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EVOLVING TRENDS IN DENGUE SEVERITY AND SEROTYPE DOMINANCE: A DECADE-LONG ANALYSIS IN RAWALPINDI, PAKISTAN

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Abstract

Dengue constitutes an alarmingly increasing Pakistani public-health issue. Longitudinal studies of case severity, serotype mechanisms and outcomes are limited. Objectives were to analyze 12 years (2013-2024) data of confirmed Dengue patients who were managed at Rawalpindi Medical University attached hospitals for; 1) trends in yearly cases, age, gender, disease severity (DF, DHF, DSS), mortality, and serotypes of circulating dengue, and 2) to determine predictors of severe disease. This cross-sectional study was conducted at RMU from January to March 2025. Data of confirmed dengue-infected patients managed at RMU-affiliated hospitals between January 2013 and December 2024 were retrieved, keeping in mind the objectives of the study. Chi2 and t-tests or ANOVA were used to compare categorical and continuous variables where relevant. Independent predictors of severe dengue (DHF/DSS) were identified using multivariable logistic regression. Of the 41196 patients (mean age 34±12.7 years; 51.4 % males), total annual cases significantly differed, with the highest number of 11942 occurring in 2019. The number of outpatient visits and hospitalization admissions varied ($p < 0.001$), as well. The percentage of DHF increased to 51.0% in 2024 compared to 27.7% in 2013 ($p = 0.003$). DSS percentage increased to 4.15% in 2024 as compared to 2.03 % in 2013 ($p < 0.05$). 122 dengue-related deaths were noted (case-fatality rate 0.29 %), with the peak in 2019 (0.34 %). DENV-II was most common during high-incidence years and occurred independently with severe dengue (adjusted OR 1.62; 95 % CI 1.282.05; $p < 0.01$). It has been concluded that dengue cases increased in frequency and severity over the last 12 years in Rawalpindi. DENV-II infection remained common. Mortality, however, remained at a low level.

Keywords: *Dengue, Dengue hemorrhagic fever, Dengue shock syndrome, Dengue virus II, Epidemiology, Pakistan*

INTRODUCTION

Dengue is the most geographically prevalent viral disease transmitted by mosquitoes. Almost half of the global population is at risk of contracting the disease. Dengue estimated leads to 36,000 deaths annually on a worldwide basis (1). Dengue infection rates have been high in the tropical and subtropical areas due to rapid urbanization, poor control of the vector, and climate that favors transmission.

Dengue virus (DENV) is a positive single-strand RNA virus that is icosahedral. It belongs to *Orthoflavivirus* genus and *Flaviviridae* family (2). DENV transmission is mainly through bite of female *Aedes aegypti* infected with virus. To some extent *Aedes albopictus* is also responsible for DENV transmission. The virus has four serotypes which are antigenically distinct i.e., DENV-1, DENV-2, DENV-3, and DENV-4 (3). Exposure to a single serotype leads to life-long immunity to the same serotype. Infections with other serotypes can however cause antibody-dependent enhancement (ADE), during which non-neutralizing antibodies help the virus enter and begin further replication, leading to more severe dengue (4). The pathology of dengue is asymptomatic to severe disease which includes dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. This differentiation is based on plasma leakage and complicating hemodynamic instability and organ impairment (5).

At a regional level, repeated dengue outbreaks in Pakistan are being noted since early nineties. DENV-2 and DENV-3 have been reported as prevalent serotypes here (6). The serotype landscape is

however changing. DENV-1 and DENV-2 infections were common when dengue patients were evaluated for serotype during 2022, Lahore epidemic (7). Serotype change has been linked to disease severity and hospitalizations (5).

Rawalpindi has served as epicenters of the dengue in Northern Pakistan because of population density, unplanned urbanization, and water storage practices due to water deficiency, seasonal monsoon, and interprovincial migration (7). There are three public tertiary-care hospitals in Rawalpindi in particular Holy Family Hospital (HFH), Benazir Bhutto Hospital (BBH), and Rawalpindi Teaching Hospital (RTH) which have to shoulder the burden of dengue outbreaks for last more than 20 years.

