Effective Preventative Measures are Essential to Lower Disease Burden From Dengue and COVID-19 Co-infection in Bangladesh

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Effective Preventative Measures are Essential to Lower Disease Burden From Dengue and COVID-19 Co-infection in Bangladesh

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ABSTRACT: Bangladesh is widely recognized as one of the dengue prone nations, and empirical evidence has consistently demonstrated an upward trend in the severity of the disease over time. With the persistent occurrence of dengue in Bangladesh and the ongoing presence of COVID-19, which has not been fully eradicated and may persist for an uncertain period of time, there is a high probability of co-infection between these 2 illnesses. Given the circumstances, the concurrent occurrence of the COVID-19 and dengue epidemics, along with the potential co-infection, may pose an overwhelming burden on healthcare systems that are already grappling with challenges in meeting the existing demand. Due to a lack of awareness, an inadequate health infrastructure, and ineffective disease prevention initiatives, the country is now more susceptible to the threat posed by a co-infection that has been found to be associated with more severe outcomes, marked by significant morbidity and mortality. The objective of this opinion piece is to explore the gravity of co-infection in Bangladesh, as well as the potential challenges to overcome and the preventative measures that need to be implemented to address the severity. This opinion piece proposes a set of modern preventative strategies that, when integrated with conventional methods, have the potential to mitigate disease severity, avert the occurrence of co-infection between COVID-19 and dengue, and halt the co-epidemics of COVID-19 and dengue.

KEYWORDS: Dengue, Corona virus, artificial intelligence, biopesticide, co-infection

Background

The dengue virus (DENV), which has a higher genetic variety in Bangladesh, is widespread and co-circulating with 4 DENV serotypes (DENV-1, DENV-2, DENV-3, and DENV-4), which raises the risk of developing severe dengue due to the antibody-dependent enhancing effect.[1] Through the bites of infected female *Aedes* mosquitoes, mostly *Aedes aegypti* and, to a lesser extent, *Aedes albopictus*, the DENV is transmitted via a human-mosquito-human cycle.[2] SARS-CoV-2, or the severe acute respiratory syndrome coronavirus 2, was identified on December 31, 2019, in Wuhan, Hubei Province, China. The COVID-19 outbreak was declared as a pandemic by the World Health Organization on March 12, 2020, as a result of the virus's subsequent global expansion.[3] When an infected person speaks, sneezes, breathes or coughs, the virus can be disseminated through their mouth or nose in tiny liquid droplets.[4] The world is affected by Alpha, Beta, Gamma, Delta, and Omicron variants of this virus during the pandemic phases of COVID-19.[5]

Co-infections, which refer to the simultaneous presence of multiple parasite strains or species within a host, are widely prevalent in various biological systems. Moreover, the correlation between various types of parasites within a host is not arbitrary, since the presence of certain parasites might enhance the likelihood of infection by other parasites. The presence of many infections has been observed to have a more detrimental impact on human health when compared to the presence of a single infection.[6] The incidence of Dengue in Bangladesh has persistently led to progressively catastrophic outcomes each year. In light of the enduring existence of COVID-19, which has not been completely eradicated and is anticipated to persist indefinitely, there exists a notable probability of concurrent infection between these 2 ailments. The presence of this probable co-infection presents a significant risk to the population of Bangladesh. This opinion piece focuses on the severity of co-infection in Bangladesh, the challenges encountered, approaches to managing it, and preventative measures aimed at mitigating the possible risks associated with co-infection.

Disease Prevalence

In order to fully comprehend the severity of co-infection, it is imperative to meticulously scrutinize and evaluate the prevalence data for dengue, COVID-19, and their simultaneous occurrence globally in various nations. This can provide us with significant insights into the potentially severe consequences of co-infection.

