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Navigating the Nexus: A Comprehensive Review of Dengue and COVID-19 Co-infection from Pathogenesis to Public Health Strategy

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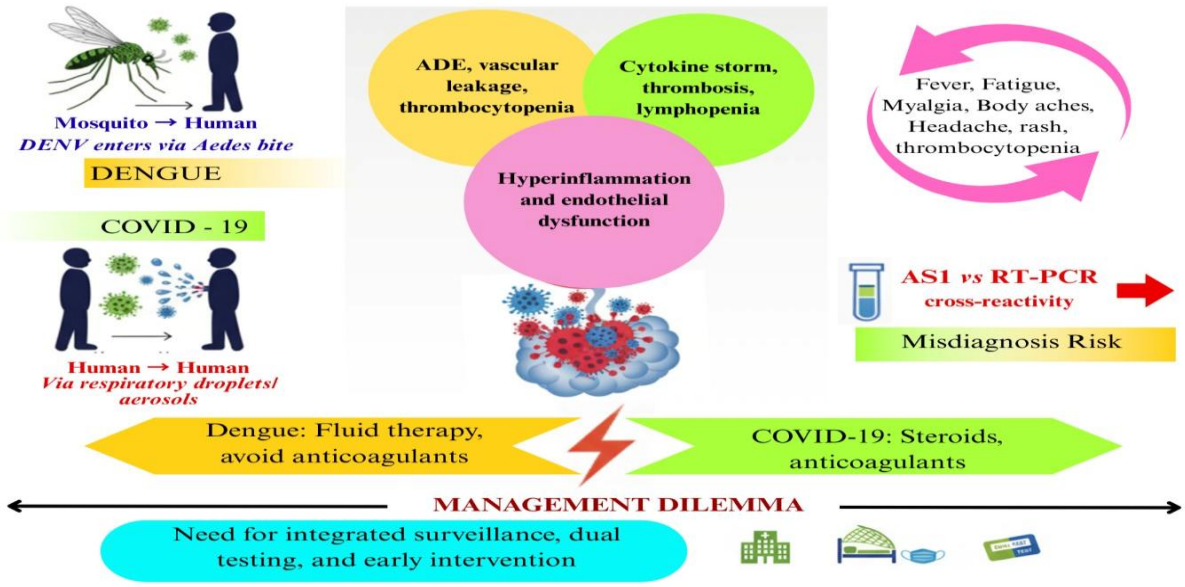
Abstract

Dengue virus (DENV) and SARS-CoV-2 co-exist in tropical and subtropical areas, which constitute a global health challenge of high importance and evolution. This review paper is a synthesis of the current evidence on the complex relationship between these two pathogens, including the pathogenesis and transmission dynamics of each, as well as their integrated effects on public health. We will initially examine the complicated immunological interactions, such as serological cross-reactivity, which make diagnosis complex and may determine the disease severity. This review subsequently examines the diagnostic issues that are caused by these overlapping clinical and laboratory abnormalities, which tend to result in misclassification and delayed treatment, and the development of multiplex molecular diagnostics. We evaluate the epidemiological data based on reported co-infection cases and analyse them in terms of geographic and demographic distribution and related prognostic factors. Moreover, the article discusses comparative trends, such as the disruptive nature of the COVID-19 pandemic on the regular dengue monitoring and management of vectors and focuses on the different approaches toward managing this disease and the pharmacological interventions. We also present the contribution of mathematical modelling in co-infection dynamics prediction and the complicated RNA dynamics of co-infected patients. The review then summarizes the findings by determining the major gaps in the literature on the real burden of the disease, pathophysiology, and optimal management of this dual infectious menace. It underlines the pressing need to possess combined surveillance, coordinated clinical guidelines, and specific research aimed at updating the effective practices in public health.

GRAPHICAL ABSTRACT



Introduction

Dengue fever is a viral disease that is transmitted by *Aedes aegypti* and *Aedes albopictus*, a negative-sense, single-stranded, non-enveloped RNA virus of the genus *Flavivirus*, and is transmitted by mosquito vectors [1, 2]. Globally, dengue burden is estimated to differ widely depending on the surveillance quality, diagnostic capacity and case definitions. Earlier estimates showed that there were about 50-100 million clinically evident infections each year in over 100 endemic countries [3, 4], but more recent modelling studies, such as those reported by the World Health Organization (WHO), suggest up to 390 million infected each year, of which almost 96-100 million infectious outbreaks are symptomatic. These inconsistencies indicate the differences between reported surveillance data, model-based projections that account for substantial underreporting and limited diagnostic infrastructures in many endemic regions. The rate of dengue has risen significantly in the last 20 years due to the high rate of urbanization, global warming, population migration, and the growth of mosquito habitats [5, 6]. Over 10,500 deaths linked to dengue and a number of millions of reported cases were reported around the world in 2023, and the WHO declared dengue a Grade 3 emergency [7]. At the beginning of 2024, the surveillance data documented about 7.6 million cases in April but the estimates were presumably low because of the regional differences in the reporting

systems and access to diagnoses. The intensity of the transmission in the very endemic areas is also likely to increase due to climate-related effects like El Niño and global interrelatedness [8-11].

Dengue is four different serotypes (DENV-1, DENV-2, DENV-3, DENV-4), each of which can cause mild febrile disease to severe dengue hemorrhagic fever, shock syndrome or death [12-15]. Its clinical manifestation involves fever, headache, myalgia, arthralgia, rash, and leukopenia that overlap with other febrile diseases, especially COVID-19. The concurrent circulation of dengue and SARS-CoV-2 in endemic regions presents significant diagnostic dilemmas, as both diseases share nonspecific symptoms (fever, headache, gastrointestinal manifestations) and haematological findings (thrombocytopenia, leukopenia), potentially leading to frequent misdiagnosis and delayed management [16, 17]. In addition, serological cross-reactivity was also described, and COVID-19 patients were sometimes false-positive in terms of dengue [18].

There is as yet no dengue antiviral therapy or globally working vaccine. The supportive care, comprising fluids and close observation, is the backbone of the treatment [19, 20]. The critical role of knowledge of its pathophysiology and diagnostic issues, particularly in the case of co-infection with SARS-CoV-2 [21, 22]. The potential impact of ADE or any other immunological interactions on the outcome of treatment is hypothetical, and it cannot be considered an endpoint. Clinical management is also complicated by conflicting therapeutic options: whereas antivirals, corticosteroids, and anticoagulants may be necessary in COVID-19, the treatment of dengue is determined by the need to take care of hydration and avoid taking drugs that increase the risk of bleeding. Also, the lockdown and other COVID-19-related public health measures could interfere with the operation of the programs on the control of the vectors, which may increase the spread of dengue onset [23–27].

The pathogenesis of dengue entails both the relationship between the virus and the host immunity, in which secondary heterotypic infections frequently result in severe disease because of antibody-dependent enhancement (ADE) [28, 29]. In this case, antibodies that are non-neutralizing with respect to previous infection aid in the entry of the virus to the host cells through Fc-receptors, amplifying viral replication and severity. Here, non-neutralizing antibodies from a prior infection facilitate viral entry into host cells via Fcγ receptors, increasing viral replication and severity. Although ADE is well described in dengue infections, the

strength of ADE in the SARS-CoV-2 co-infection is not yet demonstrated in the clinical setting and can be discussed as a hypothetical one [30–37]. The interplay of serotype order, antigenic distance, and immune response complexity further complicates disease progression and vaccine development [34]. These factors make it difficult to design a safe, broadly protective tetravalent vaccine that avoids enhancing disease severity in subsequent infections [38–41].

SARS-CoV-2 infection triggers complex immune responses, and serious illnesses are often accompanied by inflammatory reaction dysregulation and cytokine storms, resulting in dysfunction of multiple body organs [31]. Potential co-infection could also enhance or reduce immunological responses, synergies or antagonisms, but little of this is characterized by evidence that is extrapolated on the basis of mono-infection [32]. This implies that the presence of antibodies or T-cell responses to one virus may have a possible effect on the pathogenesis of the other. Moreover, cross-reactive immunity, including plasmablast activation and antibody cross-reactivity, can play a role in disease progression, although the clinical role is not established. Specifically, ADE is well established in dengue infections, but has not been proven to be beneficial in SARS-CoV-2 co-infection *in vivo* [30, 33, 36].

The epidemiology and clinical problems of dengue and COVID-19 worldwide may present distinct epidemiological and clinical challenges. Their simultaneous occurrences in the body also make their diagnosis, treatment, and public health interventions more difficult, as well as emphasizing how badly more effective diagnostic tools, therapeutic measures, and vaccines are already required. To mitigate morbidity, mortality, and the healthcare burden, a better understanding of the potential immunological interaction of the two viral infections is needed, especially in areas where both pathogens are endemic.

This narrative review was carried out after a systematic literature review to find studies that covered dengue virus (DENV), SARS-CoV-2, and co-infection. PubMed, Scopus, Web of Science, and Google Scholar were used to locate peer-reviewed articles published in the past five years (2000-2025). The search terms were a combination of Dengue, COVID-19, SARS-CoV-2, co-infection, serotype, RNA dynamics, immunology, diagnosis, clinical outcomes, and treatment. The studies were included when they touched upon immunological processes, RNA biology, clinical phenotypes, diagnostic challenges, epidemiology or therapeutic strategies.

