

Travel-associated infection presenting in Europe (2008–12): an analysis of EuroTravNet longitudinal, surveillance data, and evaluation of the effect of the pre-travel consultation



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Summary

Background Travel is important in the acquisition and dissemination of infection. We aimed to assess European surveillance data for travel-related illness to profile imported infections, track trends, identify risk groups, and assess the usefulness of pre-travel advice.

Methods We analysed travel-associated morbidity in ill travellers presenting at EuroTravNet sites during the 5-year period of 2008–12. We calculated proportionate morbidity per 1000 ill travellers and made comparisons over time and between subgroups. We did 5-year trend analyses (2008–12) by testing differences in proportions between subgroups using Pearson's χ^2 test. We assessed the effect of the pre-travel consultation on infection acquisition and outcome by use of proportionate morbidity ratios.

Findings The top diagnoses in 32 136 patients, ranked by proportionate morbidity, were malaria and acute diarrhoea, both with high proportionate morbidity (>60). Dengue, giardiasis, and insect bites had high proportionate morbidity (>30) as well. 5-year analyses showed increases in vector borne infections with significant peaks in 2010; examples were increased *Plasmodium falciparum* malaria ($\chi^2=37.57$, $p<0.001$); increased dengue fever ($\chi^2=135.9$, $p<0.001$); and a widening geographic range of acquisition of chikungunya fever. The proportionate morbidity of dengue increased from 22 in 2008 to 36 in 2012. Five dengue cases acquired in Europe contributed to this increase. Dermatological diagnoses increased from 851 in 2008 to 1102 in 2012, especially insect bites and animal-related injuries. Respiratory infection trends were dominated by the influenza H1N1 pandemic in 2009. Illness acquired in Europe accounted for 1794 (6%) of all 32 136 cases—mainly, gastrointestinal (634) and respiratory (357) infections. Migration within Europe was associated with more serious infection such as hepatitis C, tuberculosis, hepatitis B, and HIV/AIDS. Pre-travel consultation was associated with significantly lower proportionate morbidity ratios for *P falciparum* malaria and also for acute hepatitis and HIV/AIDS.

Interpretation The pattern of travel-related infections presenting in Europe is complex. Trend analyses can inform on emerging infection threats. Pre-travel consultation is associated with reduced malaria proportionate morbidity ratios and less severe illness. These findings support the importance and effectiveness of pre-travel advice on malaria prevention, but cast doubt on the effectiveness of current strategies to prevent travel-related diarrhoea.

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Introduction

Travel to, from, and within Europe is increasing. With the current projected pace of growth, there will be 1.8 billion tourist arrivals worldwide in 2030.¹ The World Tourist Organisation 2013 report shows that Europe has the largest proportion of inbound travellers (more than 563 million in 2013) and also generates over half the world's 1087 million international arrivals. Travel within Europe accounts for most international journeys. Other geographic areas with strong increased growth in 2013 include Asia (+14%), the Americas (+6%), and Africa (+3%).¹

Migration and immigration shape the infectious disease profile in Europe where the international migrant population stock (defined as the population who was

born abroad) increased from 56.2 million in 2000 to 72.4 million in 2013.² High rates of immigration into Europe lead to a strong demand to visit friends and relatives—often with importation of infections acquired when visiting the country of origin.

Travellers as tourists or occupational travellers will encounter a range of infectious agents at the destination that differ greatly from those of home especially when visiting low income, tropical countries. Travel plays a major role in the globalisation of infection as exemplified by imported cases of Ebola virus disease in Europe and associated local, hospital acquired infection. Travel within Europe also presents infection risks; northern Europeans visiting Mediterranean countries can

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encounter pathogens such as sandfly fever viruses, *Echinococcus* spp, *Leishmania* spp,³ *Rickettsia* spp, and West Nile virus and face possible emerging threats such as Crimean Congo haemorrhagic fever and *Plasmodium vivax* malaria in Greece.⁴ Visitors to northern and central Europe could be exposed to tick-borne encephalitis or Lyme disease.

Furthermore, both the destination and the source countries can be affected by travellers who might introduce a pathogen into a new geographic or ecological niche—for example, the autochthonous transmission of dengue and chikungunya viruses in Europe⁵ where the competent vector *Aedes albopictus* is widely distributed.

Travel medicine is concerned with the prevention and treatment of travel-related disease. This speciality is increasingly comprehensive and encompasses the epidemiology of travel-related infection, the pre-travel consultation with advice on prevention, vaccination, chemoprophylaxis, self-treatment during travel, and treatment of ill returned travellers or the newly arrived migrant or refugee in the context of migration medicine. In Europe, pre-travel, preventive advice follows national guidelines or WHO recommendations. An appraisal and audit of the usefulness and effect of the pre-travel consult has, so far, been insufficient.

EuroTravNet is part of the larger GeoSentinel global network that published worldwide data for travel-related disease from 2007 to 2011.⁶ Here, in this European subset, we assessed travel-associated morbidity presenting at EuroTravNet sites during the 5-year period 2008–12. Although previous papers have documented annual importation of travel-acquired disease in Europe,^{7–10} we aimed here to characterise trends in the European spectrum and risk potential of infectious disease and

with this large dataset, we show a novel evaluation of the impact and usefulness of pre-travel advice regarding certain infections and travellers types.

