# Potential antigenic cross-reactivity between SARS-CoV-2 and Dengue viruses

Yaniv Lustig Ph.D.[1], Shlomit Keler M.D.[2,3], Rachel Kolodny Ph.D.[4], Nir Ben-Tal Ph.D. [5], Danit Atias-Varon Ph.D.[2], Ekaterina Shlush M.D.[6], Motti Gerlic Ph.D. [7], Ariel Munitz Ph.D.[7], Ram Doolman Ph.D.[8,9], Keren Asraf Ph.D.[8] , Liran I. Shlush M.D., Ph.D.[10]* and Asaf Vivante M.D., Ph.D.*[2,3,11]

[1]Central Virology Laboratory, Ministry of Health, Chaim Sheba Medical Center, Ramat Gan, Israel

[2]Department of Pediatrics B, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat-Gan, Israel

[3]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

[4]Department of Computer Science, University of Haifa, Mount Carmel, Israel

[5]Department of Biochemistry and Molecular Biochemistry, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel-Aviv, Israel

[6]IVF Unit Department of Obstetric and Gynecology Galilee Medical Center, Naharia, Israel

[7]Department of Clinical Microbiology and Immunology, Sackler School of Medicine, Tel Aviv University, 6997801 Israel

[8]The Dworman Automated-Mega Laboratory, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel

[9]The Mina and Everard Goodman Faculty of Life Sciences, Bar-Ilan University, Ramat-Gan, Israel

[10]Department of Immunology, Weizmann Institute of Science, Rehovot, Israel

[11]Talpiot Medical Leadership Program, Sheba Medical Center, Tel-Hashomer, Israel

* These authors contributed equally to this work.

**Correspondence should be addressed to:**

Asaf Vivante, M.D., Ph.D.

Pediatric Department B, Edmond and Lily Safra Children's Hospital, Chaim Sheba Medical Center, Tel Hashomer and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

**Email:** Asaf.Vivante@Sheba.health.gov.il or asafvivante@gmail.com

**Summary:**

Significant serologic cross-reactivity between dengue virus and SARS-CoV-2, which can lead to false-positive dengue serology among COVID-19 patients and vice versa. Cross-reactivity between SARS-CoV-2 and dengue viruses may interfere with accurate clinical diagnosis and treatment of both diseases.

## ABSTRACT

**BACKGROUND:** COVID-19 and dengue fever are difficult to distinguish given shared clinical and laboratory features. Failing to consider COVID-19 due to false-positive dengue serology can have serious implications. We aimed to assess this possible cross reactivity.

**METHODS**: We analyzed clinical data and serum samples from 55 individuals with SARS-CoV-2 infection. To assess dengue serology-status, we used dengue-specific antibodies by means of lateral-flow rapid test as well as enzyme-linked-immunosorbent-assay (ELISA). Additionally, we tested SARS-CoV-2 serology-status in patients with dengue and performed in-silico protein structural analysis to identify epitope similarities.

**RESULTS:** Using the dengue lateral-flow rapid test we detected 12 positive cases out of the 55 (21.8%) COVID-19 patients *versus* zero positive cases in a control group of 70 healthy individuals (P= 2.5E-5). This includes nine cases of positive IgM, two cases of positive IgG and one case of positive IgM as well as IgG antibodies. ELISA testing for dengue was positive in two additional subjects using envelope-protein directed antibodies. Out of 95 samples obtained from patients diagnosed with dengue before September 2019, SARS-CoV-2 serology targeting the S protein was positive/equivocal in 21 (22%) (sixteen IgA, five IgG) *versus* four positives/equivocal in 102 controls (4%) (P= 1.6E-4). Subsequent in-silico analysis revealed possible similarities between SARS-CoV-2 epitopes in the HR2-domain of the spike-protein and the dengue envelope-protein.

**CONCLUSIONS:** Our findings support possible cross-reactivity between dengue virus and SARS-CoV-2, which can lead to false-positive dengue serology among COVID-19 patients and vice versa. This can have serious consequences for both patient care and public health.



