# **Prevalence and burden of dengue infection in Europe: a systematic review and meta-analysis.**

# **Running Title:** Dengue in Europe.

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Ali Mahmoud Ahmed1#, Abdelrahman Tarek Mohammed1#, Thao T. Vu2#, Mohammed Khattab1#, Mohamed Fahmy Doheim3, Ahmed Ashraf Mohamed1, Mai Mahmoud Abdelhamed4, Bahaa Eldin Shamandy5, Mahmoud Tamer Dawod6, Wafaa Ali Alesaei7, Mahmoud Attia Kassem8, Omar Mohamed Mattar9, Chris Smith10,11, Kenji Hirayama12, Nguyen Tien Huy13,14,\*.

1 Faculty of Medicine, Al-Azhar University, Nasr city 11651, Cairo, Egypt.

2School of Health and Biomedical Sciences, RMIT University, Victoria 3083, Australia.

3Faculty of Medicine, Alexandria University, Alexandria 21544, Egypt.

4Faculty of Medicine, Tanta University, Tanta 31511, El-Gharbiya, Egypt.

5Faculty of Medicine, Aswan University, Aswan, Egypt.

6Faculty of Medicine, Zagazig university, Zagazig 44511, El-sharkia, Egypt.

7Faculty of Medicine, Misr University for science and Technology, 6th October, Giza, Egypt.

8The Ohio State University Wexner Medical Center, Columbus, OH, 43210, USA.

9Kasr Alainy Faculty of Medicine, Cairo University, Cairo, Egypt.

10School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki 852-8523, Japan

11Department of Clinical Research, London School of Hygiene and Tropical Medicine, London, UK

12Department of Immunogenetics, Institute of Tropical Medicine (NEKKEN), School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki 852-8523, Japan.

13Evidence Based Medicine Research Group, Ton Duc Thang University, Ho Chi Minh City, 70000, Vietnam.

14Faculty of Applied Sciences, Ton Duc Thang University, Ho Chi Minh City, 70000, Vietnam.

#These authors contributed equally to the article.

\*Correspondence and requests for materials should be addressed to Nguyen Tien Huy, Evidence Based Medicine Research Group & Faculty of Applied Sciences, Ton Duc Thang University, Ho Chi Minh City, Vietnam (E-Mail: nguyentienhuy@tdtu.edu.vn).

**Summary**

Imported dengue cases are thought to be important source for transmission of autochthonous dengue in Europe. We aimed to investigate the prevalence of dengue in Europe, its severity and factors associated with it. Out of 5287 reports resulting from the search of nine electronic search engines, we included 174 reports on dengue cases in Europe. The screening processes and data extraction were performed by three independent reviewers. Meta-analysis was performed by pooling the event rate and 95% confidence interval (CI). Subgroup meta-analyses were performed to test the effect of the covariates. Among 20,284 reported cases, 130 autochthonous dengue cases were reported in eight countries with the highest number of cases reported in Israel (n=41). The highest number of imported dengue cases was in Germany (n=6,638) then France (n=6,610). Most cases were imported from South-East Asia (n=2,533) especially Thailand. Dengue infection cases increased with time, with 4,157 cases reported in 2010. Second dengue infection and dengue serotype-2 were positively associated with dengue severity. The proportion of autochthonous dengue infection increased with time to reach 14.8%. 95%CI [7.6-26.9] in 2015. The pooled proportion of severe dengue was 6.18%, 95%CI [2.7-13.3]. The United Kingdom and France had the highest rate of severe dengue (25%, 95%CI [6.3-62.3]), (21.4%, 95%CI [24.5-18.7]), respectively. This change in time and place may be due to the surveillance efforts instead of true biological phenomenon; thus, the lack of surveillance is an obvious limitation. In conclusion, imported and autochthonous dengue has been increasing in Europe. Severe dengue began to increase recently in Europe. European health authorities should pay more attention for diagnosis and control of dengue infection among returning travelers, especially the travelers with fever of unknown origin.