Methods

Study design and procedures

We analysed travel-associated morbidity in ill travellers presenting at EuroTravNet sites during the 5-year period of 2008–12. The EuroTravNet sites (n=18) constitute a daughter network of GeoSentinel sites in Europe. These are clinics specialising in travel or tropical medicine that contribute clinician-based data for ill travellers. To be eligible for inclusion in the database, the patient must have crossed an international border before presentation and the diagnosis must be considered to be travel-related by the reporting EuroTravNet physician. All confirmed and probable diagnoses are included. Every patient has at least one diagnosis (from a list of 556 possible diagnostic codes). Diagnoses are either based on recognition of a specific causative pathogen or syndrome. Syndromic codes are used when clinical indicators suggest a specific diagnosis without identification of a causative pathogen.

EuroTravNet surveillance data (collated with the GeoSentinel platform) is classified as public health surveillance by the National Center for Emerging and Zoonotic Infectious Disease at the US Centers for Disease Control and Prevention. However, Berlin and Munich required submission to local institutional review boards.

All travellers might be assigned several diagnostic codes and EuroTravNet sites use the best reference diagnostic tests available. Other data captured include demographic information (age, sex, country of birth, country of residence, and country of citizenship), travel history (recent travel and 5-year travel itineraries), reason for travel, and possible area of acquisition of the infection (georeferencing is possible if an exact location is known). Europe is defined according to the UN definition. Information about inpatient or outpatient status, and whether or not a pre-travel consultation took place are also included for each patient. Data (28 data elements) were collated prospectively and entered into a Structured Query Language database.

Only patients with final, confirmed or probable diagnoses are included. For the time trend analyses, we included only the 12 sites that reported continuously during the 5-year period (2008–12). These sites were Amsterdam, Brescia, Cambridge, Geneva, Hamburg, London, Madrid, Marseille, Munich, Oslo, Paris, and Zürich. For the analysis of the effect of a pre-travel encounter, patients whose only travel was for “immigration” and patients with an unknown pre-travel encounter status were excluded.

Statistical analysis

Data were analysed with SPSS (version 16.0). We calculated proportionate morbidity by dividing the

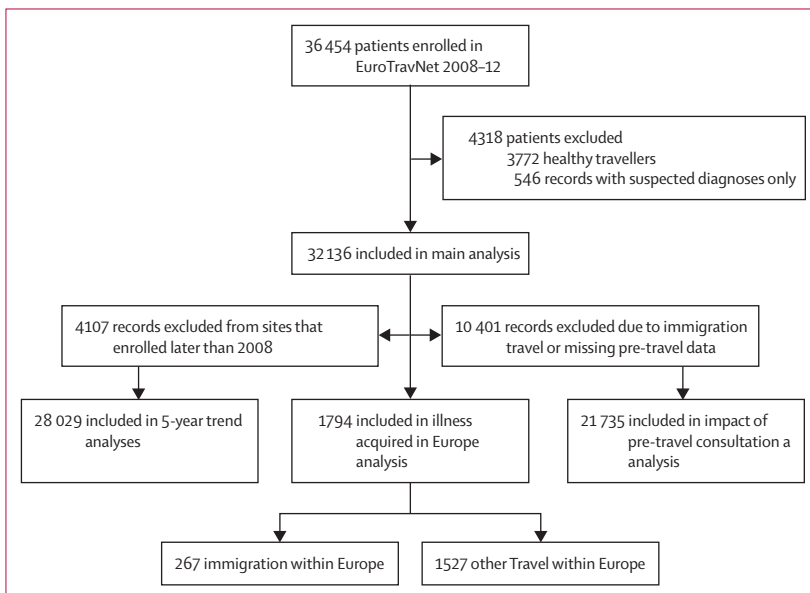


Figure 1: Trial profile

number of cases of a specific diagnosis (or of a group of specific diagnoses within a syndrome group) with all cases of returning ill travellers seen during the same time period (or to subgroups of travellers). The proportionate morbidity is reported per 1000 ill travellers, which allowed us to make comparisons over time and between subgroups. Differences in proportions between subgroups of returning ill travellers seen at EuroTravNet sites were tested using Pearson's χ^2 tests. Comparisons of proportionate morbidity for patients with or without a pre-travel encounter were based on multiple logistic regressions with age and sex as covariates with breakdown by region of exposure and reason for travel where there were more than 100 cases. 95% CIs for proportionate morbidity ratios for patients with a pre-travel encounter were compared with those who had no pre-travel encounter (the reference group). $p < 0.05$ was considered significant. This method of use of proportionate morbidity and Pearson's χ^2 to detect differences in the proportionate morbidity and use of proportionate morbidity ratios to compare exposed and unexposed groups is documented.¹¹

Role of the funding source

The funder was not involved in the current analyses or in the preparation of this report. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

32 136 patients who presented to EuroTravNet clinics during the 5-year period (2008–12) were analysed (figure 1). 16 379 (51%) were men and the median age was 35 years (range 27–48). 10 109 European travellers (32%) acquired illness from sub-Saharan Africa, 4577 (14%) from southeast Asia, 4027 (13%) from south central Asia, and 2540 (8%) from South America. 1794 travellers (6%) presenting to EuroTravNet clinics acquired their illness in Europe (1194 [4%] in western Europe and 600 [2%] in eastern Europe). Most travel was for tourism (51%) or visiting friends or relatives (14%) and 40% of all ill returning travellers reported a pre-travel health consultation. 5-year analysis of EuroTravNet patient demographics showed no significant differences in most demographics (table 1). We noted a statistically significant increase in acquisition of travel-related illness in sub-Saharan Africa and Asia; in immigration travel particularly from Africa; an increasing proportion of ill travellers treated as inpatients; and a slight decrease in the proportion of travellers who have a pre-travel encounter (data not shown).