The larger part of the available Pakistani literature focuses on individual outbreaks or even on relatively short intervals, thus opening gap in the knowledge of changing patterns over a period. Same is true for Rawalpindi; there exists paucity on longitudinal analyses of the severity patterns of the disease, altering serotype trends, and clinical implications. To bridge this gap, we evaluated 12-year RMU affiliated hospital data (2013-2024) to examine trends over time in the severity of dengue, serotype, and mortality trends associated with Dengue. The long-term prospect of the study was to note change in epidemiology, defining risk years and groups, and the clinical proportion of the predominant serotypes.

METHODOLOGY

SETTING/STUDY DESIGN

This was a cross-sectional observational study which was carried out at Rawalpindi Medical University (RMU) attached tertiary-care hospitals i.e. HFH, BBH and RTH, Rawalpindi, Pakistan. The study focused on the period from January 2013 to December 2024 (12 years of the dengue epidemic cycle).

ETHICAL CONSIDERATIONS

The Institutional Review Board (IRB) of Rawalpindi Medical University granted ethical approval. Since this was a retrospective study of anonymized data of hospital records, informed consent was not taken.

Data of all patients with confirmed dengue infection (clinical features along with one of following positive tests: 1) NS1 antigen, virus detection by PCR, IgM antibodies, or a ≥ 4-fold rise in IgG antibody titer in paired sera based on Dengue Expert Advisory Group- DEAG criteria) was retrieved. Both outpatient and admitted patients were included. Cases where there was incomplete data regarding demographics, disease severity, and outcome etc. were excluded.

The following variables were gathered: demographics (age, gender), Severity of Dengue infection (Dengue Fever- DF, Dengue Hemorrhagic Fever-DHF, Dengue Shock Syndrome -DSS), OPD visit and admission per year, mortality (expiries), and serotype results of NSI positive patients where available dengue virus. At these hospitals SD Bioline kits are used for NSI, IgM, and IgG Dengue detection. Serotyping was done by Reverse Transcriptase Polymerase Chain Reaction of DENV-I -DENV-IV). Data was entered to SPSS 24.

Data cleaning was done for missing values. Records of missing variables were excluded in analysis. Completeness checks were done for each year. A year where the % completeness of core variables was above 85 was included in inferential analysis. Frequencies and % were used to sum up the categorical variables (gender, disease classification and genotype). Continuous normal distribution variables (age etc.) were described as mean and standard deviation. Comparisons of proportions of the variables across years and between groups of severity were done using chi-square. The comparison of age and admission was predicated on independent t-tests and ANOVA. A binary logistic regression model was made to determine predictors of severe dengue (DHF/DSS). Dependent variable in this context was having severe dengue, Independent variables include: age, gender, outbreak year, circulating serotype (where applicable). Adjusted odds ratios (AOR) and 95% confidence interval (CI) were noted. P-value of < 0.05 was taken to be significant.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

There were 41196 laboratory confirmed dengue cases which were analyzed. The average patient age was 34 ±12.7 years (age range 3 to 75 years). 51.4% patients were male and 48.6% female (p value 0.46). Table I gives details in this regard. The trends of annual numbers of Dengue cases focusing gender, and mean age are presented in Figure 1.

Table I. Demographic characteristics of confirmed dengue cases (2013–2024)

Year	Total Cases	Male (%)	Female (%)	Mean age (years)	Age range (years)
2013	1223	52.1	47.9	32	5 -65
2014	1571	50.5	49.5	33	4 -70
2015	3917	51.3	48.7	29	3 -72
2016	3306	50.9	49.1	30	3 -68
2017	651	53.4	46.6	35	5 -70
2018	717	52.8	47.2	36	4 -69
2019	11942	51.7	48.3	34	4 -75
2020	38	54.0	46.0	33	10 -60
2021	3526	51.9	48.1	34	4 -67
2022	5039	50.2	49.8	35	3 -70
2023	2738	49.8	50.2	37	6 -72
2024	6528	51.2	48.8	35	3 -75

