Distinguish and Management of the Deadly Co-infection Caused by Dengue Virus and Coronavirus in Bangladesh

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
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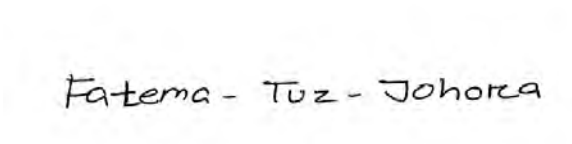
Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.



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Approval

The thesis/project titled “Distinguish and Management of the Deadly Co-infection Caused by Dengue Virus and Coronavirus in Bangladesh” submitted by Fatema-Tuz-Johora (19146041) of Summer, 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on February, 2023.

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Ethics Statement

This study comprises no human or animal trial.

Abstract

Coronavirus disease 2019 (COVID-19) infection was first diagnosed in Wuhan, China in 2019. Since then, it has become a major global concern and declared as pandemic in 2020. Bangladesh has encountered the worst outcome of COVID-19 cases in 2020. The healthcare system collapsed because of having inadequate measures to fight the pandemic. On top of that, dengue cases were on upsurge since 2020. As a result, co-infection cases led to increased fatality rate and unimaginable suffering of the patients. This review article aims to differentiate between the two infections and enlighten about managing the co-infection cases in Bangladesh. Using repurposed drugs, traditional plant treatments and development of vaccines can help fight this pandemic. Dengue infections can be prevented by taking vector control steps, making people aware of dengue and educating them about additional diagnostic tools to properly differentiate the two infections.

Keywords: COVID-19; Dengue; Repositioned drugs; Adjunctive therapies; Co-infection; Pandemic.

Dedication

This review article is dedicated to my beloved parents.

Acknowledgement

All praises to Almighty Allah. I am thankful to Him for giving me wisdom, knowledge and strength to do this project work staying in good health with full concentration.

I would like to thank my thesis supervisor, Dr. Afrina Afrose, Associate Professor, School of Pharmacy who continuously supported me throughout my work, helped me whenever I needed and showed me the right path. I am forever grateful to her for the continuous support, effort and valuable time she offered me.

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Lastly, I am thankful to my parents for their inspiration, encouragement and optimism towards me while completing this project.

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List of Acronyms

GI	Gastrointestinal
WHO	World Health Organization
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus 2.
ALT	Alanine transaminase
AST	Aspartate aminotransferase
CRP	C-reactive protein
NLR	Neutrophil-to-lymphocyte ratio
Nsp1Ag	Nonstructural Protein-1 antigen
HTN	Hypertension
DM	Diabetes Mellitus
RT-PCR	Reverse Transcription–Polymerase Chain Reaction
rRT-PCR	Real-Time Reverse-Transcriptase-Polymerase Chain Reaction
RDT	Rapid Diagnostic Test
FDA	Food and Drug Administration
MERS-CoV	Middle East respiratory syndrome–related Coronavirus
RdRp	RNA-dependent RNA Polymerase
DGHS	Directorate General of Health Services
SGPT	Serum glutamic pyruvic transaminase
ELISA	Enzyme-linked immunosorbent assay
PPE	Personal Protective Equipment

Chapter 1

Introduction

1.1 Background

Bangladesh is facing a major ultimatum as the co-infection caused by dengue virus and coronavirus has been rising since 2019 (Prapty et al., 2022). Though Bangladesh announced its first co-infection case on 15th May, 2020, the country has seen the highest number of both dengue and COVID-19 patients being hospitalized in the month of August, 2021 (Rahman et al., 2022). A study was done on a total of 11 co-infected patients divided in different groups to watch the progress of the disease. This descriptive study reported that about 45.5% of patients developed both COVID-19 and group-B dengue fever. Around 9% of patients developed group-C dengue fever and rest of the patients developed group-A dengue fever. Group-A dengue fever patients had fever, headache, muscle pain while group-B patients had increased hematocrit along with reduced platelets (Hannan et al., 2022).

Some certain symptoms like fever, pain in the muscle, severe headache, leukopenia, liver dysfunction etc. are shared symptoms of both dengue and COVID-19. Hence, the country's healthcare system is facing a major challenge in fighting the co-epidemic as the general people cannot distinguish between the signs and symptoms of the co-infection (Rahman et al., 2022).

To manage the co-epidemic, it is vital to know how to differentiate between the two viral attacks via double laboratory tests. Antigen test and PCR tests are two laboratory examinations that help identify dengue and COVID-19 infection respectively (Hasan et al., 2022).

Healthcare workers must be made aware of the complexity of the co-infection and take serious measures accordingly to monitor the patients strongly. General people should be advised to take preventive measures to fight the co-epidemic. Government must impose strong vigilance in the healthcare sector to control the outbreaks of co-infection (Prapty et al., 2022).

1.2 Research Gap

Two research gaps that I have found regarding the topic of my project:

- Endemic-prone countries are facing the co-infection cases for the first time which makes it difficult to handle the cases from the perspective of a developing country like Bangladesh. Studies and measures regarding proper management of the co-infection are not enough to fight it.
- People often misdiagnose dengue assuming it to be symptoms of normal fever or COVID-19. Symptoms of the co-infection cases are not distinguishable too. So, there is a gap in understanding the signs and symptoms of dengue or COVID-19 or the co-infection.

1.3 Objectives of the Study

The main objectives behind doing this review paper are:

- Discussing the distinguishable characteristics of the signs and symptoms of the co-infection.
- Proper management of the co-infection cases in regards to Bangladesh is displayed.
- Challenges the country is facing due to the co-infection are demonstrated.

- The impact of co-infection in a pandemic and endemic-prone country like Bangladesh is shown.

1.4 Significance of the Study

Major significance of the review paper is:

- Information on distinguishing between the signs and symptoms of the co-infection is assembled here.
- Concurrent steps to be taken to combat the challenge of a co-epidemic in the perspective of Bangladesh are displayed in this study.
- Bringing together all the available information and statistics of COVID-19 and dengue co-infection.
- Aftermath of the co-epidemic in a developing country like Bangladesh is discussed.

Chapter 2

Methodology

A systematic search was done on the websites named PubMed, Google Scholar, ScienceDirect etc. to find relevant literature matched to the project topic. Some common keywords related to COVID-19 and Dengue were used to search through these websites. Keywords include “COVID-19 and Dengue”, “Management”, “Distinguish”, “Impact”, “Pandemic”, “Symptoms of COVID-19 and Dengue co-infection”, “Treatment of Dengue during COVID-19”, “Repurposed drugs for COVID”, “Outcome of Co-infection”, “Dengue Epidemic and COVID-19 Pandemic in Bangladesh” etc. These keywords helped find literature describing management and differentiation of the co-infection and its outcome. Almost all the literature was published in the year from 2019 to 2022 which best describes the timing of the co-infection.

Inclusion criteria for the articles were:

- Co-infection of Dengue epidemic and COVID-19 pandemic.
- Clinical control of the co-infection.
- Studies that reported misdiagnosis of the co-infection.
- Outcomes of the co-infection.
- Complete studies along with conclusion.
- Drugs that were repurposed for COVID-19.
- Treatment strategies for dengue.

Exclusion criteria for the articles were:

- Studies that showed no result or conclusion.
- Incomplete studies.
- Medications and treatment options that are not used in controlling the co-infection.
- Studies having several limitations.
- Studies that were conducted before pandemic occurred.