**Keywords:** COVID-19, Dengue, West Nile

## INTRODUCTION

COVID-19, the illness caused by the recently identified severe acute respiratory coronavirus 2 (SARS-CoV-2) has rapidly spread worldwide. As of August 1st, 2020, over ten million patients have been reported globally (https://covid19.who.int/). The symptoms of SARS-CoV-2 infection vary widely, from asymptomatic disease to multisystem organ failure [1, 2]. Symptoms of COVID-19 can also be non-specific and be misdiagnosed. For instance, both dengue fever and COVID-19 are difficult to distinguish as they share similar clinical and laboratory features [3-5]. Moreover, in two cases from Singapore, it has been reported that rapid serological testing for dengue can show false-positive results among COVID-19 patients [6]. This clinical diagnostic challenge is particularly important in regions around the world with dual outbreak of both COVID-19 and dengue [7, 8].

The global burden of dengue has grown dramatically in recent decades as half of the world's population lives in dengue-endemic areas [9]. Approximately 100-400 million cases occur each year (https://www.who.int/en/news-room/fact-sheets/detail/dengue-and-severe-dengue). Laboratory diagnosis of dengue is established directly by detection of viral components in serum or indirectly by serologic means. During the febrile phase detection of the virus-expressed soluble nonstructural protein 1 (NS1) or dengue specific IgM antibodies by means of enzyme-linked immunosorbent assay (ELISA) or the lateral-flow rapid test is sufficient for a confirmatory diagnosis [9]. Lateral flow based tests are the most prevalent diagnostic method especially in dengue endemic countries since they do not require special knowledge or equipment and are not affected by high ambient tropical temperatures or humidity [10, 11]. Given that a possible cross-reactivity between dengue virus and SARS-CoV-2 could lead to false-positive results for both diseases we aimed to assess the magnitude of such possible-cross reactivity in a large cohort of individuals which were known to have either SAR-CoV-2 or dengue virus.

## METHODS

### Study participants

We included in the study clinical data and serum samples obtained from individuals with proven severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who were tested for COVID-19 in the Israeli Ministry of Health Central Virology Laboratory. The assay is based on the World Health Organization standard. It targets the SARS-CoV-2 envelope (E), N and RdRp genes [12]. Diagnosis was based on nasopharyngeal swabs which were tested for SARS-CoV-2 by reverse transcriptase–polymerase chain reaction. Only laboratory-confirmed cases were included. The institutional review board of Sheba Medical Center approved the study and waived the requirement for informed consent on the basis of preserving participants' anonymity

### Serological assays

***Serology testing to detect dengue, West Nile virus (WNV) and SARS-CoV-2 antibodies***

Antibodies against dengue virus were detected by the following commercially available immunoassays: lateral-flow rapid diagnostic test which detects antibodies against the envelope protein (RDT; SD BIOLINE Dengue IgG/IgM WB (Abbott, Chicago, USA)) and shown to be highly specific [13, 14] and by ELISA against the envelope ((Panbio® Dengue IgG and IgM Indirect ELISA (Abbott, Chicago, USA)) and nonstructural (NS)-1 (anti dengue NS1 type 1-4 IgG, Euroimmun, Germany) proteins. Detection of IgM or IgG antibodies against WNV in serum samples was performed using ELISA (WNV IgM capture DxSelect ELISA and IgG DxSelect ELISA kits by Focus Diagnostics Inc., Cypress, CA, USA). Samples were tested in all the immunoassays according to the manufacturer's instructions. WNV neutralization was performed as described [15] using a WNV strain (S42H) isolated in Israel in 2015. A dilution equal to 1:10 or above was considered neutralizing. SARS-CoV-2

IgA and IgG antibodies were detected by 2 assays: 1. A semi quantitative ELISA (anti-SARS-CoV-2 ELISA IgG, Euroimmun, Germany) performed according to the manufacturer's recommendation [16, 17]. 2. Mount Sinai Hospital Clinical Laboratory COVID-19 ELISA Antibody Test [18] which was modified accordingly: a 96 well microtiter Polysorb plate (Nunc, Thermo, Denmark) coated overnight with 1ug/ml of Receptor Binding Domain (RBD) antigen for detection of IgG and 2ug/ml for detection of IgA antibodies was blocked with 5% skimmed milk at 25ºC for 60 minutes and human serum samples (diluted 1:100 with 3% skimmed milk), were added to antigen coated wells. The plate was incubated at 25ºC for 120 minutes, washed and goat anti-human IgG horseradish peroxidase (HRP) conjugate (Jackson ImmunoResearch, PA, USA) (diluted 1:15000) or anti human IgA HRP conjugate (Abcam) was added to each well for 60 min. after addition of TMB substrate and stop solution (1M HCl) the OD of each well was measured at 450nm. ELISA index value above or equal to 1.1 was considered positive. SARS-CoV-2 RBD IgM was detected by a electrochemiluminescence serological test as described (medRxiv preprint doi: https://doi.org/10.1101/2020.06.28.20141838).

