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PERSPECTIVE

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Dengue fever coinfection in COVID-19 era: A public health concern

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Abstract

Background and Aim: Dengue and SARS-CoV-2 coinfection is commonly encountered and constantly reported in particularly the dengue-endemic regions thus posing a co-epidemic threat. Coinfection is also significantly associated with morbidity and mortality. Comorbidity risk during a coinfection is of a greater concern. Although the pathophysiologies of the two infections vary, their identical clinical symptoms during coinfection result in diagnostic and therapeutic complexities.

Methods: A literature search for the current relevant reports was carried out. The searched databases were Scopus, PubMed, Google Scholar and the Web of Science, with health agencies like the WHO. Based on the selection criteria, the most recent and pertinent reports published in English language were included for the ease of understanding, deciphering and analysing the secondary data.

Results: A delay in proper diagnosis of coinfection could result in serious complications with poor patient outcome. Whether it is a standalone dengue or COVID-19 infection or a coinfection, specific biomarkers may be utilized for its foolproof diagnosis. This article highlights the various diagnostic techniques and immune responses from the perspective of prompt and appropriate public health management for patients suffering from COVID-19 and dengue viral coinfections, both being independently or collectively capable of damaging a human body.

Conclusion: As coinfection poses significantly large burden on an already-fragile healthcare facility, constant monitoring of a coinfected patient is needed for prompt and suitable therapeutics. Also, to maintain high vigilance and invoke appropriate preventive measures particularly in dengue endemic regions, the government, healthcare authority and the general public need to collaborate and cooperate.

KEYWORDS

COVID-19, community health, coinfection, dengue, pathophysiology, public health

1 | INTRODUCTION

Dengue fever, an acute viral infection that could manifest serious complications, is primarily caused by dengue virus.[1–3] Transmitted through an arbovirus and represented as a significantly neglected tropical disease, this infection is widely distributed across various Indian states.[4] Transmitted by *Aedes aegypti* mosquito, India has witnessed the highest rate of its occurrence in this monsoon season.[5,6] The initial symptoms of the infection resembling flu, it gradually progresses as potentially fatal with complications like shock (dengue shock syndrome) and hemorrhage (dengue hemorrhagic fever).[7] Predominant in human hosts, the incidents are high especially in tropical and subtropical regions. Despite a reduction in the incidence and mortality rates of dengue virus (DENV) infection in 2021 as against 2020, its spread still persists in numerous regions that exacerbated health burden during the COVID-19 pandemic era. The global DENV infection incidents have increased significantly (30-fold) over the decade, as per the World Health Organization (WHO). It is estimated that 100–400 millions are annually DENV-infected at global level. Its steadily rising emergence and global spread suggest that half of the worldwide population is at risk.[8]

This disease is an annually recurring phenomenon in various regions. Epidemiological studies hint that DENV primarily evolved in Southeast Asian and African monkeys, spreading subsequently in humans. Its occurrence in at least 100 different countries in Asia, the Pacific, the Americas, Africa and the Caribbean is reported.[9] Additionally, individuals traveling from an endemic area are suspected carriers of the disease. On a broader scale, the seroprevalence of DENV in India is reportedly 48.7%. The regions with high seroprevalence are the South (76.9%), the West (62.3%) and the North (60.3%). The urban region has a greater (70.9%) seroprevalence as compared to the rural's 42.3%, although there is a growing concern on the severity of the infection in the rural belt.[10] The concern doubles in the wake of rapid urbanization without taking due care of hygiene and sanitation.

Dengue disease is categorized into three groups as per 2009-guidelines of the WHO: dengue without warning sign, dengue with warning sign and severe dengue. Numerous reported risk factors in relation to severe dengue include virological factors, earlier DENV exposure, old age, compromised immunity, and comorbidity like hypertension, diabetes mellitus and chronic renal failure.[11,12] The disease severity leads to serious clinical manifestations like fulminant hepatic failure, myocardial complications, encephalopathy, phrenic neuropathy, diffuse myalgia, myositis, arthritis/polyarthralgia, rhabdomyolysis, hypokalemic periodic paralysis, pleural effusion, pneumonitis, noncardiogenic pulmonary edema, acute respiratory distress syndrome, and ocular complications.[13] Clinical indications of cardiological issues vary greatly, ranging from no apparent symptoms to severe myocarditis ultimately leading to death. It raised the concern to control the mortality rate in this disease through mandatory early identification and treatment. Having a better understanding of the biological cascade following the onset of dengue for more accurate diagnosis is therefore of utmost importance.