The top diagnoses of all 32 136 patients reported as proportionate morbidity per 1000 ill travellers are shown in figure 2. Malaria and acute diarrhoea showed the highest proportionate morbidity (>60), with rates of 70.9 (95% CI 68.0–73.7) and 70.1 (67.3–72.9) proportionate morbidity per 1000 ill patients respectively, but dengue, giardiasis, and insect bites were also responsible for high proportionate

morbidity (>30). *Plasmodium falciparum* malaria was mainly acquired in sub-Saharan Africa and *P vivax* malaria in South America and south central Asia. Diarrhoeal illnesses are acquired globally with predominance in south central Asia, particularly India (figure 2).

	N (%)	Significance test
Women	15 757 (49%)	$\chi^2=6.285$, $p=0.179$
Age, years (median, IQR)	35 (26.5–47.5)	..
Reason for travel		$\chi^2=284.3$, $p<0.0001$
Tourism	16 310 (51%)	..
Visiting friends or relatives	4334 (14%)	..
Business	3501 (11%)	..
Missionary, volunteer, researcher, or aid work	3926 (12%)	..
Immigration	3107 (10%)	..
Medical tourism	98 (0%)	..
Military	301 (1%)	..
Student	559 (2%)	..
Clinical setting		$\chi^2=164.7$, $p<0.0001$
Immigration travel only	3107 (10%)	..
Seen during travel	1298 (4%)	..
Seen after travel	27 731 (86%)	..
Live in Europe	30 920 (96%)	$\chi^2=43.82$, $p<0.0001$
Born in Europe	24 625 (77%)	$\chi^2=26.38$, $p<0.0001$
Inpatient	5274 (16%)	..
Pre-travel health encounter		$\chi^2=370.8$, $p<0.0001$
Yes	12 896 (40%)	..
No	9989 (31%)	..
Don't know	9251 (29%)	..
Region of exposure		$\chi^2=1079.0$, $p<0.0001$
Antarctica	2 (0%)	..
Australia/New Zealand	111 (0%)	..
The Caribbean	867 (3%)	..
Central America	704 (2%)	..
Eastern Europe	600 (2%)	..
Middle East	754 (2%)	..
North Africa	1618 (5%)	..
North America	237 (1%)	..
Northeast Asia	381 (1%)	..
Oceania	130 (0%)	..
South America	2540 (8%)	..
South central Asia	4027 (13%)	..
Southeast Asia	4577 (14%)	..
Sub-Saharan Africa	10 109 (32%)	..
Western Europe	1194 (4%)	..
Cannot be ascertained	4285 (13%)	..

Table 1: Demographics of all analysed ill patients (n=32 136) presenting to EuroTravNet sites (2008–12)

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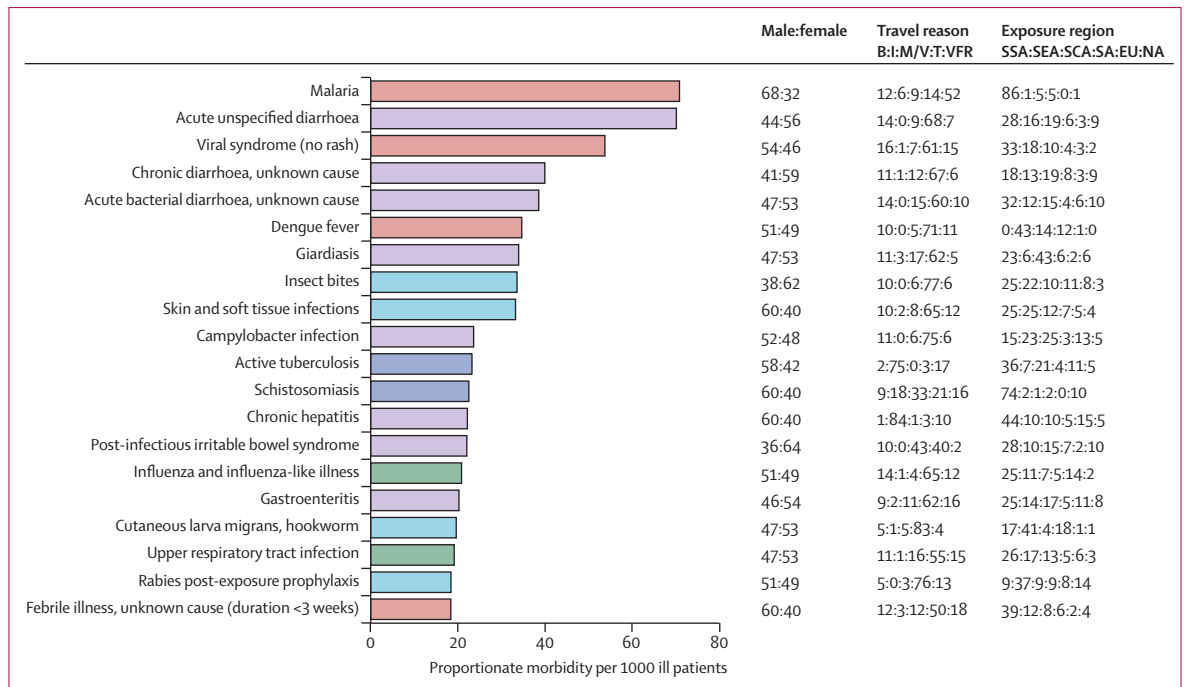


Figure 2: Top diagnoses in all ill travellers presenting to EuroTravNet clinics (N=32 136) in 2008–12

Colours: red bars are febrile illness, purple bars are gastrointestinal tract illness, light blue bars are dermatological illness, green bars are respiratory illness, and dark blue bars are infection attributable to more than one syndromic category. Travel reasons: B=business. I=immigration. M/V=missionary/volunteer. T=tourism. VFR=visiting friends and relatives. Exposure regions: SSA=sub-Saharan Africa. SEA=southeast Asia. SCA=southcentral Asia. SA=South America. EU=Europe. NA=north Africa.