Articles, editorials, commentaries, and abstracts of conferences not in full-text in non-English were excluded. Articles included in the lists of references were screened manually in order to cover widely. Since it is a narrative review, neither quality assessment nor any meta-analysis was conducted, which could add some systematic bias and restrict the possibility of direct quantitative comparison.

1. Serotypes, Transmission Cycle, and Pathogenesis

2.1. Serotypes, transmission cycle, and pathogenesis of dengue virus

Dengue viruses exist as four antigenically distinct serotypes (DENV-1 to DENV-4), creating challenges for surveillance, control, and vaccine development due to their genetic diversity [12]. Infection with one serotype provides long-term immunity against that specific serotype but only temporary cross-protection against others, predisposing individuals to severe disease during secondary heterologous infections through immunopathogenic mechanisms [42]. The pathogenesis and replication cycle of the dengue virus are illustrated in Figure 1.

The pathogen is transmitted primarily by means of bites of the infected female *Aedes aegypti* mosquitoes, and, secondarily, by Aedes albopictus. The cycle starts when the mosquitoes feed on viremic human beings; after 812 days extrinsic period the virus replicates in the mosquito which can then infect the prone hosts. In humans, the target of first infection is dendritic cells on the skin, which then extends to the local lymph nodes and is then transferred through the blood to various body organs [43].

Clinically, dengue presents as dengue fever (DF) or may progress to severe forms such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), marked by vascular leakage, thrombocytopenia, coagulopathy, and plasma leakage. The ADE, driven by cross-reactive but non-neutralizing antibodies from prior infections, promotes viral entry into Fcγ receptor-positive cells, increases replication, and worsens severity. Dengue virus also infects monocytes, macrophages, dendritic cells, mast cells, and lymphocytes, disrupting antiviral responses and driving immunopathology [43–46].

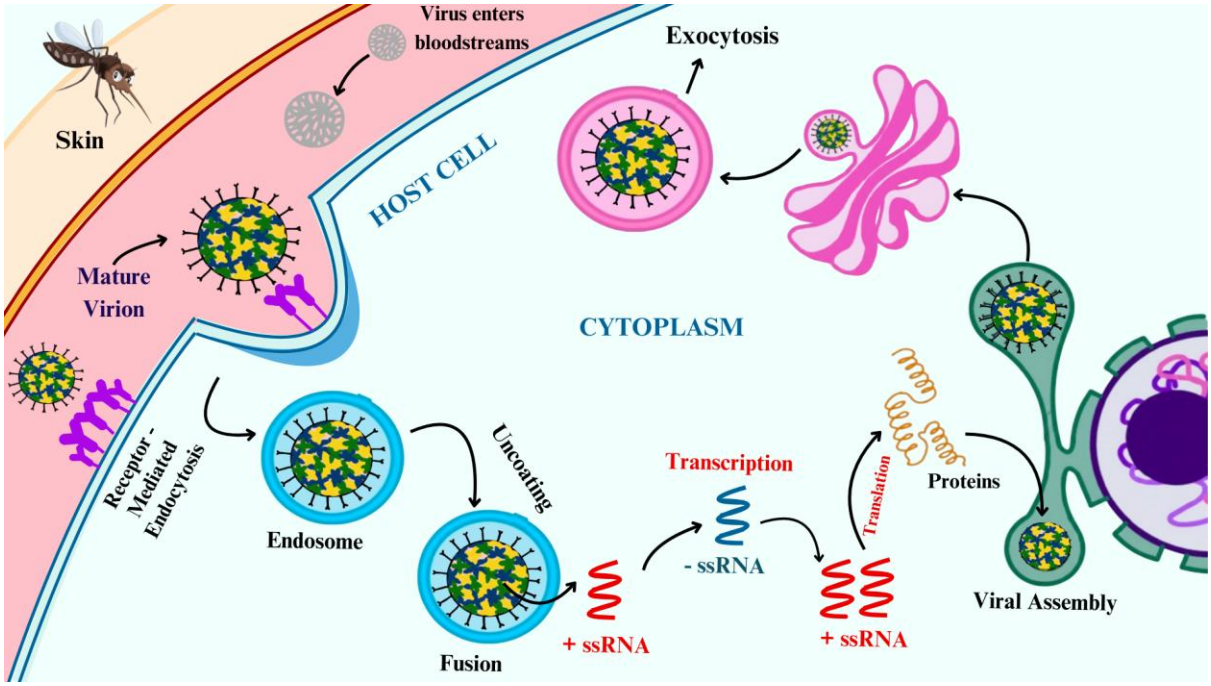


Fig. 1. Pathogenesis and replication cycle of Dengue viruses.

The virus spreads through the bite of a mosquito and enters the host's bloodstream, binding to cell-surface receptors and entering the cell via endocytosis. Membrane fusion and uncoating are caused by endosomal acidification (pH 6), which releases the +ssRNA genome into the cytoplasm. The RNA of the virus is translated and replicated, and new viral elements are brought together in the endoplasmic reticulum-Golgi network. Mature virions are then released by exocytosis, which facilitates viral spread and disease development.

2.2. Variants, transmission dynamics, and pathogenesis of SARS-CoV-2

SARS-CoV-2 is a single-stranded, enveloped, positive-sense RNA virus of the Betacoronavirus genus. Since its emergence, it has evolved into several variants of concern (VOCs), including Alpha, Beta, Gamma, Delta, and Omicron, each differing in transmissibility, immune evasion, and pathogenicity, thereby shaping COVID-19 epidemiology [8]. Transmission occurs primarily through respiratory droplets and aerosols, while fomites play a minor role. Viral entry requires binding of the spike (S) protein to the ACE2 receptor, with activation by host proteases such as TMPRSS2. Replication occurs mainly in respiratory epithelial cells, though viral RNA is also detected in extrapulmonary tissues, including gut, kidney, liver, pancreas, and brain, implicating multisystem involvement. The SARS-CoV-2 entry mechanism into human cells is illustrated in Figure 2.

Clinical outcomes range from asymptomatic infection to severe

pneumonia, ARDS, multi-organ failure, and death. Severe disease is linked to dysregulated immunity with cytokine storm (elevated IL-6, IL-1β, TNF-α, IL-10), endothelial dysfunction, coagulopathy, and microthrombosis. Lymphopenia and T cell exhaustion (PD-1, TIM-3 expression) impair viral clearance. Experimental hamster models recapitulate human disease features [47–49].

Importantly, the majority of cases of dengue-COVID-19 co-infections and immunological researches have been reported in the early pandemic waves that were characterized by the predominance of the ancestral, Alpha, or Delta variants. Therefore, the role of more recent variants like Omicron which are characterized by changes in immune escape, transmissibility and disease severity in co-infection processes is poorly specified and should be subjected to specific study.

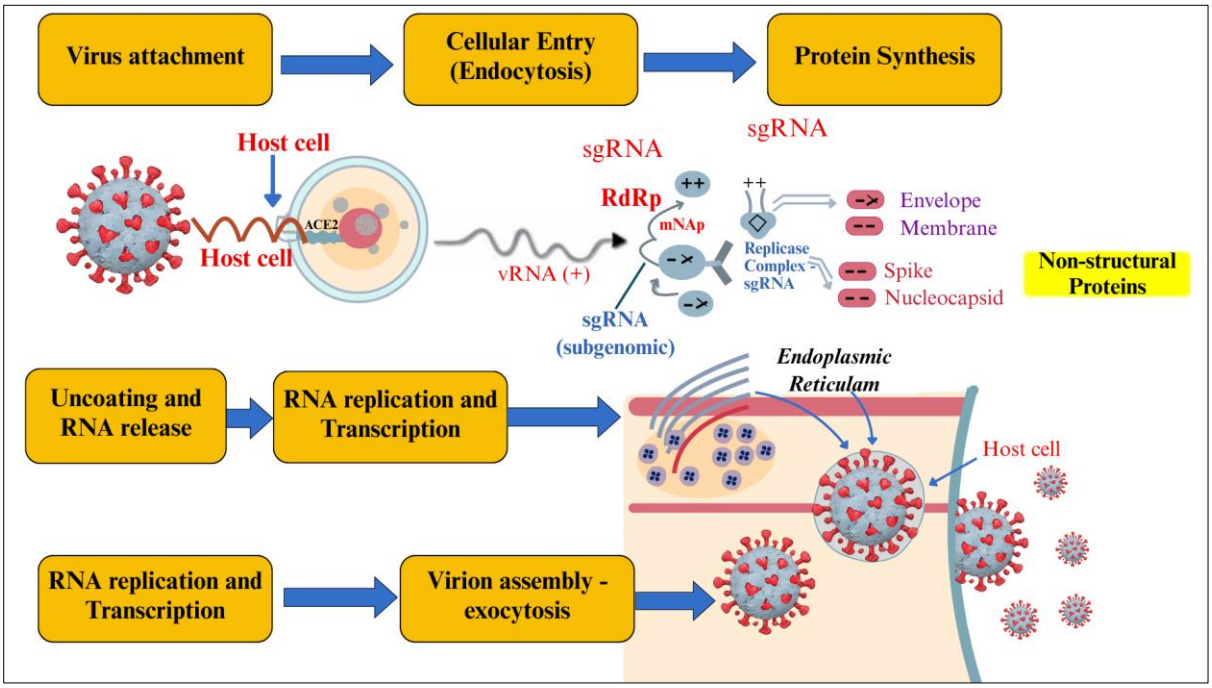


Fig. 2. Schematic illustration of the SARS-CoV-2 entry mechanism into a human cell.