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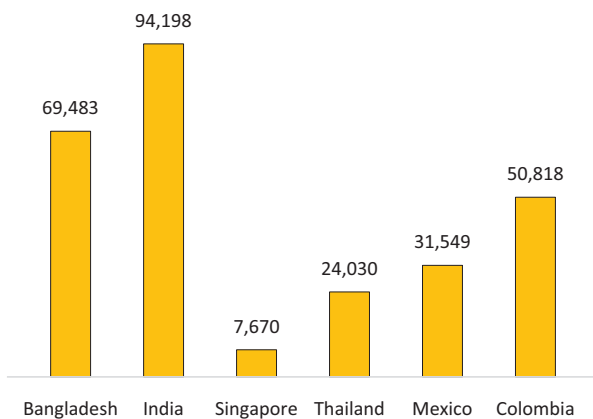
Dengue Case Report

Figure 1. Dengue cases in Bangladesh, India, Singapore, Thailand, Mexico, and Colombia during the year 2023.

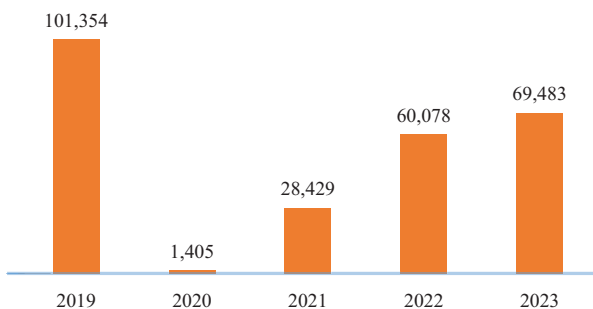**Cases of Dengue Infection in Bangladesh over the Past Five Years**

Figure 2. The prevalence of dengue infections over a 5-year period in Bangladesh.

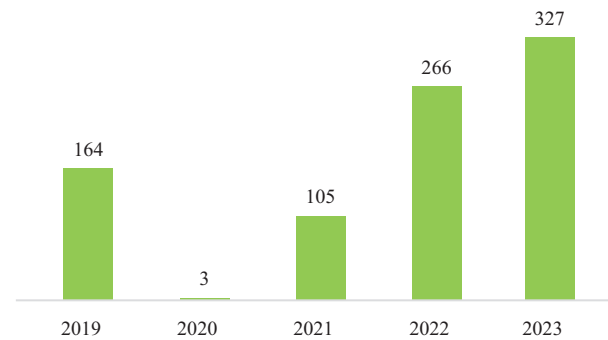**Dengue-Related Deaths in Bangladesh During the Past Five Years**

Figure 3. The prevalence of dengue-related fatalities in Bangladesh over the past 5 years.
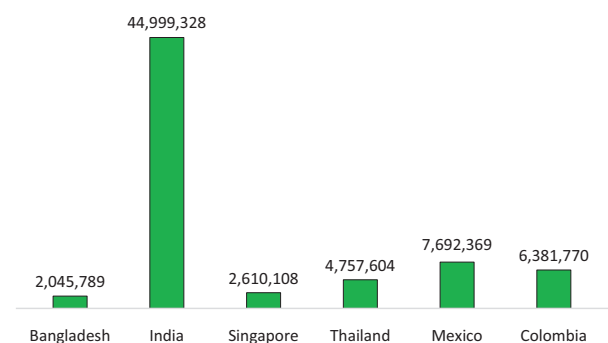
COVID-19 Case Report

Figure 4. The distribution of COVID-19 cases in Bangladesh, India, Singapore, Thailand, Mexico, and Colombia.

Annually, almost 400 million people worldwide are infected with the dengue virus. Dengue, a global epidemic, causes more than 100 million instances of illness and 40 000 fatalities annually.[7] The graph in Figure 1 displays the documented instances of dengue infection in Bangladesh (as of August 7), India (as of September 17), Singapore (as of the first 40 epidemiological week), Thailand (as of June 21), Mexico (up to epidemiological week 26), and Colombia (up to epidemiological week 25) in the year 2023.[8-12]