**Bioinformatics**

***Protein structure analysis***

We hypothesized that cross reactivity between SARS-CoV-2 and dengue virus could be the result of similarities in the structures of outer proteins of these two viruses. Such similarities could potentially cause cross reactivity if the chains that appear in the outer surface of the virus are exposed to the immune system and trigger the expansion of similar antibodies. Accordingly, we identified the outer chains of selected Flaviviruses and of SARS-CoV-2 and compared their structures (Supplementary **Table 1S**). Cross-reactivity between the different Flaviviruses is well established [19], accordingly we used this information as a positive control to test whether such cross reactivity could be observed also at the epitope similarity

level. We used the 0-1 TM-score scale to measure similarity: TM-score < 0.30 is random structural similarity, while 0.5 < TM-score implies the structures have the same fold (i.e., are similar in shape) [20]; here, we use the threshold of 0.45 to identify similar structures. TM-score reports were normalized by both aligned chains; we use the maximum among these scores. To study all similar protein chains in these viruses, we organize the data as a network and use Cytoscape [21] to visualize it.

### Statistical analysis

Descriptive statistics were used to summarize the data; results are reported as medians and standard deviations, as appropriate. Categorical variables were summarized as counts and percentages. P values were calculated using the two tails exact Fisher's test.

## RESULTS

### Clinical findings

During the period from March 17 through April 13, we identified 55 patients with confirmed COVID-19 infection. The demographic and clinical characteristics of the patients are shown in Supplementary **Table 2S**. The mean (±SD) age of the patients was 45±20 years (range, 14 to 84); 53% were men. The mean duration of symptoms before COVID-19 diagnosis was 7±8 days. Thirty-one patients were hospitalized (56%) and 24 were managed as outpatients (44%). Full clinical and laboratory details of the former group are shown in Supplementary **Table 2S**. None of the patients had recently traveled to a dengue virus endemic region.

### Dengue virus rapid test serology was positive in 12 out of 55 patients (22%) with SARS-CoV-2 infection

We first tested the study cohort for IgG and IgM antibodies using the rapid dengue virus diagnostic test (SD BIOLINE Dengue). We found nine patients positive for IgM, three

positive for IgG and one positive for both IgM and IgG out of the 55 individuals with confirmed COVID-19 (**Table 1**). In addition, we tested serum samples from a control group of 70 healthy individuals which we obtained prior to September 2019. In this cohort the dengue rapid test was negative in all samples (P= 2.5E-5). Subsequently, we assessed dengue virus serostatus using ELISA which detects antibodies directed against dengue E protein. This analysis demonstrated that out of the 12 COVID-19 patients who were positive using the dengue rapid test, only one had a weak positive IgG result and non were positive for ELISA IgM (**Table 1**). In addition, dengue IgM and IgG E based ELISA were positive in one and five patients respectively out of the 43 COVID-19 patients who were negative using the initial dengue rapid test. Dengue has known cross reactivity with the E protein of WNV. Additionally, WNV seropositivity in the Israeli population is estimated at approximately 11% [22]. Therefore, we tested these IgG dengue E positive samples for WNV E based IgG and IgM ELISA and subsequently performed WNV neutralization. Out of the five dengue positive samples, three were positive for WNV E IgG. These samples were also positive in WNV-neutralization, further providing evidence that these dengue fever positive ELISA samples represented antigenic cross reactivity with past infection with WNV. Since dengue is not endemic in Israel it is highly unlikely that these COVID-19 patients with positive E IgG dengue, negative E IgG WNV were previously infected with Dengue. Nevertheless, these samples were tested negative with a NS1 based ELISA which detects antibodies against dengue NS1 and therefore efficiently evaluate past exposure to dengue virus [23]. Overall these results suggest that cross reactivity between ELISA dengue E IgG and SARS-CoV-2 may also exist **(Table 1)**. Testing the 14 samples from dengue cross reactive COVID-19 patients with 2 ELISAs and an electrochemiluminescence serological test for IgA, IgM and IgG demonstrated that all but one sample had equivocal or positive antibodies against SARS-CoV-2.