The virus binds to the host cell with the help of ACE2 (angiotensin-converting enzyme 2) receptors and penetrates through endocytosis. Viral uncoating liberates the positive-sense RNA into the cytoplasm, where it is translated and transcribed to form structural and non-structural proteins. Replication and assembly take place in the endoplasmic reticulum-Golgi intermediate compartment and release of newly formed virions is through exocytosis and therefore infection of adjacent cells becomes possible.

3. Potential Immunological Interactions in Co-Infection

Co-infection or sequential infection with dengue virus (DENV) and SARS-CoV-2 creates a highly complex immunological scenario shaped by overlapping pathogenic mechanisms, notably cytokine storm, ADE, and endothelial dysfunction. Both viruses elicit strong innate immune responses with high levels of pro-inflammatory cytokines such as IL-6, TNF-α, IL-1β, IL-10, and IFN-γ, which are implicated in severe dengue phenotypes (dengue hemorrhagic fever, shock syndrome) and severe COVID-19 outcomes (acute respiratory distress syndrome, multiorgan failure) [43, 50]. In co-infected patients, hyperinflammatory cytokine activity may synergistically intensify endothelial activation and vascular damage, thereby exacerbating vascular permeability typical of dengue while also precipitating COVID-19-associated microvascular thrombosis, leading to complications such as respiratory distress, shock, and coagulopathy [46, 51].

ADE is a patterned characteristic of dengue immunopathology, especially in the case of secondary heterotypic infections. Sub-neutralizing or cross-reactive antibodies, particularly of the precursor membrane protein (prM), attach to immature virions and end up in cells that express Fc7 receptors, promoting viral replication and severe illness [44, 45]. ADE in SARS-CoV-2 is still hypothetically viable, and no more studies have been demonstrated *in vivo* yet. The in vitro evidence demonstrates that Fc and FcgregIIA and FcgressIIIA mediate ADE by the SARS-CoV-2 antibodies with negligible cytokine upregulation, which implies that it has minimal pathological importance in natural infection or vaccination [52]. Dengue antibodies have been found to cross-react with SARS-CoV-2 antibodies and sometimes give a false-positive serological response, a phenomenon that has been of concern in terms of immune interference. Nevertheless, there is no clinical data on ADE-related deterioration of the course in SARS-CoV-2 [51, 53].

Immunosuppressive effects such as lymphopenia and T cell exhaustion characterized by expression of PD-1 and TIM-3, leading to viral clearance impairment and possibly exacerbation of coinfection, are also caused by both viruses [43, 50, 54]. Endothelial cells are important targets in both infections: DENV provokes the release of cytokines and complement that facilitates the effusion of the plasma, and SARS-CoV-2 causes endothelial damage, inflammation, and thrombosis. Dual infection can, therefore, enhance endothelial dysfunction and immune dysregulation and requires close attention in dengue-endemic regions with COVID-

19 and additional mechanistic research to inform diagnostics and treatment [46, 50, 51, 54].

Epidemiological studies point out the increasing co-circulation and co-infection of dengue virus (DENV) and SARS-CoV-2, especially in tropical and subtropical countries, including Southeast Asia, Latin America, and island countries in the Indian Ocean. Simultaneously, early reports of Mayotte, Reunion Island and the Philippines recorded multiple infections, which highlights the difficulty of diagnosis because of overlapping symptoms such as fever, myalgia, and rash [55, 56]. In Colombia, surveillance revealed that dengue outbreaks overlapped in time with the initial COVID-19 epidemic, which is a reason to be concerned about compounded morbidity and strain on healthcare [57].

There are also very strong prevalence data, though low coverage is still seen to be under 1% to 10%, probably because of misdiagnosis and cross-reactive serology [51, 58]. Dengue antibodies cross-react with the SARS-CoV-2 antigens, which result in false-positive rapid tests and the necessity of confirmatory molecular tests [53, 59]. The clinical outcome is different; although most of the co-infected ones have mild disease, children and those with comorbidities have an increased risk of complications [46, 60]. Additional seasonal and geographic synergies, impacting dengue transmission, exist because of the COVID-19 restrictions, as witnessed in the post-pandemic dengue outbreak in Taiwan [61]. Better surveillance, dual testing and cohort studies are badly required [51, 58].

4. Diagnostic Challenges in Co-Circulation Settings

DENV and SARS-CoV-2 co-circulation in endemic areas poses a tricky diagnostic situation caused by similar clinical manifestations, immunological interactions, and testing modalities. These aspects compromise sufficient and prompt diagnosis, hence complicating patient management and interventions on population health.

4.1. Serological Cross-Reactivity and False-Positive/False-Negative Results

The cross-reactivity of serology between dengue and COVID-19 antibodies is a significant diagnostic problem. Dengue IgM/IgG can bind SARS-CoV-2 antigens and vice versa due to antigenic mimicry and give false positives [53, 62]. This issue is aggravated by rapid diagnostic tests (RDTs) in the absence of confirmatory molecular testing, particularly in acute stages, and results in false negativity [62, 63]. These misclassifications and slow treatment due to such inaccuracies are

possible. It is worth noting that research indicates that dengue antibodies have the potential to regulate the severity of COVID-19 through the activation of antibody-dependent enhancement or cross neutralization [51, 53].

4.2. *Role* of Molecular Diagnostics (RT-PCR, Multiplex Assays)

The most appropriate choice in acute detection of DENV and SARS-CoV-2 is molecular diagnostics, specifically real-time RT-PCR, which has high sensitivity and specificity without being affected by serological cross-reactivity. Multiplex RT-PCR systems permit the simultaneous identification of several pathogens, which are useful in the diagnosis of patients with emerging febrile conditions. These devices enhance efficiency, although they have issues of cost, infrastructure, and skills in resource-constrained areas [58, 64]. Hence, multiplex assays need to be validated and quality controlled with rigour, which is a requirement to ascertain reliability.

4.3. *Optimising Diagnostic Algorithms for Dengue-Endemic COVID-19 Settings*

Diagnostic algorithm optimization is critical to the management of co-circulation of dengue and COVID-19. An integrated tiered approach should combine clinical examination, epidemiological records and sequential laboratory testing. The onset of the symptoms informs the testing methods, with RT-PCR of the first five days giving priority to viral RNA testing [64]. Subsequently, the combination of NS1 antigen and IgM/IgG enhances the sensitivity to over 90 percent of both individual markers [65, 66]. Caution must be exercised in co-infection in endemic areas, and multiplex molecular or antigen-based tests must be employed where possible [58, 62]. Diagnosis is enhanced by the use of local epidemiologic patterns and patient exposure history; implementation is enhanced by increased access to molecular testing and training of healthcare workers [64]. This evidence-based strategy mitigates misdiagnosis risks, enhances patient outcomes, and supports timely interventions in dengue-endemic COVID-19 co-infection. Although there are advances in algorithms, diagnostic testing in endemic scenarios is currently limited by a lack of access to molecular testing, cross-reactive serology, and variability of test performance across systems, which are all associated with ongoing misclassification and delay in clinical decisions. The diagnostic algorithm for Dengue–COVID-19 co-infection are illustrated in Figure 3.

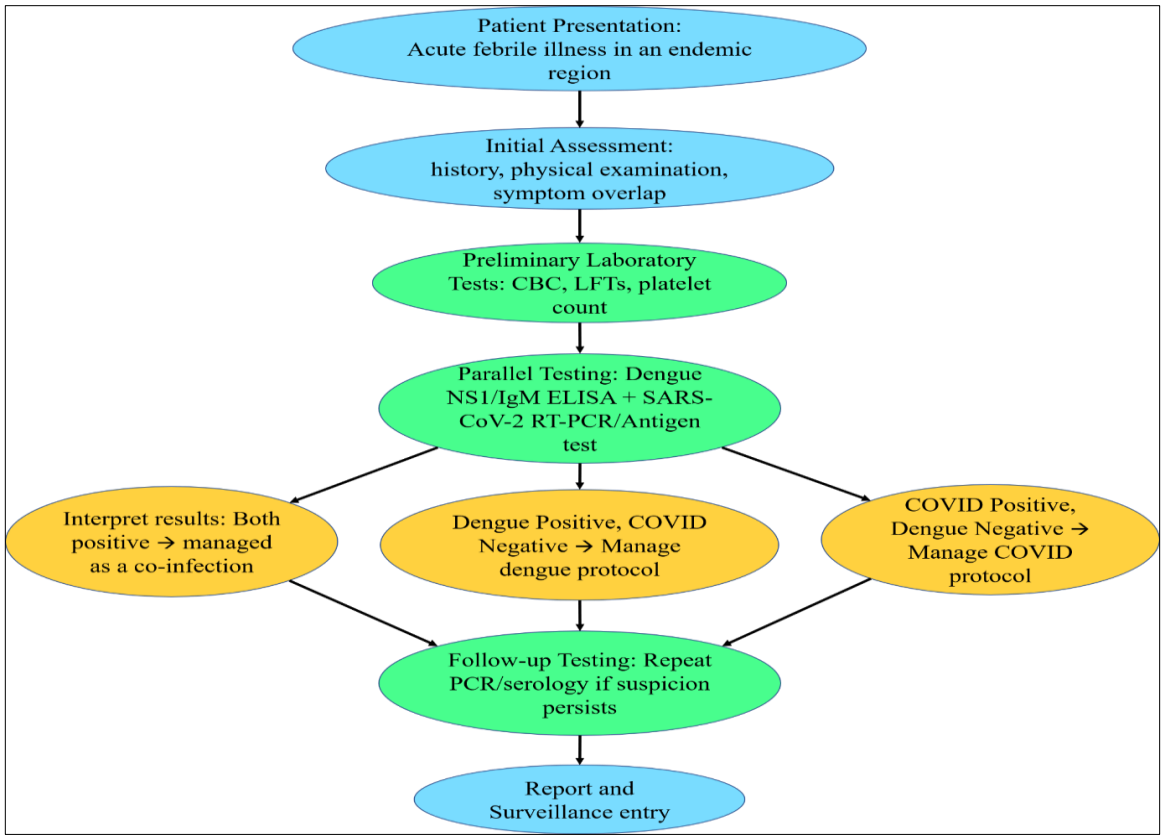


Fig. 3. A proposed diagnostic algorithm for Dengue–COVID-19 co-infection.

