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Imported dengue in Spain: a nationwide analysis with predictive time series analyses

Lidia Redondo-Bravo MD [1], Claudia Ruiz-Huerta MD [2], Diana Gomez-Barroso PhD [3,4], María José Sierra-Moros MD [5], Agustín Benito PhD [6,7], Zaida Herrador PhD [6,7,*]

[1]Servicio de Medicina Preventiva, Hospital Universitario la Paz, Madrid, Spain [2]Servicio de Medicina Preventiva, Hospital Universitario de la Cruz Roja, Madrid, Spain [3]Centro Nacional de Epidemiología, Instituto de Salud Carlos III (ISCIII in Spanish), Madrid, Spain [4]Consorcio de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain [5]Centro de Coordinación de Alertas y Emergencias Sanitarias, Dirección General de Salud Pública, Calidad e Innovación, Ministerio de Sanidad, Consumo y Bienestar Social, Madrid, Spain [6]Centro Nacional de Medicina Tropical, Instituto de Salud Carlos III (ISCIII in Spanish), Madrid, Spain [7]Network Biomedical Research on Tropical Diseases (RICET in Spanish), Madrid, Spain

To whom correspondence should be addressed. Tel: +34-91-8222012; Email: zherrador@isciii.es

Abstract

Background: Of febrile illnesses in Europe, dengue is second only to malaria as a cause of travellers being hospitalized. Local transmission has been reported in several European countries, including Spain. This study assesses the evolution of dengue-related admissions in Spain in terms of time, geographical distribution and individuals' common characteristics; it also creates a predictive model to evaluate the risk of local transmission.

Methods: This is a retrospective study using the Hospital Discharge Records Database from 1997 to 2016. We calculated hospitalization rates and described clinical characteristics. Spatial distribution and temporal behaviour were also assessed, and a predictive time series model was created to estimate expected cases in the near future. Figures for resident foreign population, Spanish residents' trips to endemic regions and the expansion of *Aedes albopictus* were also evaluated.

Results: A total of 588 dengue-related admissions were recorded: 49.6% were women, and the mean age was 34.3 years. One person died (0.2%), 82% presented with mild-to-moderate dengue and 7–8% with severe dengue. We observed a trend of steady and consistent increase in incidence ($P < 0.05$), in parallel with the increase in trips to dengue-endemic regions. Most admissions occurred during the summer, showing significant seasonality with 3-year peaks. We also found important regional differences. According to the predictive time series analysis, a continuing increase in imported dengue incidence can be expected in the near future, which, in the worst case scenario (upper 95% confidence interval), would mean an increase of 65% by 2025.

Conclusion: We present a nationwide study based on hospital, immigration, travel and entomological data. The constant increase in dengue-related hospitalizations, in combination with wider vector distribution, could imply a higher risk of autochthonous dengue transmission in the years to come. Strengthening the human and vector surveillance systems is a necessity, as are improvements in control measures, in the education of the general public and in fostering their collaboration in order to reduce the impact of imported dengue and to prevent the occurrence of autochthonous cases.

Key words: Dengue, hospitalization, imported diseases, epidemiology, Spain

Introduction

Dengue is one of the world's most important neglected tropical diseases.[1] It is endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, Southeast Asia and the Western Pacific.[2] The World Health Organization (WHO) estimates that 500 000 people with severe dengue require hospitalization each year, with the case fatality rate estimated at 2.5%.[3] In Europe, dengue is the most common imported arbovirus infection in travellers.[4] During the past 5 years, about 2000 cases of imported dengue have been reported per year in Europe.[5]

In Spain, only a few studies have been carried out on imported dengue, all focused on case series from specific hospitals.[6–8] In these studies, most of the dengue cases were Spanish tourists who had travelled to Latin America.[7] Until 2015, when it became a notifiable disease, there was no specific surveillance system for dengue in Spain.[9] In the same year, the first dengue virus detection in local mosquitoes was reported in Catalonia[10] and, in October 2018, the first six cases of autochthonous dengue were reported. In the absence of complete information on the incidence of dengue prior to 2015, the Hospital Discharge Records Database (CMBD in Spanish) of the Spanish National Health System was the only database available that provided national coverage. The CMBD is the largest administrative database of inpatients and the main source of information on morbidity in Spain.[11]

In this study, we have described imported dengue-related hospitalizations in Spain from 1997 to 2016, in terms of time, geographical distribution and individuals' disease-related characteristics. We did this using time series forecast modelling in order to assess trends in dengue importation rates and the implications for the risk of autochthonous transmission.