Number of articles identified: 116

Number of articles screened: 84

Number of articles eligible: 36

Number of articles included: 30

Number of articles excluded: 6

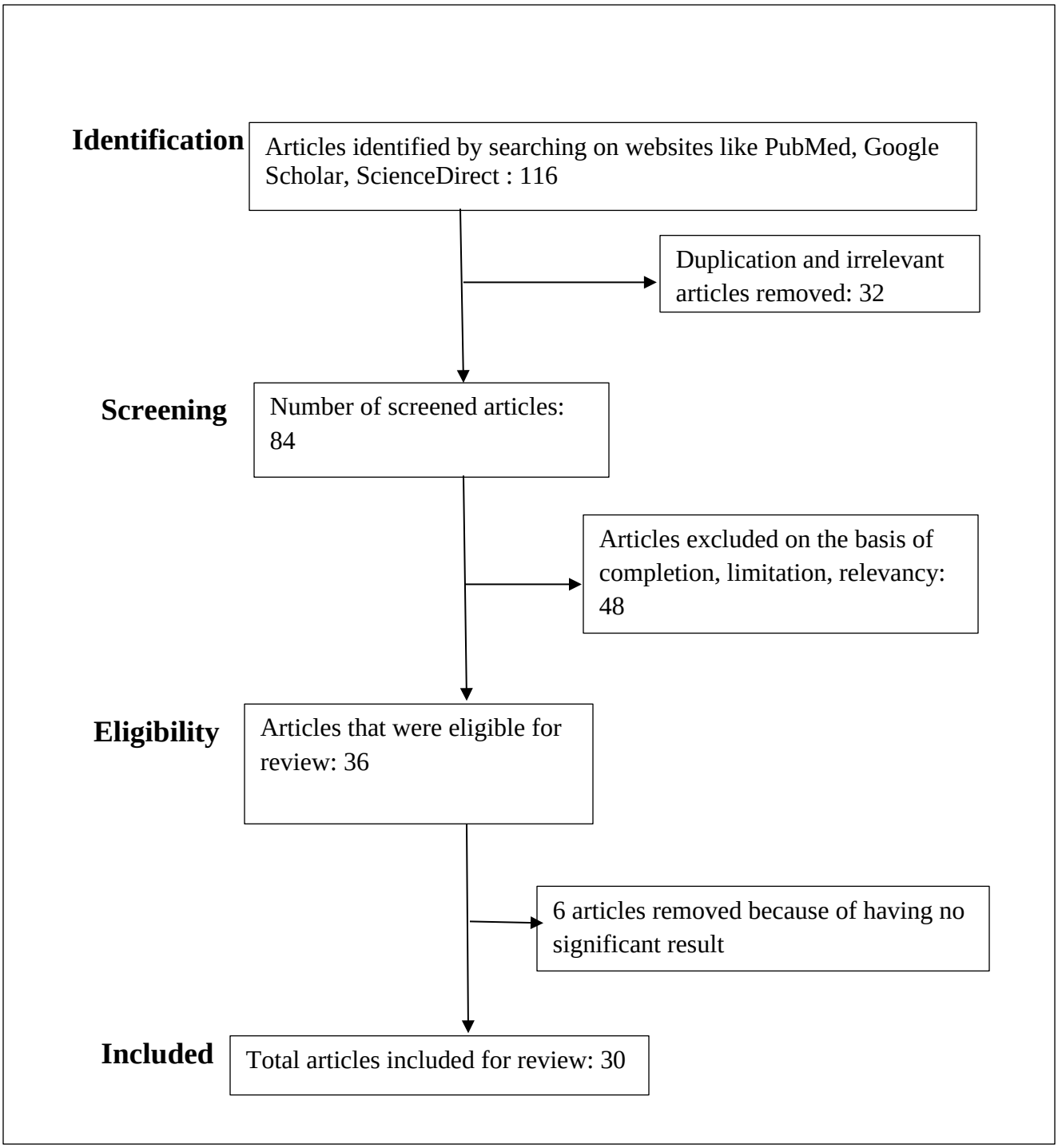


Figure 1: Flow diagram of the article selection procedure.

Chapter 3

Correlation Between Dengue Epidemic and COVID-19 Pandemic

3.1 Distinguishing Between the Signs and Symptoms of Dengue and COVID-19

Dengue occurs mainly in tropical and subtropical countries caused by either of the four dengue virus serotypes, especially *Aedes aegypti* and passed on from person to person by mosquito vectors(Harapan et al., 2021). On the other hand, SARS-CoV-2 virus is responsible for COVID-19 pandemic. These two viral infections have symptomatic similarities named fever, muscle pain, skin rashes, headache along with decreased level of platelets and leukocytes (Garg & Meena, 2021). But some case studies done in Columbia said that dengue patients suffered more from fever, rashes and GI discomforts than the COVID-19 affected patients who manifested cough and difficulty breathing mostly (Rosso et al., 2021). Hence, these infections are often misdiagnosed by the healthcare practitioners (Garg & Meena, 2021).

Some pathophysiological similarities have been found in dengue and COVID-19 infections. These include thrombocytopenia, leakage of the plasma and coagulopathy due to resemblance of the molecular changes that occur throughout the disease development. The host immune system gets activated after the attack of both dengue and SARS-CoV-2 virus. The immune cells release interleukin-6 (IL-6), inflammatory cytokines, chemokines, tumor necrosis factor (TNF) etc., which are known as immune-mediators. These events eventually lead to enhanced vascular permeability and leakage of the plasma. In case of a dengue patient, leakage of the plasma is mainly associated with direct involvement of endothelial cell surface protein with NSP1-specific antibodies (Prapty et al., 2022). The dengue virus destroys the platelets leading to thrombocytopenia and then coagulopathy in the end. On the contrary, coagulopathy and thrombocytopenia in COVID-19

patients are caused by different reasons namely destruction of the vascular endothelium, weakened growth of the bones and programmed cell death of the platelets because of SARS-CoV-2 virus (Rahman et al., 2022). The alveolar macrophages get actuated because of injured alveolar cells due to attack of SARS-CoV-2 virus. It enhances the release of various proinflammatory mediators like glycosaminoglycans (GAGs), vascular endothelial growth factor, von Willebrand factor and angiotensin II (Prapty et al., 2022). Considering that both of these viruses significantly weaken the body's immune system and have common pathophysiological characteristics, having one of them considerably raises the likelihood of having the co-infection subsequently (Rahman et al., 2022).

Patients with dengue hemorrhagic fever mainly show four criteria of symptoms as per World Health Organization (WHO). Dengue hemorrhagic fever last for 2 to 7 days approximately. Platelet count falls down to less than 100000/mm^3. Vascular permeability of the patient also gets increased which is named as Dysoria. Moreover, patient can go through dengue shock syndrome when bleeding gets increased inside the body. Some other symptoms shown by a dengue patient includes hypovolemic shock, hypertension, leukopenia, thrombocytopenia, bleeding disorders etc.(Rahman et al., 2022). But the most prominent characteristic that a dengue patient show is pain behind the eyes (Retro-orbital pain) and rashes in the skin. A considerable decrease of platelet count is a hematologic manifestation of dengue patients (Hannan et al., 2022). By contrast, patients infected with SARS-CoV-2 virus manifests clinical disorders, such as, sudden onset of fever, fatigue, loss of taste and smell, cough, headache, pharyngitis, anorexia, muscle pain, diarrhea, shortness of breath, nausea and vomiting and hepatic dysfunction (Rahman et al., 2022). However, coronavirus infection may also be asymptomatic in some patients showing no symptoms at all and range from being mild to moderate and severe infection (Saleh & Kamisah, 2021). In case of severe infection, a patient may feel continuous pain and discomfort right in the middle of his chest,

difficulty breathing, face or lips getting blue for the lack of oxygen and sometimes stroke. Critical condition of a patient is indicated by sepsis which is a life-threatening condition triggered by coronavirus infection and leads to injury of organs and tissues. Though there are symptomatic similarities between the two viral infections, it is still possible to distinguish between them (Rahman et al., 2022).

Table 1: Distinguishing between the signs and symptoms of dengue and COVID-19 (Garg & Meena, 2021; Hannan et al., 2022)

Criteria	Dengue	COVID-19
Fever	Severity: High Temperature Duration: 6 days Pattern: 2 Temperature peaks or saddle back pattern	Severity: Low Temperature Duration: 7-8 days Pattern: No definite pattern
Headache	More severe	Less severe
Cough	Dengue patients less likely to suffer from cough; 21.5% approximately.	76% of the COVID-19 patients suffer from cough.
Vomiting, abdominal pain, GI symptoms	30-55% and 16-25% of patients depending on various studies.	Only 2-5% of the COVID-19 patients suffer from GI discomforts.
Skin rashes	Very common in dengue patients.	15-20% of the COVID-19 patients show skin rashes
Thrombocytopenia	Very common. 69.51% patients or 385 among 515 patients manifested decreased thrombocyte level in their body.	A systemic review which was done on 3383 COVID-19 patients showed significant level of thrombocyte
Lymphopenia	Commonly occurs in dengue patients	Huge number of patients show the symptoms of lymphopenia
Dyspnea	Not seen in dengue patients.	More common in patients affected with COVID-19
Nasal congestion	Not seen in dengue patients.	COVID-19 patients suffer from it

3.2 Differentiating the Co-infection

At the time of ongoing COVID-19 pandemic, it became a major challenge for the healthcare professionals to differentiate between the dengue and COVID-19 infections because of their shared similarities in manifesting signs and symptoms in a patient. These challenges mostly appeared in tropical and subtropical countries where COVID-19 and dengue coexisted together. It was important to overcome the challenges in order to differentiate COVID-19 and dengue as well as to avoid misdiagnosis of these diseases so that no unwanted occurrence happens because of adopting inappropriate therapeutic approach (Rosso et al., 2021). Whether it is just COVID-19, dengue, or a co-infection, certain biomarkers generate accurate data that can be employed to identify and treat a co-infection. Biomarkers for COVID-19 and dengue infection includes increased TNF- α**,** IL-6, IL-8 and IL-10, decreased leukocyte, lymphocyte, haemoglobin and platelet, elevated creatinine level and Alanine transaminase (ALT) (Prapty et al., 2022).

