | 38 (9.5%)    | 5 (1.2%) | 0 (0%)   | 1 (0.2%)    | 0 (0%)       | 48 (0.6%)  |
| unknown            | 2 (0.0%)           | 0 (0%)       | 0 (0%)   | 0 (0%)   | 0 (0%)      | 0 (0%)       | 2 (0.0%)   |
| Missing            | 677 (13.3%)        | 384 (24.7%)  | 65 (10.0%)| 43 (6.4%)| 77 (11.6%)  | 47 (7.0%)    | 1,999 (23.6%)|

Fig. 1. Cumulative malaria cases in Switzerland 1990–2019 in relation to Plasmodium species.

Table 2. Malaria cases in Switzerland 1990–2019 – relation between Region of Exposure and Plasmodium species.
31.3 years) and male (64.5%) and the typical patient who died because of malaria was middle-aged (mean 41.5 years) and male (66.7%). Over time the mean ages increased but the sex ratio remained roughly the same. Only in the last five-year block did the sex ratio change. In 2014–2019 the typical patient was still young (mean 35.7 years) and male (61.6%), but the typical patient who died because of malaria in Switzerland was older middle-aged (mean 49.5 years) and equally male (50%) or female (50%). The total number of malaria cases in Switzerland did not change significantly over the time frame of the study (p = 0.96, 95% CI -2.85 to 3.01).

3.2. Plasmodium species

Of all the malaria cases in Switzerland, 5′102 (60.5%) were caused by *P. falciparum* and 1′554 cases (18.4%) were caused by *P. vivax* (Table 2). We observed an increase in cases caused by *P. vivax* in the years 2014–2017 (Fig. 2).

3.3. Region of exposure

The region with the highest number of acquisitions of malaria imported to Switzerland was West Africa with a total of 2′395 cases (28.4%), followed by Central Africa with 1710 cases (20.3%), East Africa with 1′486 cases (17.6%) and Asia with 493 cases (5.8%) (Table 3). We observed an increase in cases coming from East Africa in the years 2014–2017, mostly from Eritrea. The single country with the highest number of imported malaria cases to Switzerland was Cameroon (1181 cases) (Fig. 3).

3.4. Reason for travel

During the time frame of the study 1′602 malaria cases in tourists (19.0%) have been reported, 1′917 in travellers ”visiting friends and relatives” (VFR) (22.7%), 820 in business travellers (9.7%), 977 in migrants (11.6%), 567 in others (6.7%), and in 118 cases (1.4%) the reason for travel was unknown. We also observed an increase of cases in migrants between 2014 and 2017 (Fig. 4). Over the time frame of the study the total number of cases per year did not change significantly (p = 0.96, 95% CI -2.85 to 3.01), but the number of yearly cases in tourists sank significantly (p < 0.001, 95% CI -3.60 to −1.21), while the cases in VFR (p < 0.001, 95% CI 2.67 to 4.99) and migrants (p = 0.01, 95% CI 0.830 to 4.99) rose significantly. The numbers of cases in business travellers did not show a significant change (p = 0.76, 95% CI -0.638 to 0.472).

3.5. Malaria related deaths

Over the time frame of the study a total of 52 deaths were reported (0–4 deaths per year), of which 34 (65.4%) were male and 18 (34.6%) were female. The mean age was 45.4 years with a standard deviation of 15.8.

Using the total numbers of cases and deaths we were able to calculate the case fatality rate (CFR) over the time frame of the study, which overall was 0.62%. 49 of the deaths (94.2%, CFR 0.96%) were caused by an infection with *P. falciparum*, one death (1.9%, CFR 0.06%) was caused by *P. vivax*, one death (1.9%, CFR 0.73%) was caused by an unknown species and for one death (1.9%, CFR 0.10%) there was no data. 2 deaths are documented for people who supposedly were infected with malaria in Europe (3.8%, CFR 20%), East Africa accounts for 12 deaths (23.1%, CFR 0.81%), Central Africa for 10 deaths (19.2%, CFR 0.58%), West Africa for 16 deaths (30.8%, CFR 0.67%), Africa (no country specified) for 1 death (1.9%, CFR 1.75%), the Americas for 1 death (1.9%, CFR 0.55%) and for 10 deaths no data concerning the region of exposure was available (19.2%, CFR 0.50%). The total case fatality rate per year sank significantly (p = 0.01, 95% CI -0.035 to −0.005) over the time frame of the study (Fig. 5), while the yearly case fatality rate in the subgroups did not change significantly (tourists: p = 0.54, 95% CI -0.087 to 0.047; VFR: p = 0.32, 95% CI -0.016 to 0.048; business travellers: p = 0.88, 95% CI -0.038 to 0.044).