Methods

Study design and data collection

We carried out a retrospective study using CMBD data from 1 January 1997 to 31 December 2016. The CMBD database receives reports from ∼98% of public and private hospitals. All dengue cases were laboratory confirmed at regional and/or national reference laboratories.[11] We used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)[12] and ICD-10-CM[13]—the ICD versions in use during the study period—for this purpose. Registers with ICD-9-CM code 061 ('Dengue') and ICD-10 codes A90 ('dengue fever') and A91 ('Dengue hemorrhagic fever') were analysed. For each registry entry, main diagnosis (the major process that is considered the primary reason for the patient's admission) and secondary diagnoses were analysed; these can coexist with the main at the time of admission or may develop during the hospital stay. For each hospitalization, we collected sex, age, autonomous community (CCAA in Spanish) and province of residence as well as clinical data like other diagnoses such as comorbidities and clinical manifestations, average length of stay, severity and outcome. We considered as severe all hospitalizations classified as serious and extreme according to the CMBD severity classification. The CMBD uses diagnosis-related groups (DRG) to classify hospitalization severity. This DRG system groups patients with various diagnoses but similar resource consumption into case mix categories.[11] Severity level is calculated

according to the combination of DRGs, patients' characteristics and the interaction between secondary diagnoses and surgical and non-surgical procedures carried out during hospitalization. We also described the associated diagnoses commonly considered as risk factors for severe dengue in the literature.

Official population figures for the Spanish autonomous regions and municipalities were obtained from the Spanish Statistical Office (INE in Spanish).[14] Figures for resident foreign population were also obtained from the INE[15] and grouped by dengue-endemic region.[16] Travel data from the Spanish Institute of Tourism (Ministry of Industry, Trade and Tourism) were used to assess the trends in trips taken by Spanish residents to dengue-endemic regions from 1997 to 2014.[17] Since 2015, travel data have also been managed by the INE. Primary data with geographic locations for *Aedes albopictus* were obtained from a nationwide entomological survey commissioned by the Spanish Ministry of Health (MoH) in 2016 as part of the National Plan for Preparedness and Response to Vector-borne Diseases. In this survey, entomological samples were obtained through oviposition traps, BG-Sentinel mosquito traps, human landing catches and larvae sampling using filtering tools. Further details have been provided elsewhere.[18]

Statistical analysis

We used frequencies, percentages and mean ± standard deviation (SD) to summarize data. Differences in proportions were assessed by the χ^2 test, and we calculated 95% confidence intervals (95% CIs). Student's *t*-test was used to compare differences in the means. We used two-sided tests, and $P < 0.05$ was considered significant. The relation between clinical manifestations, comorbidities and inpatient stay were assessed by bivariate and multivariate linear regression. A stepwise method with backward elimination approach was used. Age and sex, considered biologically relevant, and all variables found to be associated at the $P < 0.10$ level were included in the multivariable analysis. The association measures obtained from the linear regressions were regression coefficients (B) with their corresponding 95% CIs.

The average number of hospitalizations per year by CCAA and province were calculated in order to evaluate temporal and geographical patterns. Two methods were used to assess the temporal evolution of dengue-related admissions. First, we applied a Joinpoint regression model to detect trend changes (Joinpoint software version 4.2.0.1, National Cancer Institute, Bethesda, Maryland). We generated temporal trends by fitting log-linear regression models. This technique provides estimates of annual percentage change (APC) in trends with corresponding 95% CIs. Afterwards, we used a classical approach to time series analysis to predict the evolution of annual dengue-related admission rates in subsequent years. We performed a regression analysis with the annual hospitalization rate as a dependent variable and included trend and seasonality as independent variables by using the sine and cosine functions.

The hospitalization rates by province were mapped using the Geographical Information System QGis version 3.4.3. Data analysis was performed using Stata version 15.0.