In the timeframe under analysis, we noted a significant peak in vector borne infections with increased *P falciparum* malaria ($\chi^2=37.56$, $p<0.0001$) (figure 3). Proportionate morbidity was 70 in 2010 compared with 45 in 2008 and 49 in 2012. *P falciparum* malaria was acquired mainly in sub-Saharan Africa by men and predominantly by those whose purpose of travel was visiting friends and relatives. The main countries of acquisition of malaria in 2010 (the peak year) were Comoros, Ghana, Côte d'Ivoire, Senegal, and Burkina Faso (figure 3). *P vivax* importation did not significantly differ during the 5-year period (figure 3).

The proportion of imported dengue significantly differed in the 5-year period ($\chi^2=135.9$, $p<0.0001$, with a large peak in 2010 (figure 3). Overall, the proportionate morbidity from dengue increased from 22 in 2008 to 36 in 2012, related to a large increase in imported dengue in 2009 in travellers returning from the Netherlands Antilles, in 2010 increased dengue in French tourists returning from Guadeloupe and Martinique, and in 2012, in German tourists returning from Cambodia and Thailand. Dengue cases acquired in Europe (during the outbreak on the island of Madeira in 2012) also contributed to the 2012 increase in imported dengue. There was also a significant increase in imported chikungunya infection in 2010 (the peak year; $\chi^2=24.87$, $p<0.0001$). Importantly, the areas of acquisition during the 5-years of analysis relate to the widening geographic spread of this virus. In 2008, the cases came from Comoros (n=2), Reunion (n=3), and Sri Lanka (n=2), in 2009, from India (n=3), Maldives (n=4), and

Thailand (n=5), in 2010 from India (n=12), Indonesia (n=6), and Thailand (n=5), in 2011 from India (n=2), Congo (n=1), and Malaysia (n=1), and in 2012 from Indonesia (n=4), and the Philippines (n=1). There was also an increase in leishmaniasis ($\chi^2=19.01$, $p=0.001$; data not shown) from 15 cases (proportionate morbidity 3) in 2008 to 32 cases (proportionate morbidity 5) in 2012. A regional analysis of exposure³ showed increased acquisition in western Europe (data not shown). Five cases of tick-borne encephalitis acquired in Europe were reported as were three cases of West Nile virus (one of which was acquired in Greece).

Trends in diarrhoeal disease showed a declining proportionate morbidity for chronic diarrhoea and an increasing proportionate morbidity for acute diarrhoea (figure 3). *Campylobacter* spp infection increased from 87 cases in 2008 (proportionate morbidity 15) to 128 (proportionate morbidity 23) in 2010 and 100 cases (proportionate morbidity 17) in 2012 ($\chi^2=11.82$; $p=0.19$).

Proportionate morbidity from dermatological diagnoses showed significant increases particularly in insect bites. Animal-related injuries resulting in rabies post-exposure prophylaxis (PEEP) showed an increase in the proportionate morbidity from 11 in 2008 to 23 in 2011 and 20 in 2012. Most cases were in relation to contact with dogs (217 [46%] of 472), followed by non-human primates (85 [18%]), and cats (61 [13%]; data not shown). The highest proportionate morbidity was recorded in travellers from southeast Asia (163 [34%] of 472) followed by north Africa (70 [15%]), sub-Saharan