Acute febrile patients who present in endemic areas pass through the initial assessment, which entails history, physical examination and symptom examination. Parallel (Dengue NS1/IgM ELISA) and SARS-CoV-2 (RT-PCR or antigen test) testing are performed after preliminary laboratory tests (CBC, LFTs, platelet count). Depending on the outcome, patients are treated as positive for Dengue, positive for COVID-19, or as co-infected. In case of suspicion, follow-up testing and reporting are done.

5. REPORTED CASES AND CASE SERIES

5.1. Summary of Individual Case Reports (2020–2025)

From 2020 through 2025, a growing number of case reports and case series have documented clinical instances of co-infection with DENV and SARS-CoV-2, predominantly in dengue-endemic regions experiencing concomitant COVID-19 outbreaks. These case reports mainly originate from South and Southeast Asia, including India, Malaysia, Indonesia, and Thailand, Latin America (notably Brazil, Colombia, Mexico), as well as some African countries such as Nigeria and Kenya. In these reports, patients often presented with nonspecific febrile illnesses overlapping with symptoms common to

both diseases, resulting in considerable diagnostic confusion exacerbated by serological cross-reactivity between dengue and SARS-CoV-2 antibodies [53, 62, 67]. Diagnosis RT-PCR assays or combined antigen-antibody tests to confirm co-infection, given the limitations of stand-alone RDTs, which are prone to false positives due to cross-reactivity [53, 68]. Case series from tertiary care centres have depicted clusters of co-infected patients, often with more complex clinical courses, while single case reports have highlighted the diverse spectrum of presentations, including atypical manifestations like liver injury and myocarditis [67, 69]. The recent case studies from the year of 2020 are listed in Supporting Table 1. It should be noted that the certainty of diagnostics also varied in the reports; some cases were confirmed as co-infected by RT-PCR with both viruses, whereas others were done by serological tests, or antigen-antibody tests that are vulnerable to cross-reactivity. The reported cases, therefore, constitute heterogeneous data on confirmed, probable and suspected co-infections.

Table 1.

Reported and suspected Dengue–COVID-19 co-infection cases.

Year of publication/ Country	Number of patients, age, sex	Diagnostic method for dengue	Diagnostic method for COVID-19	Major Symptoms	Treatment provided	Outcome	References
2020 / Bangladesh	1 patient, 30 M	Dengue IgM positive, IgG negative (ELISA, Panbio™ Dengue Duo)	SARS-CoV-2 RT-PCR positive	Mild COVID-19 pneumonia, heterozygous beta-thalassemia trait	IV Ringer's lactate, antibiotics, vitamins and zinc, prone positioning, supportive care	Discharged, COVID-19 negative day 21	[70]
2020 / Brazil (Brasília, Federal District)	1 patient, 56 F	NS1 antigen, RT-qPCR, IgM/IgG	RT-qPCR nasopharyngeal swab	Mild dyspnea, diffuse itchy erythemato-papular rash, worsening leukopenia, elevated aminotransferases	Chloroquine, azithromycin, anticoagulation (initial); all meds stopped after dengue diagnosis	Discharged day 6; isolation until negative SARS-CoV-2 tests on day 26	[71]
2020 / Brazil (Joinville)	1 patient, 26M	Clinical suspicion based on rash	RT-PCR (nasopharyngeal swab), IgM/IgG serology	Myalgia, dyspnea, pruritic maculopapular rash	Symptomatic treatment, social isolation	Full recovery, dengue ruled out by serology	[72]
2020 / Brazil (Presidente Prudente, São Paulo)	3 patients (Doctor- 61 M, Wife-59 F, Son-32 M)	Dengue IgG positive	SARS-CoV-2 rRT-PCR positive (Doctor), COVID-19 IgG/IgM antibodies in all	Doctor: arthralgia, diarrhea, headache, abdominal pain, back pain, dyspnea; Wife: mild back pain, headache; Son: mild rhinitis	Azithromycin Levofloxacin Methylprednisolone, supportive care	Full recovery for all	[73]

2020 / India	1 patient, 9-month-old female infant	NS1 antigen, Dengue IgM (MAC ELISA), Dengue IgM positive in CSF	Nasopharyngeal RT-PCR^{-}, Bronchoalveolar lavage RT-PCR^{+}	Seizures, rash, shock, lethargy, thrombocytopenia, elevated liver enzymes, encephalitis	Ventilation support, antiseizure meds and methylprednisolone, supportive care	Discharged neurologically normal on day 14	[74]
2020 / India (Bihar)	1 patient, 14F	NS1 antigen, IgM antibody by ELISA	Nasopharyngeal SARS-CoV-2 RNA by RT-PCR positive	Hypotensive shock, respiratory distress, raised intracranial pressure, encephalitis signs	Fluids, inotropes, ceftriaxone, azithromycin, ICP management, no antivirals	Clinical improvement and discharged	[75]
2020 / Indonesia	1 patient, 53 M	NS1 antigen test, IgM/IgG serology, PCR for dengue in some cases	RT-PCR for SARS-CoV-2, rapid antibody test in some cases	Malaise, sore throat, thrombocytopenia, rash (some), respiratory symptoms	Symptomatic treatment, supportive care, fluid resuscitation, oxygen therapy, and mechanical ventilation in severe case.	Death due to severe pneumonia, ARDS, and septic shock.	[76]
2020 / Indonesia	1 patient, 24 F	Rapid test NS1 (+), IgM (+), IgG (–); qRT-PCR DENV-2 (+)	RT-PCR SARS-CoV-2	High fever, myalgia, headache, arthralgia, retro-orbital pain, nausea, vomiting	Supportive care	Recovered and discharged	[77]
2020 / Indonesia	1 patient, 59 F	Rapid test NS1 (+), IgM (+), IgG (–); qRT-PCR DENV-3 (+)	RT-PCR SARS-CoV-2	Myalgia, arthralgia, leukopenia, thrombocytopenia, AST elevated	Fluid resuscitation	Recovered and discharged	[77]
2020 / Indonesia	1 patient, 69 F	Rapid test NS1 (+), IgM (+), IgG	RT-PCR SARS-CoV-2	Fever, myalgia, arthralgia,	Supportive care	Recovered and discharged	[77]

		(+); qRT-PCR DENV	(nasopharyngeal swab) positive SARS-CoV-2 RT-PCR (+), COVID-19 IgM & IgG (-, day 12 post-symptoms)	hyponatremia, leukopenia Thrombocytopenia, leukopenia, minor gum bleeding, bilateral basal crepitations			
2020 / Indonesia	1 patient, 58 M	Dengue NS1 (+), IgM (+), IgG (+), confirmed by commercial serology			Platelet transfusion, supportive care	Recovered, and discharged after 7 days	[78]
2020 / Indonesia (Bandung)	1 patient (10 months old girl, 7 kg)	NS1 antigen positive	RT-PCR SARS-CoV-2 (nasopharyngeal swab), positive (Ct=37)	Dyspnea, shock, gastric bleeding, melena, rash, lymphopenia, thrombocytopenia, pleural effusion	Oxygen therapy, IV fluids, paracetamol, antibiotics, vitamin, fluid resuscitation, blood transfusion	Full recovery, discharged after 16 days	[79]
2020 / Mayotte, France	1 patient, 44M	RT-PCR positive for Dengue virus serotype 1	RT-PCR positive for SARS-CoV-2	Fever, diarrhea, maculopapular rash, dysgeusia, drowsiness	Hydroxychloroquine and azithromycin for 5 days	Gradual clinical improvement	[55]
2020 / Pakistan	20 ICU patients (median age 43 years) 14M/6F	Real-time PCR (serotype-specific)	Real-time RT-PCR	Fever, shortness of breath; leukopenia, thrombocytopenia, lymphopenia	Supportive care, ICU monitoring	COVID-19 only recovered, and COVID-19 with dengue - 60% mortality	[80]
2020 / Philippines	1 patient, 62 F	Dengue NS1 antigen (RDT), IgM/IgG serology	COVID-19 RT-PCR (nasopharyngeal swab)	Hypertension, retro-orbital pain, myalgia, arthralgia, posterior-basal pneumonia	Supportive care, favipiravir 1800 mg loading then 4 tablets twice daily for 13 days	Recovered, and discharged after 10 days	[81]