Bangladesh is a nation that experiences a persistent occurrence of dengue, and over time, the intensity of these infections continues to escalate. From 2019 to August 7, 2023, the following dengue cases and fatalities were reported in Bangladesh: in 2019, 101 354 reported cases and 164 confirmed deaths; in 2020, 1405 cases with just 3 confirmed deaths; in 2021, 28 429 documented cases and 105 fatalities; in 2022, 60 078 cases resulting in 266 fatalities; in 2023, 69 483 cases with 327 deaths attributed to dengue.[1,8] In 2019, Bangladesh had a highly significant dengue outbreak, marking it as one of the most severe in the country's history. However, in 2020, there was a fortuitous decline in reports of dengue fever, possibly because of the rising trend of COVID-19 cases. Figures 2 and 3 depicts

graphically the prevalence of dengue infections and death cases over a 5-year period in Bangladesh, respectively.

As of October 12, 2023, the World Health Organization (WHO) has documented a cumulative total of 771 191 203 confirmed cases of COVID-19 globally, resulting in 6 961 014 deaths.[13] From 3 January 2020 to 12 October 2023, the recorded number of verified COVID-19 cases and deaths in different nations is as stated: Bangladesh-2 045 789 cases and 29 477 deaths; India- 44 999 328 cases and 532 034 deaths; Singapore- 2 610 108 cases and 1872 deaths; Thailand- 4 757 604 cases and 34 479 deaths; Mexico- 7 692 369 cases and 334 669 deaths; Colombia-6 381 770 cases and 142 942 deaths.[14-18] Figure 4 illustrates the distribution of COVID-19 cases.

Several countries, including Brazil, Paraguay, Bolivia, Argentina, Colombia, Mexico, Philippines, Malaysia, Singapore, Vietnam, Thailand, and Indonesia, are at a high risk of co-infection with both SARS-CoV-2 and DENV due to the COVID-19 pandemic and potential dengue outbreaks during the monsoon season. This risk has already been demonstrated by 31 confirmed cases in Brazil, Argentina, Singapore, Thailand, Maldives, India, Pakistan, Bangladesh, and a French island in the Indian Ocean, resulting in 5 deaths. The mortality rate of those co-infected with SARS-CoV-2 and DENV is 16.13%, which is considerably greater than the mortality rates

observed globally for each disease when they occur separately. The concurrent infection of SARS-CoV-2 and DENV in these places is likely to continue imposing a significant strain on the healthcare system.[19] A cross-sectional study was undertaken in Colombia, revealing that out of the 90 patients examined, 18 were found to have co-infection. Co-infection was correlated with a higher requirement for mechanical ventilation, initial management in the intensive care unit (ICU), and admission to the ICU during hospitalization, in comparison to cases of COVID-19 without co-infection. The mortality rate in the intensive care unit (ICU) was 66.6% for patients with co-infection, compared to 29.4% among patients infected solely with SARS-CoV-2.[20] A comprehensive study was carried out in the Filipino population, focusing on the simultaneous occurrence of SARS-CoV-2 and dengue infections among children. The cohort analysis involved a large group of individuals, with a total of 3341 cases of SARS-CoV-2 infection. Among these cases, it was observed that 145 individuals (4.34%) had a co-infection with dengue. This means that about 1 out of every 25 cases of SARS-CoV-2 infection also had a dengue co-infection and the co-infection resulted in a case mortality rate of 6.7%.[21] An investigation in Peru showed a total of 50 patients who were co-infected with both COVID-19 and dengue. Out of the total 50 cases, 6% had the onset of severe dengue and required admission to the ICU. Additionally, 58% of the cases exhibited dengue with warning indications, while 36% had dengue without any warning indications. Out of the entire population, 76% of the patients exhibited COVID-19 pneumonia. The group had a case fatality rate (CFR %) of 28%. Every patient afflicted with severe dengue succumbed to the illness, resulting in a 100% fatality rate.[22] In Bangladesh, the first patient to test positive for both coronavirus and dengue fever was a 53-year-old man suffering from fever, cough, muscle pain, and respiratory complications.[23] The Times of India documented an instance of a 68-year-old man who succumbed to both COVID-19 and dengue in Bhopal. Additionally, 2 individuals from Bangladesh have been documented as having a co-infection of both SARS-CoV-2 and DENV. Unfortunately, this co-infection led to the eventual demise of one of the patients.[19] A case report of a child with co-infections involving fever, shock, pneumonia-like symptoms, plasma leakage, and multiple organ dysfunction was found in Bangladesh.[24] Another case report of 11 co-infected patients was found in Bangladesh, and some of them exhibited severe COVID-19 disease, severe dengue fever, oxygen support requirements, dengue shock syndrome, and even mortality.[25]

