

DISCLAIMER

This paper was submitted to the *Memórias do Instituto Oswaldo Cruz* on 10 May 2020 and was posted to the Fast Track site on 13 May 2020. The information herein is available for unrestricted use, distribution and reproduction provided that the original work is properly cited as indicated by the Creative Commons Attribution licence (CC BY).

RECOMMENDED CITATION

Spinicci M, Bartoloni A, Mantella A, Zammarchi I, Rossolini GM, Antonelli A. Low risk of serological cross-reactivity between dengue and COVID-19 [Submitted]. *Mem Inst Oswaldo Cruz* E-pub: 13 May 2020.doi: 10.1590/0074-02760200225.

SHORT COMMUNICATION

Low risk of serological cross-reactivity between dengue and COVID-19

Michele Spinicci^{1,2*}, Alessandro Bartoloni^{1,2}, Antonia Mantella¹, Lorenzo Zammarchi^{1,2}, Gian Maria Rossolini^{1,3}, Alberto Antonelli^{1,3}

¹ Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy.

² Infectious and Tropical Diseases Unit, Careggi University Hospital, Florence, Italy.

³ Microbiology and Virology Unit, Careggi University Hospital, Florence, Italy.

*Corresponding-author: michele.spinicci@unifi.it

<https://orcid.org/0000-0002-5377-7118>

Abstract

In the near future, the overlap of COVID-19 and dengue epidemics is a concrete threat in tropical regions. Co-epidemics of COVID-19 and dengue could be an overwhelming challenge for health systems in low- and middle-income countries. In this work, we investigated potential serological cross-reactions between COVID-19 and dengue patients. Further data on accuracy of COVID-19 diagnostic test are urgently warranted.

Keywords: COVID-19; SARS-CoV-2; dengue; antibodies

Since December 2019, Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in the international scene as a major public health concern. COVID-19 pandemic is having a disrupting impact on health systems throughout Asia, Europe and America.¹ At the same time, a large outbreak of dengue is ongoing in Latin American countries, with several deaths being recorded.²

In the near future, the overlap of COVID-19 and dengue epidemics is a concrete threat in tropical regions.^{3,4} COVID-19 and dengue share several features of clinical and laboratory presentation, and differential diagnosis should rely on specific diagnostic tests.⁵ Recently, two cases of false-positive results by rapid diagnostic test (RDT) for dengue in patients with SARS-CoV-2 infection were reported from Singapore.⁶ If serological cross-reactivity between patients with COVID-19 and dengue will be confirmed, it may result in a high number of misdiagnoses, with dangerous consequences both from the patients and public health point of view.⁷

In order to further explore this possibility, we investigated potential serological cross-reactions between COVID-19 and dengue patients, by performing commercial assays for detection of anti-Dengue virus (DENV) and anti-SARS-CoV-2 antibodies on sera from well-characterized COVID-19- and dengue-positive patients, respectively.

A total of 32 anonymized sera, obtained from symptomatic patients with COVID-19 diagnosed by positive anti-SARS-CoV-2 IgM/IgG (32/32) and/or RT-PCR for SARS-CoV-2 on nasopharyngeal swab (26/32), were tested by Dengue Enzyme Linked Immune Assay (ELISA) DENV IgG-IgM (VIRCELL, Granada, Spain). Sera were collected and tested in Italy, at the Careggi University Hospital of Florence, where dengue is not endemic, and previous exposure to DENV was unlikely.

Moreover, 44 anonymized DENV-positive sera, from cases of acute dengue, were tested by using COVID-19 IgG/IgM Rapid Test Cassette (Orient Gene, Zhejiang, China) and 2019-NCoV IgG/IgM Rapid Test Cassette (ScreenItalia, Perugia, Italy). All DENV-positive sera were collected from travellers, before SARS-CoV-2 emergence.

Among 32 COVID-19 positive sera, no positive DENV IgG/IgM results were observed. On the other hand, one false-positive result was observed among 44 DENV-positive sera tested for COVID-19 antibodies with each method (in one case for IgG and IgM, and in another for IgG only), in two different samples.