2 | MATERIALS

A literature search for the current relevant reports between January 1, 2020 and December 31, 2023 was carried out. The searched databases were Scopus, PubMed, Google Scholar and the Web of Science, with 'dengue,' 'COVID-19,' 'COVID-19 and dengue coinfection' and 'immune responses related to COVID-19 and dengue' as the key search terms. Based on a combination of search and selection criteria, the most recent and pertinent reports were included. Literaure on 'dengue coinfection with COVID-19′ published in English language only were included for the ease of understanding, deciphering and analysing the secondary data. Duplicate articles, conference abstracts, protocols, studies with no laboratory diagnosis, studies in animals, and the articles in languages other than English were excluded in due process. Any discrepancy during literature selection was resolved by discussing with a third party (independent expert). A total of 30 articles were chosen for further analyses out of a total of 270 searched and shortlisted ones. Validating before citing, each literature was manually listed in the References section.

2.1 | Dengue coinfection

Although dengue manifests independently, it can potentially coexist with other illnesses that could result in critical health situation, and diagnosis and treatment complication. Coinfection in an endemic area can potentially spark a coepidemic which might further overburden the local healthcare system. Its co-occurrence with various infections on a global scale is well documented, that include rickettsial infection, malaria, chikungunya and COVID-19.[14] The concurrence of COVID-19 and dengue particularly in the tropics could threaten healthcare systems, owing to the hospitable climatic conditions for the etiological agent. Coinfection leads to illnesses with overlapping signs and symptoms, challenging the health professionals in proper diagnosis and treatment. It is necessary to cautiously diagnose suspected COVID-19 and dengue coinfection with proper care.[15] Cardiac health in both COVID-19 and dengue patients is of prime importance as both could produce interleukins due to inflammation, and lead to cytokine storm. The cytokines can be prognosis indicators in COVID-19, with variability-exhibiting impact on specific cellular targets.

Cytokine interleukin-8 (IL-8) is a class of immunity signaling molecule that is essential in inflammation associated with overactive immunological response. Often referred as 'cytokine storm,' its occurrence could be severe in COVID-19 cases. It overproduces several cytokines that can aggravate tissue damage and inflammation.[16] The immune system and inflammation are correlated with IL-8 and dengue; immune system is hyperactive during dengue, producing a number of cytokines and chemokines including IL-8, although the cytokine production pattern between the two diseases may differ (Figures 1 and 2).[17,18] To develop precise therapeutic strategies and interventions aimed to reduce the severity, comprehending these immune responses is of utmost importance.