The analysis of previous studies undertaken globally and in Bangladesh, as previously mentioned, elucidates the evident potential danger associated with co-infection. However, in general, numerous instances of co-infection are not officially documented due to the similarity of clinical symptoms, incorrect or delayed diagnosis, an inadequate healthcare system, a lack of public awareness, and other factors that are particularly evident in a less developed country like Bangladesh.

Dengue and COVID-19 Co-infection: A Threat in Bangladesh

Diagnosing, treating, and allocating resources in co-infection scenarios is challenging due to the intricate nature of different disease severities, extended periods of infection, and overlapping clinical manifestations and pathogenesis. This is especially true in developing Asian countries with a high prevalence of dengue and other arboviruses.[26] According to several research, SARS-CoV-2 and DENV co-infections cause harm to a variety of organs, particularly the lungs, liver, cardiovascular system, and central nervous system (CNS). Therefore, compared to single infections, COVID-19 and dengue co-infection correspond with more severe symptoms and worse prognoses.[19]

Dengue fever is a yearly occurrence in the tropical country of Bangladesh because of the high population density, unplanned urbanization, hot and humid climate, heavy monsoon rainfall, environmental degradation, and inadequate sanitary infrastructure that contribute to the spread of the disease.[27] With the onset of the monsoon in South Asia, dengue becomes more prevalent, posing a lethal challenge for developing nations such as Bangladesh, which have fragile health systems and congested populations.[28] The nation's yearly upsurge in dengue instances has already placed significant pressure on the healthcare system, and the continued existence of COVID-19, together with the possibility for co-infections, could worsen its vulnerability.

SARS-CoV-2 and dengue virus (DENV) have distinct modes of entry, although both pathogens elicit a systemic infection and exhibit overlapping clinical manifestations, such as fever, headache, dyspnea, cough, myalgia, nausea, asthenia, arthralgia, pulmonary edema, gastrointestinal disturbances, and frequently observed laboratory findings such as thrombocytopenia, lymphocytopenia, increased transaminase levels, and leukopenia.[19,29,30] Severe COVID-19 is distinguished by the formation of micro and macrothrombi, whereas dengue is commonly linked to a propensity for hemorrhaging.[31] Furthermore, apart from the shared clinical presentation characteristics, there exist similarities between the 2 aforementioned illnesses, encompassing endothelial dysfunction, cytokine storms, risk factors associated with the progression toward severe illness, and the occurrence of multi-organ failure. Both infections exhibit a proinflammatory immune response and a delayed and impaired type I IFN response.[32]

In regions where dengue is prevalent, it is possible to acquire false-positive results when testing for dengue virus (DENV) using serological methods. This can lead to a delayed identification of SARS-CoV-2 infection through molecular testing. As both viruses are capable of causing severe complications, predominantly through cytokine storm in lung tissue brought on by macrophage hyper-activation, this could increase the likelihood of adverse clinical outcomes.[33]