**Introduction**

Dengue, a mosquito-borne arboviral disease transmitted mainly by *Aedes aegypti*, is one of the most common viral infections that threat humans. According to the World Health Organization (WHO), the number of reported dengue cases per year increased to more than 3 million in 2013, after it was less than a thousand per year in 1950s.1,2 This number does not reflect the exact situation, where there is an annual range of 50 to 200 million of symptomatic cases including those undetermined by reporting systems. This discrepancy can be due to the clinical similarities of dengue with other infectious diseases and the short duration of infection leading to misdiagnosis.3 Previous population-based studies revealed that dengue is under-reported by surveillance systems.4,5 The most commonly reported range of globally annual dengue cases is 50-100 million with about 20,000 deaths.6

Dengue is endemic in more than 128 tropical and subtropical countries (mostly in Asia-Pacific and Americas-Caribbean) putting about 4 billion people at risk.7 It has spread, especially in the last 2 decades, to involve new areas causing outbreaks with advancing magnitude and severity.8 This geographical expansion is mainly due to changes in global climate and increased international trade and air-travel causing the spread of the disease’s vectors (*Aedes* spp.).9 These factors are explained by the dengue epidemiological triangle. The increase in air travel was concomitant with increased dengue infection in the tropics and both were responsible for the increased likelihood of health care providers, including those in European countries, confronting imported dengue cases.

Many studies at travel clinics have reported that dengue infection was the most common cause of fever in European returning travelers.10,11 Annually, the TropNetEurop collaborating centers treat about 57,000 infected patients returning from travel. According to this network, the number of imported dengue cases into Europe increased from 64 cases in 1999 to 224 cases in 2002, with the number remaining within the range of 100-170 thereafter.12 This trend is concomitant with the introduction of potential disease vectors such as *Aedes* *albopictus*, which is currently present in more than 15 European countries.13

Dengue virus (DENV) transmission can cause public health problems as infected travelers contribute to infection spread.14 This potential danger has been demonstrated recently with many reported cases of transmission of autochthonous dengue in southern Europe.15,16 Despite efforts spent to prevent dengue transmission via mosquito-control programs, European dengue infections are still increasing. Therefore, this systematic review and meta-analysis aims to highlight the exact state of dengue in Europe, evaluate its trends and severity, and propose potential solutions to overcome this problem.

**Methods**

### This study was performed in adherence with the PRISMA statement (Supplementary Table S1). The protocol was registered in PROSPERO (CRD42015015037).

### Eligibility criteria

### We included any report (published before January 2017) describing confirmed or probable human dengue cases, according to the definition of WHO for dengue infection,17 in any European country approved by the WHO (<http://www.euro.who.int/en/countries>). No restriction was made regarding publication type, language, populations, and study design. Reports highlighting dengue cases from European territories or outside the European continent were excluded. Furthermore, papers reporting suspected dengue or non-specified infection were also excluded. In addition, we omitted abstract-only reports, papers reporting dengue infection in non-human cases, reports with data that cannot be extracted, as well as overlapped datasets.

### Search strategy

We searched nine electronic search engines, including PubMed, Google Scholar, Scopus, ISI, Global Health Library, Virtual Health Library, NYAM, SIGLE, and Popline, for reports published from inception until April 2015 then the search was updated besides the manual search to include any paper reporting dengue cases in Europe until January 2017. Supplementary file S1 explains the details of the search strategy.

### Selection of the included studies

The search results were combined, and duplicates were removed using EndNote X7 software (Thompson Reuter, CA, USA). Based on the eligibility criteria, three independent reviewers initially screened the titles and abstracts, and subsequently the full text of the papers. Any discrepancy between the assessors was resolved by discussion and involvement of a senior reviewer to reach the consensus.

**Quality assessment**

Multiple quality assessment tools were used according to the study designs of the included papers. NIH quality assessment tools were used for cohort and cross-sectional studies in addition to case control studies. Having the case report or case series studies, the quality assessment was performed based on the four-domain tool proposed by Murad et al.18 These four domains were selection, ascertainment, causality, and reporting (Supplementary Sheet S1,2,3).

