Global, regional, and national burden of dengue infection in children and adolescents: an analysis of the Global Burden of Disease Study 2021

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Summary

Background Dengue remains a global threat to public health, however, its disease burden among children and adolescents has always been poorly quantified. Therefore, we aimed to systematically estimate the global, regional, and national burden and temporal trends of dengue infection in children and adolescents from 1990 to 2021.

Methods Data on the number and rate of incidence and disability-adjusted life-years (DALYs) of dengue infection among children and adolescents under 20 years were obtained from the Global Burden of Disease Study (GBD) 2021. Estimated annual percentage changes (EAPCs) of the age-standardised incidence rate (ASIR) and age-standardised DALYs rate (ASDR), by age, sex, and different countries and regions, were calculated to quantify the temporal trends of dengue burden. The association between development levels (measured using the socio-demographic index [SDI]) and dengue burden was also determined.

Findings From 1990 to 2021, the global burden of dengue incidence and its associated DALYs was consistently higher in children and adolescents than in the entire population. Globally, among children and adolescents, there were 21,641,016 incident cases in 2021, an increase of 64.43% compared to 13,241,719 in 1990. The ASIR per 100,000 population increased from 587.81 in 1990 to 812.16 in 2021, with an EAPC of 1.39% (95% confidence interval [CI], 1.13%–1.65%). Besides, the number of dengue-associated DALYs among children and adolescents increased by 16.36%, from 910,458.60 in 1990 to 1,059,428.31 in 2021. The increase in DALYs was less pronounced than incidence, with the ASDR per 100,000 population increasing from 40.17 in 1990 to 41.50 in 2021, and the EAPC was only 0.67% (95% CI, 0.40%–0.95%). The incidence and DALYs burden of dengue in children and adolescents was highest in middle SDI regions, followed by low-middle SDI regions, with the lowest burden in high SDI regions. Furthermore, Tropical Latin America had an extremely high ASIR (6040.29 per 100,000 population in 2021), and Southeast Asia had an extremely high ASDR (298.20 per 100,000 population in 2021), much higher than other regions around the world.

Interpretation The global dengue burden in children and adolescents is high and has been increasing from 1990 to 2021, even though the distribution patterns vary across different countries and territories. This study first reported the global disease burden and temporal trends of children and adolescents, which has significant implications for policymakers and public health officials, as it underscores the need for age- and region-specific strategies to mitigate the growing global burden of dengue.

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Research in context

Evidence before this study

Dengue remains a global threat to public health and is increasing at a higher rate than any other communicable disease. We used the keywords "dengue", "children", "adolescents", and "disease burden" to search Embase, PubMed, and Web of Science from database inception to 10 July 2024. Existing studies have reported the global burden of dengue based on data from the Global Burden of Disease Study (GBD) and have identified an increasing trend in global incidence and dengue deaths over the past decades. However, the limitation was that they only reported the burden for the entire population, and the disease burden of dengue among children and adolescents has always been neglected and is still poorly quantified, which is always severe in children and adolescents. To our knowledge, there is no study systematically characterising the recent trends in dengue infections and the distribution of the disease burden among children and adolescents at global, regional, and national levels.

Added value of this study

We used the latest data from the GBD 2021 to provide the most up-to-date estimates on the incidence and disability-adjusted life-years (DALYs) of dengue infection as well as the temporal trends from 1990 to 2021 among children and adolescents under 20 years at the global, regional, and country-specific levels by sex, age group, and socio-demographic index (SDI). We found that the disease burden of dengue in children and adolescents globally is enormous and has been increasing from 1990 to 2021. The distribution patterns of dengue incidence and its resulting DALYs distribution vary across different countries and territories among children and adolescents. The incidence and DALYs burden of dengue in children and adolescents was highest in middle SDI regions, followed by low-middle SDI regions, with the lowest burden in high SDI regions. Furthermore, Tropical Latin America had an extremely severe dengue incidence burden, and Southeast Asia had an extremely severe dengue DALYs burden, much more severe than other regions around the world. To our knowledge, this is the first time that the disease burden and temporal trend of dengue has been reported for children and adolescents, a population that has often been neglected in previous dengue-related studies.

Implications of all the available evidence

We believe this analysis presents the most comprehensive picture of the dengue burden among children and adolescents to date. Following the coronavirus disease 2019 (COVID-19) pandemic, communicable disease control among children and adolescents must be central to efforts to ensure sustainable development. Our study could provide an important reference value for global public health officials and policymakers to develop vaccine programmes and implement interventions to mitigate the growing communicable disease burden among children and adolescents.