It is widely acknowledged that dengue is endemic in Bangladesh, as evidenced by the escalating annual incidence and the alarming records of its worsening scenario. Consequently,

dengue has emerged as a significant public health concern inside the country. Moreover, it is highly probable that COVID-19 will persist indefinitely. The concurrent presence of COVID-19 alongside other diseases such as dengue is a common occurrence, and the likelihood of diagnostic errors cannot be discounted. One factor that contributes to the heightened risk of co-infection is the similarity in symptoms between individuals who have contracted both COVID-19 and dengue. The resemblance between symptoms of dengue and COVID-19 poses a considerable difficulty for healthcare professionals in differentiating between the 2 diseases, particularly during the early stages of infection when a definitive diagnostic test is not easily accessible. Additionally, due to the occurrence of co-infection and the overwhelming workload on healthcare workers, the likelihood of misdiagnosis and delayed diagnosis is significantly elevated, which poses a significant risk for both viral fevers.[28] Furthermore, an erroneous diagnosis at the early stages of these diseases might result in an inappropriate therapeutic strategy, ultimately leading to unfavorable clinical consequences for patients. The co-infection of dengue with COVID-19 has been associated with severe consequences, such as septic shock, acute respiratory distress syndrome, and multi-organ failure, ultimately resulting in mortality for certain individuals. Compared to patients without other chronic diseases, patients with diabetes, hypertension, and cardiovascular disease exhibited significantly more severe disease and higher case fatalities.[30] Co-infection with COVID-19 and dengue resulted in worse results in terms of fatality rates, ICU admissions, and length of hospital stay.[31]

It is noticeable that in certain nations or regions, cases of co-infection have escalated to a critical level, necessitating intensive care unit (ICU) interventions. Conversely, in other nations or regions, co-infection cases have not resulted in significant adverse outcomes. In the context of Mexico, it was observed that all patients who had co-infection, including those with notable comorbidities, exhibited a benign course, ultimately resulting in good outcomes and prognoses.[34] Conversely, in Colombia, compared to patients who had COVID-19 infection alone, co-infection was linked to worse clinical outcomes and greater mortality in ICU-admitted patients. The presence of overlapping infections and simultaneous occurrence of these diseases may contribute to an increased demand for intensive care and mechanical ventilation among affected patients.[20,33] Hence, it can be asserted that co-infection exhibits various degrees of severity in distinct areas, and the seriousness of co-infections may be influenced by several factors, including environmental circumstances, overlapping clinical symptoms, inadequate early disease detection, delayed or inaccurate diagnosis, insufficient healthcare infrastructure, failure to take promptly preventive measures, lack of public awareness, limited availability of appropriate diagnostic methods, and so forth.

The treatment of co-infections poses additional complexities, hence heightening the degree of risk. Patients with Group B and C dengue fever require continuous fluid support, although intravenous fluid is typically avoided in COVID-19 disease to prevent the danger of pulmonary edema. The use of the proper anticoagulants is necessary when COVID-19 disease results in arterial or venous thrombosis but is contraindicated in cases of dengue infection due to the risk of overt bleeding.[25]

In 2023, Bangladesh has witnessed a significant escalation in dengue epidemics, exhibiting a worsening trend. The simultaneous presence of dengue and the ongoing COVID-19 pandemic poses a considerable risk, as the country must now deal with the challenge of managing these 2 separate infections concurrently, along with the possibility of co-infections. Furthermore, the occurrence and deaths resulting from co-infection in Bangladesh have already been recorded in several case studies, some of which are mentioned before, thus emphasizing the potential severity and associated risks among the population. Nevertheless, the current lack of comprehensive prevalence data for individuals with co-infections introduces further uncertainty and exacerbates the associated dangers.

Preventive Measures and Recommendations

Bangladesh can be categorized as a least developed country with a significant population density and a constrained healthcare infrastructure. Consequently, the management of co-infection scenarios poses significant challenges, potentially exacerbating the burden on an already weakened healthcare system. Given the substantial probability of co-infection, it is crucial to promptly initiate effective measures to address these diseases. Failure to address this issue could have severe implications for the safety of the population in the foreseeable future. Old strategies have proven ineffective in tackling worst-case scenarios, therefore in addition to conventional preventive measures, it is crucial to make contemporary and innovative approaches swiftly accessible as expounded on later.

The most frequent types of containers found to be used as *Aedes* habitats in Bangladesh were vehicle parts, abandoned construction materials, tires, plastic buckets, plastic drums and coconut shells. *Aedes* larvae are produced in stagnant water, so the city corporations of Dhaka should function properly in order to clean, dispose of, and recycle these containers, and every resident should take precautions to prevent water from accumulating on the roof of the house, in the courtyard, or even in flowerpots. The use of drones for detecting stagnant water and mosquito breeding areas on rooftops is highly recommended.