### Data extraction

### Relevant data was extracted by three independent extractors using a form that was prepared after successive exploratory trials (Supplementary Sheet S5). Any discrepancy was resolved by discussion and consensus with a senior reviewer if needed. Besides the demographic data, extracted data included country, infection nature (imported or autochthonous, probable or confirmed, and primary or secondary), overseas countries of imported cases, year of study implementation, dengue virus strain, total number of patients (besides their age and sex data) stratified by the time, proportion of dengue among other imported infections, average annual attack rate (the estimated average number of cases per each year), classification of dengue cases according to either the 1997-WHO dengue fever (DF) classification; dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), or the 2009-WHO classification into dengue without warning signs, dengue with warning signs, severe dengue, and fatal dengue outcome.19

### Case definition

Based on WHO definition, dengue was defined as a febrile illness with at least two clinical findings, comprehending nausea, vomiting, arthralgia, chest pain, headache, lethargy, retro-orbital pain, rash, myalgia, hemorrhagic manifestations, liver enlargement, and leukopenia along with laboratory or epidemiological evidence of infection to confirm the condition.

The following tests were considered a confirmatory test; viral isolation and serotype identification, nucleic acid detection, and IgG detection by ELISA or neutralization test. Subsequently, antigen detection, IgM assessment by ELISA or rapid test illustrated the probability of dengue infection. The differentiation between confirmed or probable and suspected was summarized in supplementary table S2.

As for cross reactivity, high-titer neutralizing antibodies are generated against dengue viruses as a sequential effect of the second dengue virus infection. This cross reactivity produced via memory B- cells in response to dengue and non-dengue flaviviruses such as Chikungunya, and Zika viruses.

### Data analysis

### In addition to the qualitative, like frequencies in dengue virus serotype, and quantitative, like mean and standard deviation (SD) in age, assessment, proportions with 95% confidence intervals (CI) were pooled throughout years after conversion from logit event rates. Cochrane *Q* and *I2* statistics were used to investigate statistical heterogeneity among the pooled data which was considered with a *P*-value of *Q* test >0.1 or *I2* value >50%, where random effect model was implemented.20 Taking the co-variate into consideration, we tested the effect on the meta-analysis using subgroup meta-analysis and association with dengue severity using Spearman's correlation statistics. Meta-analysis was conducted using CMA X3 platform (BioStat Inc., Engelwood, New Jersey, US).

### Results

Out of 5,287 studies resulting from both the initial and the updated search, 174 studies were finally included (Figure 1; and Supplementary File S2). Among these studies, 94 studies were case reports and case series, 60 studies were cross-sectional, 15 studies were case-control studies, and five studies were reviews and editorials. We identified 20,284 dengue cases reported in 21 European countries. Among these countries, Germany and France had the highest number of dengue cases with 6,638 and 6,610 cases, respectively (Figure 2). Imported dengue was reported in 20,154 (99.36%) cases, while autochthonous dengue was reported in 130 (0.64%) cases from eight countries with the highest number reported in Israel and Croatia (41 and 36 cases, respectively). Probable dengue (2.5%) was minimal compared to confirmed dengue. Germany and France were reported to have the highest average of annual attack rate with 297.30 and 275.42 cases/year, respectively (Supplementary Table S3). Dengue in Europe is mainly imported from endemic areas. South-East Asia followed by Caribbean islands were the main sources of imported dengue infection to Europe with 3,533 and 1010 imported cases, respectively (Figure 3). Among all countries, Thailand was associated with the highest number (1515) of dengue cases imported to 15 European countries with average 52 imported cases/year (Supplementary Table S4). Southern Africa was the region of the lowest risk of dengue importation to Europe with only one case imported to Germany (Supplementary Table S5) (Figure 4).

Reported dengue infection increased with time in Europe with the highest number of cases reported in 2010 (n=4157) followed by 2014 (n=2889). Germany showed an increase in dengue cases during 2014 (n=2447) compared to France which showed no recent increase in dengue cases (Figure 5A). Dengue virus serotype 2 (DENV-2) was the highest reported serotype totally, although DENV-1 has showed an apparent increase since 2011 (Figure 5B). Regarding the type of infection, the secondary infection was lower than the primary infection. However, the percentage of the second infections increased recently compared to primary infections making the total pooled proportion 42.9%, 95% CI [39.7-46.0] of the total cases reported in the papers mentioned the type of the infection (Figure 5C).