Ethics statement

This study involves the use of patients' medical data from the CMBD. These data are hosted by the MoH. Researchers working

Table 1. Clinical characteristics of patients admitted to hospital with dengue in Spain, 1997–2016

Patient characteristics ($n = 588$)		N (%)
Sex	Women	292 (49.6)
	0–15	56 (9.5)
	16–44	407 (69.2)
Age	45–64	105 (17.9)
	>65	20 (3.4)
	Spain	522 (88.8)
Country of residence	Abroad	15 (2.5)
	Unknown	51 (8.7)
	Mild	283 (53.9)
	Moderate	201 (38.3)
Severity	Severe	38 (7.2)
	Extreme	3 (0.6)
	Home	573 (97.4)
Type of discharge	Exitus	1 (0.2)
	Others/unknown	13 (2.4)
		Mean (SD)
Inpatient stay (days)		4.4 (2.8)
Hospitalization cost (euro)		3317.5 (1177.1)

in public and private institutions can request the databases by filling in, signing and sending a request form and a confidentiality agreement—both available on the MoH website. The CMBD meets all the relevant legal and technical requirements as regards safe access and data protection. Formal ethical approval is not required for CMBD analyses.[19]

Results

Sociodemographic and clinical characteristics

Between 1997 and 2016, 588 hospitalizations with dengue in any diagnosis field were recorded in the CMBD. A total of 513

(87%) specified dengue as the main diagnosis. The second most frequent main diagnosis was fever (3%); 49.6% were women, and the mean age was 34.3 years old (SD, ±14.1). A total of 7.8% patients were admitted as urgent and five needed readmission within the first month after discharge. The length of stay ranged from 0 to 26 days (mean, 4.4; SD, ±2.9).

A total of 82.3% of hospitalizations were due to a mild episode (mild or moderate severity), with an average stay of 4.2 (±2.5) days, while 41 patients (7.8%) suffered severe dengue, with an average stay of 6.5 (±4.2) days [mean difference, 2.3 days (95% CI: 1.4–3.1; $P < 0.05$)]. One patient, representing 0.2% of the total, died (Table 1). This fatality was a 41-year-old man who was also suffering from an occlusion of the basilar artery without infarction.

Of all the comorbidities present, essential hypertension and hepatitis (any type) were the most prevalent conditions (5.8% and 2.6%, respectively) followed by asthma (1.7%). Of all the clinical manifestations, thrombocytopenia was the most frequent (17.9%) followed by leucocyte alterations (7.9%) and anaemia (3.6%). A total of 1.9% of dengue-related hospitalizations were pregnant women.

Anaemia increased the average length of hospitalization by 1.9 days (95% CI: 0.7–3.1; $P < 0.05$), pancytopenia by 3.5 (95% CI: 1.5–5.6; $P < 0.01$) and abnormal coagulation by 4.5 (95% CI: 1.7–7.2; $P < 0.01$). Chronic kidney disease (CKD) and Human immunodeficiency virus (HIV) were also associated with longer inpatient stays ($P < 0.05$). CKD increased the average length of hospitalization by 6 days (95% CI: 2.8–9.2), and HIV, by 3.6 days (95% CI: 0.4–6.8) (Supplementary Table S1).

Temporal and spatial trends

A total of 53% of dengue admissions occurred during the past 5 years (2012–2016). Dengue admissions from 1997 to 2016 in Spain presented a significant rising trend ($\beta = 0.024$; 95% CI: 0.021–0.028). According to the Joinpoint analysis, no
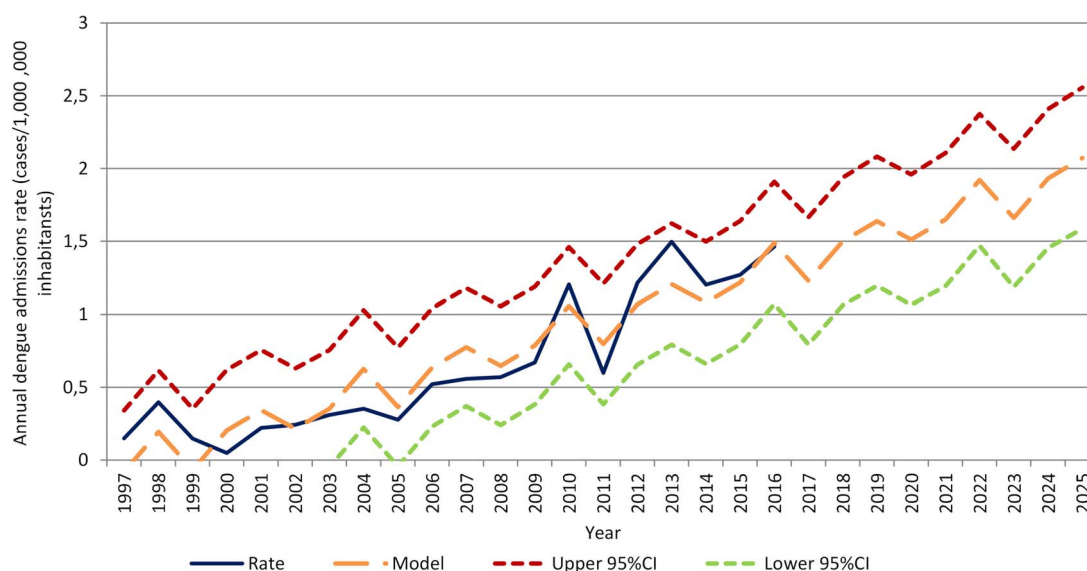