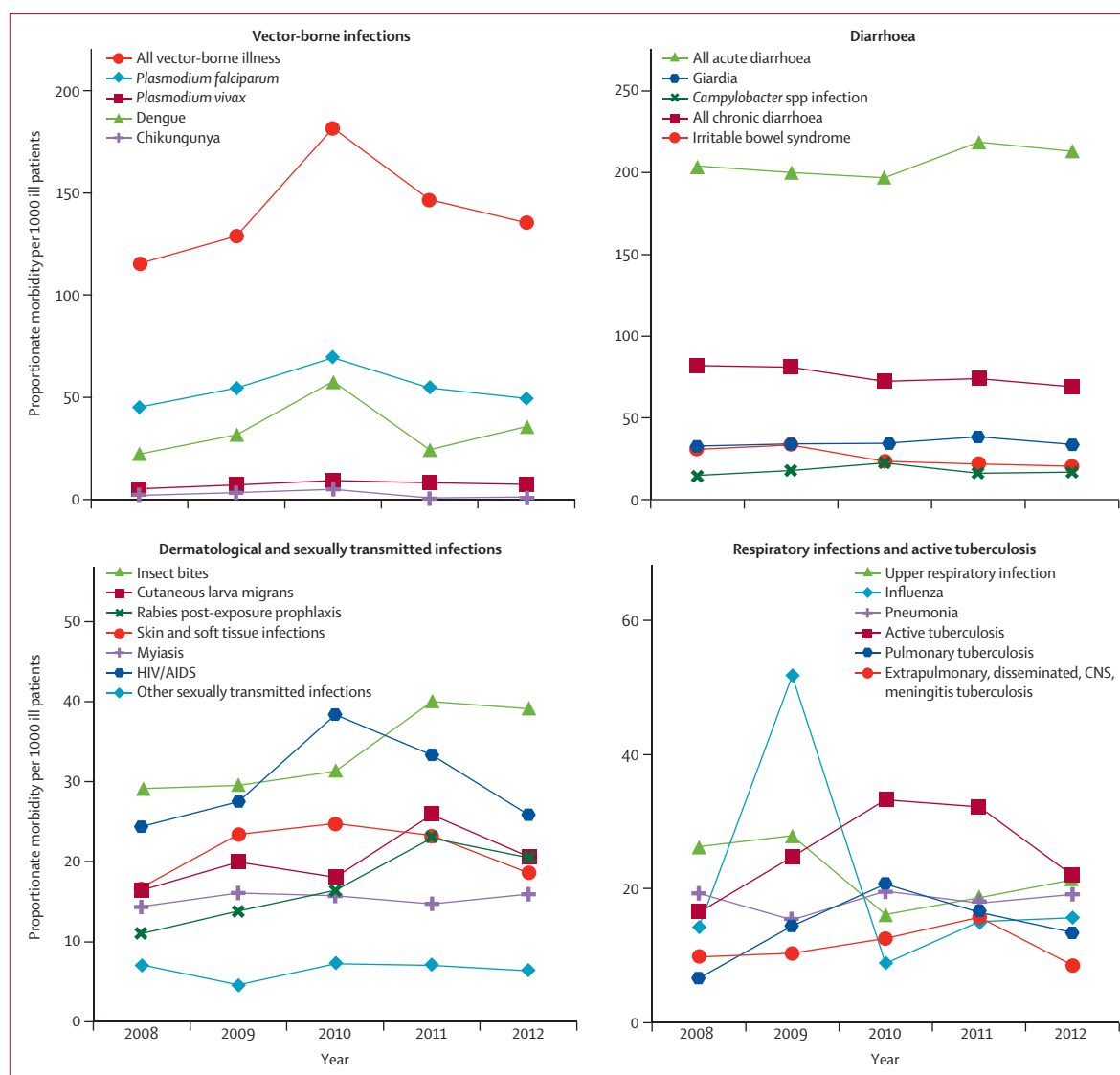


Figure 3: EuroTravNet time trends analysis (2008–12) of selected diagnoses

Africa (47 [10%]), and South America (47 [10%]; data not shown).

Respiratory infection trends were dominated by the influenza H1N1 pandemic in 2009 where cases rose to proportionate morbidity 52 compared with the 5-year average of proportionate morbidity 21 ($\chi^2=321.7$, $p<0.0001$).

The proportionate morbidity for overall active tuberculosis (pulmonary tuberculosis and extrapulmonary tuberculosis combined) varied from 16 for active (seven for pulmonary) in 2008 to a peak in 2010 (33 active, 21 pulmonary) and then declined by 2012 (22 active, 13 pulmonary) since then.

Acute hepatitis showed a continuous decline in proportionate morbidity ($\chi^2=12.41$, $p=0.015$) primarily from decreases in tourists, immigrants, and business travellers (data not shown).

The proportionate morbidities of sexually transmitted infections vary from 32 to 46 with a large proportion of these infections attributed to HIV/AIDS and a peak in 2010 (figure 3).

Illness acquired in Europe accounted for 6% of all cases. Most (1044 [58%] of 1794) travellers were tourists and 45% of exposures were in Spain ($n=351$), Germany ($n=214$), Italy ($n=142$), and Greece ($n=106$). The top ten diagnoses among patients whose travel was not for immigration are shown in figure 4. The main infections acquired in Europe overall were gastrointestinal infections ($n=634$), especially bacterial diarrhoea, followed by respiratory illness ($n=357$), including influenza. 5-year trends showed influenza proportionate morbidity was greater than 200 in 2009, but only 10–27 in other years (not shown). There was a steady increase in

proportionate morbidity for animal bites in Europe requiring rabies post-exposure prophylaxis (from 19 in 2008 to proportionate morbidity 67 in 2012). Of patients with animal bites needed rabies post-exposure prophylaxis, 13 were exposed in Romania.

The top ten diagnoses among patients whose only travel was immigration from within Europe (n=267) were chronic hepatitis C (n=56, proportionate morbidity=210),

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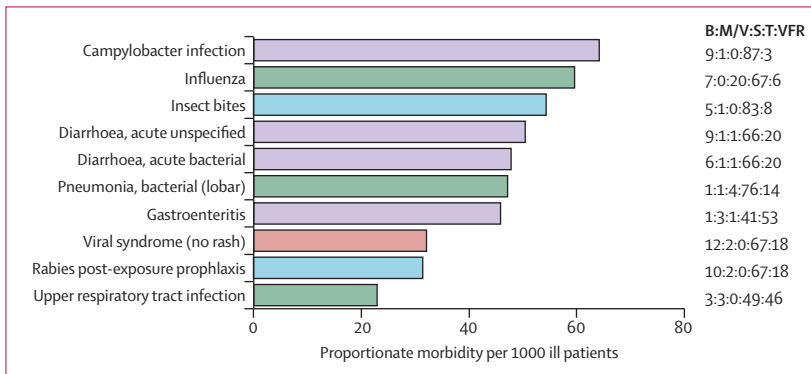


Figure 4: Top diagnoses in ill non-immigrant travellers presenting to EuroTravNet clinics with exposure in Europe (N=1527) for 2008–12

Red bars are febrile illness. Purple bars are gastrointestinal tract illness. Blue bars are dermatological illness. Green bars are respiratory illness. B=business. I=immigration. M/V=missionary/volunteer. T=tourism. VFR=visiting friends and relatives.

pulmonary tuberculosis (n=46, proportionate morbidity=172), positive PPD test (n=28, proportionate morbidity=105), asymptomatic HIV infection (n=27, proportionate morbidity=101), asymptomatic hepatitis B carrier (n=27, proportionate morbidity=101), chronic hepatitis B (n=19, proportionate morbidity=71) hepatic echinococcosis (n=16, proportionate morbidity=60), AIDS (n=15, proportionate morbidity=56), newly diagnosed, asymptomatic HIV (n=13, proportionate morbidity=49) and multidrug resistant or extensively drug-resistant tuberculosis (n=12, proportionate morbidity=45; appendix p 1).