The largest number of deaths in the entire period of the study was noted in tourists with 22 (42.3%, CFR 1.37%), followed by VFR with 9 deaths (17.3%, CFR 0.47%). Most notably, in the group of migrants no death was noted (Fig. 6). The mean age of the fatalities increased from 41.5 years (SD 16.0) in 1990–1994 to 49.5 years (SD 18.8) in 2015–2019.

The mean age of the fatal malaria cases was higher than the mean-age of all malaria-cases, 45.4 years (SD 15.8) vs. 34.4 years (SD 15.7)
Table 3

| Region of Exposure | 1990–1994 | 1995 | 1999–2000 | 2004–2005 | 2009–2010 | 2014–2015 |
|-------------------|-----------|------|-----------|-----------|-----------|-----------|
| Europe            | 10 (0.1%) | 26 (0.3%) | 1868 (17.6%) | 70 (0.7%) | 41 (0.4%) | 3 (0.0%) |
| East Africa       | 64 (4.3%) | 309 (21.3%) | 470 (24.6%) | 267 (17.1%) | 40 (2.5%) | 2 (0.1%) |
| Central Africa    | 52 (3.5%) | 271 (18.0%) | 327 (23.6%) | 235 (23.1%) | 40 (3.3%) | 3 (0.2%) |
| West Africa       | 77 (5.2%) | 486 (31.2%) | 446 (32.2%) | 437 (31.9%) | 37 (2.9%) | 10 (0.7%) |
| Africa (N/S)      | 2 (0.1%)  | 13 (0.8%)  | 22 (1.6%)  | 16 (1.2%)  | 6 (0.5%)  | 2 (0.1%)  |
| Americas          | 5 (0.3%)  | 35 (2.4%)  | 40 (2.9%)  | 40 (2.8%)  | 14 (1.2%) | 3 (0.2%)  |
| Asia              | 50 (3.4%) | 183 (11.7%) | 95 (6.9%)  | 70 (6.9%)  | 46 (4.0%) | 5 (0.4%)  |
| Oceania           | 3 (0.2%)  | 14 (0.9%)  | 16 (1.2%)  | 10 (1.0%)  | 3 (0.3%)  | 2 (0.1%)  |
| unknown           | 0 (0%)    | 0 (0%)     | 0 (0%)     | 2 (0.2%)   | 0 (0%)    | 0 (0%)    |
| Total             | 1484 (14.9%) | 1560 (15.3%) | 1386 (10.0%) | 1018 (6.9%) | 1837 (14.1%) | 1837 (14.1%) |

3.6. Increase of malaria cases in 2014

In the year 2014 we observed a marked increase of malaria cases. Differentiating the number of cases according to the reason for travel we found out that the rise was primarily caused by rising numbers of malaria cases in migrants (Fig. 7). Upon analysing the malaria cases in Switzerland in relation to the region of exposure specifically in migrants it became obvious that in the time frame 2014 to 2018 there is a peak of cases in migrants coming from East Africa. Upon further analysis of the countries of exposure, we found out that Eritrea, which is the fifth most relevant country of exposure over the whole study period (363 cases), jumped from sixth place in 2013 (9 cases) to first place in 2014 (104 cases) and 2015 (140 cases), then to second place in 2016 (42 cases) and 2017 (35 cases), and back down to eighth place in 2018 (9 cases). These data indicate that the rise in malaria cases overall and specifically in migrants are mainly caused by an increase in imported malaria in migrants from East Africa, specifically Eritrea. When differentiating the cases at the same time frame according to Plasmodium species it became clear that the increase in the total malaria cases is primarily due to an increase in P. vivax numbers in 2014, slowly decreasing until normalizing around the year 2019.