Table 2: Dengue, COVID-19 and their co-infection biomarkers (Prapty et al., 2022)

	WBC (/µL)	**Haemoglobin (g/dl)**	**Platelet count (/µL)**	**ALT (U/L)**	**AST (U/L)**	**CRP (mg/L)**
Ideal range	3500-11000	11.5-16.5	150000-450000	7-55	8-33	Less than 10
Range in Dengue patients	Less than 5000	9.5-18.8	Less than 10000	Greater than 49	Greater than 83.5	Greater than 30
Range in COVID-19 patients	8000-12000	13.5-14.2	23000-31000	26-30	28.75-33.20	Greater than 26.9
Range in Co-infection	1700-2380	16-16.9	41000-106000	75-109	45-621	7.9-109

From Table 2, it is much easier to differentiate between the two infections depending on their biomarkers. For instance, in case of COVID-19 patients the range for WBC is elevated than the dengue patients. Platelet count is lower in dengue patients than the coronavirus infected patients. Furthermore, dengue patients and co-infected patients have enhanced level of Alanine transaminase (ALT) and Aspartate transaminase (AST) than the normal level whereas, COVID-19 patients have lower range of these. Last of all, the co-infected patients have higher range of haemoglobin level than normal. The COVID-19 infected patients usually have higher neutrophil-to-lymphocyte ratio (NLR) than the dengue patients (Prapty et al., 2022).

Another effective way to differentiate between the two infections is to diagnose them properly with the reliable diagnostic tools. Coronavirus infection is usually asserted by rRT-PCR test. But Chest Computed Tomography Scan (CT Scan) may work as a primary tool to diagnose COVID-19. Repeated rRT-PCR along with CT scan can be an effective way to confirm the cases of COVID-19. On the contrary, dengue infection is affirmed by dengue RT-PCR tests, IgM capture enzyme-linked immunosorbent assay (ELISA) and by identifying Nsp1Ag (nonstructural protein-1 antigen) (Prapty et al., 2022). Rapid NS1 antigen's sensitivity and specificity were found to be correspondingly 55.5% and 92%. So, to precisely detect the diagnosis of dengue, especially in the early stages, rapid NS1 antigen and NS1 ELISA appear to be particularly reliable. However, the NS1 antigen test may not show accurate result if patient is showing fever for more than 3 days which is called the subacute phase (Kembuan, 2020). On the other hand, CBC (Complete Blood Count) test and Alanine transferase test may prove to be beneficial for patients who have the co-infection. To differentiate between the infections, the NLR value is of great use in order to interpret the occurrence of lymphocytopenia or leukopenia. Diagnostic test for dengue patients indicates enhanced hematocrit level along with gradual decrease in the leukocytes and platelets. On the other

hand, leukocytopenia as well as lymphopenia occurs as the severity of infection increases in COVID-19 patients (Prapty et al., 2022). In co-infection cases, reduced synthesis of platelet gives rise to thrombocytopenia as the virus lead to bone marrow suppression. There might be increased level of ALT rather than AST also in co-infected patients (Rosso et al., 2021).

A case series done in Holy Family Red Crescent Medical College Hospital in Dhaka, Bangladesh displayed clinical presentation of 10 patients who were diagnosed with the co-infection of dengue and COVID-19. All of them survived which assures that there is nothing to be worried about the co-infection cases in a developing country like Bangladesh. In this case series, the issue of cross-reactivity depending on rapid serology test between Coronavirus and Dengue virus was brought up (Nasir et al., 2021).

Table 3: Clinical presentation and outcome of 10 patients diagnosed with the co-infection(Nasir et al., 2021)

	NS1 antigen and rt-PCR	Anti-dengue IgM	Anti-dengue IgG	Symptoms	Outcome
Patient 1 (Age 70)	Positive	Positive	Negative	Fever, nausea, HTN, leukopenia, elevated ALT, enhanced platelet, low albumin, no plasma leakage.	Co-infected patient with HTN, fluid resuscitation given, survived.
Patient 2 (Age 49)	Positive	Positive	Negative	Fever, vomiting, dry cough, no shortness of breath, anorexia, high D-dimer, low albumin.	Co-infected patient with the history of stroke. Fluid resuscitation given.
Patient 3 (Age 32)	Positive	Positive	Positive	Fever, headache, anorexia, retro-orbital pain, pain in leg, fatigue, cough.	Co-infected patient.
Patient 4 (Age 47)	Positive	Positive	Negative	Fever, cough, low platelet and hematocrit count, low albumin, high D-dimer.	Co-infected patient, got Remdesivir injection.
Patient 5 (Age 27)	Positive	-	-	Fever, abdominal pain, nausea, vaginal bleeding, leukopenia, low hematocrit, low platelet count, SPO_2 was 92%.	Co-infected patient, high flow nasal cannula was used to supply oxygen.

Patient 6 (Age 65)	Positive	Negative	Positive	Fever, cough, SPO2 87%, low platelet count, high level of CRP, d-dimer, creatinine.	Co-infected patient with dengue fever, COVID-19 pneumonia, DM, HTN.
Patient 7 (Age 60)	Positive	Positive	Positive	Fever, body ache, cough, hypovolemic, leukopenia, low platelet, enhanced CRP and creatinine level.	Co-infected patient with bronchial asthma and history of DM and HTN.
Patient 8 (Age 42)	Positive	Positive	Positive	Fever, dyspnea, SPO_2 85%, continuous coughing, leukopenia, enhanced CRP and creatinine level, low platelet count.	Co-infected patient with HTN and depressive disorders.
Patient 9 (Age 21)	Positive	-	-	Fever, cough, vomiting, nausea, leukopenia, low platelet.	Co-infected with COVID-19 pneumonia and dengue fever. Got Remdesivir injection.
Patient 10 (Age 40)	Positive	Negative	Positive	Fever, chest pain, low platelet, high ferritin, leukopenia, enhanced SGPT.	Co-infected patient having anxiety, neurosis.

However, during the rainy season, there is a significant risk of SARS-CoV-2 and dengue virus co-infection due to the COVID-19 pandemic and potential dengue outbreaks in endemic nations such as Mexico, Brazil, Thailand, Paraguay, Argentina, Colombia, Bolivia, Singapore, Vietnam, Malaysia, Philippines, and Indonesia, as many have already emphasized by the 31 known cases in

those countries as well as in Singapore, French island, Maldives, Bangladesh, India, Thailand, Pakistan etc. When compared to the worldwide death rates of each disease's individual infections, the mortality rate from SARS-CoV-2 and dengue virus co-infection is noticeably greater at 16.13% (5 dead from 31 coinfected individuals). The mortality rate for the COVID-19 is around 2.04%, with a range of 0.8% to 2.5% (Prapty et al., 2022). Henceforth, countries where dengue is widespread disease, should conduct epidemiological studies in order to lessen the number of deaths due to the co-infection(Khairunisa et al., 2021). Here is a graphical presentation of the worldwide disease condition and death pattern of COVID-19 and dengue co-infection cases (Prapty et al., 2022).