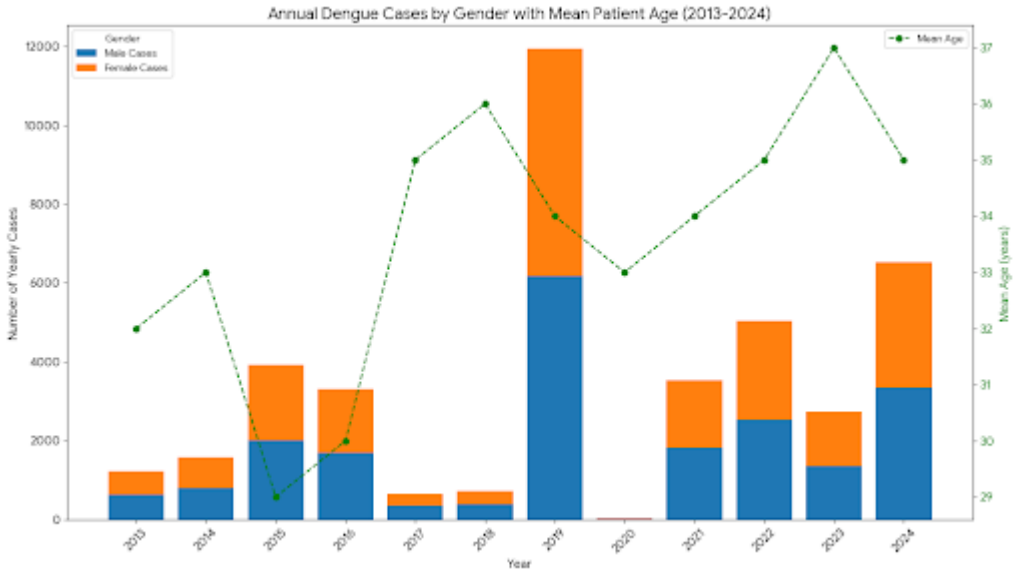

Fig. 1. Annual confirmed dengue cases gender and mean age wise (2013–2024).

OUTPATIENT VISITS AND HOSPITALIZATION

The number of outpatient department (OPD) visits and hospital admissions differed significantly between various years ($p < 0.001$). In 2019, the maximum number of OPD visits and Dengue admissions were noted. Table II gives year wise details in this regard.

Table II. OPD visits and hospital admissions (2013–2024)

Year	OPD Visits	Admissions
2013	25914	2422
2014	22126	6139
2015	44337	5258
2016	20449	2116
2017	9131	2116
2018	4516	1561
2019	87680	15479
2020	5648	350
2021	32940	5050

2022	59223	7059
2023	18637	4621
2024	50899	8386

SEVERITY OF DENGUE

Dengue situation worsened as time progressed. DHF cases in 2013 were 27.7% of Dengue cases. In 2024 this % increased to 51.02 (p value 0.003). SS cases have also shown similar incremental pattern ($p < 0.05$). Percentage wise maximum DHF and DSS cases were noted in the years 2020, 2021, and 2024 respectively. Yearly distribution of confirmed Dengue cases and its severity wise division are given in Table III.

Table III. Dengue severity patterns (year wise, DF, DHF, and DSS cases

Year	Confirmed Cases	DF Cases (%)	DHF Cases (%)	DSS Cases (%)
2013	1223	70.3	27.71	2.03
2014	1571	63.7	36.28	2.14
2015	3917	67.0	34.33	2.14
2016	3306	68.0	30.0	1.66
2017	651	64.7	33.33	1.99
2018	717	81.1	16.73	0.13
2019	11942	59.6	38.23	2.21
2020	38	48.6	48.61	2.60
2021	3526	48.7	48.61	2.60
2022	5039	57.7	40.30	2.00
2023	2738	71.5	25.96	2.41
2024	6528	44.83	51.02	4.15

MORTALITY TRENDS

During the study year, there were 122 deaths related to dengue. Case-fatality rate- CFR (no of total deaths/Total cases x 100) for 2013 to 2024 was of 0.29%. The utmost yearly mortality was noted in 2019 (11942 confirmed Dengue cases, 41 expiries, CFR: 0.34%). The CFR declined to 0.22% in 2024 even though there was a sharp increase in cases in this year. Details in this regard are given in Table IV.