3.7. Atypical transmission of malaria

According to the data from BAG ten cases have contracted malaria in Europe, but three of them had recently travelled outside Europe (Madagascar, Kenya, India). The remaining seven cases supposedly were infected in France, Italy, San Marino, Spain, and Switzerland (three cases). Two of the cases infected in Switzerland died from atypical malaria transmission and are well documented [8,10]. From the remaining five cases three were infected with P. falciparum, and one each has been infected with P. vivax and P. ovale respectively. Two deaths were documented for people who supposedly were infected with malaria in Europe, in conjunction with 10 cases (0.2%) leading to a CFR of 20% for Europe.

The two cases of death were both Swiss males living in Switzerland without history for travel outside Switzerland. They were both infected with P. falciparum in 1996 and 1999, respectively. One patient was a 54-year-old male living near the Geneva airport dying from “Introduced Malaria” after being bitten by an infected mosquito that had been brought by plane from an endemic zone [10]. The other patient was a 70-year-old male dying from “Induced Malaria” after having been operated for aortic aneurysm and coronary artery disease, necessitating transfusion of large amounts of blood. Retrospectively one of the blood donors was positive for falciparum-malaria [8].

One probable case of “Congenital Malaria”, positive Plasmodium spp. findings in a neonate during perinatal age without possibility of post-partum infection by a mosquito bite [11], could be identified but had recent travel history to Ghana. Several other possible cases were not of neonatal age and therefore may have been misclassified.

3.8. Risk of contracting malaria

The number of international travellers from Switzerland arriving in foreign countries was constantly increasing in the time frame of observation from 13.4 million travellers from Switzerland per year in 1995–1999 to 32.1 million in 2015–2019. The estimated risk of malaria in Switzerland for travellers (tourists/VFR/business travellers) sank significantly over the time frame of observation of the study (linear regression coefficient -0.060, p < 0.001, 95% CI -0.076 to -0.043).

Compared to Europe the risk of contracting malaria was higher in all other regions. It was highest in Central Africa, followed by West Africa and East Africa (Fig. 8). The single country with the highest risk to contract malaria for travellers from Switzerland was Sierra Leone with...
In this analysis of 30 years we found out that the main region from where malaria is imported to Switzerland is West Africa followed by Central Africa and East Africa, cases are mainly found in males, and the estimated risk of malaria in travellers and the total case fatality rate per year are sinking. The large time-frame of 30 years allowed us to investigate the change in the pattern of malaria over a relevant time, including the period of the European Refugee Crisis. This enabled us to identify observations as snapshots and to different them from the overall trend.

Sinking malaria cases in tourists returning to Switzerland despite increasing numbers of international travellers from Switzerland arriving in foreign countries may be connected to decreasing global malaria incidence rates, since malaria case incidence rates have decreased by 28% globally from 2000 to 2019 [1]. The sinking number of cases in tourists could alternatively suggest a rising awareness of the risk of malaria infection in tourists. As was discussed before, all travellers to endemic areas should receive professional pre-travel advice [19], which has the potential to reduce the severity of malaria associated morbidity [7]. Patients lacking a pre-travel encounter are more likely to become infected with malaria [13]. People could also be relying more on
specialized Travel clinics instead of their general practitioners, who might be struggling to keep their knowledge up-to-date [20]. We have not been able to further investigate this relationship, as information concerning pre-travel consultations was only available for a limited time period.

A possible explanation for the rising malaria cases in Switzerland in VFR could be due to them underestimating the risk of infection and rarely taking any chemoprophylaxis, making them a high-risk group for malaria infections [21]. Another possible explanation for the rise in VFR, especially after 2014, is a connection to the “European refugee crisis” between 2015 and 2017. With a higher number of migrants becoming residents and visiting their friends and relatives in their respective countries of origin, a higher number of them returning to Switzerland as VFR infected with malaria seems possible.