To lessen the incidence of dengue in Bangladesh, chemical techniques such the widespread use of long-lasting insecticide-treated nets (LLINs), indoor residual spraying (IRS), peridomestic space spraying, and mosquito repellents should be employed. However, after conducting adequate research, it may be possible to use Green Synthesized Plant-Based Metallic Nanoparticles as a potential method in the management of dengue.[35]

Biological control strategies, such as the field release of genetically modified mosquito species, bacteria (*Wolbachia* spp, *Asaia* spp), bacterial agents like *Bacillus thuringiensis* subspecies israelensis (Bti), predatory fish (*Gambusia affinnis* and *Poecilia reticulata*), protozoans (*Chilodonella uncinata*), fungi (*Beauveria bassiana*), insect growth regulators (IGRs), biopesticide spinosad and mechanical control techniques like eave tubes and attractive sugar baits, can all be used to effectively control the dengue epidemic in Bangladesh after thorough investigations.[35]

It might be possible to develop unique, innovative approaches, such a combination of COVID-19-resistant hand sanitizers and insect repellents that are efficient against arboviral diseases like dengue, which would ultimately provide protection from both infections.[36]

One study reveals that the ratio of critical care beds to population in Bangladesh is less than 1 per 10 000 people. Bangladesh has a total of 1217 intensive care unit (ICU) beds, which is significantly lower than the daily average of 15 000 COVID-19 cases and over 200 dengue cases reported in 2021. Furthermore, the healthcare facilities in Bangladesh were unable to meet the necessary oxygen demand due to a shortage in oxygen supply, highlighting the inadequacy of the healthcare system. The limited capacity of the healthcare system in the country may exacerbate the condition of co-infection. In Bangladesh, the doctor-patient ratio stands at 5.81 per capita, making it the second-lowest in South Asia.[28] Considering the current insufficiency of the healthcare system in Bangladesh, it is crucial that all hospitals including underprivileged health care units, irrespective of their location, have equitable and extensive availability of vital healthcare resources, including critical care equipment (ICU beds, ventilators, life support systems, etc.); essential medications; diagnostic facilities and an appropriate number of healthcare personnel. This is crucial to strengthen the healthcare system's capacity to manage severe co-infection scenarios.

A significant number of dengue cases went unreported because of the diverse clinical signs and the lack of a clear case classification between COVID-19 and dengue.[37] Additionally, numerous co-infection instances are still unidentified and unknown. To manage the severity of diseases and to plan and evaluate initiatives to prevent viral co-infections, epidemiological data for each disease (whether specific or associated with co-infection) is essential.[38] Therefore, this data needs to be appropriately collected.

Although the symptoms of many infectious diseases may be identical in certain situations, during the COVID-19 crisis, different countries devoted significant emphasis to the concerned sickness as it was the top priority.[39] The differentiation between the diagnoses of dengue and COVID-19 poses a notable challenge in light of the similarity in symptoms and the limited accessibility of disease-specific diagnostic tests in resource-constrained countries such as Bangladesh. During peak dengue season, it is typically advised to prioritize dengue testing based only on symptoms. Nevertheless, COVID-19 testing is not accorded same importance, which may lead to delayed and inaccurate treatment, hence worsening the gravity of the situation. To mitigate the occurrence of co-infection, it is advisable for healthcare practitioners to recommend the utilization of precise diagnostic methodologies, such as real-time reverse transcription-polymerase chain reaction (RT-PCR), or at the very least antigen detection assays, to confirm the diagnosis of these ailments. This is because antibody-based tests have the potential to yield false-positive outcomes as a result of cross-reactivity.[40] Patients exhibiting comparable symptoms, such as those with fever, should undergo testing for both dengue and COVID-19 until the dengue season concludes.