225 (83%) of 267 immigrant patients were originally from eastern Europe. The principal countries of birth were Russia (18%), Romania (17%), and Poland (12%). The number of immigrant patients increased in the 5-year period and the countries of origin changed from year to year. Immigrants from Lithuania accounted for 8% of European immigrants in 2011 and 1% in 2012. Chronic hepatitis was primarily seen in immigrants from Poland, Russia, Romania, and Lithuania. HIV/AIDS cases are primarily in immigrants from Poland, Russia, Romania, and Latvia. Tuberculosis presented predominantly in immigrants from Romania and Russia.

Patients who had a pre-travel consultation had proportionately less malaria, acute hepatitis, HIV/AIDS,

	Total (n)	Cases (n)	Proportionate morbidity per 1000	PMR (95% CI)	Men (n)	Cases (n)	Proportionate morbidity per 1000	PMR (95% CI)	Women (n)	Cases (n)	proportionate morbidity per 1000	PMR (95% CI)
Malaria												
No	8865	1064	120.02	Ref	4888	152	31.10	Ref	3973	123	30.96	Ref
Yes	12 870	683	53.07	0.44 (0.403-0.485)	6007	81	13.48	0.434 (0.332-0.566)	6852	93	13.57	0.438 (0.336-0.572)
Plasmodium falciparum malaria												
No	8865	906	102.20	Ref	4888	614	125.61	Ref	3973	292	73.50	Ref
Yes	12 870	410	31.86	0.31 (0.278-0.349)	6007	265	44.12	0.351 (0.306-0.404)	6852	145	21.16	0.288 (0.237-0.350)
Acute hepatitis												
No	8865	75	8.46	Ref	4888	50	10.23	Ref	3973	25	6.29	Ref
Yes	12 870	35	2.72	0.32 (0.215-0.480)	6007	20	3.33	0.325 (0.194-0.546)	6852	15	2.19	0.348 (0.184-0.659)
HIV/AIDS												
No	8865	126	14.21	Ref	4888	92	18.82	Ref	3973	34	8.56	Ref
Yes	12 870	42	3.26	0.23 (0.162-0.325)	6007	32	5.33	0.283 (0.190-0.422)	6852	10	1.46	0.171 (0.084-0.345)
Animal bites needing post-exposure prophylaxis												
No	8865	250	28.20	Ref	4888	152	31.10	Ref	3973	123	30.96	Ref
Yes	12 870	160	12.43	0.44 (0.362-0.537)	6007	81	13.48	0.434 (0.332-0.566)	6852	93	13.57	0.438 (0.336-0.572)
Acute diarrhoea												
No	8865	1880	212.07	Ref	4888	982	200.90	Ref	3973	895	225.27	Ref
Yes	12 870	3620	281.27	1.33 (1.26-1.39)	6007	1523	253.54	1.262 (1.18-1.36)	6852	2093	305.46	1.356 (1.27-1.45)

PMR=proportionate morbidity ratio. No=no pre-travel advice. Yes=pre-travel advice received. Ref=reference value for the groups with no pre-travel advice.

Table 2: Effect of pre-travel consultation on proportionate morbidity and proportionate morbidity ratios of specific diagnoses overall and by sex

and animal bites needing post-exposure prophylaxis than patients who had no pre-travel encounter (table 2). The most significant decrease in proportionate morbidity was with *P falciparum* malaria. Those ill travellers who had received pre-travel advice were proportionately less likely to acquire malaria and less likely to have severe illness (less likely to be inpatients) than those without a pre-travel consultation. These results held for both men and women, for all traveller types (appendix p 2), including those visiting friends and relatives and for travellers specifically to sub-Saharan Africa and south central Asia. Only 923 (21%) of the 4334 visiting friends and relatives group had pre-travel advice, compared with 7448 (46%) of the 16310 tourists. There were also decreases in the proportionate morbidity overall for acute hepatitis, HIV/AIDS, and animal bites needing rabies post-exposure prophylaxis. Conversely pre-travel consultation was associated with a higher proportionate morbidity for diarrhoea (table 2).

During the 5-year period, 11 deaths were reported; eight (73%) were men, median age was 54 years (IQR 34.5–62.0), seven (64%) were tourists, three (27%) were immigrants, and one (9%) was a missionary or volunteer. Three (27%) were exposed in western Europe and two (18%) in the Caribbean, two (18%) in eastern Europe, two (18%) in southeast Asia, and two (18%) in sub-Saharan Africa (appendix p 3).

Discussion

The surveillance of travel-associated illness in Europe is important for many reasons. First, it allows for the documentation and evaluation of the spectrum and risk potential of infectious disease related to human mobility. Second, it captures the potential of travellers as sentinels for infection transmission. Last, it serves to inform public health authorities on cross-border infection trends and threats. The profile of infection in ill travellers presenting in Europe differs somewhat from that of the global profile of travellers presenting post-travel to GeoSentinel clinics,^{6,12} highlighting the destination range of European travellers with a greater proportion of travel to Africa for visiting friends or relatives and complex migration patterns within Europe.