2020 / Reunion Island	1 patient, 18M	NS1 antigen, RT-PCR, IgM/IgG serology, DENV-1	RT-PCR (E, RdRP, N genes)	Itchy maculopapular rash, thrombocytopenia, leucopenia, lymphopenia, elevated liver enzymes	Supportive care	Discharged after 7 days	[67]
2020 / Saudi Arabia	1 patient, 63 M	NS1, IgM/IgG, PCR	PCR (+)	Fever, myalgia, dry cough, wheezing, vomiting, mild hypoxia	Oxygen, IV paracetamol, IV fluids, ondansetron, budesonide, nebulized salbutamol	Recovered and discharged after 6 days	[82]
2020 / Saudi Arabia	1 patient, 53 F	NS1, IgM/IgG, PCR	PCR (+)	Fever, watery diarrhea, shortness of breath, epigastric pain, dehydration	IV fluids, IV paracetamol, ceftriaxone, azithromycin, oxygen via nasal cannula	Recovered and discharged after 5 days	[82]
2020 / Saudi Arabia	1 patient, 48 F	NS1, IgM/IgG, PCR	PCR (+)	Fever, shortness of breath, headache, myalgia, mild hypoxia	IV dexamethasone, paracetamol, ceftriaxone, oxygen therapy	Recovered and discharged after 4 days	[82]
2020 / Saudi Arabia	1 patient, 37 M (with diabetes mellitus)	Dengue PCR	RT-PCR	Fever, nausea, vomiting, body ache, dry cough, abdominal pain, thrombocytopenia, leucopenia	Antibiotics, anticoagulants, oxygen, corticosteroids, immunomodulator, IV fluids, IV insulin	Death	[83]
2020 / Saudi Arabia	1 patient, 52 M	Dengue serology	RT-PCR	Fever, cough, shortness of breath, thrombocytopenia,	Lopinavir/Ritonavir, Ribavirin, interferon, antipyretics, DVT	Death	[83]

				leucopenia, AKI, lung involvement	prophylaxis, ICU care, CRRT, vasopressors		
2020 / Singapore	1 patient, 57 M	Dengue NS1, IgM, IgG RDT	RT-PCR nasopharyngeal swab	Fever, cough, thrombocytopenia, lymphopenia	Supportive care	Recovered and discharged	[18]
2020 / Singapore	1 patient, 57 F	Dengue IgM RDT (false positive)	RT-PCR nasopharyngeal swab	Diarrhea, thrombocytopenia, lymphopenia, abnormal liver function	Supportive care	Recovered and discharged	[18]
2020 / Taiwan	1 patient, 62 F	Dengue virus ELISA - negative	Nasal swab RT-PCR - positive	Retro-orbital pain, fever, headache, dry mouth	Hydroxychloroquine (200 mg TID), then Lopinavir–Ritonavir	Discharged day 39 after 3 negative PCRs	[84]
2020 / Thailand	1 patient, 35 M	Dengue IgM/IgG positive, NS1 antigen negative, RT-PCR negative	Nasopharyngeal swab RT-PCR positive (SARS-CoV-2)	High-grade fever, myalgia, dyspnea, thrombocytopenia, lymphopenia, elevated ALT	Supportive care; isolation in an airborne infection room	Delayed COVID-19 diagnosis, and patient hospitalized	[85]
2020 / Thailand	1 patient, 50F (flight attendant)	Dengue NS1 antigen, Dengue RT-PCR positive (DENV-2)	SARS-CoV-2 RT-PCR positive (nasopharyngeal + throat swabs)	Leukopenia, lymphopenia, mild thrombocytopenia, no warning signs of dengue vascular leak	Supportive care, close monitoring, isolation, no antivirals or specific dengue treatment	Full recovery, and discharged on day 12	[86]
2021 / Argentina	1 patient, 57F, (COPD)	DENV PCR+	SARS-CoV-2 PCR+	Abdominal pain, dyspnea, petechiae rash	Symptomatic care	Improved over 5 days	[87]
2021 / Bangladesh	11 patients, 7 F and 4 M (25–71 years)	Dengue NS1 antigen and/or antidengue IgM positive	RT-PCR	Fever, myalgia, dyspnea, skin rash, bleedingSS	Oxygen support, controlled IV fluids, anticoagulants, steroids	10 recovered without complications, 1 died (severe	[88]

						COVID-19 with dengue shock syndrome)	
2021 / Bangladesh	1 patient, 28F	Dengue IgM positive by RDT, and NS1 antigen negative	RT-PCR positive	Hemoptysis, fatigue, red rash, mild to moderate respiratory distress, ground-glass opacities on chest CT	Paracetamol, azithromycin, remdesivir, hydrocortisone, nebulization, moxifloxacin, and respiratory exercises	Full recovery, and negative RT-PCR	[89]
2021 / Bangladesh	1 patient, 8F	NS1 antigen positive	RT-PCR positive	Shock, pneumonia, plasma leakage, multiple organ dysfunction, coronary artery dilatation	Immunoglobulin, methylprednisolone, aspirin, mechanical ventilation	Gradual improvement and discharged	[90]
2021 / India	1 patient, 65M	Dengue IgM positive by ELISA, NS1 antigen negative	SARS-CoV-2 RT-PCR positive via nasopharyngeal swab	Dengue myocarditis, intermittent hematuria, erythematous rash, sinus bradycardia	Intravenous fluids, IV dexamethasone oxygen supplementation, anticoagulation	Recovered and discharged after 17 days, no residual symptoms	[91]
2021 / India	1 patient, 30 M	Dengue RDT (NS1 +, IgM+, IgG-)	SARS-CoV-2 qRT-PCR	Fever, myalgia, arthralgia, diarrhea, anosmia	Supportive care	Recovered and discharged	[92]
2021 / India	1 patient, 20 F	Dengue RDT (NS1 +, IgM-, IgG-)	SARS-CoV-2 RT-PCR	Fever, myalgia, arthralgia	Supportive care	Recovered and discharged	[92]

2021 / India	1 patient, 27 M	Dengue RDT (NS1 +)	SARS-CoV-2 qRT-PCR	Fever, myalgia, arthralgia, mild cough, runny nose	Supportive care	Recovered and discharged	[92]
2021 / India	1 patient, 19 M	Dengue RDT (NS1 +)	SARS-CoV-2 qRT-PCR	Fever, headache, myalgia	Supportive care	Recovered and discharged	[92]
2021 / India	1 patient, 20 F	Dengue RDT (NS1 +, IgM-, IgG-)	SARS-CoV-2 RT-PCR	Fever, cough, body aches, arthralgia, vomiting, sore throat	Supportive care	Recovered and discharged	[92]
2021 / Indonesia	1 patient, 23 F (Pregnant)	NS1 antigen rapid test (Rapidan reagent), IgG/IgM positive	RT-PCR (SD Biosafer reagent), Rapid IgG antibody test	Thrombocytopenia, dengue shock syndrome, multiorgan failure, intrauterine fetal death	Platelet concentrate transfusion, oxygen support, ventilator, supportive care	Death due to multiorgan failure	[93]
2021 / Indonesia	1 patient, 19 M	Dengue IgM (+), IgG (+), NS1 antigen not done, RT-PCR not done	SARS-CoV-2 RT-PCR (+)	Thrombocytopenia, elevated liver enzymes, mild hyponatremia, hypokalemia, elevated D-dimer	IV favipiravir, corticosteroid, azithromycin, vitamin C and D, Lovenox, symptomatic therapy	Recovered, discharged on day 11	[94]
2021 / Malaysia	1 patient, 62M	Dengue IgM/IgG positive, NS1 antigen negative	RT-PCR positive (Ct 19.97)	Rigors, arthralgia, myalgia, rash, bibasal crepitations	IV fluids, oral paracetamol, symptomatic treatment	Recovered, asymptomatic at 1-month follow-up	[95]
2021 / Malaysia	1 patient, 41M	Dengue NS1 antigen, RT-PCR (DENV-3)	SARS-CoV-2 RT-PCR (nasopharyngeal swab)	Lymphopenia, thrombocytopenia, elevated liver enzymes, hyperferritinaemia	Dexamethasone, piperacillin-tazobactam, corticosteroids	Discharged after 19 days, and recovered liver function	[96]

2021 / Maldives	1 patient, 39 M	NS1 negative, IgM/IgG positive, confirmed by ELISA IgM/IgG (Panbio®)	rRT-PCR positive (Ct 28.35)	Persistent high-grade fever, retro-orbital headache, right upper quadrant pain	Conservative management with oral fluids	Discharged after 14 days isolation	[97]
2021 / Maldives	1 patient, 38 M	NS1 negative, IgM/IgG positive, confirmed by ELISA IgM/IgG	rRT-PCR positive (Ct 24.45)	Intermittent fever, generalized headache, sore throat, dysgeusia, anosmia	Oral fluids; monitored for warning signs of dengue and COVID-19 severity	Discharged after 14 days isolation	[97]
2021 / Mexico	1 patient, 42 F	NS1 antigen, IgM/IgG serology, RT-PCR (DENV-1)	RT-PCR (nasopharyngeal and oropharyngeal swabs)	Odynophagia, myalgia, arthralgia, petechiae, thrombocytopenia, hepatomegaly	Ivermectin (single dose), ciprofloxacin, loratadine, paracetamol, chlorpheniramine	Discharged after 24 days	[98]
2021 / Philippines	1 patient, 38M	SD BIOLINE Dengue Duo (NS1, IgM, IgG), DENV-1-4 RT-PCR	SARS-CoV-2 RT-PCR	Arthralgia, slight myalgia, thrombocytopenia, liver enzyme elevation, pneumonia	Supportive care, isolation, monitoring, no hospitalization	Full recovery after 3 weeks, and discharged	[56]
2021 / USA (travel from Pakistan)	1 patient, 30 F,	Dengue RT-PCR+ (DENV-2)	SARS-CoV-2 RT-PCR Negative	Myalgia, ageusia, loose stools	Hydration, antipyretics	Discharged	[99]
2023 / India	24 patients, ~67.5 years, 13 M	NS1 antigen, IgM/IgG antibody test	Not specified	Vomiting, dyspnea, altered sensorium	Supportive care, symptom management	16 recovered, 3 deaths	[100]

2023 / Russia	1 patient, 14F	Rapid antigen test, PCR for dengue virus DNA	Serology (IgM positive), PCR for M. pneumoniae (DNA negative)	Sore throat, rash, nosebleeds, abdominal pain, liquid stools, catarrhal symptoms	Infusion therapy (Meglumine sodium succinate), antipyretics, IV ceftriaxone, antihistamines, interferon inducer	Clinical improvement, discharged after 7 days	[101]

* Diagnostic confirmation varied across studies.