In the year 2019 46.4% of the malaria cases in Switzerland were in VFR and 13.3% were in tourists. In the UK, instead 84% of the malaria cases were in VFR and only 7% were in tourists. 87% of the travellers from the UK had not taken chemoprophylaxis [22]. While there is no data available concerning chemoprophylaxis in travellers from Switzerland, it remains unclear whether chemoprophylaxis might be causative for the difference. Another possible explanation is a different composition of the migrant population living in the UK compared to Switzerland. Relevant malaria prevention strategies include pre-travel
consultation and malaria chemoprophylaxis, but the existing data did not provide consistent information allowing us to investigate the relation between pre-travel consultation, use of chemoprophylaxis, and malaria cases or outcomes. Other inconsistency in the data include the specific place of acquisition (e.g. province of the respective country) and the duration of travel. These circumstances created challenges to statistical analysis and are most probably caused by the long timeframe of the study, during which the report forms changed several times. Similar obstacles could be prevented in the future by further clarification of the report forms and inclusion of mandatory fields in a digitalized reporting system.

Most of the reported deaths were caused by *P. falciparum*. The increasing age of the death-cases over the time frame of the study may be caused by a change in the tourist demographics, including more and elderly people travelling to remote places and putting themselves at risk of a malaria infection. Reassuringly, the number of deaths is sinking over the time frame of the study, indicating a rising awareness of malaria in the travellers and travel medicine practitioners, possibly increased use of chemoprophylaxis in high-risk areas, and awareness of malaria risk in returning travellers which is crucial for correct and timely diagnosis and treatment.

Despite rising numbers of cases in travellers, the sinking case fatality rate implies a rising awareness concerning imported malaria if not in the prevention, then at least in diagnosis and treatment. Despite VFR
showed a relevant proportion of malaria cases (88%) in 2015 are estimated to have occurred in Africa. In almost all sub-Saharan African countries, and there is evidence of rights situation is cause for concern. The observed increase in malaria cases in Switzerland during this time might be further increased by a higher suspicion of malaria.

*P. falciparum* and *P. vivax* are the primary causes of malaria in humans, the main species causing malaria infection in Switzerland is *P. falciparum*. This finding is consistent with Africa being the main continent on which the imported malaria originates, as *P. falciparum* is the most prevalent malaria parasite in Africa, accounting for more than 99% of estimated malaria cases in 2019. *P. vivax* instead is rarer in sub-Saharan Africa, globally the highest proportion of the *P. vivax* burden is in South-East Asia instead. Our own data in contrast showed a relevant proportion of *P. vivax* cases imported from East Africa.

Data from returning travellers suggests a low endemicity of *P. vivax* in almost all sub-Saharan African countries, and there is evidence of *P. vivax* from 18 countries, including all countries of the “Horn of Africa”, containing Eritrea. The areas of higher endemicity of *P. vivax* in Africa were shown to be Northeast Africa and Madagascar.

In the year 2014 we observed an increase of malaria cases attributed to an increasing number of migrants from Eritrea infected with *P. vivax*. 2014 also was the beginning of the “European refugee crisis”, and between 2015 and 2017 the European Union (EU) underwent a major crisis. According to the United Nations High Commissioner for Refugees (UNHCR), in 2014 Eritrea was part of the five top source countries of asylum seekers, together submitting 45% of all asylum applications recorded among all industrialized countries. The number of Eritrean asylum claims more than doubled compared to a year earlier.

Eritrea, which is situated in north-eastern Africa, is one of the areas with the highest endemicity of *P. vivax* in Africa. Since most of the malaria cases (88%) in 2015 are estimated to have occurred in Eritrea, we interpret the increase in refugees from Eritrea, infected with *P. vivax*, during the European refugee crises as the most likely source of the observed increase in malaria cases in Switzerland during this time period.