Our analyses show 5-year infection trends in European travellers and confirm that travel-related illness relates to local and global disease trends with some exceptions. For example, we noted a rise in imported mosquito-borne infections that mirrored the increased transmission of dengue fever (figure 3), particularly in 2010, which is also shown in regional and national reports.^{13–15} We also noted a significant change in imported chikungunya infection with new areas of acquisition including many European overseas countries and territories, such as la Réunion (French overseas department),¹⁶ suggest the widening geographic spread of this virus. Improvements in diagnostic procedures and rapid tests might have contributed to the observed increased numbers of dengue diagnoses. Although global trends suggest reduced

transmission of malaria, especially in Africa,¹⁷ our data, by contrast, show an increase in imported malaria, which could be attributed to the European immigration trends: a large proportion of migrants and travellers visiting family and friends who presented to EuroTravNet sites (25% of all travellers) came from highly endemic areas for malaria in sub-Saharan Africa (including Ghana 5%, Somalia 3%, Cameroon 4%, Nigeria 4%, Ethiopia 2%, and Eritrea 1%). The immigration pattern from Africa to Europe is multidimensional and is affected by turmoil in the country of origin and regional upheavals. The resulting non-continuous linear changes in countries of origin and thus in exposures makes examination of trends over time very complicated.

With regard to illness associated with travel within Europe, substantial differences were related to the type of traveller. The main infections acquired in Europe by patients who had not travelled for immigration were bacterial diarrhoea followed by respiratory illness including influenza. Migration within Europe has a different profile of infection (appendix p 1). Tuberculosis is a dominant infection associated with immigration within Europe. 68 cases of active tuberculosis were diagnosed during the 5 years of this analysis in travellers developed in eastern Europe. Tuberculosis ranks prominently in the the top 10 diagnoses of infections acquired in Europe. From the high proportion of extra-pulmonary tuberculosis, it is assumed that a substantial proportion of tuberculosis episodes could have evolved in (earlier HIV-infected) HIV-positive individuals, but our data do not allow verification of this hypothesis. Immunosuppressant therapy, particularly with anti-TNF drugs,¹⁸ microenvironmental circumstances (such as exposure to patients with tuberculosis during clinical work abroad^{19,20}); and direct exposure to fellow travellers with pulmonary tuberculosis²¹ enhance the mean risk of exposure, infection, and subsequent disease. However, the latency period of tuberculosis varies widely; to that end, it cannot be deduced from the post-travel or post-immigration diagnosis that infection occurred during the temporally related travel episode preceding the diagnosis. The most commonly imported infections in the European immigrant populations were chronic hepatitis and tuberculosis. Because both hepatitis C and tuberculosis are easily transmittable diseases, clinicians should have a high index of suspicion in this population to timely diagnose patients, link them to care, and prevent further transmission.

Our analysis shows a low but constant burden of sexually transmitted infections in ill travellers presenting in Europe where the proportionate morbidities from sexually transmitted infections vary from 32 per 1000 to 46 per 1000 travellers with a large proportion of these infections attributed to HIV/AIDS (figure 3). The main factors associated with travel-related acquisition of sexually transmitted infections are male sex, immigration travel, visiting friends and relatives, and business travel—

Panel: Research in context**Systematic review**

We searched Medline using the title/abstract terms “travel” and “infection”, and “pre-travel advice” for studies published between Jan 1, 1990, and July 31, 2014, with no language restrictions. Several papers focused on single infections in travellers,^{31–34} or on travellers with specific medical disorders,^{35,36} or on travellers returning from a specific region.^{37,38} One review focused on the need for surveillance of travel-associated infection to improve the evidence base for pre-travel advice.³⁹ A more recent paper on surveillance data for imported illness in Europe during 2011 did not assess the effect of pre-travel advice.⁷ A systematic review examined the effect of pre-travel advice on risky sexual behaviour abroad, but did not find a clinical study on the effect of a standard pre-travel sexually transmitted infection discussion.⁴⁰

We did not find any studies assessing the usefulness of pre-travel advice with respect to a broad range of travel-related infections and specific risk groups. We searched national travel medicine websites for information about evidence that pre-travel advice affects imported infection, but did not find any scientific evidence establishing the value of pre-travel consultation.

Interpretation

Our large study shows the profile of travel-related infections imported into Europe during 5 years, identifies trends and risk groups and evaluates, for the first time to our knowledge, the effect of pre-travel advice on the proportionate morbidity of infections. The changing spectrum of illness presenting in Europe relates to the areas of acquisition of infection, migration trends, and purpose of travel. The results of the trend analyses show that surveillance of infection in travellers is useful to inform on cross-border changes and infectious disease threats especially mosquito-borne infection. Pre-travel consultation results in reduced proportionate morbidity for several infections, particularly malaria. These findings support the importance and effectiveness of pre-travel malaria prevention strategies. However, pre-travel advice does not seem to be useful in the prevention of travellers' diarrhoea.

such factors corroborate a large cross-sectional study of the GeoSentinel database.²² Travel related, sexually transmitted diseases are probably under-represented in tropical-disease units; individuals with self-recognised risk exposures or characteristic genitourinary symptoms might seek care in other settings.

The number of presentations related to arthropod bites showed a significant increase ($p < 0.0001$). Animal-related injuries requiring PEEP are also common among travellers seen at EuroTravNet clinics. However, this finding is most probably an underestimate because only 13 (72%) of 18 EuroTravNet clinics reported rabies PEEP. The incidence of rabies PEEP among travellers has been estimated at 0.4% per month of stay, according to a meta-analysis of more than 1 270 000 individuals²³ making rabies exposure one of the most frequent health threats that international travellers might encounter. We noted a small but significant rise in the proportion of travellers requiring rabies PEP, which might relate to the overall trend toward increased proportions of international arrivals in countries with emerging and developing economies, particularly in Asia and Africa—continents in which many countries have endemic rabies, which parallel a recent increase of rabies cases among

travellers.²⁴ Most travellers with animal bites were exposed in tropical areas, but animal bites also occurred frequently during travel in Europe, in areas where rabies remains endemic such as in Eastern Europe (Romania) and in some areas of recent reintroduction such as Italy²⁵ and Greece.²⁶