The pooled proportion of imported dengue among all imported infections was 10.4% (95% CI [9.1-11.9]). This proportion increased with time to reach its peak in 2015 (18.8%, 95% CI [11.3-29.8]). Furthermore, the pooled proportion of the autochthonous dengue among all reported dengue infections was relatively minimal (0.7%, 95% CI [0.3-1.4]), albeit this proportion increased recently to reach 14.8% (95% CI [7.6-26.9]) in 2015 (Figure 5D). The pooled proportion of severe dengue cases (DSS and the 2009 WHO severe dengue), DHF, DF, dengue with warning signs, and dengue without warning signs were 21%, 95% CI [18.3-23.8]; 21.2%, 95% CI [18.6-24.2]; 55.4%, 95% CI [51.8-59]; 13.5%, 95% CI [4.4-34.5]; and 14.8%, 95% CI [5.1-35.9], respectively. Severe dengue increased with time to reach the highest proportion in 2016, while dengue without warning signs did not appear to increase in the current decade compared with DF in the last decade. It was obvious that the new 2009 dengue classification was used prominently after 2010 rather than the old 1997 classification (Figure 5E).

United Kingdom and France reported to have the highest proportion of dengue severity (25%, 95% CI [6.3-62.3]); (21.4 95% CI [18.7-24.5]), respectively. Dengue with warning signs was highest in Russia (98.08%) and DHF was highest in UK (50%), while Italy had the highest proportion of dengue without warning signs (89.02%) (Figure 6A).

France and Germany were reported to have similar proportions of dengue among all imported infections (21.96% and 19.78%, respectively), while Russia had a higher proportion. Therefore, there was no correlation between imported dengue proportion and dengue severity (Figure 6B). There was a positive correlation between second infection and dengue severity (r=0.779, *P*=0.008) (Figure 6C). DENV-2 was significantly associated with dengue severity (r=0.791, *P*=0.034) with concomitant increase in countries of high severity category (UK, France and total) (Figure 6D).

**Discussion**

### This study highlights that Europe is not protected from the risk of dengue. After the 1928 Greece epidemic, dengue was rarely reported in Europe until the establishment of *Aedes spp* during the 90th of the last century.21 Since then, dengue has been on a continuous rise to the extent that Europe faces an increasing threat of an epidemic.22

### We reported 20,284 dengue cases with 130 autochthonous cases in Europe. Our data shows that dengue expansion increased recently from the beginning of the 21th century in Europe, especially in Germany and France. Nevertheless, the burden of the disease in Europe is still low compared with other endemic areas including South-East Asia and Western Pacific which account for around 75% of the global burden of the disease.23 Dengue expansion is attributed to many factors including advancement in surveillance systems and testing, climatic change, viral evolution, globalization, travel, increase the awareness of physicians in travel clinics, and socioeconomic factors.24

### Dengue transmission is highly sensitive to climate change through the effect on the dengue epidemiological triangle; the *Aedes* vector (*Aedes spp)*, dengue virus, and human.14 Historically, the increase in dengue outbreaks in the last century was simultaneous with the global average rise of temperature by 0.75°C.25 Climate change enhances dengue spatio-temporal expansion to non-endemic areas.24 Higher temperature increases vector capacity by increasing the average biting rate, probability of infectivity per bite either for the human or the vector, and rate of mosquito development.26 Therefore, it is related with the appearance of autochthonous cases and this explains the recent inflation in autochthonous dengue. Relative humidity and rainfall are other climatic factors can affect dengue transmission through their positive effect on larval development and harvesting.27

### Climate changes significantly altered the vector competence in Europe. The literature revealed that both Ae. Aegypti and Ae. albopictus were infested Europe throughout the entire period (2006-2015). However, the pattern of distribution of either type is different; in particular, Ae. albopictus infested mainly in the Mediterranean area but expanding northward, while only three areas, Georgia and southwestern portions of Russia, have recently reported the infestation of Ae. Aegypti. Generally, at the optimum temperature, Ae. Aegypti showed higher intensity relative to Ae. albopictus.27

### Despite its effect on the epidemiological triangle, travel, trade, along with globalization associated with climate change may be the main driver of dengue expansion.28 Traveling to South-East Asia and Caribbean islands accounted for more than half of imported cases that constitute more than 99% of European dengue. A stay for one week in Thailand during the peak season of dengue is associated with a 0.2% risk for dengue infection.29 The longer the duration of stay, the higher risk of infection. The risk of travel is not restricted to Europe; it affects other low-risk areas like Japan, USA and Latin America.22,28 Overseas travel was associated with establishment of the *Aedes* vector in Europe during the 90th of the last century through breeding of the mosquito larvae in used tyres.22 In addition to cross-border travel, inside-country travel from rural to urban areas contributes to dengue expansion through increased urbanization.28 These findings highlight the importance and the need for effective control of travel-associated dengue infection as a major cause of dengue expansion all over the world.