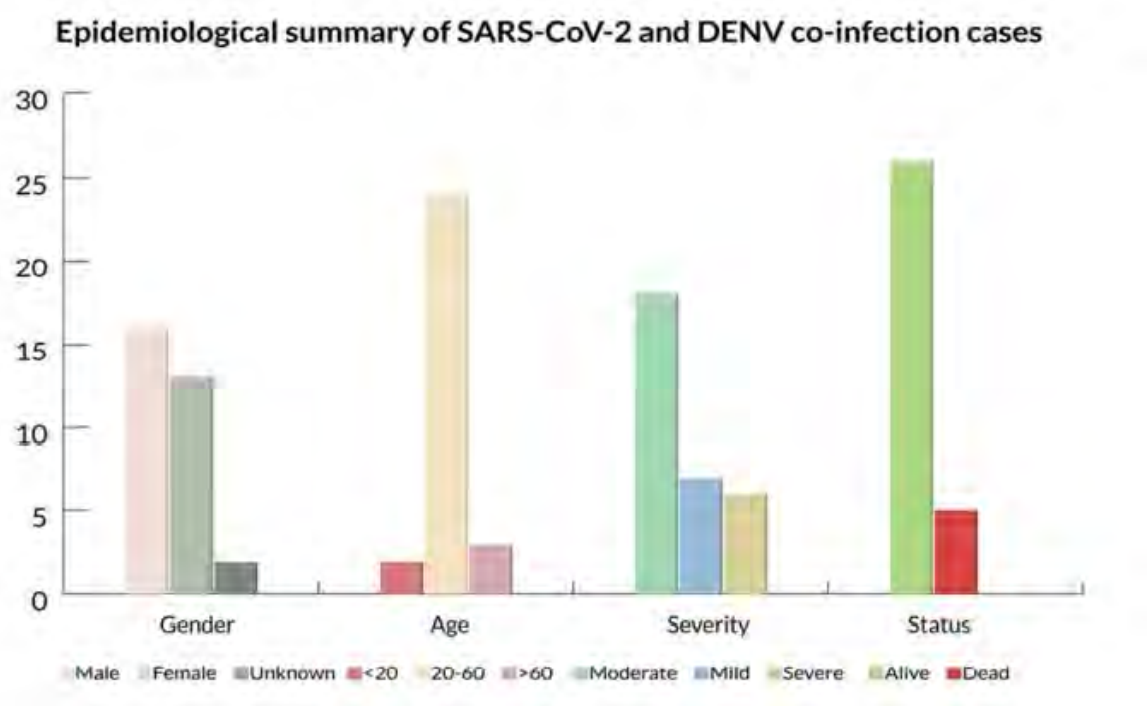


Figure 2: Graphical representation of the epidemiological data of COVID-19 and dengue virus co-infection cases (Prapty et al., 2022).

Chapter 4

Misdiagnosis

Doctors and physicians of dengue-endemic countries face greater challenge to combat COVID-19 infections as these two infections have shared symptoms. In addition, cross-reactivity between the two viruses results in false positive serology. South East Asian nations have already confirmed of the misdiagnosis of COVID-19 as dengue infection in its early stages as dengue is widespread in these countries (Khairunisa et al., 2021). Clinical signs and symptoms, such as, fever, muscle pain, rash and fatigue create dilemma in physicians while diagnosing between the COVID-19 and dengue infections. That is why, depending only on clinical manifestation it becomes difficult to diagnose and differentiate the two infections(Harapan et al., 2021). Besides, initial diagnostic tests including blood tests may often exhibit same pattern for both of the infections which ultimately increase the risk for misdiagnosis (Kembuan, 2020). This is primarily due to the fact that over 80% of the COVID-19 infections are mild to severe cases with asymptomatic patients that resemble dengue fever (Masyeni et al., 2021).

Apart from the same clinical demonstration, COVID-19 and dengue might be misdiagnosed based on serological cross-reactivity between the two life-threatening viruses. False positive test for dengue may have two reasons. First one is, the patient who was previously attacked by dengue virus own anti-dengue virus antibodies. Coronavirus antigens are cross-reactive with these antibodies (Harapan et al., 2021). IgG remains in the bloodstream longer, typically ranging from six months to 2 years following the first dengue infection, whereas IgM stays inside the bloodstream for up to 2 to 6 months. Additionally, IgG reacts faster, with elevated amounts, and over a longer circulating time in response to secondary infection. So, it can be concluded by saying

that the post-infection dengue antibody response can be persistent for a very long time (Khairunisa et al., 2021). And the second reason is, coronavirus and dengue virus may have similarities in their antigens. That is why, when the human body is attacked by SARS-CoV-2 virus, it produces antibody for dengue virus which is obtained from memory B cells (Harapan et al., 2021).

Some misdiagnosis cases of dengue endemic countries like Indonesia. Singapore, Italy, Thailand were reported during the COVID-19 pandemic (Harapan et al., 2021). In Singapore, a patient was diagnosed with dengue fever with the help of positive serological test of dengue and received treatment according to that. Eventually when his symptoms got worse, additional tests confirmed the patient was infected with coronavirus (Khairunisa et al., 2021). To add with it, a case report from Thailand also talked about misdiagnosis where a patient was thought to have dengue as he had rashes and small red or purple spots in his skin. But later on, he was diagnosed with COVID-19 tested by RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction) when he suffered from respiratory abnormalities (Garg & Meena, 2021). The potential of misdiagnosis exists due to the findings that COVID-19 was able to conceal itself throughout the initial stages of the infection and the prolonged duration of developing severity (Khairunisa et al., 2021). If COVID-19 is misdiagnosed as dengue then the necessity for isolating the infected patient is also diminished which increases the danger of airborne transmission of COVID-19 to other patients (Wiyono et al., 2021). A case study supporting this hypothesis depicts that a co-infected patient manifested dengue fever in the initial stage of the infection. After 5 days, he showed the symptoms for COVID-19 (Garg & Meena, 2021). On the other hand, there were three cases of co-infection in Bali, Indonesia saying that the patients were positive for Dengue virus NS1Ag test and IgG/IgM dengue fever antibody tests. But their condition worsened on the next week of diagnosis. As a consequence, further tests were done and it was reported that the patients were positive for

COVID-19 infection. This case confirmed dengue and COVID-19 co-infection (Masyeni et al., 2021). Also in Indonesia, five COVID-19 RDTs (Rapid Diagnostic Test) were conducted on 60 RT-PCR-evaluated dengue tests and 95 RT-PCR-evaluated COVID-19 examples on dengue RDTs to determine the cross-reactivity across dengue and COVID-19 antibodies. Cross-responsiveness, false-positive results, and unexpected co-infection cases between dengue and COVID-19 illness were found in the study (Garg & Meena, 2021).

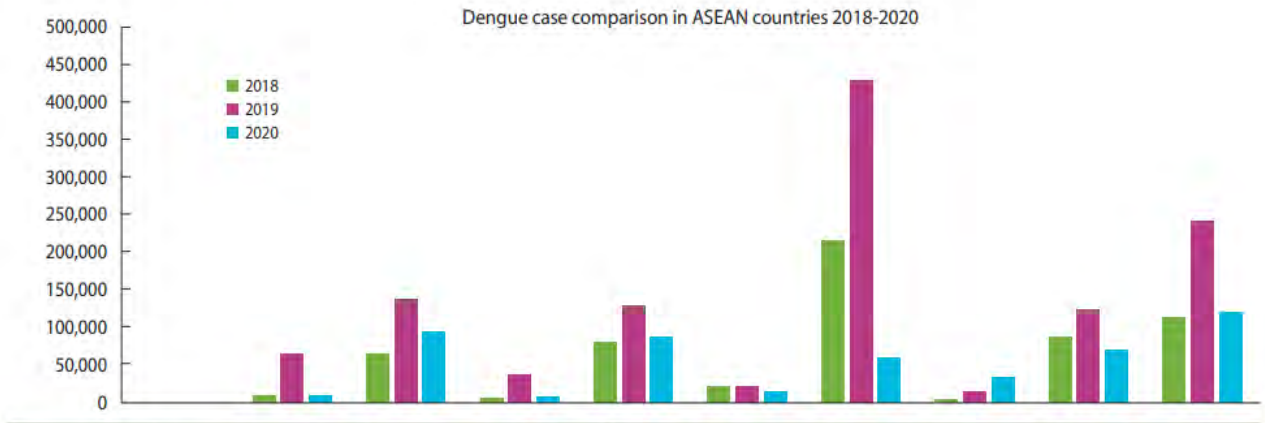
To eradicate the complication of misdiagnosis cases it is very important to choose the correct diagnostic tool to detect the coronavirus or dengue virus co-infection. As per WHO, the responsiveness of antigen dependent RDT is 34%-80% for detecting COVID-19 (Harapan et al., 2021). But it is advisable for physicians to use Real-Time PCR test than using serological RDT as it often leads to misdiagnosis as mentioned in the above cases. Therefore, RT-PCR test is considered as the reference standard test for detecting coronavirus infection (Khairunisa et al., 2021). In addition, to detect dengue infection it is recommended to use NS1Ag result as all flaviviruses generate the NS1 glycoprotein, which is released from the cells of mammals and is frequently utilized in rapid testing kits to diagnose dengue virus infection early (Kembuan, 2020). Besides, a systematic review reported of incorrect pooled findings of IgA, IgG, IgM, IgG/IgM and total antibodies for 15,976 samples using ELISA, lateral flow assays and chemiluminescence immunoassays combinedly (Masyeni et al., 2021). However, the PCR dependent technique can be used for diagnosing patients for both types of infection (Khairunisa et al., 2021).