Eritrea is one of the poorest countries of the world and its human rights situation is cause for concern. Since the border conflict between Eritrea and Ethiopia in 1998–2000, all Eritreans are obliged to perform a timely unlimited national service without prospect of release, with conditions comparable to forced labour. Deserters face arbitrary punishment. The Swiss asylum policy concerning deserters from Eritrea changed at the end of 2005, granting them asylum as a rule. Following this, Switzerland became one of the most important destination countries for Eritrean refugees due to the large existing diaspora. The applications for asylum of Eritrean nationals started rising relatively in 2006 and then more than tripled between 2013 and 2015 to almost 10 000 per year. In 2016 the asylum policy changed again, granting asylum only to people who deserted the national service and not to individuals who left the country before being recruited. This excluded all minors and individuals who had already completed national service. From 2016 the applications for asylum of Eritrean nationals started sinking again to reach about the same level as 2013 in 2019.

A similar situation was observed in Germany in the years 2014/2015 where a distinct increase in the malaria case numbers was noted compared to the preceding years. In the same timeframe likewise an obvious species-shift in favour of *P. vivax* became notable. Afterwards the number of cases remained constant. In contrast the United Kingdom did not observe a relevant increase in malaria case numbers in this timeframe. The total number of malaria cases reported in the UK each year between 2010 and 2019 instead fluctuated around a mean which was lower than the mean for the previous 10 years. Most notably the number of *P. vivax* cases kept sinking after 2011, indicating that the UK did not experience a similar immigration from Eritrea as Switzerland and most probably Germany.

The European Refugee Crisis induced a rise in *P. vivax*-malaria in Switzerland due to migrants from Eritrea. Other waves of migrants might be arriving in Switzerland, probably from Afghanistan, where *P. vivax* is the main species. Afghanistan together with Pakistan is responsible that about one quarter of the malaria cases in the eastern Mediterranean region are infected with *P. vivax*.

A major obstacle in the treatment of *P. vivax*-malaria is the fact that it is able to persist in the liver as a hypnozoite able to relapse after months. The main treatment for hypnozoites is Primaquine, which is hard to procure in Switzerland and many European countries. A new possibility of treatment can be Tafenoquine which has recently been introduced in Europe.
approved in the United States and Australia and may soon be available in Europe.

Although sustainable malaria transmission in central Europe still seems to be unlikely [9], the malaria vector, *Anopheles* spp., especially *A. atroparvus* is present in southern Europe and the Mediterranean region and could as a result of rising temperature spread northwards and possibly extend the area and season of malaria transmission. Imported malaria cases from endemic areas could contribute to an increased infectious parasite reservoir [36] and therefore promote the risk to establishing endemic malaria transmission with *P. vivax* in Switzerland.

All fatal malaria cases diagnosed in Switzerland and acquired in Europe could be identified as atypical transmission of malaria instead of travel-associated malaria. This leads to the conclusion that the high case fatality rate of 20% does not reflect the actual risk for travellers to die from malaria while travelling to Europe.

In contrast none of the patients that the data claimed to have atypical malaria transmission really qualified for this category and instead were most probably infected while travelling to a malaria risk area. This limitation of the data prevented us from further investigating atypical transmission of malaria.

Despite the huge increase in the total number of outbound international travellers from Switzerland, the increase in the number of travellers to malaria free regions (Europe) or to malaria low-risk regions (Americas, Asia, Oceania) was higher than the increase of travellers to malaria high-risk regions (Africa). In addition, the global malaria case incidence rates were decreasing, and there may be a higher awareness of the malaria risk in tourists, and better availability of effective malaria-chemoprophylaxis. These circumstances can explain that despite the huge increase in the total number of outbound international travellers from Switzerland the number of malaria cases did not change significantly and therefore the risk of malaria for travellers from Switzerland sank significantly.

The World Tourism Organization’s (UNWTO) data concerning outbound tourism of specific countries are based on arrivals in destination countries and are therefore subject to variable quality and availability, some countries are missing completely and for some other countries data does not exist for all years. Despite this limitation, the major advantage is the availability of the data for a long timeframe, since 1995 in the case of Switzerland. Because of the limitations mentioned, the data has to be interpreted in relative terms instead of absolute terms.

The reporting forms of the Swiss Federal Office of Public Health (BAG) are typically filled by physicians who are not necessarily specialists in the field of malaria. This seems to be a limitation of the data source, as we encountered several misclassifications especially concerning atypical transmission of malaria. However, the errors in atypical transmitted malaria classification stopped in 2006, indicating a change in the reporting forms. To date the report forms still mention the categories congenital-, induced-, and introduced malaria but clearly indicate that these options are only valid for individuals who did not visit a malaria endemic area prior to infection [15].