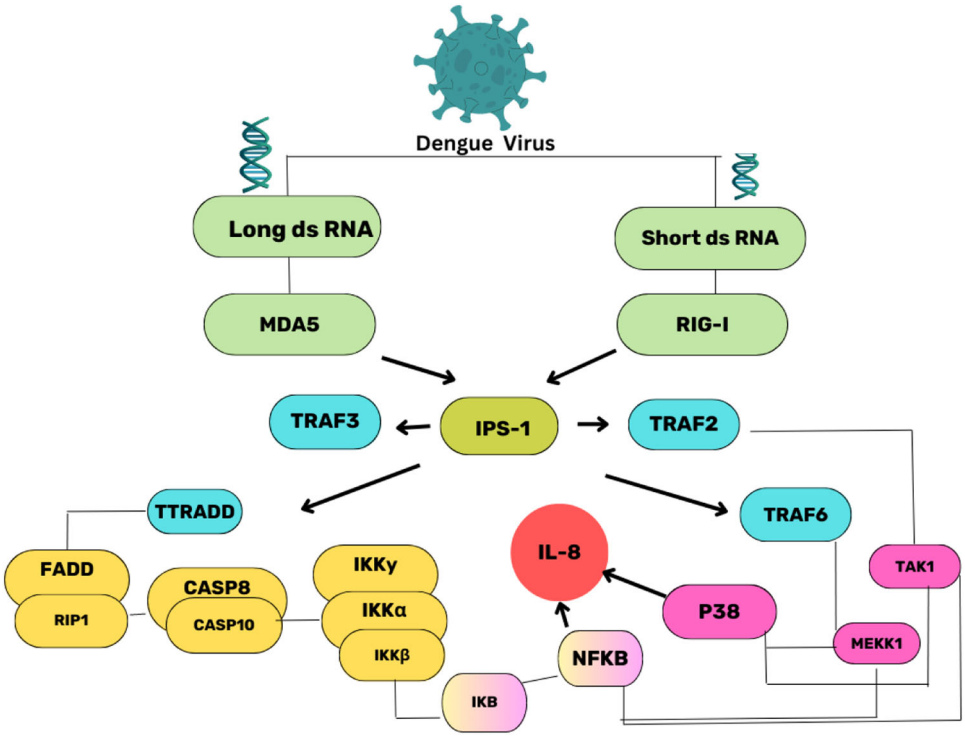

FIGURE 1 Interleukin-8 synthesis following the RIG pathway in dengue viral infection.

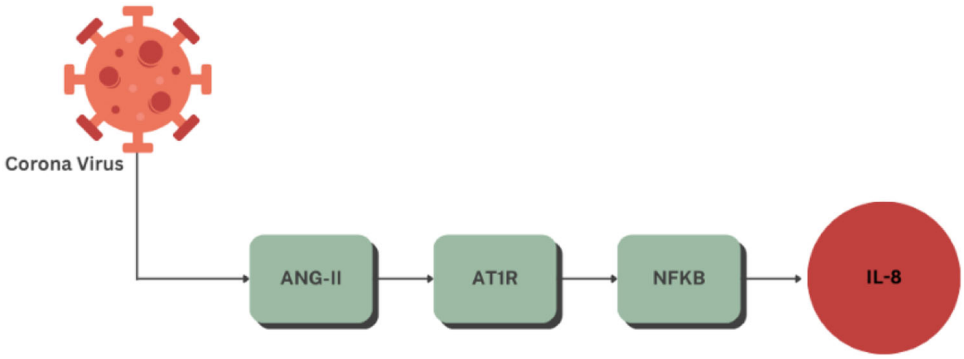

FIGURE 2 Interleukin-8 synthesis following the AT1R pathway in COVID-19 viral infection.

Figure 1 depicts IL-8 synthesis in dengue viral infection, following the RIG pathway. IL-8 production during dengue occurs through RIG pathway. RIG-I pathway is crucial in immune response against an infection. RIG-I is structurally altered after interacting with viral RNA, exposing its caspase activation and recruitment domains (CARDs). Conformational alteration facilitates the interaction of RIG-I with the signaling molecules. RIG-I CARDs interact with mitochondrial antiviral signaling protein, known as IPS-1. RIG-I and IPS-1 engagement initiates diverse signaling cascades encompassing the synthesis of type I interferons (IFNs) and pro-inflammatory cytokines. MAVS facilitate the recruitment and activation of various (TANK-binding kinase 1, IκB kinase ε) kinases including TBK1. TBK1 and IKKε are liable to phosphorylate transcription factors like interferon regulatory factors (IRFs) and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). Translocation of phosphorylated IRFs to the nucleus activates the gene expression, specifically for type I interferons (IFN-α and IFN-β) production, that is crucial in immune response against viral infections. NF-κB activation upregulates the pro-inflammatory cytokines including IL-8.

Figure 2 depicts IL-8 synthesis in COVID-19 viral infection, through AT1R pathway. IL-8 production in COVID-19 occurs through AT1R pathway. AT1R pathway is important in COVID-19 infection. In this cellular cascade the binding of SARS-CoV-2 spike protein to ACE2 allows the virus to enter the host cell and infect. This ACE2 enzyme acts to counterbalance the effects of angiotensin II type 1 receptor (AT1R). This process could destruct the infected cells and trigger an immune response, causing inflammation due to the produced IL-8.