Chapter 5

Management of Dengue and COVID-19 Co-infection from the perspective of Bangladesh

5.1 Treatment Options for Dengue

Southeast Asian countries are more prone to dengue-endemic than the other nations. In the middle of COVID-19 pandemic these countries have faced greater hurdle to tackle both COVID-19 and dengue infection together as it affected the human health and economy of the country at the same time. The infection cases for dengue also rose as the pathogen-host-vector relationship was disturbed because of the change in human's way of behavior due to COVID-19 pandemic. Here is graphical representation of observed dengue cases in ASEAN region during the year of 2018 to 2020 amidst COVID-19 pandemic (Wiyono et al., 2021).



Year	Brunei[1]	Cambodia	Indonesia	Lao PDR	Malaysia	Myanmar[1]	Philippines	Singapore	Thailand	Vietnam
2018	75	9,885	65,600	6,204	80,615	23,000	216,190	3,285	88,005	113,850
2019	119	66,461	137,760	38,026	130,101	23,203	430,282	15,998	125,235	241,863
2020	74	10,464	95,893	8,305	88,000	15,820	59,675	34,844	71,292	121,398

Figure 3: Correlation of observed dengue infection cases in various ASEAN countries between the year 2018 to 2020 (Wiyono et al., 2021).

Therefore, it was essential to control the dengue infections to reduce the mortality rate and to lessen the burden imposed on the nation's economy. There are 2 types of treatment option available in order to combat dengue infection. One type is dengue vaccines for patients who were already infected with dengue virus. The name of a widely available vaccine is Dengvaxia but the disadvantage of this vaccine is, it cannot be used by people who were not initially infected by dengue virus because it causes dengue fever in healthy individuals after receiving the vaccine (Wiyono et al., 2021).

The second type of treatment option is the use of medicinal plants to improve the health condition of the dengue patient. These plant extracts are not only effective against type 1 and 2 dengue virus but also type 3 and 4. Several kinds of plant parts like leaves, flowers, stem, bark and roots are used in various preparation of medicine to cure the infection (Saleh & Kamisah, 2021). The most adverse health condition that the patient suffers in dengue is decreased platelet count as a result of dengue virus infection (Rahman et al., 2022). Leaf extracts of the Papaya plant, also known as *Carica papaya* is used to increase the platelet count in dengue patients. Some other widely used plants are *Euphorbia hirta, Aternanthera sessillis, Ipomea batata* and *Eurycoma longifolia* which shows similar effects as Papaya plant. Such plants have the potential to elevate platelet level in the bloodstream (Saleh & Kamisah, 2021).

In addition, some other effective treatment options for the management of dengue patient are providing with oral rehydration saline and intravenous fluid to keep the patient hydrated, prescribing a diet full of fluids and advising the patient to take proper bedrest (H. T. Hossain et al., 2021).

5.2 Repositioning of Drugs for COVID-19

Drug repositioning, another name for drug repurposing, assists in discovering new applications for authorized or investigational medications that deviate from their intended indications. Repositioning of drugs can save a huge cost for discovering and developing a totally new drug component as well as saves time for research and approval and aids in emergency situation (De et al., 2021). The proposal for using repositioned or repurposed drugs comes from the fact that there is no currently available effective medicine to combat COVID-19 and treat critically ill patients. Repositioning of drugs was proposed and approved by the FDA before any effective vaccine was developed. Repositioned drugs include antibiotics, anti-inflammatory drugs, antiviral drugs, corticosteroids, anti-arthritis drugs, convalescent plasma therapy, RNA synthesis inhibitors and Neuraminidase inhibitors (Wu et al., 2020).

The drug repositioning approach is classified into three kinds:

- Approach related to Experimental biology
- Approach related to Computational method
- Mixed approaches (Singh et al., 2020).

Several repositionable therapeutic candidates that attack the host proteins work to inhibit the coronavirus replication and disease development after infection. A vast antiviral medication repertoire would also make it harder for the virus to evolve resistance mutations opposed to the antiviral drugs. Moreover, combination therapy containing two or more drugs can be effectively used in treating COVID-19 patients which also increases the chances of survival of a patient. By combining them with other recognized antiviral medications, several repurposed medications can also be tested in patients infected with coronavirus (De et al., 2021).

5.2.1 Dexamethasone

Dexamethasone is a steroid which stimulates the immune system just like corticosteroid drugs. In accordance with the research findings of the RECOVERY trial, which was carried out in the United Kingdom, the World Health Organization (WHO) acknowledged the use of anti-inflammatory medicine, dexamethasone on severe COVID-19 patients on June 16, 2020 (Vohra et al., 2021). Dexamethasone is a 30 times more potent broad-spectrum immunosuppressant which has extended effect than cortisone (Ledford, 2020). Wide usage of Dexamethasone is seen in patients with serious inflammation and allergic condition (Vohra et al., 2021). Treatment of coronavirus infected patients with Dexamethasone has increased after the RECOVERY study which demonstrated that fatalities in critical COVID-19 patients can be successfully reduced by it (Ledford, 2020). Moreover, nano-formulation of Dexamethasone has been proposed to treat COVID-19 patients and help them surviving critical condition. Nano-formulation of Dexamethasone can be used to treat a number diseases like inflammatory bowel disease, liver fibrosis, healing of the wound, multiple sclerosis, rheumatoid arthritis, cancer etc. But these nanomedicines could be costly and complex in composition to manufacture if we see from the perspective of our country. However, nano-formulation of it may result in greater performance by reducing the need for ventilation and ICU which eventually cuts off the cost for expensive hospitalization (Lammers et al., 2020).

5.2.2 Chloroquine (CQ)

Chloroquine is mainly an antiviral drug which can be repurposed to be used against coronavirus (De et al., 2021). It is also widely known for its anti-plasmodium effect (Singh et al., 2020). The main indications for Chloroquine are rheumatoid arthritis, lupus erythematosus and malaria (Wu

et al., 2020). Chloroquine and its corresponding products potentially inhibit the infection of coronaviruses (Singh et al., 2020). It is cost effective as well as widely available in comparison to other antiviral drugs (Kotecha Bsc et al., n.d.). By interrupting with ACE2 receptor glycosylation and its adhering to spike protein, Chloroquine can inhibit coronavirus entry and prevent viral cell fusion. This suggests that Chloroquine therapies may be more beneficial in the early phases of infection, before COVID-19 decrease ACE2 expression and activity. It is also proven that Chloroquine helps to decrease cytokine storm which is known as the main reason for death of COVID-19 patients due to respiratory failure (Wu et al., 2020). That is why, FDA has granted authorization for the usage of Chloroquine in emergency situations to treat COVID-19 patients (De et al., 2021).

5.2.3 Hydroxychloroquine (HCQ)

Hydroxychloroquine is a repositioned anti-malarial drug approved by the US and French authorities for the treatment of COVID-19 patients as it has strong antiviral effect and no other effective treatment for COVID-19 is still developed (Kotecha Bsc et al., n.d.). Hydroxychloroquine provides the same effect as Chloroquine but it has less toxicity due to having a hydroxyl group (Wu et al., 2020).

Although the viral load in COVID-19 patients was dramatically lowered by therapy with Hydroxychloroquine, the addition of azithromycin to the treatment led to more effective virus eradication outcomes. That is why, Hydroxychloroquine sulphate 200 mg was given to the COVID-19 patients 3 times per day for 10 days along with 500 mg azithromycin for day 1 and then 250 mg per day for the next 4 days. Even after therapy, one of the patients receiving only

Hydroxychloroquine had the viral infection, therefore azithromycin was given to treat the infection as soon as possible (De et al., 2021).

5.2.4 Favipiravir

Favipiravir is an antiviral drug previously used against Ebola virus infection. This drug was approved for use against coronavirus infection on February 15, 2020 as it significantly reduced the illness in COVID-19 affected patients (Singh et al., 2020). It has been used to treat RNA virus-based infectious illnesses such as, Ebola, influenza, norovirus etc. (Wu et al., 2020).

