# Dengue Reinfection and Co-infection: A Study of Incidence and Outcomes in Adults Admitted to a Tertiary Care Hospital, Karachi, Pakistan

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***Authors' contributions***

*This work was carried out in collaboration among all authors. Author SH designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author AJ helped with analysis of the study, literature search and writing the manuscript. Authors RA and RI managed data collection, literature search and reviewing the manuscript. All authors read and approved the final manuscript.*

*Original Research Article*

## ABSTRACT

**Aim:** To determine the occurrence of re-infection and co-infection with dengue among the adult population in Karachi, Pakistan. In addition, to determine the frequency of various medical complications among dengue patients with or without co-infection and reinfection. And to identify possible risk factors associated with dengue reinfection.

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**Study Design:** Retrospective cross-sectional study.

**Place and Duration of Study:** Department of Internal Medicine, Aga Khan University Hospital, Karachi, Pakistan, between January 2022 and August 2022.

**Methodology:** A total of 500 adult patients aged 18 years or above; admitted with a confirmed diagnosis of dengue were included in the study. Information was collected regarding clinical and demographic data using structured questionnaire. Data was analyzed using SPSS version 25.

**Results:** The current study reported an incidence of 3.8% for dengue re-infection and an incidence of 19% for co-infection among adult dengue patients. The most common clinical symptoms were fever, nausea, vomiting, and abdominal pain while bleeding, acute kidney injury, and nosocomial infection were the most common complications with a proportion of 10.6% (n=53), 7.8% (n=39) and 4.2% (n=21). The study could not find any statistical association between the socio-demographic factors and disease-related characteristics.

**Conclusion:** This study determines a low incidence proportion of dengue re-infection and co-infection among adult patients admitted with a confirmed diagnosis of dengue infection at a private tertiary care hospital in Karachi. Bleeding, nosocomial infection, and acute kidney injury were identified as the most frequent medical complications among hospitalized dengue patients. The study did not show any statistically significant risk factors associated with dengue re-infection. Large scale multi-center studies are warranted with sufficient sample size and objective assessment methods to determine the incidence of dengue re-infection and co-infection as well as for the identification of risk factors associated with dengue re-infection among the adult population of Pakistan.

## 1. INTRODUCTION

Dengue is a vector-borne viral disease, transmitted by female Aedes mosquito. There are 4 serotypes of this virus. Every year millions of people suffer from this illness. However, the severity of the illness varies from mild symptoms like fever and body aches to severe dengue hemorrhagic shock syndrome [1]. Transmission of this viral illness is greatly influenced by temperature, rainfall, and urbanization. The primary pathophysiology of the disease is capillary leakage and hemoconcentration. This viral illness is known for causing multi-organ damage such as encephalopathy, respiratory distress syndrome, acute liver injury, renal failure, coagulopathy, and much more. Previously thought to be a pediatric disease has now shown a trend in the young adult population [2]. In Pakistan rapid urbanization, climate change, population growth, and various socioeconomic factors have resulted in increased burden and more frequent outbreaks of dengue infection [3,4]. Early identification of the disease is important in countries like Pakistan which are endemic for dengue and other illnesses that have similar clinical spectra such as malaria or acute viral hepatitis, early recognition and treatment may sometimes be delayed. Various studies have also shown the incidence of various viral and non-viral co-infections in patients with dengue fever. Such simultaneous infections not only complicate the diagnosis but also the treatment and overall outcome [5,6]. The rising burden of dengue infection also increases the likelihood of dengue re-infection which is known for relatively more severe illness and poor prognosis. Previous studies from Pakistan conducted in Lahore and Mardan have reported severe illness and relatively poor prognosis among dengue patients with re-infection or when patients had a positive history of previous dengue infection [7,8,9,10].

Various small-scale studies from Pakistan have reported the incidence of dengue and associated seasonal variation. However, there is a dearth of evidence regarding dengue re-infection and co-infection. Therefore, this study aims to determine the incidence of re-infection and co-infection with dengue among the adult population in Karachi, Pakistan. The study also aims to determine the frequency of various medical complications among dengue patients with or without co-infection and reinfection as well as possible risk factors associated with dengue reinfection.