Introduction

Dengue is a mosquito-borne disease that causes flu-like symptoms and is common in warm tropical climates.[1] The threat of dengue has been increasing for decades.[2] Dengue is increasing at a higher rate than any other communicable disease, increasing by 400% over 13 years (2000–2013).[1] It is estimated that around 400 million people get infected with dengue every year, of which about 25% were clinically apparent and accounted for 1.1 million disability-adjusted life-years (DALYs) globally,[3,4] and approximately half of the world's population are at risk of contracting dengue.[5] It is predicted that globally 2.25 billion more people will be at risk of dengue in 2080 compared to 2015, bringing the total population at risk to over 6.1 billion, or 60% of the world's population.[6] Dengue has been listed as one of the ten threats to global health in 2019 by the World Health Organization (WHO).[7] Since not all dengue viruses (DENVs) have been documented in official reports and many endemic countries do not have robust detection and reporting mechanisms, the true global burden of dengue is likely to be underestimated. In May 2024, the WHO assessed the overall risk of dengue at the global level as still high, and therefore dengue remains a global threat to public health.[8]

Dengue is caused by the DENV, which is a single-stranded, positive-sense ribonucleic acid (RNA) virus of the genus Flavivirus (family Flaviviridae) and has four serotypes (DENV-1, DENV-2, DENV-3, DENV-4).[2,4] The most common cases following infection are asymptomatic or result in mild febrile illness. However, some cases will develop severe dengue, which may involve shock, severe bleeding, or severe organ damage.[8] DENV is mainly transmitted through the bite of infected mosquitoes, most commonly *Aedes aegypti* (*Ae. aegypti*) and *Aedes albopictus* (*Ae. albopictus*) mosquitoes.[8] This virus and its vectors have spread rapidly around the globe, mainly in tropical and subtropical regions, with over three billion people living in *Aedes*-infested areas, the transmission of dengue is now present in every

WHO region of the world and more than 125 countries are known to be dengue endemic.[9]

Recent research highlights the increasing geographic range of dengue, including previously non-endemic regions, such as the autochthonous dengue outbreak in Rome, Italy, in 2023, demonstrating the disease's growing presence in Europe.[10] Furthermore, dengue is increasingly affecting international travelers.[11] Globally, there has been an increase of the reported cases of dengue among international travelers over the past two decades, which is part of the increasing dynamics of the global dengue burden that is expected to continue in the coming decades under the combined impact of climate change, urbanization, and international connectivity.[6,12,13] Although dengue has caused significant public health impacts, is increasingly attracting public attention and has been accompanied by growth in research funding, dengue is still regarded as a neglected tropical disease (NTD), reflecting ongoing gaps in research funding and prevention strategies.[14] While many NTDs have seen declining incidence and mortality over recent decades, dengue continues to rise, contributing substantially to the overall burden of NTDs worldwide.[15] From 1990 to 2019, among common NTDs, dengue had the largest increase in incident cases, and was the only NTD with rising mortality.[15]

The disease burden of dengue has always been severe in children and adolescents. Du et al. reported on the global burden of dengue using data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 and found that the peak age of dengue incidence globally was in adolescents and young adults aged 10–25 years, followed by young children aged 5–10 years.[16] Because of the immaturity of the hemodynamic system, children (especially infants) are susceptible to severe dengue.[17] National surveillance data from Asian countries showed that infants under one year of age and children aged 4–9 years were consistently at highest risk of severe dengue.[18] An estimated 500,000 cases of severe dengue require hospitalization each year, of which a very large proportion is in children.[19] Therefore, the control of dengue and other arboviruses remains a critical global health priority due to the persistent and growing burden they pose,[20] particularly among vulnerable populations such as children and adolescents.

Existing studies have reported the global burden of dengue and have identified an increasing trend in global incidence and dengue deaths over the past decades.[16,21,22] However, the disease burden of dengue among children and adolescents has always been poorly quantified and under-recognised in terms of focused research and specific preventive strategies for these age groups. Therefore, based on data from GBD 2021 for children and adolescents under 20 years of age, this study systematically analysed the epidemiological status and temporal trends of the incidence and DALYs of dengue across age groups, sexes, and geographic regions between 1990 and 2021, to provide comprehensive and comparable analyses of the burden of dengue in children and adolescents and to help formulate targeted dengue prevention strategies globally.