5.2. Geographic and Demographic Patterns in Co-Infection

Geographically, co-infected cases predominantly reported in urban and peri-urban tropical zones where both diseases exhibit endemic or epidemic transmission, with temporal peaks notably overlapping during dengue seasons coinciding with COVID-19 waves. Indicatively, the Valle del Cauca region of Colombia recorded a high number of cases of dengue and COVID-19 in the first 20 epidemiological weeks of 2020 emphasizing the vulnerability of the region to concurrent cases [57]. Co-infections were reported among cases in adults in the age group 20-50 years with slight dominance by males which might be attributed to occupational exposures and place of movement activities in endemic regions. Most of the vulnerable subpopulations targeted include healthcare workers and the socioeconomically disadvantaged populations, which are disproportionately impacted as they are more exposed [51, 102]. Pediatric and elderly are also rarely reported, but diagnosed cases are more likely to have a severe disease outcome [103]. These patterns are also affected by the socio-ecological factors, such as population intensity, urbanization, and inequality in access to healthcare.

5.3. Outcomes and Prognostic Indicators in Published Cases

There is a significant variation in clinical outcomes reported in DENV and SARS-CoV-2 co-infections. Though a minority of the cases are mild or asymptomatic, about 15-20 percent of the reported case series develop severe complications, such as acute respiratory distress syndrome (ARDS), severe vascular leakage, disseminated intravascular coagulation, liver dysfunction, and hemorrhagic syndromes that are synonymous with dengue shock, further complicated by the COVID-19 related pulmonary and systemic outcome. Patients have been reported to be admitted to the ICU at approximately 7.8% with hospital mortality reported up to 19.1% in some series but direct comparisons cannot be made due to the study design and reporting bias. The presence of advanced age, comorbid conditions, including diabetes mellitus, hypertension, and cardiovascular disease, high levels of inflammatory biomarkers (CRP, ferritin, D-dimer), coagulopathy, and continuously decreasing platelet counts are considered common prognostic factors of poor outcomes. Diagnostic ambiguity with a combination of clinical and laboratory features frequently leads to a delay in treatment which worsens the prognosis and is caused by the presence of diagnostic ambiguity

[51, 62, 103]. It is worth noting that coinfections may also increase the hospital stay; as in the case of dengue patients, the length of stay is longer in patients initially assigned to COVID-19 isolation wards than in non-isolated patients [102]. The key to optimum management is related to early and precise multiplex diagnostics and attentive clinical observation because the interactions of pathophysiology in co-infected individuals are complicated. It is advised by mathematical and control modeling that combined vaccination methods against COVID-19 and focused dengue measures should be applied to minimize cases and serious outcomes in endemic regions [104]. Overall, the 2020 body of literature proves that the co-infection of DENV and SARS-CoV-2 is not ubiquitous yet poses a serious clinical and public health problem characterized by a lack of diagnostic criteria, a broad spectrum of the clinical manifestation, high morbidity and mortality rates, and the necessity to integrate management and surveillance strategies according to the specifics of the context.

Markedly, there is unanimous reporting of clinical outcomes of dengue-COVID-19 co-infection. Whereas some case series show a higher occurrence of severity, ICU admission, and mortality than mono-infections, other reports show a similar outcome as dengue or COVID-19. Such inconsistencies are likely to indicate heterogeneity in study design, sample size, time and sequence of infection, variants of viruses circulating, host immune status, and capacity of the healthcare system. Causal inference is further undermined by the fact that mostly case reports and small observational studies are used to illustrate the true meaning of the outcome risk, thus necessitating well-designed prospective cohort studies.

6. Comparative Trends: Pre-Pandemic vs Pandemic Period

The comparison between pre-pandemic (2015–2019) and pandemic periods (2020–2025) reveals significant shifts in dengue virus (DENV) epidemiology, surveillance, diagnosis, clinical management, and public health strategies under the influence of SARS-CoV-2 emergence (Table 2).

6.1. Epidemiological and Surveillance Trends

Before COVID-19, DENV transmission followed predictable seasonal and cyclical patterns in endemic tropical and subtropical regions with relatively robust surveillance systems monitoring outbreaks. Vector control efforts and community engagement were consistent components of prevention programs. However, during the pandemic, many dengue-endemic countries

experienced apparent declines in reported dengue incidence, which have been attributed largely to disruptions in routine surveillance mechanisms, healthcare-seeking behaviors, and laboratory testing capacity because of lockdowns and resource diversion to COVID-19. For instance, Thailand experienced a reduction of 7 to 158 percent from 2020 to 2021 in the dengue incidence relative to forecasting on the basis of data in the pre-pandemic period, with fewer spatial clusters detected during the pandemic [105, 106]. On the contrary, there were also recorded concomitant outbreaks of COVID-19 and dengue cases in certain countries such as Brazil, Colombia and the Philippines, which demonstrates the continued active transmission through other environments, underreporting [57, 58].

6.2. Diagnostic Misclassification in Surveillance Data

Clinical algorithm as the main method of pre-pandemic dengue diagnosis was accompanied by antigen (NS1) and serological (IgM/IgG) tests, which offered acceptable sensitivity and specificity [68]. The pandemic brought some complexities in diagnoses because of the overlapping symptomatology of the COVID-19 and dengue [51]. In addition, serological cross-reactivity of DENV and SARS-CoV-2 antibodies also turned out to be a major confounder, which leads to false-positive outcomes in rapid diagnostic tests (RDTs) of either infection [53, 62]. The research revealed that the use of antigen-antibody testing enhanced the sensitivity of dengue diagnosis to 93 percent, indicating the advantages of using multiplexes to minimize false classification [65]. However, misdiagnosis delays affected timely clinical management and procedure of infection control in 2020-2022 [102].

6.3. Vector Control and Programmatic Disruptions

The strategies to control vectors that had been put in place before the pandemic, such as the use of insecticides, sanitation of the environment, and community mobilization, were badly interrupted by the movement restrictions and resource redistribution of the pandemic in most endemic areas. These disturbances enabled rebounds of Aedes mosquito population, which may increase the risk of dengue transmission although the number of cases was reportedly low. Also, alterations in human habits and city crowding during lockdowns could have impacted the rates of the human-vector contact in an unpredictable way [105, 106]. These dynamics brought weakness to the algorithm of controlling vectors and the program requires strengthening during the

recovery period after the pandemic and post-pandemic.

6.4. Clinical Management and Health System Burden

In endemic regions, the triage and treatment guidelines of dengue were clearly outlined and strengthened the pre-pandemic clinical management of the disease. The pandemic placed the COVID-19 caseloads on the healthcare system, as a result of which the dengue patient did not have access in time and complex isolation regimes [67, 102]. The pre-COVID period of dengue and COVID-19 co-infections were uncommon, and exhibited patterns of more severe, higher ICU admissions, longer hospitalization, and high mortality rates. An example here is that the ICU admission rates on the co-infected patients were as high as 7.8 %, and mortality was up to 19.1 % documented in certain reviews [69, 104]. Moreover, the dengue patients admitted to COVID-19 isolation wards were discharged more than one day earlier than the patients who were not subjected to hospital isolation policy [102]. The combination of these related clinical dilemmas required combined diagnostic algorithms and cross-disciplinary management interventions.

6.5. Public Health Strategic Adaptations

The pandemic has increased the rate of digital transformation of infectious disease surveillance and disease integration, and there is more timely tracking of febrile illnesses and co-infections based on the use of more mobile health platforms and syndromic surveillance as a shift in pre-pandemic siloed disease surveillance systems. The demand to use holistic or One Health strategies that are climate sensitive, include the ecology of vectors and health systems resilience have become prominent to address overlapping epidemic risks [51, 102]. Furthermore, COVID-19 and optimal dengue control interventions with increased level of vector control and community participation are increasingly suggested to be implemented as synergistic interventions [104].