Favipiravir is a prodrug which enters the infected cells via endocytosis where it undergoes phosphoribosylation and phosphorylation to be converted into an active form of favipiravir ribofuranosyl phosphates (Wu et al., 2020). The drug inhibits RdRp (RNA-dependent RNA polymerase) which prevents incorporation of nucleotide during the replication of viral RNA (Singh et al., 2020). This disruption in replication of virus results in huge number of mutations by replacements of nucleotides (Adenine in place of Guanine, Thymine in place of Cytosine, Uracil in place of Cytosine). It destroys the viral RNA from being formed (Wu et al., 2020). Favipiravir works in a dose-dependent way to provide antiviral activity. With more clinical trial findings, however, the use of this medication might be permitted (Singh et al., 2020).

5.2.5 Lopinavir-Ritonavir

Lopinavir along with Ritonavir are used in combination named Kaletra (brand name) that is used as an anti-retro-viral against HIV infection. Lopinavir cannot be used alone as it is destroyed by host proteases in the human body. That is why, Ritonavir is used in a small dose along with it to protect the drug inside human body as Ritonavir exerts its protective action by inhibiting the

proteases and Cytochrome P450 which is a metabolizing enzyme. The randomized controlled studies have indicated that the combination therapy of 400 mg lopinavir and 100 mg ritonavir twice daily for 14 days is beneficial for COVID-19 patients, but they have also showed some gastrointestinal side effects (Singh et al., 2020).

5.2.6 Remdesivir

Remdesivir was designed to work against Ebola virus infection which is mainly an antiviral drug. Despite the drug's ineffectiveness against the Ebola virus, preliminary findings from preclinical research, as well as case reports, point to its effectiveness against the coronavirus (Singh et al., 2020). According to studies conducted on animals, remdesivir can significantly lower the infection of virus in mice infected with MERS-CoV, enhance activity of the lung, and lessen pathological lung tissue destruction (Wu et al., 2020).

The typical dosage regimen of Remdesivir for COVID-19 patients should be 200 mg on first day and dosage for the rest of the 2-10 days should be 100 mg (De et al., 2021). Nearly 70% of patients who received Remdesivir through compassionate use in the USA showed improvement in their oxygen needs, and several patients who were on mechanical ventilation were extubated. Remdesivir's strong antiviral effect on the improved clearing of viral loads in the respiratory system is still too early to form any conclusions, but it does suggest a pretty important therapeutic effect (Wu et al., 2020).

5.3 Adjunctive Therapy for COVID-19 Patients

Adjunctive therapies are widely used by physician to combat COVID-19 infection since currently there is no effective drug still developed to fight this virus. Some adjunctive therapies that were

proved to be beneficial are corticosteroid therapy, ascorbic acid, azithromycin, convalescent plasma, tocilizumab, sirolimus etc. (Wu et al., 2020).

Corticosteroids

Corticosteroids are anti-inflammatory drugs that are used in combination with other drugs. The oxygen saturation was restored with corticosteroid and interferon-1 combination therapy. In COVID-19 patients, corticosteroid treatment has the ability to increase the rate of survival by reducing the cytokine storm of interleukins (IL), interferons and tumor necrosis factor (TNF) that is triggered by acute viral respiratory infections and causes tissue damage (De et al., 2021). Recently, medical experts think corticosteroids, particularly methylprednisolone, may help the dysfunctional immune response brought on by sepsis (Wu et al., 2020).

Ascorbic Acid

Ascorbic acid is proved to be a potential adjunctive therapy for the treatment of COVID-19 patients as it is a strong antioxidant which works against influenza virus infection. Numerous studies shown that vitamin C has a favorable impact on T lymphocyte and NK (natural killer) cell proliferation and maturation. It increases immune response against viral infections. In China, hospitalized patients were administered with intravenous vitamin C which enhance oxygen index of the patients and they were readily discharged after getting recovered (Wu et al., 2020).

Azithromycin

Another supporting agent that improved patient condition in COVID-19 infection is azithromycin as it is used to prevent the replication of virus and generation of IL-6 (Singh et al., 2020). It reduced viral load in patients by rapidly clearing the infection from patient's nasopharynx when

administered in combination with Hydroxychloroquine. By inhibiting IL1-beta, IL2 and TNF, azithromycin also demonstrates anti-inflammatory effects. As a result, it aids in managing the elevated immune response in the case of COVID-19 infection (De et al., 2021).

Convalescent Plasma

A minority of coronavirus infected patients are treated with convalescent plasma as it contains neutralizing antibodies that are COVID-19 specific (De et al., 2021). This type of therapy can be used not only to prevent the disease but also to cure the infection. It acts in the human body by binding of the infused antibodies to the infectious pathogen. Therefore, the pathogen gets directly neutralized or cytotoxicity occurs. Several clinical reports from China, Taiwan, Hong Kong and South Korea supports administration of convalescent plasma for optimal benefits (Wu et al., 2020).

Tocilizumab

Tocilizumab is a monoclonal antibody which was generated for the treatment of arthritis patients. According to research in China, Tocilizumab was administered in 21 critically ill COVID-19 patients. 20 patients were fully recovered by the drug and 1 was in the ICU on his way to show positive outcome (Wu et al., 2020).

Sirolimus

Sirolimus acts as an immunosuppressant drug which is also known as Rapamycin. It is used to cure lymphangioleiomyomatosis (LAM). It showed positive result when treating influenza patients. Sirolimus was discovered as one of the 16 prospective choices for curing COVID-19 patients in at least one in silico investigation combining information from other human coronavirus infections (Wu et al., 2020).

5.4 Plant Derived Medicines for COVID-19

As there is no currently available effective medication to treat COVID-19, herbal medicinal plants can be a good source to fight this pandemic. Such herbal plants can prevent the coronavirus from binding to angiotensin-converting enzyme 2 (ACE-2) which acts as a receptor for the virus. If the activity and expression of ACE-2 gets increased then it alters the cytokine levels which are known to cause inflammation. A traditional Chinese medication that was authorized for the treating the SARS-CoV outbreak in 2003 represents one of the plant-based organic products. It has led to the use of plant-based medicine to combat current COVID-19 pandemic. Some widely available plants that are known to prevent viral replication are extracts of *Houttuynia coedata* whole plant, *Toona sinensis* leaves, *Euphoria nerifolia* leaves, extracts of Chinese herbs like *Cibotium barometz, Gentiana scabra, Cassia tora, Dioscorea batatas and Taxillus chinensis, extracts of istatic indigotica roots* etc. (Saleh & Kamisah, 2021). Moreover, some injections are proved to have immunosuppressive action such as *Re Du Ning* and *Shen Fu* injections which are used as traditional Chinese medicine. These medicines decrease the level of cytokines, interleukins and TNF- α, thereby decreasing the chances of lung inflammation. Some Chinese and Korean guideline suggested to have *Qingfei Paidu* decoction which is a herbal remedy targeting the lung and spleen in COVID-19 patients and boosts immunity as well as decreases inflammation (Wu et al., 2020).

Medicinal plant derived drugs are used instead of repositioned drugs because they are less toxic than the repositioned drugs. Medicinal whole plants and their leaf, root, bark extracts have shown to be effective against viral infection in many clinical trials. Besides, these plants have been used for hundreds of years for their anti-inflammatory properties. It is therefore, essential to repurpose the alternative medicinal plant-based treatment or medications to suit the current situation because

it takes a long time to manufacture new vaccines and synthetic drugs. It will also pave the path to combat the current pandemic situation (Saleh & Kamisah, 2021).

5.5 Vaccines for COVID-19

A crucial tool for stopping the spread of coronavirus infection and ultimately ending the pandemic is vaccination. Safe and efficient vaccines are therefore necessary to fight the pandemic and maintain patient compliance. The WHO has given approval to a total of 10 vaccines from 153 vaccines for use in emergency as the infection cases were increasing overwhelmingly (Li et al., 2022). When compared to the traditional vaccines established earlier for other diseases, the COVID-19 vaccines were produced using multiple platforms which required substantially less time in the various development stages (De et al., 2021).