**SARS-CoV-2 serology status among patients with dengue fever**

To test the possibility of false positive SARS-CoV-2 serology in patients diagnosed with dengue fever, we assessed SARS-CoV-2 serology status in serum samples obtained prior to September 2019 from patients with clinical and serological diagnosis of acute (IgM) and past (IgG) dengue fever. Using the Euroimmun ELISA which detects antibodies against the S protein, we found 21 out of 95 samples to be positive or equivocal for SARS-CoV-2 IgG or IgA antibodies. This is significantly higher FP rates as compared with rates detected in 102 healthy controls (4% vs 22%, P = 1.6E-4) and in prior studies [16, 17] (Supplementary **Table 3S**). We next examined if the cross reactivity observed was a general or more specific phenomenon by testing samples from acute (IgM) and past (IgG) dengue fever patients with an ELISA which detects antibodies against the RBD antigen. Results (Supplementary **Table 3S**) show higher, although not statistically significant, FP rates for samples obtained from past dengue fever patients as compared with healthy controls. To further explore such cross reactivity between SARS-CoV-2 and dengue virus we hypothesized that although they belong to different families of viruses they might share structural similarities.

**In-silico protein structure analysis reveals possible similarity between SARS-CoV-2 spike protein and dengue envelope protein**

Since sequence similarity could not explain the observed cross reactivity (Supplementary **Figure 1S)** we hypothesized that structure similarity might expose regions in the outer protein chains that can explain the immune cross reactivity. We focused our analysis on the comparison of folds of chains and structures that are known to be in the outer surface of a protein, because it is estimated that antibodies identify epitopes which are in specific folds. Based on these assumptions we propose that structure similarity might correlate with positivity rate. Indeed, very high similarity (TM score 0.75-1.0) was found between many chains of the different Flaviviruses **(Supplementary figure 2S, Figure 1 panel A**). The same

analysis between Flaviviruses and SARS-CoV2 identified high similarity between the SARS-COV-2 6LVN chains which are part of the HR2 domain of the spike protein and several chains in the envelope protein of both dengue (4CBF, 4UIF, 5A1Z etc) and Zika viruses (6JFI, 5YGH, etc). The similarity between SARS-CoV-2 6LVN chains and WNV were not with chains of the envelope protein but rather with chains of the NS1 protein (4O6C) of WNV (**Figure 1 panel B**). Few other SARS-CoV-2 chains from the spike protein (6LXT, 6VSB, 6VXX etc) demonstrated high similarity with chains from the envelope protein of both Zika and dengue viruses, while such similarity could not be apparent with chains from WNV (**Figure 1 panel B**). Altogether, we identified structure similarities between chains of the SARS-CoV-2 spike protein and chains of the envelope protein of both Zika and dengue but not with WNV. Such similarities could potentially explain the cross reactivity between SARS-CoV-2 and dengue virus.

## DISCUSSION

Here we provide lines of evidence to support cross-reactivity between dengue and SARS-CoV-2 which can lead to false-positive dengue serology among patients with COVID-19. Failing to consider COVID-19 infection because of a positive dengue result can have serious consequences for both patient care as well as for public health policies.

Dengue fever and COVID-19 are difficult to distinguish because they share clinical and laboratory features [3-5]. Yan G et. al. recently described two cases which were wrongly diagnosed as dengue but later confirmed to be COVID-19 [5]. In addition, it has been recently reported in Brazil and other regions that both viruses spread simultaneously as co-pandemics [7, 24]. In these regions, diagnostic misclassification can be highly problematic. Cross-reactivity between SARS-CoV-2 and dengue viruses may interfere with accurate

clinical diagnosis and treatment, understanding of undelaying pathomechanisms and possible development of vaccine.