2.2 | Public health perspective

As dengue occurs in the tropics and subtropics seasonally, cocirculation of COVID-19 in these regions could result in coinfections. In the absence of specific therapeutics to treat the infections, it can potentially develop severe complications, increased morbidity and mortality. Both the viral diseases influence immune responses and lead to inflammatory alterations that is damaging to the host cell, tissue and organ. Although both have distinct pathological signs, there are commonalities in their clinical manifestations and laboratory findings. It could thus lead to infection misdiagnosis and/or mismanagement of the coinfection as evident from a Filipino case where a COVID-19 patient developed dengue when SARS-CoV-2 pandemic had peaked. The patient had fever and myalgia but did not show any respiratory issues like commonly encountered dyspnea in COVID-19 infection. The patient also did not develop any visible rash or any bleeding as dengue infection peculiarities. A mild thrombocytopaenia (145×10^9/L) developed in the patient suggested dengue infection. Chest X-ray showed the evidence of pneumonia that suggested COVID-19 infection. And, also the lab findings through reverse transcription polymerase chain reaction (RT-PCR) established a COVID-19 and dengue coinfection. This case also highlights the fact that the patient did not reveal specific signs and symptoms of either COVID-19 or dengue thereby complicating the clinical diagnosis. A co-circulation of SARS-CoV-2 and any other endemic infection complicate the clinical diagnosis. Hence, clinicians could be careful in diagnosing the patients for endemic infections through extensive laboratory observations and monitoring the patient's history.[19]

Similar COVID-19 and dengue coinfection in a Thai patient had nonspecific symptoms and signs as seen in most coinfected patients.[20] The study showed that the patient had fever and myalgia with no visible concerns in the chest X-ray that could confirm lungs infection. The observation highlighted the significance of hospitalization and constant observation based on lab-findings to minimize the complications of the coinfection and provide the patient with improve health management. These two case reports highlight a need of laboratory diagnosis and hospitalization for better management of a coinfected patient. However, such cases need to be handled with caution with respect to the disease diagnosis and management due to the overlapping of several clinical manifestations of dengue and COVID-19 infections, including pathophysiology, innate immune responses and humoral immune responses. Additional drawbacks include false positive serological tests due to cross-reactivity and overlapping of the laboratory findings that confuse the diagnosis and complicate patient management.[21]

A comparative analysis carried out on dengue cases during pre-COVID-19 and the pandemic period showed a 44% reduction in dengue incidence during the pandemic.[22] Similar reduced dengue incidents was observed in Sri Lanka during the COVID-19 pandemic.[23] The pandemic has entered a phase wherein SARS-CoV-2 may again prevail, and thus an increase in dengue cases and simultaneous coinfections in dengue endemic regions is potentially high. On the contrary, studies in Singapore and Bangladesh reported increased dengue cases during the COVID-19 pandemic.[24,25] The Singapore study found a 37% increase, attributing it to being restricted at homes, urban living condition and high vector density. The Bangladesh study reported a rise primarily due to clinical and laboratory misdiagnosis owing to overlapping of dengue and COVID-19 disease manifestations. The study also cautioned of potential increase in coinfection, hospitalization and an imminent healthcare burden. This study emphasized on awareness among physicians and healthcare workers about dengue and SARS-CoV-2 co-circulation, and a potential rise in coinfection cases.

2.3 | Recommendations

Misdiagnosis of a disease could aggravate the illness, deteriorate patient's health condition and could pose an additional burden on the healthcare system. In this context, differential diagnosis holds a significant importance especially within the gamut of coinfection condition during an ongoing pandemic. Given the viral-infection associated significant morbidity and mortality potentials, prompt appropriate disease management measure is crucial.

Dengue-COVID-19 dual threat may effectively be managed by using an outbreak-monitoring and disease-tracking system by digitizing all the confirmed cases.[26] Telemedicine is suggested especially for remote locations to control the disease transmission and prevent coinfections. Immunoassays for potential false positive cases is suggested to analyse and minimize cross-reactivity of dengue and COVID-19 antibodies.[27] The study suggested that RBD (receptor binding domain) based test that is limited by cross-reaction could be replaced by S1 and N protein-based assay that is least affected by antibody cross-reactivity and the returned results are reliable.