## 2. MATERIALS AND METHODS

### 2.1 Research Design, Site and Population

A retrospective cross-sectional study was conducted at Aga Khan University Hospital Karachi, from January 2022 till August 2022. All

the adult patients of age 18 years or above; admitted with a confirmed diagnosis of dengue i.e., either through antigen or antibody test for dengue infection through the emergency department or out-patient-department were included in the study. Patients who were not admitted to the hospital despite medical advice and could not be followed were excluded from the study.

## 2.2 Data Collection and Analysis

Patients` personal and relevant clinical information was obtained from the existing Health Information Management System established at Aga Khan University Hospital. Basic demographic characteristics, disease signs, symptoms and complications, laboratory investigations, critical care unit stay, treatment offered, demographic data, and disease outcome were recorded as the main study variables. All the data was collected using a purposefully designed structured questionnaire. Out of 520 patients, 500 patient records fulfilling the eligibility criteria were included in this study.
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Data was analysed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics were calculated using mean or median for quantitative continuous variables and frequency or proportions for categorical variables. Incidence proportion was

calculated for dengue re-infection and co-infection. The frequency of various medical complications was also calculated. The chi-square test of significance was also applied to identify possible factors associated with dengue re-infection and co-infection.

## 3. RESULTS

A total of 500 eligible dengue patients were included in the study. The median age of patients was 36 years with an IQR of 22 years. 76.8% (n=384) of the patients were between ages of 19-44. Around 59.4% of all dengue patients were male and 40.6% (n=203) were females. The majority of the patients were residents of Karachi. 60.8% (n=304) of all patients were diagnosed based on positive rapid antigen test while 33.4% (n=167) of all dengue patients were diagnosed with positive IgM test. However, 1% of all IgM tests showed equivocal results and for 4.8% (n=24) of the lab-confirmed dengue patients the information regarding the type of test applied for diagnosis was not available as were tested outside before admission. 73.8% (n=369) of all dengue patients included in this study were tested and diagnosed with dengue at Aga Khan University Hospital. Hypertension was the most common co-morbid followed by Diabetes Mellitus with a proportion of 18% (n=90) and 13.4% (n=67) respectively. Fever was the most reported symptom followed by vomiting, nausea, diarrhoea, and generalized weakness (Table 1).

**Table 1. Socio-demographic characteristics of the adult dengue patients presenting at a private tertiary care hospital in Karachi, Pakistan**

(n=500)

| Variable | Frequency (n) | Percentage (%) |
|---|---|---|
| Median Age: 36 years (IQR; 22 years) | | |
| **Age (in completed years)** | | |
| 19- 34years | 223 | 44.6 |
| 35-50years | 161 | 32.2 |
| 51-66yeras | 80 | 16.0 |
| 67-82 years | 31 | 6.2 |
| 83 years and above | 05 | 1.0 |
| **Sex** | | |
| Male | 297 | 59.4 |
| Female | 203 | 40.6 |
| **Residence** | | |
| Rural Sindh | 06 | 1.2 |
| Baluchistan | 09 | 1.8 |
| KPK | 05 | 1.0 |
| Punjab | 01 | 0.2 |
| Karachi | 479 | 95.8 |
| **Dengue diagnosed on:** | | |

| Variable | Frequency (n) | Percentage (%) |
|---|---|---|
| Positive Rapid antigen test | 304 | 60.8 |
| Positive IgM test | 167 | 33.4 |
| Equivocal result on IgM test | 05 | 1.0 |
| Not sure about the diagnostic test applied | 24 | 4.8 |
| **Dengue diagnostic test conducted at:** | | |
| Aga Khan University Hospital | 369 | 73.8 |
| Outside Aga Khan University Hospital | 131 | 26.2 |
| **Co-morbids** | | |
| Hypertension | 90 | 18.0 |
| Diabetes Mellitus | 67 | 13.4 |
| Ischemic Heart Disease | 27 | 5.4 |
| Chronic Kidney Disease | 10 | 2.0 |
| **Symptoms** | | |
| Fever | 479 | 95.8 |
| Headache | 57 | 11.4 |
| Shortness of breath | 26 | 5.2 |
| Nausea | 106 | 21.2 |
| Vomiting | 161 | 32.2 |
| Diarrhea | 89 | 17.8 |
| Abdominal Pain | 80 | 16 |
| Generalized weakness | 78 | 15.6 |
| Jaundice | 03 | 0.6 |
| Dizziness | 26 | 5.2 |
| **Clinical signs on examination** | | |
| Pallor | 09 | 1.8 |
| Edema | 05 | 1.0 |
| Bruises | 22 | 4.4 |
| Hepatomegaly | 02 | 0.4 |
| Splenomegaly | 04 | 0.8 |
| **Disease outcome** | | |
| Recovered and discharged | 476 | 95.2 |
| Left against medical advice | 13 | 2.6 |
| Died | 11 | 2.2 |