Methods

Study population and data source

Data on dengue burden from 1990 to 2021 were obtained from the GBD 2021 using the Global Health Data Exchange (GHDx) results tool.[23] GBD 2021 provided comprehensive estimates of the global burden of 371 diseases and injuries, 288 causes of death, and 88 risk factors in 204 countries and territories from 1990 to 2021, utilizing the most recent epidemiological data and enhanced standardised methodologies.[24] The general methodological approaches to estimate the mortality were described elsewhere.[24–26] We defined the study population as children and adolescents aged <20 years.[27] Data on the number and rate of incidence of dengue infection and dengue-associated DALYs were extracted from the GBD 2021. In this study, we selected the following four age groups to analyse: <5 years, 5–9 years, 10–14 years, and 15–19 years, to summarise the age distribution of the dengue burden of children and adolescents. To compare the disease burden of dengue in children and adolescents with the entire population, data on the population of all ages were also extracted. This research adhered to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER).

The socio-demographic index (SDI) is developed by GBD researchers and represents the combined level of health-related social and economic conditions in each region.[28] The SDI is the geometric mean of 0–1 indices of the total fertility rate in females younger than 25 years, mean education (years of schooling) in people aged 15 years and older, and the country's lag-distributed income per capita. As a composite, a location with an SDI of 0 would have a theoretical minimum level of development relevant to health, while a location with an SDI of 1 would have a theoretical maximum level.[28] The 204 countries and territories in GBD 2021 are grouped into quintiles (low, low-middle, middle, high-middle, and high) based on country-level estimates of SDI (Table S1).[28] Besides, GBD 2021 produced estimates for 204 countries and territories, grouped into 21 GBD regions, which are geographically close, epidemiologically similar, and share similar distributions of causes of death.[24]

Ethics statement

For GBD studies, the Institutional Review Board of the University of Washington reviewed and approved a waiver of informed consent (https://ghdx.healthdata.org/gbd-2021).[24]

Statistical analysis

Numbers of incidence and DALYs with 95% uncertainty intervals (UIs), and their corresponding age-standardised rates (ASRs) were the main indicators used to describe the dengue burden of children and adolescents. We calculated the age-standardised incidence rates (ASIR) and age-standardised DALYs rates (ASDR) based on the GBD World Standard Population using the following formula: $ASR = \frac{\sum_{i=1}^{N} a_i w_i}{\sum_{i=1}^{N} w_i}$, where a_i is the ASR in the ith age group and w_i represents the number of people (or the weight) in the same age group among the GBD standard population. N is the number of age groups.[29,30]

The relative changes in incidence and DALYs of dengue from 1990 to 2021 were defined as $\frac{Number_{2021} - Number_{1990}}{Number_{1990}} \times 100\%$.[16] To evaluate the long-term and average changing trends in the dengue burden of children and adolescents over the entire study period from 1990 to 2021, we calculated the estimated annual percentage change (EAPC) in ASIR and ASDR, which was widely used in secondary analysis based on GBD studies. To assess the assumptions underlying the linear regression model, the linear relationship between the natural logarithm of ASR and the calendar year was verified through scatterplots and residual diagnostics, independence was tested by the Durbin–Watson statistics, normality was tested through the distribution of residuals examined by histograms and Q–Q plots, homoscedasticity was tested by the residuals vs. fitted values plots.[31] The test results showed that our data met the assumptions underlying linear regression. Therefore, following the previous common research method,[30,32] the natural logarithm of ASR is assumed to fit the linear regression model $y = \alpha + \beta x + \varepsilon$, where $y = \ln(ASR)$, $x = calendar\ year$, β coefficient represents a geometric mean ratio, and ε is the error term, which is assumed to follow a normal distribution with a mean of zero and constant variance. Then, EAPC was estimated as $100 \times (e^{\beta} - 1)$, with 95% confidence intervals (CIs) obtained from the linear regression model.[30] An ASR was determined to represent an increasing or decreasing trend over time if both the EAPC and its 95% CIs were above or below 0, respectively. When the 95% CIs included 0, the change in ASR was considered statistically non-significant, meaning that the observed trend was not statistically different from no change.[30]

Finally, we examined the shape of the association between ASIR and ASDR of dengue and the SDI using the Locally Estimated Scatterplot Smoothing (LOESS) method.[33] We used a span of 0.75, which provided a balance between capturing the non-linear trends and avoiding overfitting. The LOESS method used a tri-cube weighting function, which assigns more weight to points closer to the target point in the local regression, and could model the potentially complex relationship between SDI and the disease burden of dengue. All the statistical analyses were performed using R software (version 4.2.1).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study, and the corresponding authors had final responsibility for the decision to submit for publication.