7. Management and Therapeutic Strategies for Dengue–COVID-19 Co-infection

Dengue-COVID-19 co-infection is quite a challenge as the two diseases share symptoms and have different methods of treatment. Both infections are accompanied by fever, myalgia, headache, and rash, which makes the early diagnosis important and challenging to direct treatment and limit morbidity [56, 106, 107]. Dengue management focuses on close fluid balance to avoid leaking of the plasma and shock,

observation of platelets in case of thrombocytopenia, as well as avoiding NSAIDs or anticoagulants to minimize the risks of bleeding. On the contrary, treating the severe COVID-19 cases in most cases involves the use of corticosteroids, antivirals, and anticoagulation to contain the hyperinflammation and thromboembolic complications [69, 107, 108]. These paradigms are contradictory, since anticoagulation towards COVID-19 can exacerbate dengue bleeding, whereas steroids can affect the elimination of the virus or increase the severity of dengue. Co-infection also predisposes to hypovolemic shock, coagulopathy and pulmonary edema due to the mismanagement of fluids or compounded vascular dysfunction [67, 69, 103].

The parallel molecular and serological tests are required to detect the disease at a very early stage to avoid administering the wrong treatment [103, 107]. The individualized fluid therapy with constant hematological surveillance is the fundamental aspect. Without standardized guidelines, management depends on vigilant supportive care and individualized risk assessment [67, 69, 103]. Concurrent epidemics strain health systems, highlighting the need for integrated surveillance, vector control, and coordinated prevention programs [109-113].

Table 2

Summary of Clinical Management Strategies for Co-infection.

Clinical Scenario	Recommended Diagnostic Workflow	Supportive Care	Disease-specific Interventions	Monitoring & Follow-up Recommendations	References
Dengue-dominant	Rapid NS1 antigen / IgM/IgG serology, CBC, liver function tests- Rule out COVID-19 via RT-PCR	Hydration (oral/IV)- Fever management (avoid NSAIDs)- Bed rest	Symptomatic management; Careful fluid replacement to prevent shock	Daily CBC and hematocrit- Monitor (bleeding, plasma leakage)- Follow-up until platelet recovery	[71, 114]
COVID-dominant	SARS-CoV-2 RT-PCR / rapid antigen test, chest imaging if respiratory symptoms- CBC, CRP, liver/kidney function	Oxygen therapy as needed, antipyretics, nutritional support	Antivirals (Paxlovid, Remdesivir) per protocol- Corticosteroids if indicated- Thromboprophylaxis	Monitor oxygen saturation, vital signs- Repeat labs as clinically indicated, and telemedicine follow-up if mild	[115, 116]
Severe co-infection	Combined testing: NS1/IgM/IgG + SARS-CoV-2 RT-PCR- CBC, LFTs, renal function.	ICU-level supportive care, IV fluids guided by hemodynamics, oxygen/ventilatory support	Dengue (cautious fluid and resuscitation), COVID-19 (antivirals, corticosteroids, thromboprophylaxis)	Continuous monitoring, CBC, coagulation, LFTs, renal function checkup, and Multi-disciplinary follow-up	[117, 118]

7.1. Mathematical Modelling and Optimal Control Approaches for Co-Infection Management

The conceptual perspective of mathematical model results can give an understanding of the population-level of dengue and COVID-19 co-infection, especially in an endemic area, and the results are not applicable in individual clinical decision-making but in public health planning. Extended-term SEIR-like (Susceptible-Exposed-Infectious-Recovered) models have been created to include mono- and co-infections as well as the notion of recovery, where transmission dynamics and hypothetical immune interactions can be built across a range of conditions. More complex methods, such as an overall extension of Atangana-Baleanu derivatives to the fractional-order model, aim to model the effect of memory in disease behaviour, and optimal control theory has been used to assess the intervention measures of interest, including COVID-19 vaccination, treatment of dengue, and sustained vector control, as well as isolation of the patient [104, 111].

Based on the Maximum Principle by Pontryagin, these models assume that interventions that are implemented jointly, especially when they include vaccination against COVID-19 and control of dengue, can lead to an overall decrease in disease prevalence, rather than that of a specific disease. Parameters that are always found sensitive in the sensitivity analyses include: the rate of biting the vectors, the vaccination coverage, diagnostic latency, and also the access to healthcare. Other models analyze the theoretical effect of policy responses, such as lockdowns and redistribution of resources, on co-infection dynamics [104, 111]. Nevertheless, such modelling studies are based on simplifying assumptions, limited empirical data, and heterogeneous parameter estimates, and most of them have not been tested on large real-world co-infection data. Their findings, therefore, can only be viewed as exploratory and hypothesis-generating, but not predictive. These shortcomings notwithstanding, the models indicate the possible societal health utility of built-in tracking, coordinated vaccination plans, and protracted control of vectors in locations where both dengue and COVID-19 are circulated [53, 62, 104]. The summary of Mathematical Models Applied to Dengue–COVID-19 Co-infection were listed in Table 3.

Table 3.

Summary of Mathematical Models Applied to Dengue–COVID-19 Co-infection.

Model Type / Framework	Key Assumptions	Parameters Included	Optimization Approach	Main Findings	References
Agent-Based Model	Individual-based simulation, heterogeneous mixing	Individual behaviours, contact rates, vaccination status	Simulation-based optimization	Simulates individual interactions to predict disease spread and evaluate interventions	[119]
Fractional-Order Differential Equation Model	Non-integer order derivatives, memory effects	R_0, fractional-order derivatives, transmission rates	Optimal control theory	Fractional-order models provide more accurate predictions for co-infection dynamics	[120]
Multi-Strain / Multi-Pathogen Model	Multiple strains or pathogens co-circulating	Strain-specific transmission rates, cross-immunity	Multi-strain modeling techniques	Models interactions between multiple strains or pathogens	[121]
Network-Based Model	Disease spreads through contact networks	Contact patterns, transmission rates, and recovery rates	Network analysis	Models disease spread through social or contact networks	[122]
Optimal Control Model	Control strategies to minimize disease spread	Isolation rate, treatment rate, vaccination rate	Pontryagin's Maximum Principle	Identifies optimal strategies for controlling co-infection	[104]

SEIR Model with Co-infection Compartments	Homogeneous mixing, constant population	R_0, vector biting rate, vaccination coverage, isolation rate	Pontryagin's Maximum Principle	Combined vaccination and vector control can significantly reduce co-infection prevalence	[113]
SIR Model with Co-infection Compartments	Homogeneous mixing, constant population	R_0, vector biting rate, vaccination coverage, isolation rate	Pontryagin's Maximum Principle	Combined vaccination and vector control can significantly reduce co-infection prevalence	[113, 119]
Stochastic Model	Randomness in disease transmission	R_0, transmission rates, recovery rates	Stochastic differential equations	Incorporates random fluctuations in disease spread, useful for small populations	[124]

7.2. RNA Dynamics in Dengue–COVID-19 Co-infection

The analysis of RNA dynamics during dengue virus (DENV) and SARS-CoV-2 co-infection highlights a complex interplay between viral genomes, host RNA-binding proteins, innate immune pathways, and resulting immunopathology, shaping replication efficiency and disease severity. Both DENV and SARS-CoV-2 are positive-sense single-stranded RNA viruses which use host machinery and viral RNA-dependent RNA polymerases (RdRp) to replicate. The 10.7 kb genome of DENV is self-coding and contains 5 mRNA-like UTR elements (stem-loops and pseudoknots), which avoid exonuclease Xrn1, and generate subgenomic flaviviral RNA (sfRNA) as a result of exon deletion [124, 125]. Conversely, the relative genome size (~29.9 kb) of SARS-CoV-2 has replicase ORFs (1a/1b) and subgenomic RNAs produced by discontinuous transcription through transcription regulatory sequences (TRSs), which coordinate protein expression and avoid RNA sensing [126, 127]. In co-infection, the viruses are competing over ER-derived replication complexes, ribosomes, nucleotides and RNA-protein interaction networks and may result in one virus prevailing or synergistic regulation of host responses.

The RNA-binding proteins (RBPs) act as a host for this interplay. To ensure the stability of the RNA and immune suppression, DENV recruits more than seventy RBPs, such as G3BP1, hnRNPs, and translation initiation factors. On the same note, nucleocapsid protein of SARS-CoV-2 interacts with helicases such as DDX3X and stress granule elements, which control viral RNA metabolism [128]. Competition for these RBPs in co-infected cells may alter replication dynamics and immune modulation. Both viruses encode RNA associated proteins that antagonize the innate RNA sensing pathways, such as DENV sfRNA blocks RIG-I signaling, while NS4B inhibits STAT1 nuclear translocation. SARS-CoV-2 proteins such as Nsp15 and ORF6 impede dsRNA sensing and IFN-STAT pathways [124, 127, 128]. Combined suppression in co-infection may enhance replication and worsen clinical outcomes.

Cross-talk between viral RNAs adds complexity. DENV-induced mitochondrial DNA release activates TLR9, influencing innate immunity during SARS-CoV-2 co-infection [129]. The RNA-mediated suppression of innate sensing as well as interferon signalling may indirectly amplify the downstream cytokine responses observed in severe dengue and COVID-19, potentially exacerbating the inflammation during the co-infection [130].

The potential influence of pre-existing dengue antibodies on SARS-CoV-2 infection has been proposed, but the immunological implications of ADE are discussed in detail in Section 3 and are not primarily RNA-driven [51]. Structural elements such as DENV's duplicated 3′ UTR dumbbell motifs (DB1, DB2) influence replication in mosquitoes and humans [125], while SARS-CoV-2 subgenomic RNAs enable flexible adaptation to host pressures.