Figure 1. Dengue admission rates 1997–2016 and predictive model for expected admissions up to 2025 in Spain

Table 2. Time series analysis parameters for the series of patients admitted for dengue in Spain, 1997–2016

Rate	Coefficient	Standard error	95% CI		P value
			Lower	Upper	
Cosine (3y)	0.135	0.059	0.010	0.259	0.036
Year	0.072	0.007	0.056	0.087	0.000
Constant	−144.117	14.703	−175.138	−113.096	0.000

change in trend occurred during the study period, showing it to be consistent, with an APC of 18.98% (P < 0.05). The year with the fewest dengue-related admissions (n = 2) was 2000, while the highest number of hospitalizations were recorded in 2013 (n = 70). Admissions mostly occurred in late summer (August and September). Seasonality was also detected in the time series; 3-year cycles were found to be statistically significant (P < 0.05). According to the predictive model, a constant increase can be expected in the near future—an increase of 65% in the worst case scenario (upper 95% CI) by 2025 (Figure 1, Table 2).

The annual resident foreign population from dengue-endemic countries in Spain from 1998 to 2016 is shown in Figure 2. Immigration from American dengue-endemic countries was predominant during the whole period, with a progressive increase until 2010, when it presented a slight decrease. Population from Asian and African dengue-endemic countries represented a smaller proportion but with a consistent increase during the whole study period.

The number of trips made by Spanish residents to dengue-endemic regions, 1999–2016 is shown in Figure 3. Overall, there is a fluctuating increase until 2010, when trips decreased in each of the three subsequent years. However, the travel dynamics differed by destination region, with different peaks and slopes; Asian tourism seems to have steadily increased during the past few years, while trips to America and Africa have fluctuated more, but have shown a rise in recent years.

Regarding the regional distribution, all the CCAA reported dengue admissions throughout the study period, but not all provinces (Figure 4). Northeastern regions seemed to experience higher rates; provinces in the Basque Country and Navarra were those with the highest hospitalization rates, followed by provinces in Madrid and Catalonia (Supplementary Table S2).

The distribution of *Ae. albopictus* detections in Spain is shown in Figure 4. The highest vector density was observed in the area next to the Mediterranean coast from north to south (Catalonia, Valencian Community and Murcia) and the Balearic Islands, with the highest concentration in the autonomous region of Catalonia.