We cannot exclude the possibility that the phenomenon seen in this study is assay specific false positive and not true antigenic cross reactivity. Our results demonstrating cross reactivity of samples from COVID-19 patients on the dengue RDT as well as samples from dengue patients with the Euroimmun ELISA in addition to our in-silico protein structure analysis suggests that at least some specific antigenic cross reactivity exists. However, the results of the dengue ELISA and SARS-CoV-2 Mount Sinai RBD-ELISA demonstrating only minimal cross reactivity suggests that this cross reactivity is not due to a significant antigenic similarity. It is possible to speculate that the existence of minor structural similarities between dengue and SARS-CoV-2 may result in selected epitopes identity. As a consequence only assays detecting antibodies targeting these epitopes will show differential cross reactivity. Nevertheless, both the dengue rapid test (RDT) and the SARS-CoV-2 ELISA are widely used worldwide and therefore the issue of cross reactivity with these assays have huge implications. One interesting example is the RDT dengue by SD bioline (shown here to detect 22% of COVID-19 patients): This assay was shown by us and others to be highly specific with ~95-100% specificity, with sensitivity that depends on the time since symptom onset [13, 14]. The SD bioline test is one of the most used in the world for dengue diagnosis because it is cheap and available to test in resource-poor settings. It is widely used in South East Asia and South America - areas endemic to dengue with most dengue infections, and much less used in developed countries which mostly see only returning travelers infected with dengue. Moreover, with the introduction of the Sanofi dengue vaccine and the increased risk for severe disease within dengue naïve individuals, it is now mandatory to test for dengue antibodies before immunization [24]. Therefore, in South East Asia and South America, which have co-circulation of dengue and COVID-19 [7, 23] 22% of COVID-19 infections

may be falsely identified as dengue. This may lead to spread of COVID-19 infections due to lack of isolations as well as vaccination of dengue naïve individuals.

Furthermore, antigenic cross-reactivity between dengue and COVID-19 raises questions regarding the possibility of protective immunity overlap between these two diseases, on the one hand, or worsening of the disease through antibody dependent enhancement on the other hand. This question should be addressed in future studies. Finally, our observations of structure similarity of specific SARS-CoV-2 and dengue protein structures could explain the observed cross reactivity. Interestingly, our bioinformatics structure similarity does not predict cross-reactivity with WNV, and indeed we could not observe such cross-reactivity. Our results also predict potential cross reactivity with Zika virus, which needs to be further validated. These results suggest that protein structure similarities regardless of genetic distance could predict cross reactivity between viruses from distant phylogenetic lineages.

Altogether, our results highlight the importance of recognizing false-positive dengue serology results in patients with COVID-19 and vice versa.

**Acknowledgments:** We thank Ravit Koren, Shiri Katz-Likvornik, Osnat Helpern and Mayan Yitzchaki for facilitating COVID-19 sample analysis. YL is supported by the Nehemia Rubin Excellence in Biomedical Research – The TELEM Program. LIS is an incumbent of the Ruth and Louis Leland career development chair. This research was also supported by the Sagol Institute for Longevity Research, the Barry and Eleanore Reznik Family Cancer Research Fund, Steven B. Rubenstein Research Fund for Leukemia and Other Blood Disorders, the Rising Tide Foundation and the Applebaum Foundation. RK and NB-T acknowledge the support of ISF grant 450/16 of the Israeli Science Foundation (ISF). NB-T's research is supported in part by the Abraham E. Kazan Chair in Structural Biology, Tel Aviv University.

**Disclosures:**

Competing interests: AM and MG filed a patent application regarding antibodies that were presented in this study. They report grants from Biological Industries for development of the electrochemiluminescense COVId-19 IgM. All other authors have no additional competing interests.