Inactivated Vaccines

Inactivated vaccines are generated by utilizing chemical reagents to inactivate the in vitro cultivated viruses. BBIBP-CorV (Sinopharm), CoronaVac (Sinovac Biotech) and COVAXIN (Bharat Biotech International) are three of the inactivated vaccines (Li et al., 2022). BBIBP-CorV and CoronaVac were developed in China, whereas, COVAXIN was developed in India(De et al., 2021). These three vaccines got approval from WHO to be used against coronavirus infection (Li et al., 2022).

Live-attenuated Vaccines

Live attenuated vaccines are developed using viruses with reduced virulence through reverse genetics or adaptability. To protect the upper respiratory tract, these vaccines can encourage mucosal immunity by inhaling through the nose. As of March 28, 2022, COVI-VAC and MV-014-

212, two potential COVID-19 live attenuated vaccines, have received approval for clinical trials (Li et al., 2022).

Viral Vector Vaccines

AZD1222 (AstraZeneca-University of Oxford) Ad26.COV-2-S (Johnson & Johnson) are two viral vector vaccines that have received WHO approval. As of March 28, 2022, 25 candidates for COVID-19 viral vector vaccines have their clinical trials approved, four of which used replicating vectors whereas, 21 made use of non-replicating vectors (Li et al., 2022).

Protein Subunit Vaccines

These vaccines are dependent on viral peptides or proteins that are systemically expressed utilizing a variety of systems which are cell-expressing, including bacteria, yeasts, insects and mammalian cells. The WHO has approved just one COVID-19 protein subunit vaccine for emergency use (NVX-CoV2373: (Novavax)) (Li et al., 2022).

mRNA Vaccines

The foundation of mRNA vaccines is mRNA enclosed by vectors, typically lipid nanoparticles, viral proteins, or polypeptides created during translation in the host cells. As of March 28, 2022, a total of 28 prospective COVID-19 mRNA vaccines have been licensed for clinical studies by the WHO, including the BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) two types of mRNA vaccines. These two vaccines are being widely used in our country (Li et al., 2022).

In contrast to vaccination efficacy, vaccine effectiveness refers to the decreased risk of infection or disease among vaccine recipients. This may be affected by population-dependent vaccine effects, vaccination regimens, and vaccine administration and handling. Following COVID-19

vaccination, local or systemic mild acute responses, like injection discomfort, soreness, redness, lethargy, headache, joint and muscle pain are frequently reported (Tregoning et al., 2021).

5.6 Management of the Co-infection Cases in Bangladesh

5.6.1 Challenges of the Co-infection

Our country is a dengue-endemic region which has caused overlapping outbreak of COVID-19 and dengue infections during the pandemic period (Harapan et al., 2021). It has imposed a huge burden on the healthcare system of our country, as well as on the government. Dengue infections are on the rise along with COVID-19 pandemic which has created a devastating situation for the dengue-endemic regions (Hasan et al., 2022). Furthermore, it is difficult to distinguish between dengue fever and COVID-19 infections due to their similar laboratory and clinical characteristics; as a result, misdiagnosis would be more often (Lorenz et al., 2020). Practitioners struggle to distinguish between dengue and COVID-19 infections because of their similar symptoms and false-positive test results for COVID-19 in dengue patients. Due to a deadly third wave of the coronavirus, the healthcare system of our country was already in turmoil. It was made worse by an upsurge in dengue cases, which placed a double burden on the healthcare system (Hasan et al., 2022).

5.6.2 Outcome of the Co-infection in People

Patients who are infected with both dengue and coronavirus are vulnerable to death as both the infections are deadly and serious (Hasan et al., 2022). The first co-infection case that was detected in Bangladesh was on May, 2020. The patient was 53 years old, elderly man with high fever, breathing problems, cough and muscle ache. He was admitted into Intensive Care Unit (ICU)

because of being in a serious state. The risk of death and disabilities in people with these two disorders together could be multiplied. Therefore, if the dengue outbreak could not be controlled quickly, the government might have to pay a high price for this (Lorenz et al., 2020). This is not the only challenge for our country. All the well-equipped hospitals are on the urban area which makes it difficult for rural patients to access the healthcare services easily. Moreover, there are a few ventilators for COVID-19 infected patients in the hospitals. An estimation shows that only one ventilator against 93,273 patients is available (Hasan et al., 2022). In some countries, dengue prevention activities may have been suspended and community vector control efforts may have diminished during the pandemic (Harapan et al., 2021). Bangladesh is a hotspot for the creation of a severe dengue risk due to the existence of all of these conditions. As the number of patients with COVID-19 viral infections already weighed heavily on the hospitals. With pandemics, dengue cases are double as common. Since January 2021, Bangladesh has reported more than 15,000 cases of dengue and roughly 57 fatalities. At such crucial time, the WHO has stressed the need for effective measures to prevent, identify and address vector-borne diseases like dengue as case numbers rise in a number of countries, putting people at the highest risk for both illnesses (Hasan et al., 2022).

5.6.3 Accurate Determination of the Infection by Additional Testing

Due to the cross-reactivity of dengue virus and COVID-19 antibodies, additional laboratory testing may be useful as a diagnostic tool to assist distinguish between the two infections. Beyond this, Bangladesh's limited capacity for diagnostics and healthcare remains a key concern, therefore expanding the quantity and accessibility of laboratories can be helpful (Hasan et al., 2022).

For early and appropriate detection of infecting pathogens, highly reliable and accessible COVID-19 and dengue diagnostic tests, coupled with ongoing observation of individuals exhibiting clinical signs, are advised (Miah & Husna, 2020). The government should make it mandatory for all the COVID-19 patients to test for dengue infection also. In rural areas, where people have little access to healthcare facilities, the government should establish temporary clinics and healthcare centers for COVID-19 and dengue patients. The general public should be made aware of dengue prevention and management techniques as well as COVID-19 preventative techniques through both print and electronic media (Lorenz et al., 2020).

5.6.4 Managing Dengue Infection Cases

For controlling dengue infection cases, vector control is the first and foremost measure to adapt. Dengue surveillance system and house-to-house inspection system should be digitized in order to control larvae production because these two measures were stopped during the pandemic (Wiyono et al., 2021). By encouraging neighbors to lessen mosquito breeding grounds in and around houses, is one of the most practical solutions to reduce dengue cases (Harapan et al., 2021). When there are lockdowns and individuals are instructed to stay indoors, community involvement in mosquito control efforts should be boosted (Wilder-Smith et al., 2020).

5.6.5 Managing COVID-19 Infection Cases

COVID-19 precautions that must be followed include keeping social distance and practicing great personal cleanliness. Healthcare professionals need to be made aware of the complication of co-infection cases and the importance of taking personal precautions. In order to administer the various medications necessary due to the differing pathophysiology of the infections on time, the co-infection patients need also be continuously monitored (Prapty et al., 2022). Healthcare

providers should always use sanitizers, masks, gloves and PPE. Flu like symptoms should never be ignored. Our country needs better preparedness for dengue as well as for COVID-19 if we want to overcome a devastating phenomenon in future (Chowdhury et al., 2020).

5.6.6 Managing the Co-infection Cases

An effort must be made for a differential diagnosis of the infection in laboratories in each of the dengue and COVID-19 affected locations. The healthcare providers should be equipped with the necessary drugs, equipment, and testing labs to strengthen the healthcare system and prepare for the anticipated increase in dengue infection cases due to the growing number of COVID-19 cases. Some symptoms that are easily distinguishable for COVID-19 and dengue infection cases like fatigue, stomach pain, accumulation of fluid in the body, vomiting should be given importance for managing the co-infection. To ensure that dengue patients receive sufficient clinical care throughout the pandemic, strong contamination avoidance and management procedures must be implemented at all levels of healthcare (Hasan et al., 2022). Although more research is required to determine any complex association between the dengue and COVID-19 vaccines, vaccination programs should be enforced and appropriately delivered with integrity and in accordance with objective policies to promote acceptability of the vaccines by general people (Wiyono et al., 2021). The government of Bangladesh has already introduced a hotline for COVID-19 infected patients. If there is another hotline opportunity for dengue patients, then it would be easier to provide effective treatment to the co-infected patients (Lorenz et al., 2020).