5. Conclusions

The malaria risk for travellers from Switzerland and the CFR for malaria in Switzerland sank significantly over the timeframe of the study, which is mainly due to large increase in numbers of travellers to countries with no high risk of malaria transmission as well as to a rising awareness of the malaria risk in tourists, and better availability of effective malaria-chemoprophylaxis. The main geographic origin of malaria in Switzerland is Africa, more specifically West Africa, therefore travel medicine should focus its efforts on this region. Fatal cases were associated with *P. falciparum* in all but one case, and were exclusively found in travellers (tourists, VFR, business travellers), indicating a higher suspicion of malaria as well as a residual semi-immunity in migrants. Future waves of migrants might be from Afghanistan where *P. vivax* is the main species. In course of the climate change an increased infectious parasite reservoir could facilitate establishment of endemic malaria transmission with *P. vivax* in Switzerland. Furthermore, the travel trend in the time following the Covid 19 pandemic possibly could change towards a higher proportion of VFR which could increase the numbers of malaria cases. Raising awareness in clinicians and preparedness for malaria in travellers and migrants as well as awareness in public health authorities can help to reduce morbidity and mortality of malaria in Switzerland by implementing mitigation strategies.

Inconsistency in the data have been observed which could be prevented in the future by clarification of the report forms and inclusion of mandatory fields in a digitalized reporting system.

**Funding**

No involvement of funding in this paper.

**CRediT authorship contribution statement**

**Bodo Giannone:** Data Collation, Analyses, Interpretation of analyses, writing and revisions.

**Nachda Hedrich:** Statistics, Interpretation of analyses, writing and revisions.

**Patricia Schlagenhauf:** Concept, Study design, Interpretation of analyses, writing and revisions.

**Declaration of competing interest**

None.

**Acknowledgements**

Prof. Dr. Ulrike Held (University of Zürich, Epidemiology, Biostatistics and Prevention Institute, Department of Biostatistics) supported the initial statistical analyses. Thank you to Dr. Catherine Bourquin (Swiss Federal Office of Public Health) and Nicole Gysin (formerly Swiss Federal Office of Public Health) who provided access to the BAG data. Prof. Dr. Schlagenhauf is supported in part by MilMedBiol, a collaboration between the University of Zürich and the Swiss Armed Forces.

**References**

[1] World Health Organization. World Malaria Report: 20 years of global progress and challenges. WHO/HTM/GM; 2020.

[2] World Health Organization. World malaria report 2019. World Health Organization; 2019.

[3] Christen D, Steffen R, Schlagenhauf P. Deaths caused by malaria in Switzerland sank significantly over the timeframe of the study. Furthermore, the area in Switzerland. Furthermore, the malaria risk for travellers from Switzerland and the CFR for malaria in Switzerland sank significantly over the timeframe of the study, which is mainly due to large increase in numbers of travellers to countries with no high risk of malaria transmission as well as to a rising awareness of the malaria risk in tourists, and better availability of effective malaria-chemoprophylaxis. The main geographic origin of malaria in Switzerland is Africa, more specifically West Africa, therefore travel medicine should focus its efforts on this region. Fatal cases were associated with *P. falciparum* in all but one case, and were exclusively found in travellers (tourists, VFR, business travellers), indicating a higher suspicion of malaria as well as a residual semi-immunity in migrants. Future waves of migrants might be from Afghanistan where *P. vivax* is the main species. In course of the climate change an increased infectious parasite reservoir could facilitate establishment of endemic malaria transmission with *P. vivax* in Switzerland. Furthermore, the travel trend in the time following the Covid 19 pandemic possibly could change towards a higher proportion of VFR which could increase the numbers of malaria cases. Raising awareness in clinicians and preparedness for malaria in travellers and migrants as well as awareness in public health authorities can help to reduce morbidity and mortality of malaria in Switzerland by implementing mitigation strategies.

Inconsistency in the data have been observed which could be prevented in the future by clarification of the report forms and inclusion of mandatory fields in a digitalized reporting system.