## References


1. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med **2020**.
2. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. N Engl J Med **2020**.
3. Nunthavichitra S, Prapaso S, Luvira V, Muangnoicharoen S, Leaungwutiwong P, Piyaphanee W. Case Report: COVID-19 Presenting as Acute Undifferentiated Febrile Illness-A Tropical World Threat. The American journal of tropical medicine and hygiene **2020**.
4. Janah H, Zinebi A, Elbenaye J. Atypical erythema multiforme palmar plaques lesions due to Sars-Cov-2. Journal of the European Academy of Dermatology and Venereology : JEADV **2020**.
5. Bokhari S, Mahmood F, Bokhari S. Case Report: Diagnosis of Novel Coronavirus Disease (COVID-19) versus Tropical Diseases in Pakistan. The American journal of tropical medicine and hygiene **2020**.
6. Yan G, Lee CK, Lam LTM, et al. Covert COVID-19 and false-positive dengue serology in Singapore. The Lancet Infectious diseases **2020**; 20(5): 536.
7. Magalhaes T, Chalegre KDM, Braga C, Foy BD. The Endless Challenges of Arboviral Diseases in Brazil. Tropical medicine and infectious disease **2020**; 5(2).
8. Lam LTM, Chua YX, Tan DHY. Roles and challenges of primary care physicians facing a dual outbreak of COVID-19 and dengue in Singapore. Family practice **2020**.
9. Simmons CP, Farrar JJ, Nguyen v V, Wills B. Dengue. The New England journal of medicine **2012**; 366(15): 1423-32.
10. Phommasone K, Sengvilaipaseuth O, de Lamballerie X, et al. Temperature and the field stability of a dengue rapid diagnostic test in the tropics. The American journal of tropical medicine and hygiene **2015**; 93(1): 33-9.
11. Blessmann J, Winkelmann Y, Keoviengkhone L, et al. Assessment of diagnostic and analytic performance of the SD Bioline Dengue Duo test for dengue virus (DENV) infections in an endemic area (Savannakhet province, Lao People's Democratic Republic). PloS one **2020**; 15(3): e0230337.
12. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin **2020**; 25(3).
13. Lee H, Ryu JH, Park HS, et al. Comparison of Six Commercial Diagnostic Tests for the Detection of Dengue Virus Non-Structural-1 Antigen and IgM/IgG Antibodies. Ann Lab Med **2019**; 39(6): 566-71.
14. Matusali G, Colavita F, Carletti F, et al. Performance of rapid tests in the management of dengue fever imported cases in Lazio, Italy 2014-2019. Int J Infect Dis **2020**.
15. Lustig Y, Mannasse B, Koren R, et al. Superiority of West Nile Virus RNA Detection in Whole Blood for Diagnosis of Acute Infection. Journal of clinical microbiology **2016**; 54(9): 2294-7.
16. Tang MS, Hock KG, Logsdon NM, et al. Clinical Performance of Two SARS-CoV-2 Serologic Assays. Clinical chemistry **2020**.
17. Krüttgen A, Cornelissen CG, Dreher M, Hornef M, Imöhl M, Kleines M. Comparison of four new commercial serologic assays for determination of SARS-CoV-2 IgG. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology **2020**; 128: 104394.
18. Amanat F, Stadlbauer D, Strohmeier S, et al. A serological assay to detect SARS-CoV-2 seroconversion in humans. Nat Med **2020**; 26(7): 1033-6.
19. Rathore APS, St John AL. Cross-Reactive Immunity Among Flaviviruses. Frontiers in immunology **2020**; 11: 334.
20. Zhang Y, Skolnick J. TM-align: a protein structure alignment algorithm based on the TM-score. Nucleic acids research **2005**; 33(7): 2302-9.

21. Shannon P, Markiel A, Ozier O, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome research **2003**; 13(11): 2498-504.
22. Bassal R, Shohat T, Kaufman Z, et al. The seroprevalence of West Nile Virus in Israel: A nationwide cross sectional study. PloS one **2017**; 12(6): e0179774.
23. Nascimento EJM, George JK, Velasco M, et al. Development of an anti-dengue NS1 IgG ELISA to evaluate exposure to dengue virus. Journal of virological methods **2018**; 257: 48-57.
24. 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 medicine and infectious disease **2020**: 101656.

## FIGURE LEGENDS

**Figure 1. Structural similarities between Flaviviruses and SARS-CoV-2**

Nodes represent outer protein chains, colored based on their virus. Edges connect chains in two viruses that are structurally similar (max TM-score > 0.45) and colored based on the TM-score, with darker edges representing more similar structures

**Panel A** shows extensive structural similarity among the outer proteins of the three Flaviviruses. To compare the structural similarities between Corona virus and the three Flaviviruses, we first cluster the protein chains: two chains are grouped into the same cluster if they belong to the same virus, their sequences are more than 90% identical, and the structures of the aligned residues are essentially the same (less than 1A RMSD). Supplementary Table 1S lists the number of clusters for each virus.