Following appropriate clinical trials, the development of an effective dengue vaccine and antiviral medications for all age groups and conditions should be regarded as a top priority and made promptly available worldwide, particularly in dengue-endemic nations such as Bangladesh. A clinical experiment evaluating the efficacy of a dengue vaccine was conducted in Bangladesh, yielding promising outcomes in terms of its potential to mitigate the viral disease. Currently, there are ongoing phase III efficacy trials investigating the potential of the tetravalent dengue vaccine candidate TV005. This particular vaccine has demonstrated the ability to elicit immunological responses against all 4 serotypes of dengue. In light of these findings, it is imperative that more research be conducted promptly to expedite the availability of this vaccine.[41]

The corona virus undergoes frequent and rapid mutations, and its rate of evolution is often unanticipated.[5] The WHO's announcement that COVID-19 is no longer a global health emergency increased the risk of the virus spreading because there was a noticeable drop in interest in heeding health safety recommendations and receiving the vaccine following the announcement, and the effectiveness of previously administered vaccines without booster doses is gradually declining, which may have contributed to the recent COVID-19 outbreak. Up-to-date vaccination requirements and other relevant actions should be implemented in order to stop the spread of COVID-19, which will eventually stop the co-infection with dengue.

To lessen the occurrence of co-infections, a vaccination that offers defense against multiple viral infections urgently needs to be developed. A vaccine adjuvant may reduce or eliminate any unfavorable side effects while enhancing the vaccination's efficacy, immunogenicity, and longevity.[5] It may also be able to combat newly altered variants of viruses and shield against multiple viral infections.

Modern technologies in conjunction with appropriate research can be used to control diseases brought on by the COVID-19 and dengue viruses, including artificial intelligence (AI) technology to screen the population and provide medical assistance, warnings, and recommendations; the internet of

things (IoT) to monitor and detect *Aedes* mosquito outbreaks in vulnerable regions; and surface acoustic wave technique for frequency-based identification of female *Aedes* mosquitoes so that they can be eradicated as soon as possible.[42,43]

A key component of managing and preventing dengue and COVID-19 co-infections is raising community awareness. This can be accomplished through community health workers making personal visits to affected areas, radio broadcasts featuring public figures and medical experts to promote the use of preventive measures, social media campaigns, seminars in both urban and rural settings. Regular dissemination of health alerts via social media, in conjunction with traditional media, could boost mass participation of the inhabitants in order to increase awareness about the severity of co-infection cases, refute myths, and promote early detection of new cases. Public awareness campaigns play a significant role as they equip individuals with knowledge about the key indicators and symptoms of the disorder, enabling them to promptly seek medical attention for an early diagnosis. Bangladesh may require financial assistance from organizations such as the World Bank and WHO in order to conduct the required investigations, modern initiatives, awareness campaigns, immunization programs, in addition to all other essential preventative measures.

Conclusion

As dengue is an annual occurrence in Bangladesh, the probability of co-infection with COVID-19 in this region is significantly elevated. Hence, if Bangladesh is compelled to manage 2 epidemics simultaneously with the co-infection of these 2 diseases, the country's fragile healthcare infrastructure could result in a catastrophe. The coexistence of SARS-CoV-2 and dengue virus in an individual might lead to significantly negative consequences, including heightened morbidity and fatality rates, particularly in individuals with pre-existing risk factors. The presence of similar clinical and laboratory characteristics in each disease poses a significant challenge in effectively diagnosing and managing infections. Early detection could potentially mitigate the adverse consequences associated with these illnesses. We aimed to elucidate the inherent risks associated with co-infections, highlight the challenges that need to be addressed, and recommend some effective, contemporary strategies, such as immunizations; epidemiological data collection; precise diagnostic methodologies; advanced research; cutting-edge technologies; biological, chemical, and mechanical methods. These preventative measures should be promptly implemented in conjunction with conventional preventative measures to efficiently prevent and control the burden of these diseases, thereby alleviating the strain on healthcare system.

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Author Contributions

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethic Statement

Not applicable.

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