**Funding**

No involvement of funding in this paper.

**CRediT authorship contribution statement**

**Bodo Giannone:** Data Collation, Analyses, Interpretation of analyses, writing and revisions.

**Nachda Hedrich:** Statistics, Interpretation of analyses, writing and revisions.

**Patricia Schlagenhauf:** Concept, Study design, Interpretation of analyses, writing and revisions.

**Declaration of competing interest**

None.

**Acknowledgements**

Prof. Dr. Ulrike Held (University of Zürich, Epidemiology, Biostatistics and Prevention Institute, Department of Biostatistics) supported the initial statistical analyses. Thank you to Dr. Catherine Bourquin (Swiss Federal Office of Public Health) and Nicole Gysin (formerly Swiss Federal Office of Public Health) who provided access to the BAG data. Prof. Dr. Schlagenhauf is supported in part by MilMedBiol, a collaboration between the University of Zürich and the Swiss Armed Forces.

**References**

[1] World Health Organization. World Malaria Report: 20 years of global progress and challenges. WHO/HTM/GM; 2020.

[2] World Health Organization. World malaria report 2019. World Health Organization; 2019.

[3] Christen D, Steffen R, Schlagenhauf P. Deaths caused by malaria in Switzerland 1988-2002. Am J Trop Med Hyg 2006;75:1188-94.

[4] D’Acremont V, Landry P, Mueller I, Pecoud A, Genton B. Clinical and laboratory predictors of imported malaria in an outpatient setting: an aid to medical decision making in returning travelers with fever. Am J Trop Med Med Hyg 2002:66:481-6. https://doi.org/10.4269/ajtmh.2002.66.481.

[5] Eperon G, Durieux-Paillard S, Mauris A, Chappuis F, Gysin N. Malaria cases in Switzerland from 2005 to 2015 and recent rise of imported Plasmodium vivax malaria. Swiss Med Wkly 2017;147:w14510. https://doi.org/10.4414/smw.2017.14510.

[6] Schlagenhauf P, Gробус MP, Hamer DT, Angeleht M, Schrenkel M, Eperon G, et al. Area of exposure and treatment challenges of malaria in Eritrean migrants: a GeoSentinel analysis. Malar J 2018;17:443.

[7] Schlagenhauf P, Weld L, Ghoorhuis A, Gaertet P, Weber R, von Sonnenburg F, et al. Travel-associated infection prevention in Europe (2008-12): an analysis of EuroTravNet longitudinal, surveillance data, and evaluation of the effect of the pre-travel consultation. Lancet Infect Dis 2015;15:55-64.

[8] Frey-Wettstein M, Maier A, Markwardt K, Munch U. A case of transfusion transmitted malaria in Switzerland. Swiss Med Wkly 2001;131:320.

[9] Pondofer SG, Jaeger VK, Scholz-Kreidlmayr F, Horn J, Krumkamp R, Kreuels B, et al. Risk estimation for air travel-induced malaria transmission in central Europe - a mathematical modelling study. Trav Med Infect Dis 2020;21:100014. https://doi.org/10.1016/j.tmaid.2020.100014.

[10] World Health Organization. International notes: airport malaria - Switzerland. World Heal Organ Wkly Epidemiol Rep 1996;71:558.

[11] Romani L, Pane S, Severini C, Menegon M, Foglietta G, Bernardi S, et al. Challenging diagnosis of congenital malaria in non-endemic areas. Malar J 2018; 17:470. https://doi.org/10.1186/s12936-018-2614-9.
[12] Bacaner N, Stauffer B, Boulware DR, Walker PF, Keystone JS. Travel medicine considerations for North American immigrants visiting friends and relatives. JAMA 2004;291:2856–64. https://doi.org/10.1001/jama.291.23.2856.

[13] Leder K, Black J, O’Brien D, Greenwood Z, Kain KC, Schwartz E, et al. Malaria in travelers: a review of the GeoSentinel surveillance network. Clin Infect Dis 2004;39:1104–12. https://doi.org/10.1086/424510.