**Panel B** shows a network, where the nodes are clusters of chains, colored based on their virus and edges connect two clusters of chains which include structurally similar chains; the width of the edge is proportional to the number of structurally similar chain pairs within the two clusters. The chains in each node are described herein :**Blue nodes West-Nile virus**: 1) 4O6C_A, 4O6C_B, 4O6C_C, 4O6C_D, 4O6C_E, 4O6C_F, 4O6D_B, 4TPL_B; 2) West Nile: 4O6D_A, 4TPL_A. **Purple nodes for Zika virus**: 3) 5YGH_A, 5YGH_B; 4) 6C44_A, 6C44_B; 5) 5GS6_A, 5GS6_B; 6) 5K6K_A, 5K6K_B; 7) 5IRE_E, 6JFI_E,6JFH_E; 8) 5IRE_C, 6JFI_C, 6JFH_C; 9) 5GZR_A, 5GZR_B, 5GZR_C, 5IZ7_A, 5IZ7_B, 5IZ7_C, 5H30_A, 5H30_B, 5H30_C, 5H37_A, 5H37_B, 5H37_C; 10) 5IRE_A, 6JFI_A, 6JFH_A; 11) 5U4W_G, 5U4W_I, 5U4W_K; **Yellow nodes Dengue virus**: 12) 3J27_A, 3J27_C, 3J27_E, 3J2P_A, 3J2P_C, 4CBF_A, 4CBF_C, 4CBF_E, 4UIF_C, 4UIF_E, 5A1Z_C, 5A1Z_E; 13) 4UIF_A, 5A1Z_A; 14) 3J27_B, 3J27_D, 3J27_F, 3J2P_B, 3J2P_D, 4CBF_B, 4CBF_D, 4CBF_F, 4UIF_B, 4UIF_D, 4UIF_F, 5A1Z_B, 5A1Z_D, 5A1Z_F; **Red nodes SARS-COV-2 :** 15) 6LXT_A, 6LXT_B, 6LXT_C, 6LXT_D, 6LXT_E, 6LXT_F; 16) 6VSB_B, 6VSB_C, 6VXX_A,6VXX_B, 6VXX_C, 6VYB_A, 6VYB_C; 17) 6VSB_A, 6VYB_B; 18) 6LVN_A, 6LVN_B, 6LVN_C, 6LVN_D.