The study found an incidence proportion of only 0.6% for dengue-reinfection and an incidence proportion of 3.8% for dengue co-infection. The highest incidence for dengue co-infection was observed with bacterial infections and viral Hepatitis-A infection with an observed incidence of 2.4% and 0.8% respectively (Fig. 1).

Bleeding and acute kidney injury (AKI) were the most frequent complications among dengue patients with a proportion of 10.6% (n=53) and 7.8 %(n=39); however, the overall mortality due to dengue infection was only 2.2.% (n =11) (Fig. 2).

## 4. DISCUSSION

To the best of our knowledge, this is the first study estimating the incidence proportion for dengue re-infection among adult patients with laboratory-confirmed cases of dengue infection. The considerably higher frequency of dengue cases among the male sex as compared to the female sex is consistent with previous local evidence [7,8].

### 4.1 Burden of Re-infection and Co-infection in Dengue

However, the incidence of dengue re-infection and co-infection in this study was 3.8% i.e.3.8 re-infection cases per 100 patients which was considerably low as compared to the frequencies of re-infection given in previous studies i.e. (ranging between 9.6 to 39.5%) can be attributed to differences in the study population, age group selected and sample size of the study [8-12]. However, the overall burden of co-infection in our sample was 19% i.e. 19 dengue cases with co-infection per 100 cases of dengue infection which

was considerably lower as compared to previous local as well as international evidence. These differences can be explained by the selection of dengue patients from a hospital representing a privileged population with a relatively higher socioeconomic class, good health literacy, and better living conditions. The most common co-infection was bacteraemia followed by Hepatitis A infection. On the contrary to previous local evidence, the incidence of co-infection with Malaria in the current study was too low which can be explained by again the specific socioeconomic background of the study population [13]. It is obvious that difference in socioeconomic class is the main factor playing a direct role in malaria transmission owing to improved infrastructure and better environmental conditions. Not a single case of Chikungunya as co-infection is reported in our study. However, studies from public sector healthcare settings in Pakistan have shown a considerable burden of 11.1% of co-infection with Chikungunya [11]. The differences in the epidemiology of dengue and other co-infections within Pakistan can be well explained by geographical and environmental condition within the country as well as differences in lifestyle.