Results

Global burden and trend of dengue in children and adolescents

From 1990 to 2021, the global burden of dengue incidence and its associated DALYs was consistently higher in children and adolescents than in the entire population (Tables S2 and S3, and Fig. S1). Globally, the incidence of dengue infections among children and adolescents increased gradually from 1990, peaking around 2015 before showing a slow decline, and thereafter a small increase in 2020 and 2021 (Table S2 and Fig. S1A). However, it remained on the rise overall. There were 21,641,016 incident cases in 2021, an increase of 64.43% compared to 13,241,719 in 1990. The ASIR per 100,000 population of dengue increased from 587.81 in 1990 to 812.16 in 2021, with an EAPC of 1.39% (95% CI, 1.13%–1.65%) (Table 1). The DALYs number due to dengue infection increased by 16.36%, from 910,458.60 in 1990 to 1,059,428.31 in 2021. The increase in DALYs was less pronounced than incidence (Table S3), with the ASDR per 100,000 population increasing from 40.17 in 1990 to 41.50 in 2021, and the EAPC was only 0.67% (95% CI, 0.40%–0.95%) (Table 2).

From 1990 to 2021, the incidence rate of dengue in all age groups among children and adolescents showed an overall increasing trend, with EAPCs and their 95% CIs >0 (Table 1). The number and incidence rate of dengue were lowest in children less than 5 years of age, with similar incidence trends and burdens in the remaining three age groups of children and adolescents (Fig. 1A and B, and Fig. 2A). The opposite was true for dengue-associated DALYs, with more than half of the burden of DALYs being in children less than 5 years of age with the highest DALYs rate. This was followed by the 5–9 years age group, with a lower burden of DALYs in children and adolescents older than 10 years (Table 2, Fig. 1C and D, and Fig. 2B). Further analyses of children <5 years of age showed that those infants <28 days had the lowest ASIR but the highest ASDR (Fig. S2).

By sex, the pattern of ASIR and ASDR per 100,000 population between 1990 and 2021 was similar among males and females. The burden of dengue incidence was consistently higher in females than in males, but