Table IV. Expiries, DHF and DSS segments, and predominant dengue virus serotype-year wise

Year	Expiries	Expiry %	DHF cases (%)	DSS cases (%)	Predominant genotype	Predominant genotype %
2013	7	0.57	27.71	2.03	DEN-2	100%
2014	2	0.12	36.28	2.14	DEN-3	85.9%
2015	8	0.20	34.33	2.14	DEN-2	62%
2016	3	0.09	30.0	1.66	DEN-2	45.16%
2017	3	0.46	33.33	1.99	DEN-2	72%
2018	2	0.27	16.73	0.13	N/A	-
2019	41	0.34	38.23	2.21	DEN-2	100%
2020	0	-	48.61	2.60	N/A	-
2021	24	0.68	48.61	2.60	DEN-2	23%
2022	23	0.44	40.30	2.00	DEN-2	60%
2023	-	-	25.96	2.41	DEN-1 (71%), DEN-2 (29%)	
2024	9	0.13	51.02	4.15	DEN-2 (90%), DEN-1 (10%)	

PREVALENT GENOTYPES AND THEIR IMPACT

Serotype data show that DEN-I and II infections were there in years with the highest number of dengue infections e.g. 2019, 2022, and 2024. Except for 2014 when Den-III was common, in other years DEN-I and II infections were predominant ones. The statistical evaluation showed significant association of DEN-II infection with Dengue severity ($p < 0.01$). Table IV gives further details.

DISCUSSION

This large cohort study of focused 41,196 confirmed dengue cases diagnosed and treated during several epidemic events in last twelve years at Rawalpindi, Pakistan. This study is of interest considering the trend in the global dengue burden, especially in the highly populated and climatically favorable areas of Southeast Asia where frequent epidemics create considerable burden on the health system (8, 9). With extensive information focusing demographic, outpatient visits, hospitalization rate, the severity of disease, mortality rates, and the most common serotypes of dengue virus (DENV), this data set will be an invaluable source of reference when approaching dengue dynamics and planning future preventive measures and allocation of healthcare resources (10).

The cases of dengue registered per year in Rawalpindi displayed a lot of variation with a sharp rise in 2019 and another in 2024. This variability can probably be explained by many factors and conditions that can be contributory. Climatic conditions, monsoon rains promoting mosquito breeding, dense population, deficient civic facilities, deficient public health interventions, lack of community awareness and participation, and the change of serotypes that can create varying immunity in the population are important of these factors (11, 12). The graphical pattern makes it possible to perform predictive modeling of future infections, showing that the years that have been like 2019 and 2024 are at risk of an outbreak. This kind of prediction is needed to effectively undertake preemptive preparation of the care of the population and the mobilization of resources, which can prevent epidemics in the future (13, 14).

Our noted demographics of Dengue cases are comparable to results of studies conducted in Southeast Asian population where it has been found that dengue affects younger people, with an average patient age of slightly below 34 years (15, 16). Dengue patient's age noted in various related Pakistani studies is given in Table V.

Gender information the gender breakdown in our study co-relates with data from others regional countries that show widespread nature of the disease regardless of gender (17, 18). In various Pakistani studies male predominance has been noted in Dengue cases (Table V). It is to be noted that gender-based differences in context of Dengue in our region are attributed to; 1) hospital based nature of studies i.e. only problematic patients go to hospital and these studies do not represent total infected patients, and 2) females seek medical attention less compared to males (19).

About 25% of dengue infections are symptomatic termed as Dengue Fever (F) (20). As per World Health Organization (WHO) fact sheet 2023 focusing dengue and severe dengue, ~500 000 cases of severe dengue (including DHF/DSS) occur each year. This corresponds to 0.5-1% of total worldwide Dengue infections (21). Country specific data show that 3-5% of DF cases are complicated by DHF/DSS. In our study comparatively very high % of DI were complicated. This is explainable on; 1) hospital-based nature of study, and 2) only problematic patients attend public sector hospital set up like ours.

Our severity analysis showed a disturbing upsurge in severe dengue presentation or dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) from 2013 to 2024. The augmented severity coincides with similar observations in research work from India and Bangladesh. It is considered that there is an augmented prevalence of DHF and DSS attributable to the alterations in serotype, secondary infections, and changing virulent patterns of circulating dengue virus (22, 23).

The patterns of mortality in our study, where the overall case fatality rate (CFR) was 0.29%, support the international data. Table V, and VI provide comparison with reference to local and international studies. Important point to note in positive sense is that CFR has been low despite high disease severity. Improvement of clinical management protocols, early diagnosis, increased community awareness, increasing experience of treating teams, and better healthcare facilities have helped in reducing mortality in recent years, even though proportion of severe cases increased (19,24).