## 4.2 Symptoms and Indicators of Severity

In this study, fever was the most common symptom followed by gastrointestinal (GI) symptoms including nausea vomiting, abdominal pain, and diarrhoea. A similar trend in symptoms is observed in other studies conducted in Karachi, Pakistan reporting fever, vomiting abdominal pain as the most reported symptoms [12,14,15]. The latest dengue classification by the World Health Organization (WHO); introduced in 2009 also identifies the presence of GIT symptoms as an indicator of disease severity [16]. A meta-analysis of 39 published articles comprising 1790 records; published in 2021 concluded that vomiting, abdominal pain or tenderness, pleural effusion, ascites, epistaxis, gum bleeding, GI bleeding, lethargy or restlessness, and hepatomegaly (>2 cm) were associated with higher risk of severe dengue [17]. However, the actual frequency of various commonly reported GI and non-GI dengue symptoms was relatively different in our study sample as many of them were partially treated outside at other facilities; hence may have passed the initial phase of illness usually identified by fever, myalgia, and headaches.
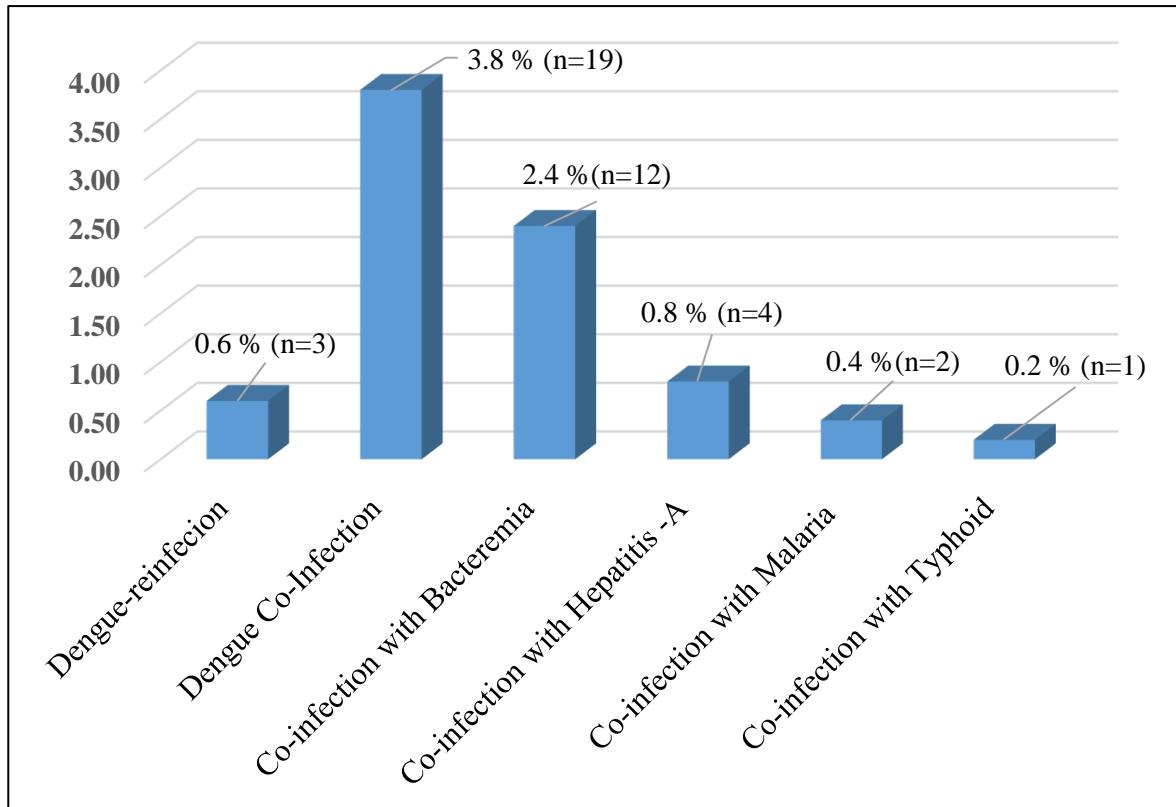


**Fig. 1. Incidence Proportion of Dengue Re-infection and Co-infection among adult dengue patients admitted at a private tertiary care hospital in Karachi, Pakistan (n=500)**
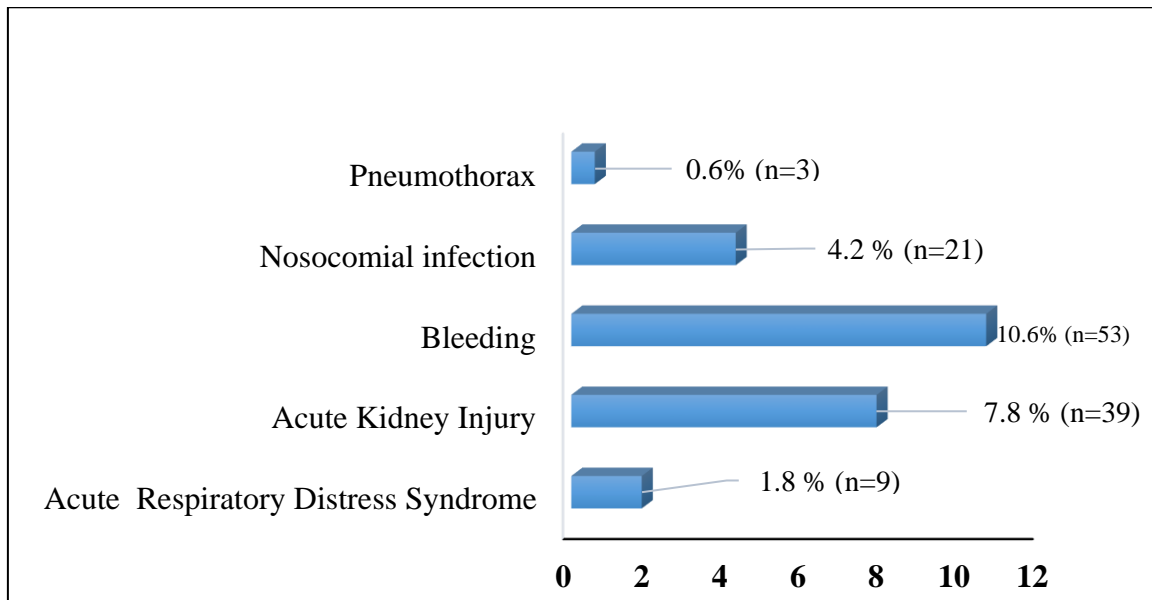
**Fig. 2. Frequency of various medical complications among adult dengue patients admitted at a private tertiary care hospital in Karachi, Pakistan (n=500)**