### Autochthonous dengue in Europe is very low but its presence indicates increased risk for dengue transmission and outbreaks, given other variables like climate change, travel, and trade.22,30 Autochthonous dengue was found mainly in Croatia, Israel, France, and Italy. These countries are at risk of future outbreaks in Europe.

Human and socio-economic factors, such as population growth and rapid urbanization, are other factors that may contribute to dengue expansion.28 Dengue prevalence may vary between neighboring countries, even between neighboring cities inside the same country despite the same climate suitability, population density, and the vector predominant. The obvious discrepancy between Germany and Poland, also France and Spain, could be attributed to socio-economic factors and increased travel rate in Germany and France.31 In 2010, nearly 5.8 million airline travelers joined Europe from dengue-affected areas worldwide. There was a significant correlation between the travel rate and the incidence of dengue infection.31

The high rate of reported severe dengue can be attributed to the high rate in France and UK, however it was much lower in other countries. Dengue severity depends on several factors, such as secondary infection 32, vector competence33, age, gender, and genetic factors.34 The positive correlation between dengue severity and second-dengue infection can be attributed to the antibody-dependent enhancement (ADE) theory. Following primary viral infection, dengue cross-reactive antibodies raise and bind with other viruses to format immune complex. Consequently, the number of viral infected cells increase with elevated levels of cytokines leading to plasma leakage and shock.34 Most reported cases were of primary infection but primary followed by secondary carries more risk for developing severe dengue. This can explain why France and UK had the highest rate of severity. France and UK had the highest rate of dengue infection in the last decade, which may consequently result in appearance of secondary cases with higher risk of severity.

Dengue severity was well-explained in both 1997 and 2009 classifications; however, both classifications are largely different from each other from both application and conceptual views. For the clinical usage, the 2009 classification is easier. For epidemiological and pathological research, it is also easy to be applied with increased sensitivity and international compatibility.35 Therefore, it is expected to be widely used after it had been introduced in 2009 as our result showed.

The high prevalence of DENV-2 in Europe can be attributed to its high prevalence in tropical and subtropical areas from which dengue is imported.36,37 We report that infection with DENV-2 increases the tendency to cause severe dengue. Some authors approved that association between DENV-2 and disease severity in South-East Asia.36,38 The underlying mechanism is not fully clear but it is reported that DENV-2 is associated with increased Nitric Oxide (NO) levels and activity causing vascular leakage.39 That is not only for serotypes, even genotypes of the same serotype can affect. African and American genotypes of serotype 2 and 3 were found to be less virulent than Asian genotypes of the same serotypes.40 However, genotypes detected in Europe are of low epidemiological impact, and epidemic is less likely, Europe is a continent of diverse-ethnic populations, and travel from Asia increases the risk of transmission of more virulent genotypes.40,41 Furthermore, phylogenetic and epidemiological studies suggested that more virulent genotypes are now transmitted frequently over those with lower epidemiological impact, which perhaps due to effect of viral genetics on vector competence suppressing the vector innate immune response against the infecting virus.22 Quantitative trait loci genes play a key role in directing the vector innate immune response resulting in vector competence or refractory outcome.41,42

Knowledge of the status of dengue in Europe, effective prevention, and control strategies should be focus of European health-care agencies. Comprehensive understanding of the dynamics of the epidemiological triangle gives us solutions to mitigate the current burden and control the future expansion. Being an important driver of dengue transmission in Europe, control of travel associated dengue is a must.43