As COVID-19 and dengue both could lead to severe complications and death, molecular diagnosis like RT-PCR is suggested to detect the infection early and initiate specific treatment even with a suspected coinfection.[28] As an alternative to differential diagnosis of dengue and COVID-19, neutrophil counts, platelet counts, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio, and neutrophil-lymphocyte-platelet ratio was suggested.[29] It was opined that neutrophil count, platelet count and NLR could discriminate COVID-19 from dengue with greater acuracy and specificity. Increased surveillance, vector control strategies and public awareness would help control outbreaks, transmission and coinfection of dengue and COVID-19.[30]

3 | CONCLUSION

COVID-19 and dengue coinfections pose serious threat to patient prognosis and diagnosis. Both infections damage various body parts, either separately and collectively. Coinfection is also associated with significant morbidity and mortality. As clinical and laboratory attributes of the infections overlap, an accurate diagnosis and

treatment of infected cases is challenging. A coinfected patient needs constant monitoring for suitable treatment provisions in time. Coinfection presents significant challenges with enormous burden on the healthcare system. Delayed diagnosis of a coinfection may result in serious patient complications with poor outcome. The general public, healthcare authorities and the government must work together to maintain high vigilance and take preventive measures against such cases particularly in the dengue endemic regions as much as practicable.

AUTHOR CONTRIBUTIONS

Soumya Jal: Writing–original draft. **Sangeeta Chhotaray**: Writing–original draft. **Gurudutta Pattnaik**: Conceptualization; Writing–original draft. **Snehasish Mishra**: Writing–review and editing. **Ranjan K. Mohapatra**: Conceptualization; writing–review and editing. **Venkataramana Kandi**: Supervision; writing–review and editing. **Md. Kudrat-E-Zahan**: Writing–original draft.

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CONFLICT OF INTERESTS STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

ETHICS STATEMENT

The authors have nothing to report.

TRANSPARENCY STATEMENT

The lead author Ranjan K. Mohapatra, Md. Kudrat-E-Zahan affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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REFERENCES

1. Ravi K, Kumar NK, Malagi AD. The lipid profile as a marker for predicting the severity of dengue fever. *IJAM*. 2021;8(5):691.
2. Mohapatra RK, Kandi V, Seidel V, Rabaan AA. Editorial: reemergence of neglected tropical diseases amid the COVID-19 pandemic: epidemiology, transmission, mitigation strategies, and recent advances in chemotherapy and vaccines. *Front Pharmacol*. 2023;14:1265803. doi:10.3389/fphar.2023.1265803
3. Mohapatra RK, Kutikuppala SLV, Kudrat-E-Zahan M, et al. Resurging dengue cases among the Rohingya refugees in Bangladesh amid COVID-19 pandemic: A SouthEast Asia healthcare concern. *Ann Med Surg*. 2022;84:104962.
4. Guzman MG, Harris E. Dengue. *Lancet*. 2015;385385(9966):453-465. doi:10.1016/S0140-6736(14)60572-9
5. Biswas S, Kumar P, Tansir G, Biswas A. Case report: cardiac tamponade in dengue hemorrhagic fever: an unusual manifestation of a common disease. *Am J Trop Med Hyg*. 2019;101(2):448-450. doi:10.4269/ajtmh.19-0153
6. Jagtap S, Pattabiraman C, Sankaradoss A, Krishna S, Roy R. Evolutionary dynamics of dengue virus in India. *PLoS Pathog*. 2023;19(4):e1010862.
7. Mohapatra RK, Bhattacharjee P, Desai DN, et al. Global health concern on the rising dengue and chikungunya cases in the American regions: countermeasures and preparedness. *Health Sci Rep*. 2024;7(1):e1831.
8. WHO, dengue and severe dengue. 17 March 2023. https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue
9. Messina JP, Brady OJ, Golding N, et al. The current and future global distribution and population at risk of dengue. *Nat Microbiol*. 2019;4(9):1508-1515. doi:10.1038/s41564-019-0476-8
10. Wilder-Smith A, Ooi EE, Horstick O, Wills B. Dengue. *Lancet*. 2019;393(10169):350-363. doi:10.1016/S0140-6736(18)32560-1
11. St John AL, Rathore APS. Adaptive immune responses to primary and secondary dengue virus infections. *Nat Rev Immunol*. 2019;19(4):218-230. doi:10.1038/s41577-019-0123-x
12. Niriella MA, Liyanage IK, Udeshika A, et al. Identification of dengue patients with high risk of severe disease, using early clinical and laboratory features, in a resource-limited setting. *Arch Virol*. 2020;165(9):2029e35.
13. Kamath V, Radhakrishnan B, Markanday K. Atypical manifestations of dengue. *APIK J Intern Med*. 2022;10:146-152.
14. Kamath V, Ganguly S, Avinash B. A comparative study of concurrent infections of rickettsial infection, malaria, typhoid, and chikungunya with dengue. *APIK J Intern Med*. 2019;7:120-126.
15. Wu D, Lu J, Liu Q, et al. To alert coinfection of COVID-19 and dengue virus in developing countries in the dengue-endemic area. *Infect Control Hosp Epidemiol*. 2020;41(12):1482. doi:10.1017/ice.2020.187
16. Kesmez Can F, Özkurt Z, Öztürk N, Sezen S. Effect of IL-6, IL-8/CXCL8, IP-10/CXCL 10 levels on the severity in COVID 19 infection. *Int J Clin Pract*. 2021;75(12):14970. doi:10.1111/ijcp.14970
17. Juffrie M, van der Meer GM, Hack CE, et al. Inflammatory mediators in dengue virus infection in children: interleukin-8 and its relationship to neutrophil degranulation. *Infect Immun*. 2000;68:702-707.
18. Prapty CNBS, Rahmat R, Araf Y, et al. SARS-CoV-2 and dengue virus coinfection: epidemiology, pathogenesis, diagnosis, treatment, and management. *Rev Med Virol*. 2023;33(1):2340. doi:10.1002/rmv.2340
19. Prapty CNBS, Ahmed N, Araf Y, et al. Coinfection of COVID-19 and dengue: a case report. *Front Med*. 2022;9:872627. doi:10.3389/fmed.2022.872627
20. Nasomsong W, Luvira V, Phiboonbanakit D. Case report: dengue and COVID-19 coinfection in Thailand. *Am J Trop Med Hyg*. 2021;104(2):487-489. doi:10.4269/ajtmh.20-1340
21. Alla D, Alla SSM, Vempati R, et al. Dengue & COVID-19: a comparison and the challenges at hand. *Cureus*. 2022;14(11):e31877. doi:10.7759/cureus.31877
22. Md Iderus NH, Singh SSL, Ghazali SM, et al. The effects of the COVID-19 pandemic on dengue cases in Malaysia. *Front Public Health*. 2023;11:1213514. doi:10.3389/fpubh.2023.1213514
23. Surendran SN, Nagulan R, Sivabalakrishnan K, et al. Reduced dengue incidence during the COVID-19 movement restrictions in Sri Lanka from March 2020 to April 2021. *BMC Public Health*. 2022;22(1):388. doi:10.1186/s12889-022-12726-8
24. Lim JT, Chew LZX, Choo ELW, et al. Increased dengue transmissions in Singapore attributable to SARS-CoV-2 social distancing measures. *J Infect Dis*. 2021;223(3):399-402. doi:10.1093/infdis/jiaa619