Discussion

Epidemiology of imported dengue in Spain

Between 1997 and 2016, there were 588 dengue-related hospitalizations in Spain. We found a significant increase in the number of dengue-related hospitalizations in Spain during the study period. This increase is not surprising considering (i) the increase in immigrant population (except from Latin America in
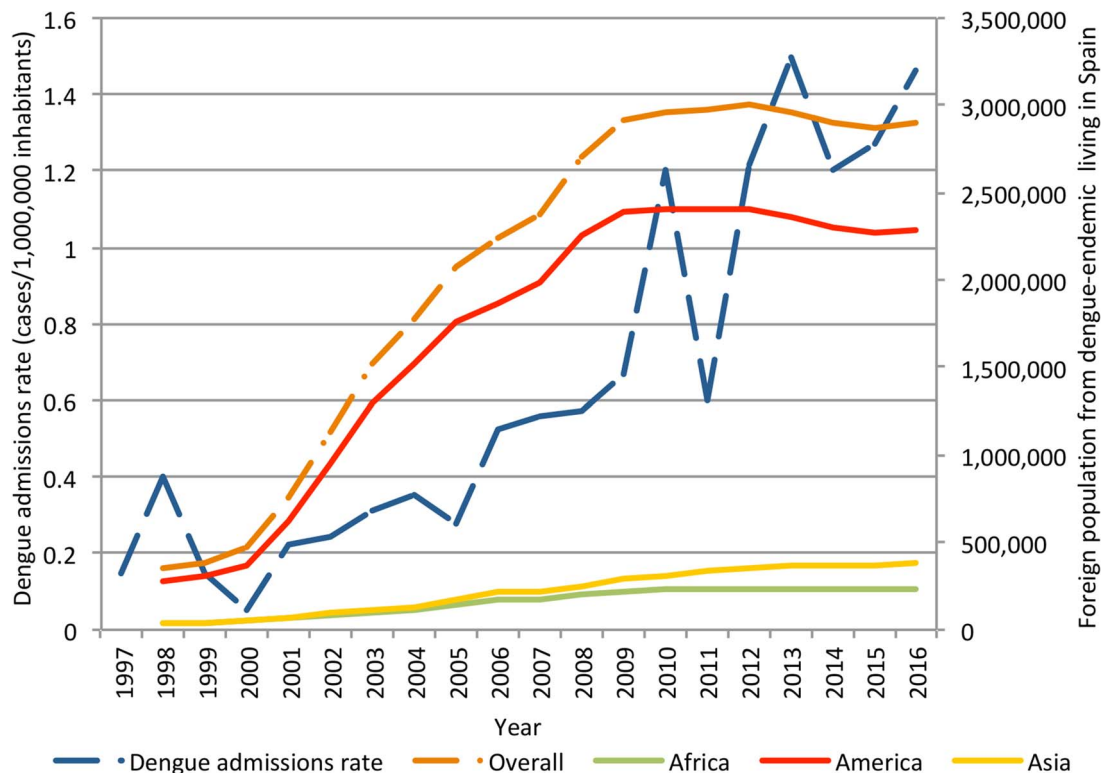