Dengue commonly shares symptoms with other febrile illnesses, especially during first stages of the disease, making the early detection difficult.43 The under-recognition of dengue contributes to the state of underestimation worldwide specially in non-endemic areas like Europe.43,44 This raises the importance of increasing clinical awareness among communities and health-care providers about the risk of travel and other risk factors associated with dengue expansion.43 This is a simple and effective way to reduce the state of underestimation in Europe, as early detection of cases and subsequently, reduction in rates of severe dengue and mortalities associated, particularly in the light of the evolution in dengue diagnostic tools.45 Serological tests are the most suitable screening tests for travelers being rapid, feasible, less expensive, dengue confirmatory, and able to differentiate between primary and secondary infection. Other diagnostic methods like viral isolation and viral RNA detection have the advantages of being more specific with the ability to detect the serotypes and genotypes of the virus but these methods cannot differentiate between primary and secondary infections, besides being expensive, time consuming, and the need of highly equipped laboratories.45,46 Absence of established vaccine and failure of environmental and vector control to prevent dengue expansion necessitate the usage of all epidemiological triangle aspects for prevention.47

Although this study highlights the risk of dengue on Europe, the obvious limitation is that we could not count the exact number of cases due to underreporting. In our data, we depended on published reports to compare past with present. However, many cases might not be reported. Moreover, the expansion factor cannot be calculated due to unavailability of negative surveillance studies in Europe which are recommended.

Despite current control and prevention measures, reports of imported dengue are increasing in Europe which in turn results in autochthonous cases. Severe dengue began to increase recently in Europe. DENV-2 is the most prevalent serotype in Europe. Infection with DENV-2 and secondary dengue are associated with severe dengue. Improved dengue prevention and control strategies should be carried out through *Aedes* vector,48 dengue virus,49 and human.50 Furthermore, dengue should be considered in the clinical diagnosis of fever of unknown origin in travelers returned from tropics or subtropics. Furthermore, surveillance and entomological surveillance studies are needed for autochthonous dengue cases in high risk areas.

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**Declaration of interests:**

The authors declare that there are no conflicts of interest

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**Figure legends**

1. Figure 1: PRISMA flow diagram showing study selection process. Content not satisfying criteria;1254 report in the first round (title and abstract screening) and 233 in the second round (full text screening) distributed as follow; Papers reporting cases outside Europe (n=649 and 94, respectively), papers reporting non-specific infection or dengue cases with expected dengue (n=476 and 79, respectively), papers with data that cannot be extracted (n=49 and 26, respectively), overlapped datasets (n=73 and 34, respectively), and papers reported non-human cases (n=3 and zero, respectively)).
2. Figure 2: Geographical classification of European countries regarding the distribution of the dengue cases
3. Figure 3: Geographical classification of the world destinations (world countries) from where dengue cases come to Europe according to the density of traveled cases.
4. Figure 4. Number of cases imported to each European country and the source of infection for each case. Each arrow indicated the number of cases imported from any place in the world to each European country. (A) Number of cases imported to Norway, Sweden, Finland, Russia, Turkey, Israel, Romania, and Poland. (B) Number of cases imported to Spain, Portugal, Italy, Switzerland, Czech Republic, and Denmark. (C) Number of cases imported to United Kingdom, Netherland, Belgium, Germany, and France.
5. Figure 5: The trend of dengue infection in Europe over the years. (A) distribution of total, Germany, and France cases, (B) provide the total proportion of cases with serotype data available, (C) provide the total proportion of cases with primary vs secondary infection data available, (D) distribution of both pooled proportion of imported dengue among all imported infections (like Chikungunya virus, West Nile virus, yellow fever, gastroenteritis, malaria, hepatitis A, B, C, and E, respiratory infection, urinary infection, tuberculosis, typhoid and paratyphoid, skin infection, and other infections) and pooled proportion of autochthonous dengue among all reported dengue, (E) demarcate the change in WHO definitions on the timeline. provide definitions in caption.
6. Figure 6. Distribution and impact of dengue severity in Europe. (A) The pooled rates of the different dengue classes in each country, (B) The correlation between the proportion of imported dengue among all imported infections and dengue severity, (C) The correlation between secondary dengue and dengue severity, (D) The impact of dengue serotypes on dengue severity.

**Abbreviation list**

DF; Dengue Fever, DHF; Dengue Hemorrhagic Fever, DSS; Dengue Shock Syndrome, CI; Confidence Interval, DENV-1; Dengue Virus Serotype 1, DENV-2; Dengue Virus Serotype 2, UK; United Kingdom, NO; Nitric Oxide.