Characteristics	Number of incident cases		Percentage change, % 1990–2021	ASIR (per 100,000 population)		EAPC, % (95% CI) 1990–2021	P value
	1990 (95% UI)	2021 (95% UI)		1990	2021		
Global	13,241,719 (2,104,209, 25,791,668)	21,641,016 (5,291,719, 39,972,109)	63.43	587.81	812.16	1.39 (1.13, 1.65)	<0.0001
Sex							
Female	6,951,988 (1,083,348, 13,417,308)	11,288,930 (2,788,165, 20,630,701)	62.38	632.63	873.98	1.39 (1.13, 1.66)	<0.0001
Male	6,289,731 (818,899, 12,358,506)	10,352,085 (2,122,024, 19,383,134)	64.59	545.12	754.00	1.40 (1.15, 1.65)	<0.0001
Age							
<5 years	2,453,922 (4,738,099, 421,639)	3,472,146 (6,437,718, 863,287)	41.49	395.83	527.54	1.10 (0.88, 1.32)	<0.0001
5–9 years	4,034,700 (7,862,962, 624,546)	6,102,335 (11,245,012, 1,511,495)	51.25	691.43	888.19	1.22 (0.99, 1.46)	<0.0001
10–14 years	3,720,778 (7,224,913, 577,901)	6,306,112 (11,679,274, 1,528,194)	69.48	694.59	945.96	1.45 (1.13, 1.76)	<0.0001
15–19 years	3,032,320 (5,889,016, 474,875)	5,760,423 (10,690,380, 1,393,055)	89.97	583.79	923.17	1.75 (1.45, 2.05)	<0.0001
Socio-demographic index							
High SDI	113,433 (16,372, 282,381)	121,406 (27,327, 262,234)	7.03	44.55	51.82	1.05 (0.04, 2.07)	0.042
High-middle SDI	506,649 (62,518, 1,356,816)	851,353 (359,046, 1,470,903)	68.04	136.60	275.31	3.24 (2.75, 3.72)	<0.0001
Middle SDI	6,479,343 (419,745, 14,193,515)	10,068,558 (3,509,110, 17,853,483)	55.39	847.15	1321.16	2.01 (1.68, 2.35)	<0.0001
Low-middle SDI	4,904,791 (518,300, 10,527,333)	8,608,611 (873,352, 18,835,962)	75.51	837.94	1115.67	1.16 (0.99, 1.34)	<0.0001
Low SDI	1,231,866 (711,076, 1,851,003)	1,983,732 (65,527, 4,974,222)	61.03	451.16	341.71	−1.51 (−2.24, −0.79)	0.00018
GBD region							
Andean Latin America	61,684 (7161, 145,702)	149,905 (61,999, 254,785)	143.02	326.24	630.46	2.26 (1.86, 2.66)	<0.0001
Australasia	1913 (133, 5646)	4757 (1471, 11,432)	148.65	30.26	62.27	3.69 (2.85, 4.52)	<0.0001
Caribbean	64,330 (1889, 195,777)	75,543 (9187, 219,658)	17.43	427.73	491.05	0.62 (−0.10, 1.34)	0.087
Central Asia	NA	NA	NA	NA	NA	NA	NA
Central Europe	NA	NA	NA	NA	NA	NA	NA
Central Latin America	593,338 (98,329, 1,192,445)	1,019,043 (635,886, 1,428,916)	71.75	720.22	1177.94	2.81 (1.68, 3.94)	<0.0001
Central Sub-Saharan Africa	42,349 (512, 273,388)	137,651 (6552, 791,799)	225.04	140.52	188.07	1.10 (0.99, 1.20)	<0.0001
East Asia	14,118 (1390, 46,931)	13,626 (3792, 32,521)	−3.48	3.09	3.88	0.87 (0.69, 1.05)	<0.0001
Eastern Europe	NA	NA	NA	NA	NA	NA	NA
Eastern Sub-Saharan Africa	912,024 (69,402, 2,370,882)	193,572 (3190, 705,951)	−78.78	844.45	85.45	−9.90 (−12.23, −7.58)	<0.0001
High-income Asia Pacific	72,243 (10,673, 188,938)	96,723 (21,391, 223,351)	33.89	141.04	314.90	3.03 (1.78, 4.27)	<0.0001
High-income North America	90 (15, 308)	326 (10, 1673)	260.18	0.11	0.36	6.28 (4.87, 7.69)	<0.0001
North Africa and Middle East	9696 (3224, 30,581)	24,868 (7401, 89,833)	156.49	5.51	10.46	2.31 (1.39, 3.22)	<0.0001
Oceania	12,869 (2844, 34,722)	29,465 (13,159, 57,891)	128.96	386.69	469.31	1.24 (0.92, 1.55)	<0.0001
South Asia	6,390,743 (66,042, 13,639,094)	12,124,954 (669,988, 25,695,836)	89.73	1188.20	1743.60	1.43 (1.36, 1.49)	<0.0001
Southeast Asia	1,359,733 (263,358, 3,808,724)	2,341,381 (1,657,128, 3,697,610)	72.19	616.54	1010.45	2.06 (1.76, 2.37)	<0.0001
Southern Latin America	16,015 (338, 55,579)	26,061 (5816, 61,225)	62.72	82.46	130.71	1.99 (1.51, 2.47)	<0.0001
Southern Sub-Saharan Africa	417 (20, 2754)	585 (31, 3928)	40.40	1.58	1.86	−1.85 (−2.76, −0.94)	0.00024
Tropical Latin America	3,287,610 (197,468, 8,524,869)	4,040,170 (1,268,260, 8,073,272)	22.89	4691.84	6040.29	1.55 (1.03, 2.08)	<0.0001
Western Europe	NA	NA	NA	NA	NA	NA	NA
Western Sub-Saharan Africa	402,548 (248, 1,416,465)	1,362,386 (65,148, 4,637,231)	238.44	386.04	513.78	1.03 (0.94, 1.12)	<0.0001

Abbreviations: UI, uncertainty interval; ASIR, age-standardised incidence rate; EAPC, estimated annual percentage change; CI, confidence interval; SDI, socio-demographic index; GBD, Global Burden of Diseases, Injuries, and Risk Factors Study; NA, not available.

Table 1: **Number of incidence and age-standardised incidence rates per 100,000 population of dengue infection among children and adolescents in 1990 and 2021 and their temporal trends from 1990 to 2021.**

the burden of dengue-induced DALYs was reversed (Table 1, Table 2, Fig. 2C and D).