Figure 2. Annual dengue admission rate and foreign population from dengue-endemic countries living in Spain, grouped by region, 1998–2016
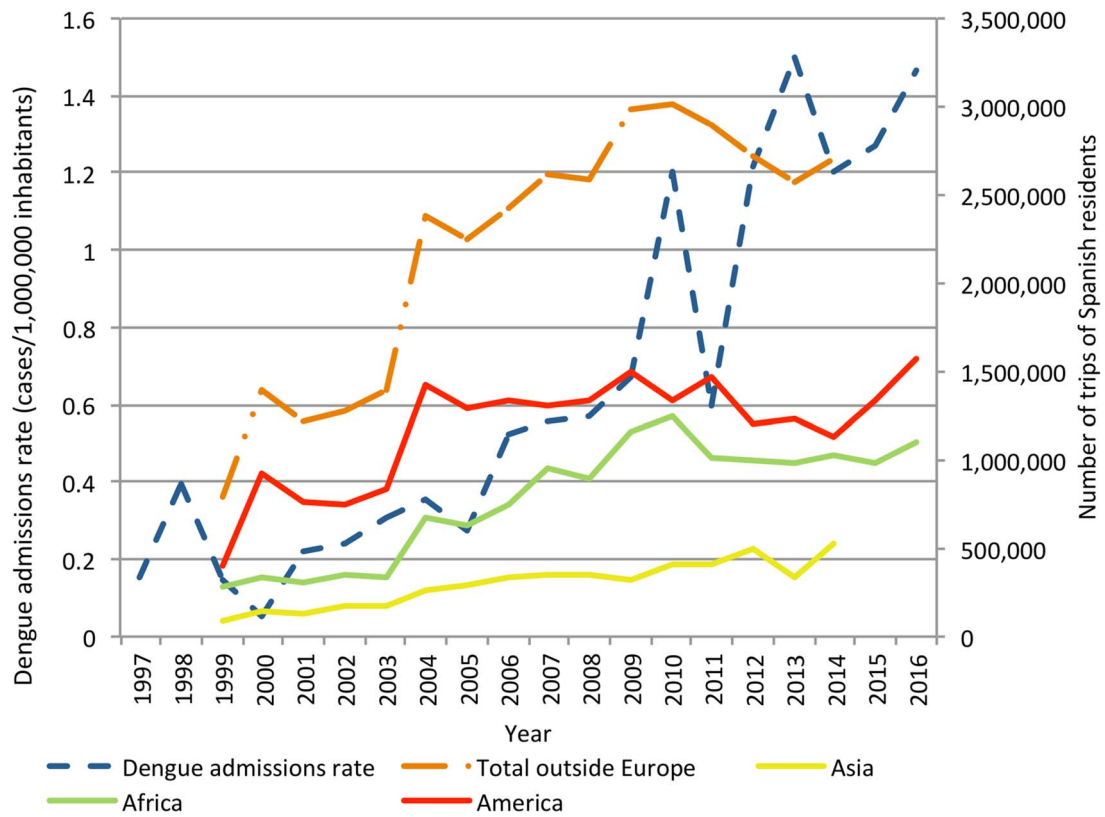
Figure 3. Annual dengue admission rate and annual trips by Spanish residents (1997–2016), total and by dengue-endemic region. Trip data for years 2015 and 2016 were collected from the INE database. In this source, tourism data for Asia were not available.
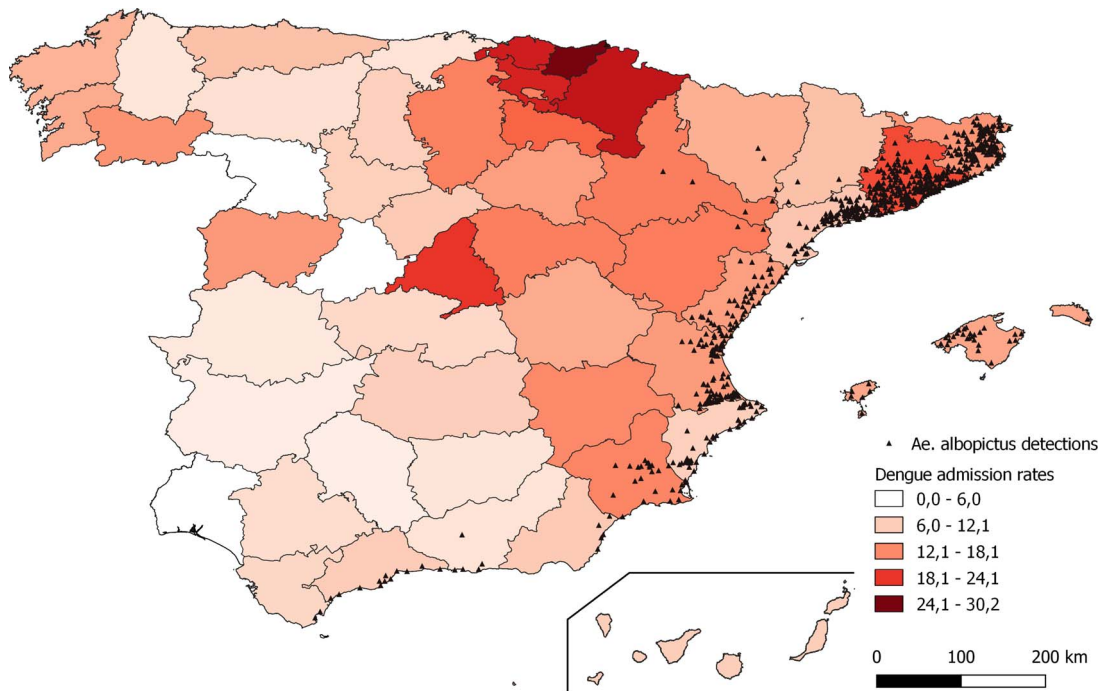

Figure 4. Dengue admission rates 1997–2016 and *Ae. albopictus* detection distribution as of 2016, in Spain. This map was created with free software QGis version 3.4.3. The map was plotted by L.R. for this article.

the past decade)[15], (ii) a substantial number of travellers enter Spain every year from the tropics and subtropics and (iii) the number of cases in disease-endemic regions has increased in the recent years.[3] Four relevant peaks were identified in the time series analysis: 1998, 2010, 2013 and 2016. A large peak was detected worldwide in 1998,[20] followed by a decline in