[14] Smith JL, Auala J, Haindongo E, Uusiku P, Gosling R, Kleinschmidt I, et al. Malaria risk in young male travellers but local transmission persists: a case-control study in low transmission Namibia. Malar J 2017;16:70. https://doi.org/10.1186/s12936-017-1718-x.

[15] Bundesamt für Gesundheit. Meldeformulare für meldepflichtige Infektionskrankheiten [n.d.].

[16] Bundesamt für Gesundheit. BAG-Bulletin [n.d.].

[17] United Nations Statistics Division. Geographic regions [n.d.].

[18] Tourism Statistics. Switzerland: country-specific: outbound tourism 1995 - 2019 2020:(1), p.

[19] DeVos E, Dunn N. Malaria prophylaxis. StatPearls 2020. https://www.ncbi.nlm.nih.gov/books/NBK551639/. [Accessed 27 February 2020].

[20] Hatz C, Krause E, Grundmann H. Travel advice: a study among Swiss and German general practitioners. Trop Med Int Health 1997;2:6–12. https://doi.org/10.1046/j.1365-3156.1997.d01-130.x.

[21] Matteelli A, Colombini P, Gulletta M, Castelli F, Carosi G. Epidemiological features and case management practices of imported malaria in northern Italy 1991-1995. Trop Med Int Health 1999;4:653–7. https://doi.org/10.1046/j.1365-3156.1999.00468.x.

[22] Public Health England. Malaria imported into the United Kingdom: 2019 2019:14.

[23] Mischlinger J, Ronberg C, Álvarez-Martínez MJ, Bühler S, Paul M, Schlagenhauf P, et al. Imported Malaria in countries where malaria is not endemic: a comparison of semi-immune and nonimmune travelers. Clin Microbiol Rev 2020;33. https://doi.org/10.1128/CMB.00104-19.

[24] Howes RE, Battle KE, Mendis KN, Smith DL, Cibulskis RE, Baird JK, et al. Global epidemiology of Plasmodium vivax. Am J Trop Med Hyg 2016;95:15–34. https://doi.org/10.4269/ajtmh.16-0141.

[25] Howes RE, Reiner RCJ, Battle KE, Longbottom J, Mappin B, Ordanovich D, et al. Plasmodium vivax transmission in Africa. PLoS Neglected Trop Dis 2015;9:e0004222. https://doi.org/10.1371/journal.pntd.0004222.

[26] Gehring FW, Elzanar IRF, Moyes CL, Smith DL, Battle KE, Guerra CA, et al. A long neglected world malaria map: Plasmodium vivax endemicity in 2010. PLoS Neglected Trop Dis 2012;6:e1814. https://doi.org/10.1371/journal.pntd.0001814.

[27] Stockemer D, Niemann A, Unger D, Speyer J. ‘The refugee crisis’, immigration attitudes, and euroscepticism. Int Migr Rev 2019;54:883–912.

[28] United Nations High Commissioner for Refugees. Asylum trends 2014. United Nations High Commissioner for Refugees; 2015.

[29] World Health Organization. World malaria report 2015. World Health Organisation; 2015.

[30] Eidgenössische Schweizerische, Der Bundesrat. Eritrea: analyse der Situation und Skizzierung mittelfristiger politischer Ansätze. 2016.

[31] Staatssekretariat für Migration. Asylsuchende aus Eritrea [n.d].

[32] Bundesamt für Migration. Asylstatistik 2006 2007.

[33] Staatssekretariat für Migration. Asylgesuche nach Nationen. 2021. 1986 bis 2021.

[34] Robert-Koch-Institut. Infektionsepidemiologisches Jahrbuch meldepflichtiger Krankheiten für 2015; 2015. https://doi.org/10.1016/j.jkhinf.2014.09.017.

[35] Robert-Koch-Institut. Infektionsepidemiologisches Jahrbuch meldepflichtiger Krankheiten für 2020 2020.

[36] Fischer L, Gütekin N, Kaelin MB, Fehr J, Schlagenhauf P. Rising temperature and its impact on receptivity to malaria transmission in Europe: a systematic review. Trav Med Infect Dis 2020;26:101815. https://doi.org/10.1016/j.tmaid.2020.101815.