**Table 1. Serology characteristics of 14 patients with covid-19 and false positive Dengue serology**

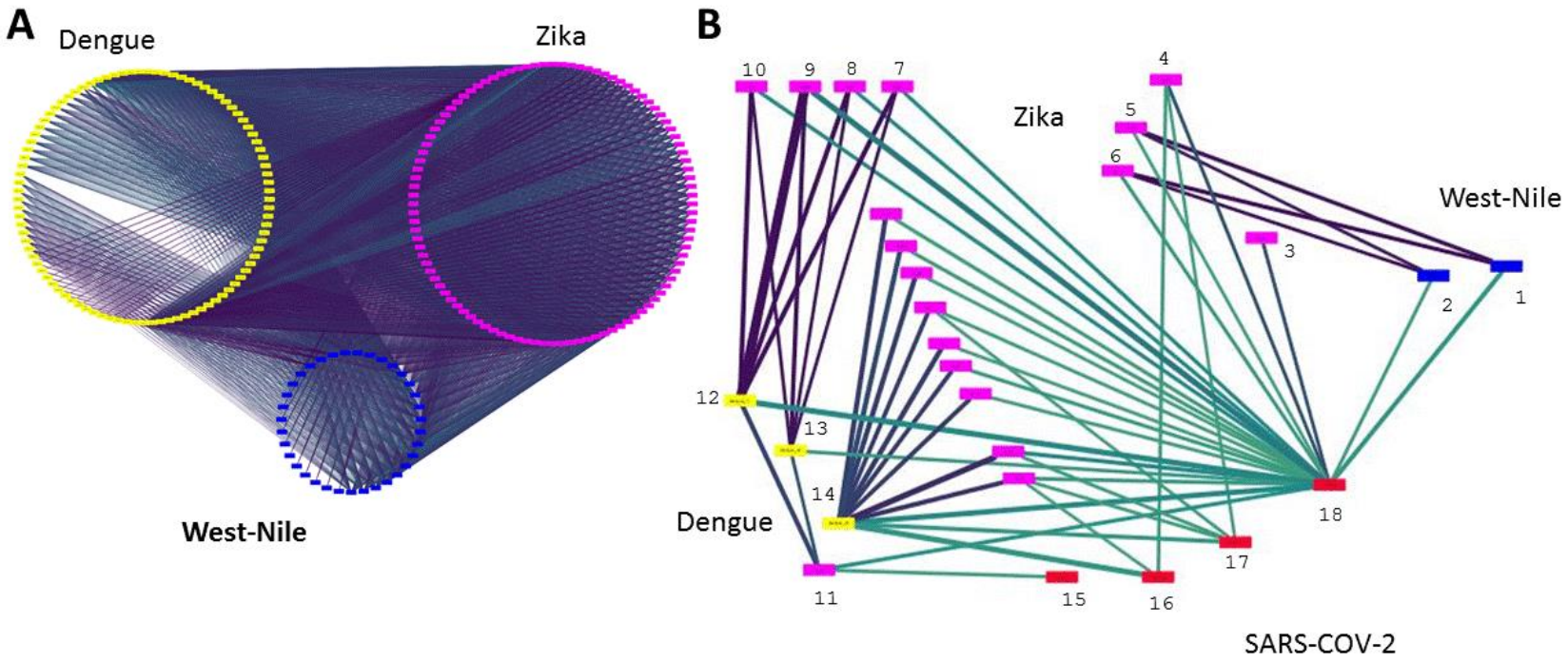
| Index Case # | Positive Covid-19 PCR to sample collection (days) | Dengue Rapid | | Dengue E-ELISA | | Dengue NS1-ELISA | WNV E-ELISA | | West-Nile neutr-alization Assay [d] | Euroimmun SARS-CoV-2 ELISA | | Electrochemiluminescence SARS-CoV-2 ELISA | Mount-Sinai ELISA | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IgM | IgG | IgM | IgG | IgG | IgM | IgG | | IgA | IgG | IgM | IgA | IgG |
| **3** [a] | 4 | **Positive** | Neg | Neg | Neg | Neg | Neg | **Positive** | <1:10 | Neg | Neg | Neg | Neg | Neg |
| **515** | 24 | **Positive** | Neg | Neg | Neg | Neg | Neg | Neg | - | **Positive** | **Positive** | N/A | **Positive** | **Positive** |
| **35** [a] | 4 | **Positive** | Neg | Neg | Neg | **Positive** | Neg | **Positive** | 1:320 | Neg | Neg | Neg | Equ | Neg |
| **67** [a,c] | 6 | **Positive** | Neg | Neg | Neg | Neg | Neg | Neg | - | **Positive** | Neg | N/A | **Positive** | **Positive** |
| **523** | 34 | **Positive** | Neg | Neg | Neg | Equ | Neg | Neg | - | Neg | Neg | **Positive** | Neg | Neg |
| **41** [a,b] | **0** | **Positive** | Neg | Neg | Neg | Neg | Neg | Neg | - | **Positive** | Neg | **Positive** | **Positive** | **Positive** |
| **516** | 20 | **Positive** | Neg | Neg | Neg | Neg | Neg | Neg | - | Neg | Neg | Equ | Neg | Neg |
| **518** | 20 | **Positive** | Neg | Neg | **Positive** | Neg | Neg | **Positive** | 1:320 | Neg | Neg | Equ | Neg | Neg |
| **514** | 22 | **Positive** | Neg | Neg | Neg | Neg | Neg | Neg | - | Equ | **Positive** | **Positive** | **Positive** | **Positive** |
| **519** | 19 | **Positive** | **Positive** | Neg | Neg | Neg | Neg | Neg | - | **Positive** | **Positive** | **Positive** | **Positive** | **Positive** |
| **62** [a,b] | 3 | Neg | **Positive** | Neg | Neg | Neg | Neg | Neg | - | **Positive** | Neg | Equ | **Positive** | Neg |
| **2** [a] | 17 | Neg | **Positive** | Neg | Neg | Neg | Neg | Neg | - | Neg | Neg | **Positive** | Neg | Neg |
| **527** | 19 | Neg | Neg | Neg | **Positive** | Neg | Neg | Neg | - | **Positive** | **Positive** | **Positive** | **Positive** | **Positive** |
| **517** | 6 | Neg | Neg | Equ | **Positive** | Neg | Neg | Neg | - | Neg | Neg | Equ | Neg | Neg |

[a] These patients were hospitalized; [b] These patients required invasive ventilation; [c] This patient passed away. [d] A dilution equal to 1:10 or above was considered neutralizing.

Neg, Negative; Equ, Equivocal; N/A, Not available.

^Died *Required invasive ventilation

Figure 1


A
Dengue
Zika
West-Nile
B
10
9
8
7
4
Zika
5
6
West-Nile
3
2
1
12
13
14
Dengue
18
17
11
15
16
SARS-COV-2