1999–2000 and a steady increase in overall activity since then. Dengue cases reached historically high levels in 2010 in several Latin America regions.[21] In 2013, dengue outbreaks were reported in many countries, such as Brazil (double the deaths as compared with 2012), Singapore and Thailand (the worst in 20 years).[22,23] The year 2016 was also characterized by large dengue outbreaks worldwide.[20] Our results may reflect the dynamics of the worldwide dengue trends in relation to Spain's imported cases. These kinds of results have been described as being beneficial by the WHO, since data for imported cases reported in non-endemic countries can act as sentinel data and enable countries with weaker surveillance systems to detect outbreaks earlier. On the other hand, the slope described in our time series analysis seems to be more pronounced than that for cases worldwide. This can be explained by an increase in the number of travellers returning from endemic countries during the study period, as reflected in our time series analysis of international travellers. Moreover, changes to immigration patterns could also be influencing this trend.

Admissions mostly occurred in late summer (August and September), with significant seasonality shown by 3-year peaks. Similar seasonal patterns have been described previously.[24–26] In Southeast Asia, dengue cases generally peaked between June and September in typical non-epidemic years.[27,28] In Latin America and other southern hemisphere countries, the majority of cases were reported in the first half of the year, while in the northern hemisphere, most cases occurred in the second half. This may be related with the rainy seasons in these countries and other meteorological factors that may affect the vectors.[29] Moreover, we know that monthly incidence may vary more notably in outbreak years.[28] Unfortunately, we cannot segregate dengue admissions in Spain by returned travellers' region travelled to, as this information is missing from the CMBD dataset. We only know that the number of Spaniards travelling to dengue-endemic areas peaks during the summer vacation season, which may also go towards explaining our results. For all these reasons, mention of dengue seasonality should be considered as part of pre-travel advice for travellers visiting dengue-endemic countries.

The CCAAs with the highest dengue admission rates were the Basque Country and Navarra, followed by Madrid and Catalonia. According to INE data, Madrid, Navarra and the Basque Country were the CCAAs with the highest number of trips/person made between 2015 and 2017 (data before 2015 were not available).[30] Madrid and Catalonia were also the regions with the highest immigration rates from dengue-endemic regions during the study period. Thus, it seems that some of the travellers from these regions could match the visiting friends or relatives (VFRs) profile, identified as that of the highest risk for travel-related health problems.[31–34] These two facts together could explain the higher admission rates observed in these territories. In addition, regions where the vector is present may have had more sensitive surveillance and greater awareness when making diagnoses. However, we should take into account some other factors that could explain our results. These include purchasing power differences between CCAAs—which may influence travel destinations, levels of adherence to prevention measures and the ease with which pre-travel medical advice may be obtained.

Clinical features of imported dengue fever in Spain

The majority of admissions occurred in the 16–44 age group, similar to data from other studies.[36]

This can be explained several ways. First, those aged 25–34 years had the highest number of international tourist visits during the study period.[36] Combined with the greater likelihood of participating in outdoor activities, this might increase the risk of contracting dengue. Second, some of these hospitalizations may have been returning migrant travellers who had been VFRs.[32,33] We know that in Spain the migrant population is generally young, mostly due to work-related reasons.[37,38]

We observed a fatality rate of 0.2% among our cases. According to the WHO, early detection and access to proper medical care lowers fatality rates below 1% across all dengue cases.[3] However, Spain's low fatality rate could be related to the fact that imported dengue cases are most probably travellers who have contracted primary dengue infections.[39] Only a minority of travel-acquired cases are due to secondary dengue infection.[40] Secondary infections are more frequent in endemic countries due to the circulation of different dengue virus serotypes; thus, their populations are at higher risk of severe outcomes.[41]

The most frequent comorbidities were essential hypertension, hepatitis and asthma. The liver is frequently affected by dengue infections.[42] On the other hand, chronic hepatitis, asthma and diabetes are risk factors for severe organ involvement.[43,44] In our study, none of these—with the exception of HIV and CKDs—were associated with longer inpatient stay. Being immunocompromised has been described as a risk factor for severe dengue previously,[35] and renal disorders have also been linked to dengue severity; however, this has mostly referred to acute episodes rather than chronic conditions.[45]

Dengue fever in Spain: what can we expect?