In our 5-year analysis of European surveillance data, we assessed the effect of pre-travel consultation (tables 2, 3) and reported that patients with pre-travel advice were diagnosed with proportionately significantly less malaria than those patients who did not have pre-travel advice. This finding was also valid for men who had pre-travel advice showing that protective measures can mitigate the gender bias in travellers' malaria. Previous research has shown that men are likely to acquire arthropod-borne infections and less likely to have pre-travel advice than women.²⁷ Reduced malaria proportionate morbidity after pre-travel advice was shown for all traveller groups, including those visiting friends or relatives, tourists, business and volunteer travellers, and across regions of travel. These comparisons are restricted by insufficient data for travellers who received pre-travel consultation and who did not become ill. However, the consistent pattern of travellers with pre-travel consultations being diagnosed less often with malaria than the ill-travellers who did not have a pre-travel encounter, even when region of exposure, sex, and purpose of travel are controlled for, suggests strong support for pre-travel interventions. In particular, these data suggest that anti-malaria interventions will be effective in high-risk groups such as those visiting friends or relatives in sub-Saharan Africa, who most frequently import malaria. This group is least likely to have a pre-travel consultation. Thus, we speculate that effective interventions, such as malaria chemoprophylaxis, should be recommended for those attending pre-travel consultations.

Conversely, morbidity from diarrhoea including acute diarrhoea, chronic diarrhoea, *Giardia* spp infection, and *Campylobacter* spp infection increased as a proportion of morbidity in the group with pre-travel advice. The proportionate morbidity ratios for acute diarrhoea in south central Asia was 1.51 showing the failure of the pre-travel consultation in the prevention of travellers' diarrhoea. An earlier study also showed that pre-travel consultation was associated with increased rates of travellers' diarrhoea.²⁸ This seemingly paradoxical effect is difficult to explain and might simply be a result of surveillance data being limited to patients who sought medical care. However, travellers with pre-travel advice could be more likely to visit higher-risk destinations. Furthermore, there are no proven effective interventions to prevent travellers' diarrhoea. Prevention can be discussed in the pre-travel consultation and advice given on food, water, and personal hygiene, but no effective vaccine or preventive medication is available. A recent assessment of a patch vaccine containing heat-labile toxin from *Escherichia coli* against travellers' diarrhoea

showed that this intervention did not protect travellers.²⁹ Some protection against travellers' diarrhoea is conferred by an older, oral cholera vaccine, but this is rarely recommended and is not registered for this indication.³⁰ The current advice pre-travel is that the traveller should practice hygiene and carry an antimotility medication such as loperamide. For some travellers, carriage of antibiotics is recommended, but the palette of effective antibiotics is geographically restricted because of the spread of resistance, which might also contribute to the increased travellers' diarrhoea proportionate morbidity in returning travellers despite pre-travel advice. This situation of no effective intervention is a major deficit in travel medicine because diarrhoeal illness is the most common illness in travellers. These findings suggest that travel medicine needs constant audit to identify areas of strength and weakness (panel).

The limitations of travel illness surveillance by EuroTravNet are manifold; only patients presenting to specialised clinics are included, whereas healthy returning travellers and those who present to primary care are missed. Because of the absence of denominator data, the absolute risk of an illness or infection cannot be determined. Further, because these data are anonymised surveillance data, adjustments cannot be made for clusters of patients who had travelled together. Because clinics have joined the network since 2008, the 5-year trend analysis could only be done on a subset of 12 of the 18 clinics. Without complete data, whether any biases were introduced cannot be determined, although all 12 of the clinics were very heterogeneous and only one new site country was added. Furthermore, some changes in traveller demographics could have affected the trends. Despite these limitations, our analysis is a robust evaluation of more than 32 000 ill travellers presenting during a 5-year period at major reference centres throughout Europe who were assessed with best quality reference diagnostic tests, and thus our results are useful to show changes in patterns of morbidity caused by travel related infectious disease.

The demographics of travellers presenting to EuroTravNet sites are changing, reflecting increased immigration travel, increased acquisition of illness in Asia and sub-Saharan Africa, increased proportion of inpatient treatment, and a slight decrease in the proportion of those seeking pre-travel advice. The profile of travel-related infections is multidimensional and varies according to the area of acquisition of infection and the traveller type. Trend analyses are useful to inform public health authorities on cross-border infection threats and generally do reflect global trends—except for imported *P falciparum* malaria, for which we noted an increase in cases imported in Europe compared with reduced numbers in endemic areas. Pre-travel advice is associated with reduced proportionate morbidity for several infections. The most significant decrease in proportionate morbidity and

absolute numbers of cases was seen for *P falciparum* malaria in all traveller types. Decreases in the proportionate morbidity ratios overall for acute hepatitis, HIV/AIDS, and animal bites needing rabies PEEP were also noted. By contrast, pre-travel consultation was associated with an increased proportionate morbidity for diarrhoea. Surveillance data provide a powerful approach to identify threats of infectious diseases and can be used to identify areas of strength and weakness in pre-travel advice.

Contributors

PS together with MG, AG, PP, and LW co-conceived and designed the study. PS was involved in data analysis and interpretation with LW, MG, AG, PP, and PG. PS drafted the first version of the report, did the literature search with LW, MG, AG, PP, and PG, and prepared the final paper for submission. All authors contributed data, participated in interpretation of the analyses and reviewed and approved the final report.

Declaration of interests

We declare no competing interests. In the past 3 years, PS has received research funding and honoraria from F Hoffmann-La Roche and travel and speaker honoraria from Sigma Tau.

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