Dengue in children and adolescents among different SDI regions

For SDI regions, incidence numbers of dengue in children and adolescents increased most remarkably in low-middle SDI regions (75.51%), followed by high-middle (68.04%), low (61.03%), middle (55.39%), and high (7.03%) SDI regions (Table 1). Both the largest number of dengue incidence (10,068,558 cases) and the highest ASIR (1321.16 per 100,000 population) were observed in middle SDI regions in 2021 (Table 1 and Fig. 2E). From 1990 to 2021, the ASIR increased in all SDI regions except high SDI regions (EAPC = −1.51%, 95% CI, −2.24% to −0.79%), with the highest EAPC in high-middle SDI regions (EAPC = 3.24%, 95% CI, 2.75%–3.72%) (Table 1 and Fig. 3A).

Characteristics	Number of DALYs		Percentage change, % 1990–2021	ASDR (per 100,000 population)		EAPC, % (95% CI) 1990–2021	P value
	1990 (95% UI)	2021 (95% UI)		1990	2021		
Global	910458.60 (628036.13, 1243518.75)	1059428.31 (554478.43, 1557409.57)	16.36	40.17	41.50	0.67 (0.40, 0.95)	<0.0001
Sex							
Female	421279.84 (285999.68, 572338.94)	471327.77 (246106.84, 725284.37)	11.88	38.26	37.93	0.57 (0.25, 0.88)	0.00094
Male	489178.76 (290499.22, 724095.80)	588100.54 (301336.76, 844682.62)	20.22	41.94	44.85	0.77 (0.52, 1.02)	<0.0001
Age							
<5 years	532201.04 (908501.71, 313581.29)	534201.16 (783000.94, 280713.02)	0.38	85.85	81.16	0.29 (0.06, 0.53)	0.017
5–9 years	217842.78 (286691.91, 151563.13)	248830.22 (370002.17, 137335.12)	14.22	37.33	36.22	0.62 (0.29, 0.95)	0.0061
10–14 years	81960.55 (138677.74, 40098.49)	138101.14 (242013.44, 56690.26)	68.50	15.30	20.72	1.88 (1.45, 2.31)	<0.0001
15–19 years	78454.23 (125744.84, 39100.97)	138295.79 (232989.55, 59976.45)	76.28	15.10	22.16	1.56 (1.29, 1.83)	<0.0001
Socio-demographic index							
High SDI	1309.53 (271.01, 3217.84)	1268.78 (273.45, 3035.81)	–3.11	0.52	0.54	0.80 (–0.16, 1.77)	0.10
High-middle SDI	66223.17 (42133.30, 102992.91)	56474.76 (33109.21, 80411.45)	–14.72	18.88	20.09	0.50 (0.07, 0.93)	0.025
Middle SDI	479412.45 (309116.44, 698468.86)	579234.91 (336431.04, 826724.81)	20.82	64.17	82.05	1.54 (1.20, 1.88)	<0.0001
Low-middle SDI	321180.49 (220586.40, 428328.88)	362268.88 (155257.25, 591056.11)	12.79	52.37	48.78	0.16 (–0.04, 0.36)	0.11