Chapter 6

Impact of the Co-infection in Bangladesh

COVID-19 was announced as a global pandemic by the WHO on March 11, 2020. When the situation was becoming worse, Bangladesh went under lockdown from March 26, 2020 (Chowdhury et al., 2020). On top of that, the WHO has alerted about dengue infection cases as it has increased over 8-fold since the last 2 decades. Bangladesh has encountered a sharp increase in dengue infection cases in 2021 when it imposed a countrywide lockdown due to the fatal Delta variant of coronavirus (Khan et al., 2022). Since January 2021, there have been around 15,000 dengue cases and roughly 57 fatalities in Bangladesh. The DGHS reports that 88% of all cases since January occurred in Dhaka which makes it the epicenter of dengue (Hasan et al., 2022). So, the country's healthcare system was devastated because of the ongoing pandemic and dengue epidemic. The co-infection of COVID-19 and dengue suggests that, given the nature of coronavirus and the appearance of mutations and variations, global population management of COVID-19 may be a time-consuming task. Moreover, dengue would continue to be an epidemic in the majority of Asia's resource-constrained nations, in addition to the COVID-19-related emergency situation (Khan et al., 2022).

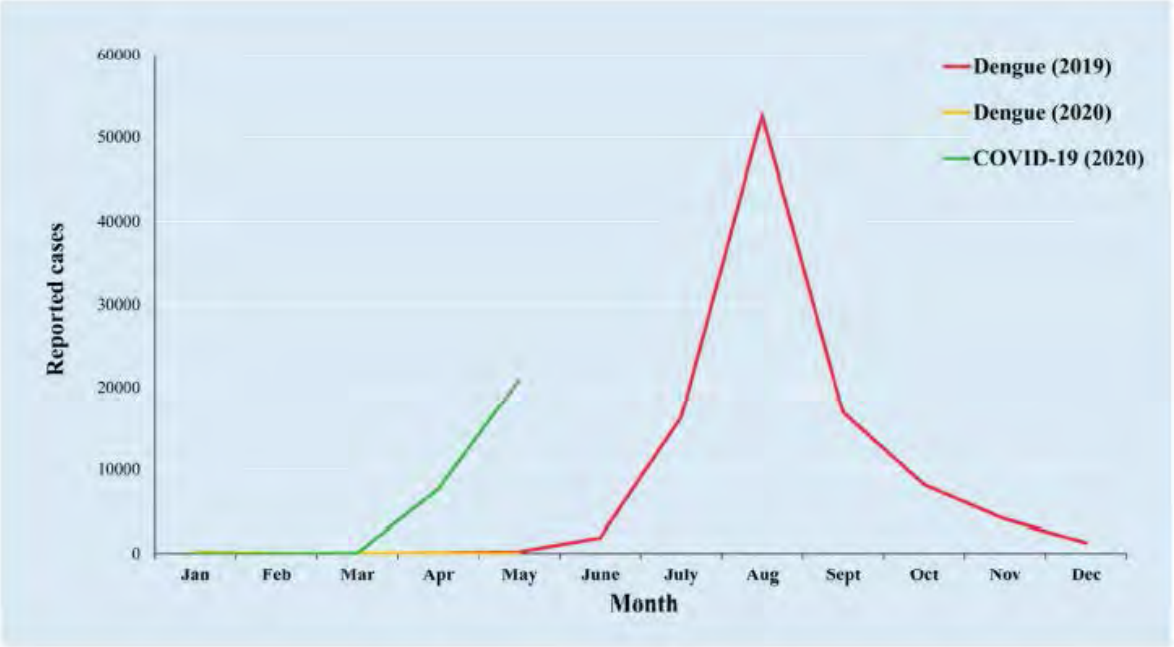


Figure 4: Upsurge of dengue cases (2019 and 2020) and COVID-19 cases (2020) in Bangladesh (Chowdhury et al., 2020).

Because of having an ongoing pandemic and dengue epidemic at the same time, the healthcare sector is now currently facing a hard time dealing with these infection cases. As both of the infections have similar symptoms, people are often misdiagnosing dengue as COVID-19 infection. In this case, if COVID-19 and dengue remain prevalent among individuals during the monsoon, the existing health crisis would worsen and lead to further health problems (Sultana & Alam, 2020).

The impact of this ongoing pandemic has greatly affected the people of our country. Global print and online media outlets have emphasized COVID-19 due to its fatality and strong transmissibility. But it has also ignited unnecessary fear and panic among mass people. Even in areas where cases are not formally confirmed or where few cases are recorded, it has sparked panic attack in people, racism, assaulting people and distrust. For instance, before reporting of the first case from

Bangladesh, people are breaking family ties in fear of getting infected with COVID-19, fleeing from hospitals when they heard of a patient admitted with flu-like symptoms etc. (M. S. Hossain et al., 2020). On top of that, there was a scarcity of COVID-19 testing kits and health services during the early stage of coronavirus outbreak. Because the healthcare institutions lacked proper protective equipment, even the COVID-19 treatments took longer than expected. As a result, 35 recorded cases of doctor fatalities and a high infection rate among healthcare professionals were noted (Chowdhury et al., 2020). Moreover, there are not enough ICU beds and COVID-19 medical team members to care for more than 160 million individuals in our country. DGHS has reported of having only 564 ICU beds in government hospital which is not adequate at all for over millions of people of Bangladesh (Sultana & Alam, 2020). Furthermore, reports claim that the sudden inflow of patients led to a delay in the identification of dengue and other diseases. Bangladesh, a lower-middle-income nation, is struggling with all of these challenges since COVID-19 has already depleted its little healthcare resources. The country has been badly hit by the COVID-19 and dengue outbreaks due to inadequate healthcare infrastructure, insufficient surveillance and further socioeconomic inequalities. Predisposing conditions have been worsened by current issues such as a monsoon season that favors breeding sites, urban population density, a lack of healthcare infrastructure, dengue outbreak history, cross-reactivity of COVID-19 and dengue infections as well as symptom similarities. To successfully address this situation, initiatives at improved diagnostic testing, public awareness programs and development of good healthcare infrastructure are required (Hasan et al., 2022).

Chapter 7

Conclusion, Limitations and Future Recommendations

7.1 Conclusion

Amidst the ongoing COVID-19 pandemic, repeated outbreaks of dengue infection cases would pose a new challenge for the healthcare sector of Bangladesh. Similar symptoms of COVID-19 and dengue make it complicated to diagnose the infection. In addition, COVID-19 and dengue co-infection cases increase the fatality in patients. Moreover, Bangladesh being a developing country, is facing a hurdle to accommodate co-infected patients in hospitals, let alone giving them the best possible care. But it is a matter of pleasure for us that the COVID-19 vaccines have already been developed and people from all background can take it which costs them not a single penny. As a result, COVID-19 cases are now under control in 2023 and government has withdrawn lockdown back in 2022. Dengue infection cases have lessened in number too as people are now taking preventive measures to fight it beforehand. Cross-reactivity between dengue and COVID-19 can be prevented too if physicians can guide the patient to take the correct tests at correct time. To conclude, dengue and COVID-19 cases can be easily distinguishable with proper tests. In addition, managing the co-infection cases is also possible if people are alert of their lifestyle as well as take precautions of maintaining personal hygiene. Co-infected patients need to be in constant monitoring of the healthcare professionals. In order to maintain high vigilance and take the most effective preventative measures against dengue and coronavirus infection, the general people, healthcare facilities and the government must work together hand-in-hand.

7.2 Limitations

1. The COVID-19 pandemic began almost three years ago. In such short time, doing enough research and tests for managing the pandemic was a very difficult task to accomplish since the virus is undergoing mutations constantly. Still, new variants of coronavirus are being discovered. Many scientists are working very hard to develop greater vaccines and medicines to fight the deadly infection. That is why, effective and reliable information on managing this co-infection of dengue and COVID-19 were not available which resulted in lack of adequate data in this study.
2. Furthermore, only endemic-prone countries are struggling on finding the best cure for the co-infection that is making it difficult for the developing countries to manage the co-infection. Also, distinguishing and management of this co-infection will vary from country to country due to socio-economic status and geographical location. As a result, co-infection management data are discussed from the perspective of only endemic-prone countries.

7.3 Future Recommendations

1. COVID-19 pandemic is now under control due to the development of effective vaccines and awareness of people beforehand. But still there might be possibilities that this virus can mutate as it did earlier and become more dangerous than ever causing another pandemic. So, it is the duty of scientists and researchers to be aware of such consequences and be prepared for facing the challenge. They should not only work for developing vaccines but also effective medicines need to be developed and made accessible to public.
2. More researches regarding COVID-19 infection and dengue fever needs to be done to be able to clearly distinguish between the two infections.

3. The world must also come forward to fight the COVID-19 and dengue co-infection as it is not only confined to endemic-prone countries now. General people must be aware of taking constructive management programs to control this co-infection together.

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