Autochthonous transmission re-emerged in Europe in 2010 in France and Croatia; prior to this, the last major outbreak was in Turkey in 1945, and southern Europe has not been dengue endemic since 1930.[46,47] In 2012, the island of Madeira (Portugal) had a large outbreak of dengue with more than 2000 cases associated with *Aedes aegypti*. This species was also identified in a very limited area of the island of Fuerteventura (Canary Islands, Spain) in 2017, although the risk of the vector establishing itself was considered low.[48] In 2018, there was a widespread outbreak of unusual magnitude on the island of Reunion (France), with more than 6600 cases, with *Ae. albopictus* as the implicated vector.[49] According to the European Centre for Disease Prevention and Control risk assessment, the implication of this secondary dengue vector in the Reunion outbreak increases the likelihood of sustained local transmission in continental Europe.[50]

In October 2018, the first six cases of autochthonous dengue in Spain were reported. Three of these belonged to the same family, two were living in Murcia and the other in Madrid. The first three had travelled around the region of Murcia and around Cádiz (Andalusia). Another two cases were diagnosed in Murcia with epidemiological links to one of the first cases and the sixth lived in Catalonia, but none of these latter cases had relevant recent travel histories.[48] Although it seems that there

was an epidemiological link to the Murcia region (except for the last case), it was not possible to establish where the infection was acquired with certainty. All these cases were considered autochthonous as there was no history of travel to dengue-endemic countries. According to our results, Murcia—where *Ae. albopictus* was first identified in 2011[50]—had medium dengue admission rates, while Barcelona is one of the provinces with the highest admission rates and also has significant vector density. In Spain, *Ae. albopictus* was first detected in Catalonia (2004).[48] Since then, *Ae. albopictus* has spread throughout the whole Mediterranean coastal region of Spain. In addition, the vector was recently identified in a number of other regions such as the Basque Country (2014),[51] Aragon (2015)[52] (probably due to proximity to Catalonia), Madrid (2017)[53] and Extremadura (2018).[54] In these regions away from the Mediterranean Sea, the introduction of the mosquito may have been through ground or air transportation from coastal areas.[49] On the other hand, the dengue virus periodically enters into non-endemic countries via travellers from endemic countries, especially during the summer holidays, which coincide with the months of the highest vector activity.[49] Finally, we know that environmental and demographic changes can also facilitate the autochthonous transmission of the virus.[49,55] For all these reasons, we believe that it is likely that new autochthonous cases will appear in Spain in the near future.

Conclusion

This study has several limitations. First, our results only include dengue cases admitted to hospitals; therefore, they do not reflect the many asymptomatic dengue infections or dengue requiring medical intervention while travelling. As a consequence, it is likely that we have underestimated the number of dengue cases in our territory and therefore the magnitude of the reservoir. The mandatory reporting of this disease from 2015 on may have partially resolved this problem in Spain, as it is generally agreed that worldwide dengue reporting systems still underestimate dengue's real incidence. Furthermore, dengue may not be suspected during the first examination due to health professionals' lack of experience with tropical diseases. Another important limitation is the lack of sociodemographic information and travel background available in the CMBD database; unfortunately, data provided by the Spanish CMBD do not include patients' place of origin, which would have allowed for further comparisons between immigrants and those born in Spain. After a long absence, dengue has re-emerged in the WHO European region, driven by the increase in imported cases and the invasion of the mosquito vector species. According to our predictive model, a permanent increase in imported dengue cases can be expected. This, added to wider vector distribution, and the recent reports of six autochthonous cases[49] could lead to a higher risk of autochthonous dengue transmission. To reduce this risk, the key elements included in the National Preparedness and Response Plan Against Vector-borne Diseases should be reinforced. This includes strengthening the surveillance system (boost clinical awareness, make improvements in laboratory capacity and ensure rapid notification of cases), improving the education of and fostering collaboration from the general public, as well as strengthening mosquito surveillance and vector control

measures.[18] Finally, an effective travel vaccination against dengue could provide protection for travellers and thus reduce the risk of autochthonous transmission.[56]

Conflict of Interest

None declared.

Author Contributions

Z.H., D.G.B., L.R.B. and C.R.H. contributed to the conception and design of the study. L.R.B., C.R.H. and Z.H. drafted the manuscript, carried out statistical analysis, interpreted the data and helped with the revision of the manuscript. D.G.B. contributed to the design of the study, interpretation of data and revision of the manuscript. A.B. and M.J.S.M. contributed to the conception of the study and critically revised the manuscript. All the authors read and approved the final manuscript.

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