Low SDI	41351.83 (28703.38, 58524.95)	59231.10 (16421.60, 117621.52)	43.24	14.21	10.08	–0.91 (–1.19, –0.62)	<0.0001
GBD region							
Andean Latin America	813.33 (192.96, 1937.15)	1754.48 (748.51, 3264.75)	115.72	4.28	7.40	2.56 (1.35, 3.77)	0.00015
Australasia	19.71 (1.25, 66.15)	49.58 (12.80, 129.73)	151.56	0.31	0.65	3.74 (2.90, 4.58)	<0.0001
Caribbean	875.96 (179.73, 2340.26)	985.36 (187.14, 2570.05)	12.49	5.82	6.45	1.03 (–0.60, 2.66)	0.21
Central Asia	NA	NA	NA	NA	NA	NA	NA
Central Europe	NA	NA	NA	NA	NA	NA	NA
Central Latin America	8055.18 (2779.01, 16328.72)	18549.46 (10285.44, 29396.58)	130.28	9.74	22.20	3.79 (2.79, 4.79)	<0.0001
Central Sub-Saharan Africa	436.08 (7.97, 2719.26)	1500.72 (69.85, 8695.77)	244.14	1.44	2.05	1.18 (1.09, 1.27)	<0.0001
East Asia	3271.88 (1960.67, 4645.40)	305.89 (115.64, 552.46)	–90.65	0.76	0.09	–6.74 (–7.16, –6.32)	<0.0001
Eastern Europe	NA	NA	NA	NA	NA	NA	NA
Eastern Sub-Saharan Africa	9625.10 (939.31, 24891.92)	3882.29 (1238.57, 9711.32)	–59.66	8.86	1.70	–7.13 (–9.24, –5.02)	<0.0001
High-income Asia Pacific	744.70 (98.20, 2030.96)	973.52 (174.66, 2442.38)	30.73	1.47	3.17	2.98 (1.74, 4.23)	<0.0001
High-income North America	4.47 (2.81, 6.92)	23.34 (10.64, 45.91)	422.20	0.01	0.03	7.75 (6.80, 8.69)	<0.0001
North Africa and Middle East	677.07 (346.49, 1174.38)	388.65 (125.70, 1145.52)	–42.60	0.37	0.16	–0.71 (–3.35, 1.93)	0.59
Oceania	654.96 (490.07, 935.28)	346.36 (154.52, 729.18)	–47.12	18.97	5.51	–0.34 (–1.45, 0.76)	0.53
South Asia	223743.04 (123118.19, 350728.03)	328890.16 (89556.11, 620486.94)	46.99	40.55	49.38	1.18 (0.90, 1.45)	<0.0001
Southeast Asia	623743.00 (357516.79, 1055418.06)	643160.29 (415469.06, 893790.85)	3.11	287.66	298.20	0.67 (0.43, 0.90)	<0.0001
Southern Latin America	167.72 (5.81, 632.21)	267.62 (49.13, 722.08)	59.57	0.86	1.34	1.89 (1.42, 2.37)	<0.0001
Southern Sub-Saharan Africa	4.86 (0.56, 30.22)	6.57 (0.58, 42.85)	35.15	0.02	0.02	–1.75 (–2.63, –0.86)	0.00037
Tropical Latin America	33575.16 (2886.21, 86308.83)	44809.16 (15063.28, 96643.35)	33.46	48.01	67.12	2.11 (1.55, 2.67)	<0.0001
Western Europe	0.29 (0.17, 0.42)	0.11 (0.04, 0.21)	–62.95	0.00032	0.00013	–0.67 (–1.83, 0.49)	0.25
Western Sub-Saharan Africa	4046.09 (49.34, 15303.30)	13534.75 (633.13, 47068.89)	234.51	3.87	5.10	1.06 (0.96, 1.17)	<0.0001