## 4.3 Complications of Dengue Infection with or without Co-infection and Re-infection

The study did not show any statistical differences in the frequency of dengue re-infection based on differences in demographic characteristics such as age groups, sex, and place of residence. Similarly, no statistical differences were noted in the presence of comorbidity i.e. diabetes mellitus, hypertension, ischemic heart disease, and acute kidney injury among dengue patients with and without dengue re-infection. This can be explained by relatively very few numbers of cases with re-infection. This study found statistically significant differences in the frequency of acute respiratory distress syndrome and acute kidney injury as complications of dengue fever among patients with and without diabetes mellitus type 2. This finding is supported by a previous study conducted in Punjab and KPK by Faiz Ahmed and colleagues reporting more severe disease among dengue patients with diabetes mellitus [11].

Our study has some intrinsic limitations, such as providing information from only one private sector, tertiary care hospital in Karachi, which limits its generalizability. Moreover, as this data was taken from patients admitted to the hospital hence it cannot represent less severe dengue cases that were asymptomatic and never required hospital admission as well as the general community. Similarly, the findings of this study may be different from previous studies

conducted in public sector hospitals due to differences in healthcare environment as well as differences in the socio-demographic status of patients attending public sector hospitals. All these differences further limit the generalizability of the study findings. Moreover, this study assessed re-infection based on patients` self-reported medical history and didn't assess serum IgG test for confirmation of previous dengue infection. This limits the internal validity of the study and may have resulted in underestimation of the re-infection of dengue possibly due to recall issues as well as in cases where physicians had treated them without identifying the dengue infection due to overlapping symptoms and self-limiting nature of the disease. Similarly, no data was available to assess concurrent dengue infection which can be described as simultaneous infection with two different strains of dengue virus. In addition, the probability of underestimating co-infection in this study cannot be ruled because a mild co-infection with dengue infection can be easily masked due to overlapping signs and symptoms and no-specific laboratory investigations, especially among those who had no complications and overall stable hospital course.

Nevertheless, this study offers a valuable addition to the local evidence and provides a further basis to conduct large-scale studies in a community where dengue has become more like a regular occurrence rather than a seasonal infection. The researchers also need to study the

factors associated with this changing behavior of the disease.

## 5. CONCLUSION AND RECOMMENDA-TIONS

This study determines a low incidence proportion of dengue re-infection and co-infection among adult patients admitted with a confirmed diagnosis of dengue infection at a private tertiary care hospital in Karachi. Fever and GIT symptoms were among the most reported symptoms. Bleeding, nosocomial infection, and acute kidney injury were identified as the most frequent medical complications among hospitalized dengue patients. Our study could not identify any statistically significant risk factors associated with dengue re-infection. Large-scale multi-center studies are warranted with sufficient sample size and objective assessment methods to determine the incidence of dengue re-infection and co-infection as well as for the identification of risk factors associated with dengue re-infection among the adult population of Pakistan.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

Ethical approval for this study was obtained from the Ethical Review Committee of Aga Khan University, Karachi (Ethical board review number 2022-8101-23102). This study involved no direct interaction between the patient and the researcher. However, standard practices were followed to ensure anonymity and confidentiality of the study participants. Patients were assigned unique randomly generated three-digit codes to organize the data and no personal identifying information (including names and Medical Record numbers) was formally recorded. Access to the coded identifiers will be granted upon request only to those involved in data review and analysis upon request and a logbook will be maintained to keep track of requests.

## DISCLAIMER (ARTIFICIAL INTELLIGENCE)

I, Sadaf Hanif being the first author of the study, hereby declare that none of the AI tools have been used while writing or editing this manuscript.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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