Therapeutically, viral RdRps (DENV NS5, SARS-CoV-2 nsp12) are prime drug targets for nucleoside analogues (e.g., remdesivir) and structure-based inhibitors [127, 131]. RNAi approaches using siRNAs against conserved regions, ASOs disrupting sfRNA pseudoknots or TRS sequences, and CRISPR-Cas13 RNA cleavage show promise [124, 132]. RNA aptamers and immunomodulatory RNAs may restore interferon responses and mitigate cytokine storms [129, 130].

8. Pharmacological Interventions for Dengue and Covid-19

Currently, two dengue vaccines have been licensed, Dengvaxia(r) (Sanofi) and Qdenga(r) (Takeda). Dengvaxia (CYD-TDV) is a tetravalent, live attenuated, recombinant vaccine with a yellow fever 17D virus attenuated backbone (incorporating genes prM and E of all four serotypes of dengue virus). It is only given by three doses (0, 6 and 12 months) and shows a moderate level of efficacy (~60 or ~80) in the seropositive population, but increases the risk of severe dengue in naive seronegative vaccinees because of ADE. Due to this, the WHO and the U.S. FDA limited its use to those 9-16 years of age who are seropositive in endemic regions. Qdenga 1 1 2 (TAK-003) is the live attenuated tetravalent vaccine designed against dengue based on DENV-2 backbone, harbouring the prM and E genes of DENV-1, 3 and 4. Administered in two doses three months apart, it shows ~80% efficacy in both seropositive and seronegative individuals with a favourable safety profile, eliminating the need for pre-vaccination screening. Approved in Indonesia, Brazil, and the EU (2022–2023), it offers a practical tool for broad dengue prevention. While neither vaccine protects against SARS-CoV-2, widespread dengue vaccination can indirectly reduce co-infection risk and associated diagnostic challenges [51, 128, 130, 133]. The limitations of Dengvaxia in areas with overlapping dengue and COVID-19 epidemics are due to logistical difficulties in conducting serological screening and the safety of an attenuated vaccine, but Qdenga has a better profile, which can be used as a convenient tool of widespread dengue prevention [67, 111]. Table 4 provides a list

of the comparison of dengue vaccines (Dengvaxia and Qdenga) [133-135].

Table 4.

Comparison of dengue vaccines.

Vaccine	Dengvaxia® (CYD-TDV)	Qdenga® (TAK-003)
Manufacturer	Sanofi	Takeda
Vaccine Type / Platform	Tetravalent, Recombinant, and Live attenuated, yellow fever chimeric	Live attenuated, DENV-2 backbone
Backbone Virus	Yellow fever 17D vaccine	Dengue virus serotype 2
Composition Details	prM and E genes from all 4 DENV serotypes on the YF17D backbone	DENV-2 backbone expressing prM/E from DENV-1, 3, 4
Serostatus Dependence	Yes, only seropositive recommended due to ADE risk	No, safe and effective regardless of serostatus
Efficacy	~60–80% in seropositive individuals	~80% overall
Dosing Schedule	3 doses (0, 6, 12 months)	2 doses (0, 3 months)
Target Age Group Approved	9+ years (varies by country)	4+ years (varies by country)
Regulatory Status	WHO prequalified; approved in multiple endemic countries	EMA; approved in multiple endemic countries
Usefulness	Requires pre-vaccination screening for safe use; limited in dengue-naive populations	Broad population use without screening; simplified immunization program

Supporting this notion, a case-control study carried out among 293 adults diagnosed with dengue and malaria in Mangaluru, India, in 2024 supports this idea. The presence of dengue and malaria was established using standard laboratory tests, whereas previous COVID-19 infection was obtained in terms of medical

history. One hundred and eighty-one percent of severe dengue cases and eighty-five point seven percent of severe malaria cases among the participants had a history of COVID-19 infection. The patients had a problem of fever, aches in the bodies and other symptoms of the diseases whose vectors were the vectors. Standard hospital care such as supportive treatment was given. Results indicated that factors that predicted a more severe dengue and malaria were previous COVID-19 infection [136]. Interestingly, the acceptance rate of dengue vaccines in Puerto Rico rose significantly in post-COVID-19 period indicating a change in prevalence rates from to 73.4% to 84.5 and 75.6%n to 85.5% among the adults and their children, respectively [137]. In the case of dengue, the only currently approved methods of prevention include vaccination and supportive care because no direct-acting antiviral agents have been approved [138]. By comparison, COVID-19 control is advantaged by the availability of multiple vaccines that have strong real-world data that show a decrease in morbidity and mortality, especially in populations at high risk. Antiviral drugs have been reported to be effective in treating COVID-19 with remdesivir, molnupiravir, and nirmatrelvir/ritonavir, as well as monoclonal antibodies [139-141]. Nevertheless, the safety, efficacy, and clinical benefit of these antiviral agents in the dengue-COVID-19 co-infection are not studied, and specific clinical research is necessary.

9. Research Gaps and Future Perspectives

The complexity of dengue–COVID-19 coinfection is a challenge that highlights important flaws in trial design, diagnosis, and understanding of the mechanism. Traditional methodologies do not reflect the patient heterogeneity, different interaction of pathogen, and the swiftly changing epidemiology. Master protocol biomarker-driven stratification and adaptive enrichment and Bayesian updating are provided by innovative clinical trial designs, including basket, umbrella, and platform designs, in multifactorial disease situations. Their use is however, hampered by poor mechanistic justification, statistical impression, and type I error control problems [142-144]. Digital technologies, such as mobile health systems, wearable devices, and AI analytics can be integrated to overcome the delays in the recruitment process, the high operational cost, and the low generalizability [145]. Decentralized pragmatic trials are capable of reaching more representative cohorts and being regulatory compliant in consent, privacy, and security. Blending digitization and adaptive trial designs may create scalable

and responsive and cost-effective emerging coinfection research ecosystems.

studies are required on large scale, multicentre cohort studies in endemic areas that would capture super-strain variability as well as host genetics, comorbidities. Standardized biospecimen collection is necessary to support high-resolution immunopathogenic studies, such as antibody-dependent enhancement and common pathways, such as hyperinflammation and endothelial dysfunction. Precision trial design can be informed with immunologically relevant endpoints by sophisticated methodologies such as single-cell transcriptomics and immunophenotyping. Immune cross-reactivity that results in diagnostic uncertainty requires the creation of multiplex and point-of-care tests that can detect SARS-CoV-2 and DENV with non-cross-reactive targets simultaneously [51, 67, 145]. The diagnostic accuracy can be improved with the help of AI-assisted algorithms that combine clinical and laboratory data. Epidemiologically, overlapping outbreaks strain healthcare systems, hinder diagnosis due to serological cross-reactivity, and disrupt vector control under lockdowns [57, 111]. Integrated surveillance, rapid molecular diagnostics, and dual-targeted therapies are essential. Future research should emphasize single-cell transcriptomics, interactome mapping, ribosome profiling, and organoid-based validation to unravel co-infection dynamics and advance RNA-based therapeutics. Predictive modelling that assimilates epidemiological, climatic, vector ecology, and immunological data can forecast co-epidemic dynamics, optimise resource allocation, and support targeted public health interventions in co-endemic regions.

On a methodological level, there are still a number of limitations and gaps in research. Although they do have some emerging insights, there still exist considerable knowledge gaps as a result of the dearth of co-infection-specific clinical trials, little longitudinal data and because usage of heterogeneous case reports and observational studies, which is likely to be skewed towards rare or positive results. The lack of diagnostic algorithms and the existence of validated biomarkers restricts the comparative analysis and the synthesis of evidence. The solution to these gaps will entail congruent study designs, durable multicentre relations, and the background of prospective data-collections to reduce the bias and to increase the reproducibility, especially in the co-endemic areas.

10. Conclusion

Dengue and COVID-19 are two overlapping infectious diseases, which

have complicated clinical and population health conditions. The overlapping clinical similarity and the immunological cross-reactivity makes it a great challenge with regard to the diagnosis and the prognosis. The disturbances of the COVID-19 pandemic on the long-established dengue surveillance and control programs contribute to the intensification of these complications as well due to the misclassification and underreporting of the actual disease burden. There is the need to address this nexus of viral threats in a multi-faceted and integrated way. The ability to detect and forecast instructions can be improved through the development of multiplex molecular diagnostics and mathematical modelling. However, gaps in the research remain severe, particularly when it comes to the pathophysiology of co-infection in particular and its long-term consequences. The suggested future research study has to be involved with big epidemiological studies as well as clinical trials to maximize the management approaches. Lastly, integrated surveillance and global ready response to health should be enhanced to enable proper management of co-infection of dengue and COVID-19.

Conflict of interest

The author declares no conflict of interest, financial or otherwise.

Declaration of generative AI in scientific writing

During the preparation of this manuscript, the authors used generative AI tools solely for reference formatting and organization. The authors reviewed and verified all outputs and take full responsibility for the accuracy and integrity of the content.

Authorship contribution statement

Selvakumar Muruganantham: Writing – original draft, Supervision, Conceptualization. **Shanmugarathinam Alagarsamy**: Writing – original draft, Supervision, Conceptualization. **Dhanasekar Jayakumar**: Writing – review & editing, Writing – original draft. **Dineshkumar Palanivel**: Writing – original draft. **Sowbagaya Lakshmi Ramesh**: Writing – original draft, review and editing.

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