



Enfermedades Infecciosas y Microbiología Clínica

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Editorial

How should we generalise the diagnosis of dengue as it spreads to more and more regions of the world?



¿Cómo deberíamos aumentar las oportunidades diagnósticas de dengue a medida que la infección se extiende a mas regiones del mundo?

In recent decades, the incidence of arbovirus (arthropod-borne viruses) infections has increased dramatically worldwide, often associated to international outbreaks causing great concern to public health authorities and citizens.¹ In 2022, the World Health Organization (WHO) launched the Global Arbovirus Initiative with the aim of raising the global alarm about the risk of arbovirus epidemics and the potential risk of pandemics.² The main priority actions are (1) monitor risk and anticipate, (2) prevention and prepare for epidemic, (3) enhance innovation and new approaches and (4) strengthening vector control. The most important and the fastest growing vector-borne disease is dengue, which is currently endemic in more than 100 countries distributed in five WHO regions.³ Last year, around 4 million cases of dengue disease were reported, but the suspected cases are many more.⁴ However, the actual data are unknown or underestimated because in many cases there is not capacity to perform an accurate diagnosis, because many infections are asymptomatic, and they are not diagnosed. In fact, according to WHO data, about half of the world population is now at risk of dengue with an estimated 100–400 million infections occurring each year.³ In the European Region, a non-endemic area, 20,959 dengue cases were reported between 2010 and 2020, (1348 in Spain). These cases have been mainly related to imported cases from epidemic regions. The first European autochthonous case was detected in France in 2010 and since then, 145 autochthonous cases have been reported.⁵ A total of 13 autochthonous cases have been described in Spain; the first one was detected in 2018 and the most recent autochthonous cases in 2023.⁶

This epidemiological change is linked to a wider extensive geographical distribution of the vectors involved in dengue virus (DENV) transmission. These expansions are attributed to favourable climatic conditions that facilitate vector survival and enable the mosquito biological cycle to be sustained upon their introduction. *Aedes aegypti* is present in the area around the Black Sea, and recently in Cyprus, while *Aedes albopictus* is well established in many European countries, particularly in the Mediterranean basin. In fact, all autochthonous Spanish cases have been detected in the Mediterranean region, where *Ae. albopictus* was first

established.⁷ However, the most recent ECDC report detected a stable presence of the vector in the communities of Aragon, Madrid, Castilla la Mancha, Extremadura, Navarre, the Basque Country and La Rioja in addition to those already described in the Mediterranean region (Catalonia, Balearic Islands, Valencian Community, Murcia and Andalusia).⁷ Moreover, *Ae. aegypti*, which is the most efficient vector for transmitting dengue, was detected in the Canary Islands during 2017 and 2022–2023, causing concern. Additionally, *Aedes japonicus* was found in Asturias in 2018 and subsequently detected in Cantabria (2019) and Basque Country (2020).⁸

Given the increasing incidence of dengue cases worldwide, those European countries such as Germany, France, UK, and Spain receive the highest number of travellers, migrants, and visiting friends and relatives (VFR) from endemic regions; and the other hand those European countries with a stable presence of the vector (Greece, Turkey, Croatia, Italy, France, and Spain) are particularly vulnerable to the introduction and transmission of DENV. Spain possesses the required conditions for the emergence of additional imported and autochthonous cases of dengue in a larger region of the national territory in the coming future and should take measures such as strengthening diagnostic and surveillance systems to prevent the spread of the disease.⁷ Recently, the Spanish Ministry of Health, in collaboration with other institutions of the General State Administration, the authorities of Public Health of Autonomous Communities, and the scientific societies, has elaborated a National Plan for the Prevention, Surveillance and Control of Vector-Borne Diseases aims to reduce the risk and minimise the global impact of these emerging diseases from a “One Health perspective” including a diagnostic working group.⁹ This plan includes dengue and other arboviral diseases such as chikungunya or zika. The National Plan aims to strengthen a greater understanding of the disease and raise awareness of the need to increase diagnostic capabilities for human arbovirus infections. In addition to these recommendations, this SEIMC editorial suggests a stratification of the detection strategies according to the complexity of the care centre and the required response that each of these clinical scenarios, but also improving the diagnostic opportunities through the implementation of a national surveillance programme.

The gold standard for direct DENV diagnosis is nucleic acid amplification tests (NAATs).¹⁰ However, this approach has several

DOI of original article: <https://doi.org/10.1016/j.eimc.2022.12.009>

<https://doi.org/10.1016/j.eimc.2023.09.003>

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limitations. One of these is that in many places this strategy is inaccessible, as the samples must be sent to reference laboratories, and the time between the first visit and diagnosis could be too long. This time would be particularly critical in those regions where the presence of the vector is known, because of the increased possibility of transmission chains among the autochthonous population. An alternative strategy is detection of NS1 antigen (NS1Ag). Although the optimal methods for NS1Ag detection are based on ELISA methods, rapid tests are also available. The point of care approach based on rapid NS1Ag detection tests (RDT) is accessible to different health systems, it is easy to perform and interpret, it does not require complex equipment, and the time on the test is minutes. A number of studies have evaluated different RDT for dengue. In general, these tests have satisfactory results in non-endemic areas, such as Spain, but with a limited utility in endemic areas.^{11,12} Several studies have assessed the potential benefits of RDT for diagnosing dengue in travellers.¹³ Rapid tests combining antigen and antibody detection may achieve sensitivity and specificity values close to 90%,¹⁴ making them a good option for extended surveillance. However, as the prevalence of dengue infections is highly variable depending on the annual prevalence and the target population, positive and negative predictive values could be also high variability.