Serological test for dengue are known to be affected by cross-reactivity issues in areas where multiple Flavivirus, such as Zika, Yellow fever or Japanese encephalitis virus are circulating. The risk of false-positive results is reduced when dengue IgM/IgG testing is paired with NS1 antigen capture.⁸

According with our results, the concern about false-positive dengue serology in COVID-19 patients could be downsized, at least when an ELISA is used. On the other hand, COVID-19 false-positive results are possible in patients with DENV infection, although at a low rate and variably using different RDTs for COVID-19. It should be also considered that these COVID-19 false-positive results may reflect different specific cross-reactivity, not necessarily related to DENV-specific antibodies.⁹

In low- and middle-income countries, where arboviroses and other common tropical diseases are highly endemic, SARS-CoV-2 spread will represent an additional challenge for clinicians.^{10,11} In particular, co-epidemics of COVID-19 and dengue could be an overwhelming situation for health systems.¹² Further studies are warranted to better elucidate the accuracy of commercially available

RDTs for SARS-CoV-2 antibodies detection and their role within the strategy for COVID-19 diagnosis and control.

Acknowledgements: This article has been supported by funds of “Ministry of Education, University and Research (Italy) Excellence Departments 2018–2022” Project for the Department of Experimental and Clinical Medicine.

Author's contribution: MS, AB, LZ, GMR contributed to the study design. AA and AM performed laboratory tests. All authors contributed to data analysis, interpretation and critically reviewed the paper

References:

1. World Health Organization 2020. Coronavirus disease (COVID-2019) situation reports. Available at: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/>
Last access: 9th May 2020.
2. Pan American Health Organization / World Health Organization. Epidemiological Update: Dengue. 7 February 2020, Washington, D.C. PAHO / WHO.
3. Navarro JC, Arrivillaga-Henríquez J, Salazar-Loor J, Rodriguez-Morales AJ. COVID-19 and dengue, co-epidemics in Ecuador and other countries in Latin America: Pushing strained health care systems over the edge. *Travel Med Infect Dis.* 2020 Apr 5:101656.
4. Lorenz C, Azevedo TS, Chiaravalloti-Neto F. COVID-19 and dengue fever: A dangerous combination for the health system in Brazil. *Travel Med Infect Dis.* 2020 Apr 9:101659.

5. Lam LTM, Chua YX, Tan DHY. Roles and challenges of primary care physicians facing a dual outbreak of COVID-19 and dengue in Singapore. *Fam Pract*. 2020 May 6. pii: cmaa047.
6. Yan G, Lee CK, Lam LTM, Yan B, Chua YX, Lim AYN, et al. Covert COVID-19 and false-positive dengue serology in Singapore. *Lancet Infect Dis*. 2020 Mar 4. pii: S1473-3099(20)30158-4.
7. Li R, Pei S, Chen B, Song Y, Zhang T, Yang W, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2). *Science* 2020:eabb3221.
8. Muller DA, Depelseñaire AC, Young PR. Clinical and Laboratory Diagnosis of Dengue Virus Infection. *J Infect Dis*. 2017;**215**(suppl_2):S89-S95.
9. Sethuraman N, Jeremiah SS, Ryo A. Interpreting Diagnostic Tests for SARS-CoV-2. *JAMA*. 2020 May 6. doi: 10.1001/jama.2020.8259.
10. Bokhari SMMA, Mahmood F, Bokhari SMSA. Case Report: Diagnosis of Novel Coronavirus Disease (COVID-19) versus Tropical Diseases in Pakistan. *Am J Trop Med Hyg*. 2020 May 5. doi: <https://doi.org/10.4269/ajtmh.20-0356>.
11. Joob B, Wiwanitkit V. COVID-19 can present with a rash and be mistaken for dengue. *J Am Acad Dermatol*. 2020 May;82(5):e177.
12. Wu D, Lu J, Liu Q, Ma X, He W. To alert co-infection of SARS-COV-2 and dengue virus in developing countries in the dengue-endemic area. *Infect Control Hosp Epidemiol*. 2020 May 4:1-6.