The high prevalence of DENV-II serotype with severe dengue outcomes in our study is like studies conducted in countries where dengue is endemic. Similar results were noted in Southeast Asia and Latin America where severe clinical presentation was noted with DENV-II infection (25, 26). There is a need to

improve surveillance systems, vector control, and community participation to slow down transmission of the disease (27, 28).

Keeping in mind the findings of our study it can be interpreted that dengue case management at hospital is satisfactory however disease prevention has issues. Disease prevention has not been focus of this study. However, without improving it, hospitals may not be able to manage annually increasing dengue patients with severe disease. Proactive, multidimensional, community-based prevention strategies need to be implemented (9, 29).

This research has several limitations which need to be kept in mind. The analysis was retrospective and relied on the hospital records that can be incomplete. Clarity of reporting severity and distribution of serotypes may not be accurate, therefore. Moreover, some epidemiological parameters including socioeconomic status, and vector control practices etc. were not focus of the study. This constrained the level of analysis on these potentially influential factors (30).

Large sample size and focus on 12 years period are strengths with reference to internal validity of study that makes observed trends and associations more reliable. External validity is limited to some extent because the results are from RMU Teaching hospitals only. There are other tertiary care hospitals and health care facilities where Dengue patients are also managed to some extent. Our study results are unique for Rawalpindi that has many issues discussed earlier that contribute to almost yearly Dengue outbreaks. However, based on the characteristics of Rawalpindi as an urban center with a significant healthcare infrastructure, our results will have generalizability to other areas of Pakistan and Southeast Asia (7, 31-32).

Table V. Comparative epidemiology of major dengue epidemics in Pakistan (2017-2022)

Year/ Location	Total confirmed cases	Total deaths	Case fatality rate (CFR)	Predominant age group	Male: female ratio	Severity breakdown	Predominant serotype(s)	Key reference
2017 / KPK	24,938	70	0.28%	16-30 years (45%)	~2:1	Not Available	DENV-2 (Inferred)	23
2019 / National	54,386	95	0.17%	Not Available	~1.6:1 (General)	DF: 74.4%, DHF: 24.1%, DSS: 1.5% (General)	Not Available	7
2021 / National	48,906	183	0.40%	16-30 years (37%)	~1.8:1	Not Available	DENV-2 (45.8%) & DENV-3 (50.4%) co-circulation (in KP)	2
22/02 / National	25,932 (by Sep)	62	0.25%	20-29 years (27%)	~2.1:1	Mild: 75%, With Warning Signs: 11%, Severe: 1.4% (in Karachi)	DENV-1 (34%) & DENV-2 (45%) co-circulation (in Karachi)	17

The consistent overrepresentation of young adult males

Table VI. Epidemiological characteristics of the 2019-2020 dengue epidemics in selected Southeast Asian Nations

Country (Year)	Total confirmed cases	Total deaths	Case fatality rate (CFR)	Predominant serotype(s)	Key demographic findings	Severity breakdown (% Severe)	Key reference(s)
Philippines (2019)	420,453	1,565	~0.37%	DENV-3 (>64%)	Children (5-9 years) most affected	Not Available	7
Malaysia (2019)	130,101	176	~0.14%	All 4 co-circulating	Adolescents & children high incidence; Elderly high mortality	Proportion of severe cases decreasing despite peak incidence	7
Vietnam (2019)	320,702	54	~0.017%	DENV-2 (73%)	Young adults (18-29 years) most affected	Most cases mild, primary infection	7
Bangladesh (2019)	101,354	129-164	~0.13-0.16%	DENV-3 (Re-emergent)	Young adults (19-29 years) & avg. age 33.3	~10% of hospitalized adults developed severe dengue	7
Singapore (2020)	35,315	32	~0.09%	DENV-3 (Shift from DENV-2)	Working-age adults most affected	0.15% DHF	33
Sri Lanka (2019)	105,049	90	~0.085%	DENV-3 then DENV-2	Children (<16 years) 55.3% of viraemic samples	~21% with severe features	7

CONCLUSION

In this 12-year analysis of dengue cases, we noted progressive annual increase in disease frequency and severity, with major epidemics in 2019 and 2024. Despite this, case fatality rate declined. Virus evaluation consistently identified DENV-II as predominant serotype and main reason for disease severity. This is indicative that disease management is up-to the mark and disease prevention needs to be improved that is the main step to reduce dengue related morbidity and mortality.

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