A recent study by Camprubí-Ferrer et al., published in *ENFERMEDADES INFECCIOSAS Y MICROBIOLOGÍA CLÍNICA* (EIMC) journal analysed the availability of RDT in the emergency department (ED) of a tertiary hospital and its impact on the management of patients requiring hospitalisation and antibiotics in a Spanish hospital. This proposal is a good example for increase the screening and diagnosis of dengue infections. They found that the implementation of NS1Ag for dengue in the management of travellers with undifferentiated non-malarial fever returning to Spain would reduce the number and duration of hospitalisation (9.7% vs 32% in RDT-AgNS1 vs standard protocol respectively), the need for additional tests while awaiting a definitive diagnosis, the prescription of empirical antibiotics (46% received unnecessary antibiotics), and the cost per patient (cost savings between 290 and 546 €/patient).¹³ This work reveals added benefits to previously commented in this editorial. Similar proposals to Camprubí-Ferrer et al. have been implemented with success in ED but also in less complex hospitals or Primary Care (PC) during COVID pandemic, although the clinical and epidemiological scenario are very different.

In this editorial, we raise the following issues for discussion: Are the necessary conditions for this diagnostic strategy met in our country? Should the use of RDT be exported to PC and other non-specialised health centres in Spain? Finally, we will address the question of whether the decentralised diagnosis requires governance. In response to the first question, as we have explained previously, Spain is considered a hot spot for arboviral emergence, and the health authorities are strengthening the surveillance and diagnosis. Many tertiary hospitals have access to molecular diagnostics in Microbiology Departments, and several of them have on-call microbiologists for testing including RDT. Currently, in less complex hospitals or PC, the management of suspected cases without worrying signs is based on biochemical and haematological markers. Parameters suggestive of arboviral infection such as low leucocyte count or tourniquet test may be one of the few diagnostic options available in PC.¹⁵ These approaches are very nonspecific. Therefore, many dengue cases may be undiagnosed or incorrectly diagnosed. This leads us to the second question, should the use of RDTs be exported to PC and other non-specialised health centres in Spain? Clearly, the availability of RDTs for dengue diagnosis in these scenarios could be an interesting public health intervention. Many potential travellers from endemic areas will present to PC or non-specialised health centres with mostly mild symptoms.¹⁶ In this context, a rapid diagnosis would facilitate timely and effective

clinical management, and it could prevent unnecessary referrals to hospitals, and reduce ED visits. However, it is important to remember that a negative NS1Ag test in a patient with high suspect of dengue infection should be followed by specific dengue RT-PCR testing in a reference laboratory.

There are several examples in the literature of the use of RDT for the diagnosis of DENV especially in resource-limited settings.¹⁷ This strategy has also been implemented in PC in the context of an outbreak.¹⁸ Recently, in the Peruvian outbreak, the public health authorities indicated that there was an increased need for point-of-care testing to strengthen epidemiological surveillance.¹⁹ In addition to this, it is important to ensure that RDT for malaria are also available in all health centres even in the case of a positive dengue RDT. As malaria, being much more often a life-threatening disease than dengue, it is imperative to rule out malaria first when diagnosing dengue.²⁰

In these models, decentralisation of diagnosis has advantages for outbreak control. Could we then implement RDT in Spanish PC for early diagnosis and prevention of autochthonous cases? We can accept the national risk of an endemic situation in three decades or less and we must start implementing plans for the prevention, surveillance, and control of vector-borne diseases. However, this optimal proposal may be unrealistic because the current impact on public health may not be cost-effective. On the contrary, this measure could be evaluated through a sentinel surveillance programme (as is done for the surveillance of respiratory viral infections, such as influenza), especially in those Spanish regions where the presence of competent vectors for DENV transmission has been confirmed, at least during the period of high vector circulation and the highest flow of travellers or migrants from endemic areas. The delay in reporting imported cases to health authorities is the main factor facilitating the autochthonous spread of dengue.²¹ In this sense, several European reference laboratories suggest that preparedness plans need to look beyond national reference laboratories for strengthening of local capacity through a network of laboratories with different diagnosis capacities.²² This decentralised strategy would improve dengue diagnosis and a reinforcement of surveillance and prevention programmes.

According to this explanation, the last question: Does decentralised diagnosis require governance? Our answer must be in the affirmative. The knowledge of DENV and other tropical diseases was previously limited to specialised health areas, and it would be globalised in all health areas where these types of patients are attended. Improving the diagnosis is a good proposal as suggested by the work of Camprubí-Ferrer et al. However, the diagnosis of arbovirus infections is complicated because there are overlapping clinical manifestations between different arboviruses (for example, in the 2016 outbreak in Burkina Faso, only 25% of dengue-positive cases were clinically suspected¹⁸), and there could be cross-reactivity between related arboviruses.²² For this to happen, PC, ED, and laboratory professionals must be provided with the necessary training and resources to strengthen knowledge about DENV and arbovirus infections to enable an adequate interpretation of RDTs and appropriate clinical management. Decentralisation requires proximity reference laboratories for those clinical settings (PC and ED) with RDT-NS1Ag capacity, to which all specimens should be sent, regardless of clinical decisions, for confirmatory diagnosis in suspected cases or for more complex surveillance works. On the other hand, the Ministry of Health, the National Centre of Microbiology and Epidemiology, together with a network of reference and expert laboratories representing the different Autonomous Communities, should establish the governance of a national network for arboviral diagnosis and surveillance programme.

In conclusion, the Spanish epidemiological situation respect to arbovirus disease suggests the implementation of national plan of surveillance including a network of reference laboratory for early

detection tests for dengue in febrile travellers from endemic areas but also a network sentinel for surveillance in regions with high risk of autochthonous dengue cases. Both requirements appear to be a promising approach to improve disease management, while recognising its limitations and difficulties.

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