25. Rahman FI, Ether SA, Islam MR. Upsurge of dengue prevalence during the third wave of COVID-19 pandemic in Bangladesh: pouring gasoline to fire. *Clin Pathol*. 2022;15:2632010X221076068. doi:10.1177/2632010X221076068
26. Cheema HA, Mujtaba RS, Siddiqui A, et al. Singapore's dengue outbreak amidst the COVID-19 pandemic: challenges, responses, and lessons. *Infect Drug Resist*. 2023;16:1081-1085. doi:10.2147/IDR.S397407
27. Adnan N, Haq MA, Tisha TA, et al. Optimizing SARS-CoV-2 immunoassays for specificity in Dengue-Co-Endemic areas. *Cureus*. 2023;15(10):e47683. doi:10.7759/cureus.47683
28. Zepeda-Carrillo EA, Soria Saavedra FM, Mercado Villegas MB, López Alvarado A, Regla-Nava JA, Torres-Valadez R. SARS-CoV-2 and dengue virus coinfection in a Mexican pediatric patient: a case report from early molecular diagnosis. *Pathogens*. 2022;11(11):1360. doi:10.3390/pathogens11111360
29. Osuna-Ramos JF, Reyes-Ruiz JM, Ochoa-Ramírez LA, et al. The usefulness of peripheral blood cell counts to distinguish COVID-19 from dengue during acute infection. *Trop Med Infect Dis*. 2022;7(2):20. doi:10.3390/tropicalmed7020020
30. Wiyono L, Rocha ICN, Cedeño TDD, Miranda AV, Lucero-Prisno DE. Dengue and COVID-19 infections in the ASEAN region: a concurrent outbreak of viral diseases. *Epidemiol Health*. 2021;43:e2021070. doi:10.4178/epih.e2021070

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