Abbreviations: DALYs, disability-adjusted life-years; UI, uncertainty interval; ASDR, age-standardised DALYs rate; EAPC, estimated annual percentage change; CI, confidence interval; SDI, socio-demographic index; GBD, Global Burden of Diseases, Injuries, and Risk Factors Study; NA, not available.

Table 2: **Number of DALYs and age-standardised DALYs rates per 100,000 population of dengue infection among children and adolescents in 1990 and 2021 and their temporal trends from 1990 to 2021.**

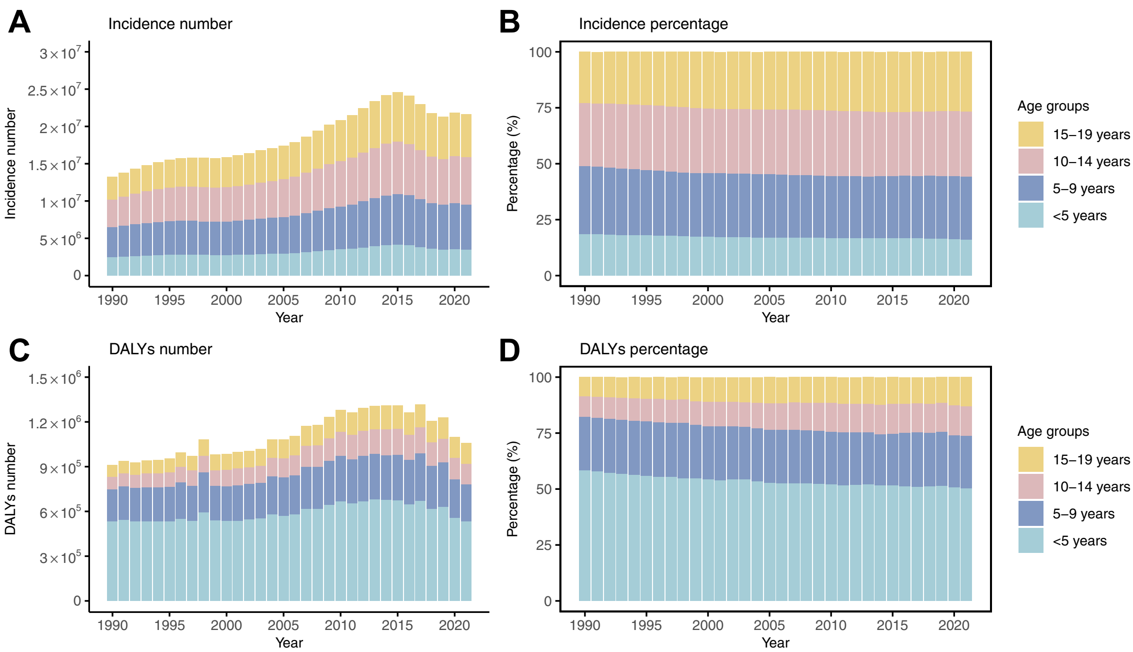

***Fig. 1:* Number and percentage of incidence and DALYs of dengue among children and adolescents grouped by age groups from 1990 to 2021. Number (A) and percentage (B) of incidence cases. Number (C) and percentage (D) of DALYs**. DALYs, disability-adjusted life-years.

From 1990 to 2021, dengue-associated DALYs number in children and adolescents increased in low (43.24%), middle (20.82%) and low-middle (12.79%) SDI regions, but decreased in high-middle (−14.72%) and high (−3.11%) SDI regions (Table 2). As same as incidence, both the largest number of dengue-associated DALYs (579234.91) and the highest ASDR (82.05 per 100,000 population) were observed in middle SDI regions in 2021 (Table 2 and Fig. 2F). From 1990 to 2021, the ASDR increased in middle (EAPC = 1.54%, 95% CI, 1.20%–1.88%) and high-middle (EAPC = 0.50%, 95% CI, 0.07%–0.93%) SDI regions, decreased in low (EAPC = −0.91%, 95% CI, −1.19% to −0.62%) SDI regions (Table 2 and Fig. 3B).

Dengue in children and adolescents among different GBD regions

According to GBD 2021, dengue incident cases were recorded in 17 of the 21 GBD regions worldwide, and dengue-associated DALYs were recorded in 18 GBD regions.

The incidence number of dengue was highest in South Asia, with 12,124,954 in 2021 (Table 1). From 1990 to 2021, the greatest growth in the number of dengue incidence was in High-income North America by 260.18%, followed by Western Sub-Saharan Africa (238.44%) and Central Sub-Saharan Africa (225.04%) (Table 1). Among all GBD regions, Tropical Latin America consistently had the highest burden of dengue incidence, with an ASIR of 6040.29 per 100,000 population in 2021, followed by South Asia (ASIR = 1743.60 per 100,000 population) and Central Latin America (ASIR = 1177.94 per 100,000 population) (Table 1 and Fig. 4A). From 1990 to 2021, of the 17 GBD regions with recorded dengue incidence, 14 showed an increasing trend in ASIR, the highest increasing trend was in High-income North America (EAPC = 6.28%, 95% CI, 4.87%–7.69%), and only two regions showed a decreasing trend in ASIR (Eastern Sub-Saharan Africa [EAPC = −9.90%, 95% CI, −12.23% to −7.58%] and Southern Sub-Saharan Africa [EAPC = −1.85%, 95% CI, −2.76% to −0.94%]) (Table 1 and Fig. 3A).

Among all GBD regions, the burden of DALYs due to dengue in Southeast Asia is consistently the largest, with the highest DALYs number (643,160.29 in 2021) and ASDR (298.20 per 100,000 population in 2021) (Table 2, Fig. 3B, and Fig. 4B). From 1990 to 2021, the number of dengue associated DALYs in High-income North America increased the most by 422.20%, followed by Central Sub-Saharan Africa (244.14%) and Western Sub-Saharan Africa (234.51%) (Table 2). Of the 18 GBD regions recording dengue-induced DALYs, 11 GBD regions showed an increasing trend in ASDR, with the largest increasing trend in High-income North America (EAPC = 7.75%, 95% CI, 6.80%–8.69%), and three GBD regions showed a decreasing trend in ASDR, with Eastern Sub-Saharan Africa showing the largest decrease (EAPC = −7.13%, 95% CI, −9.24% to −5.02%), followed by East Asia (EAPC = −6.74%, 95% CI, −7.16% to −6.32%) (Table 2 and Fig. 3B).

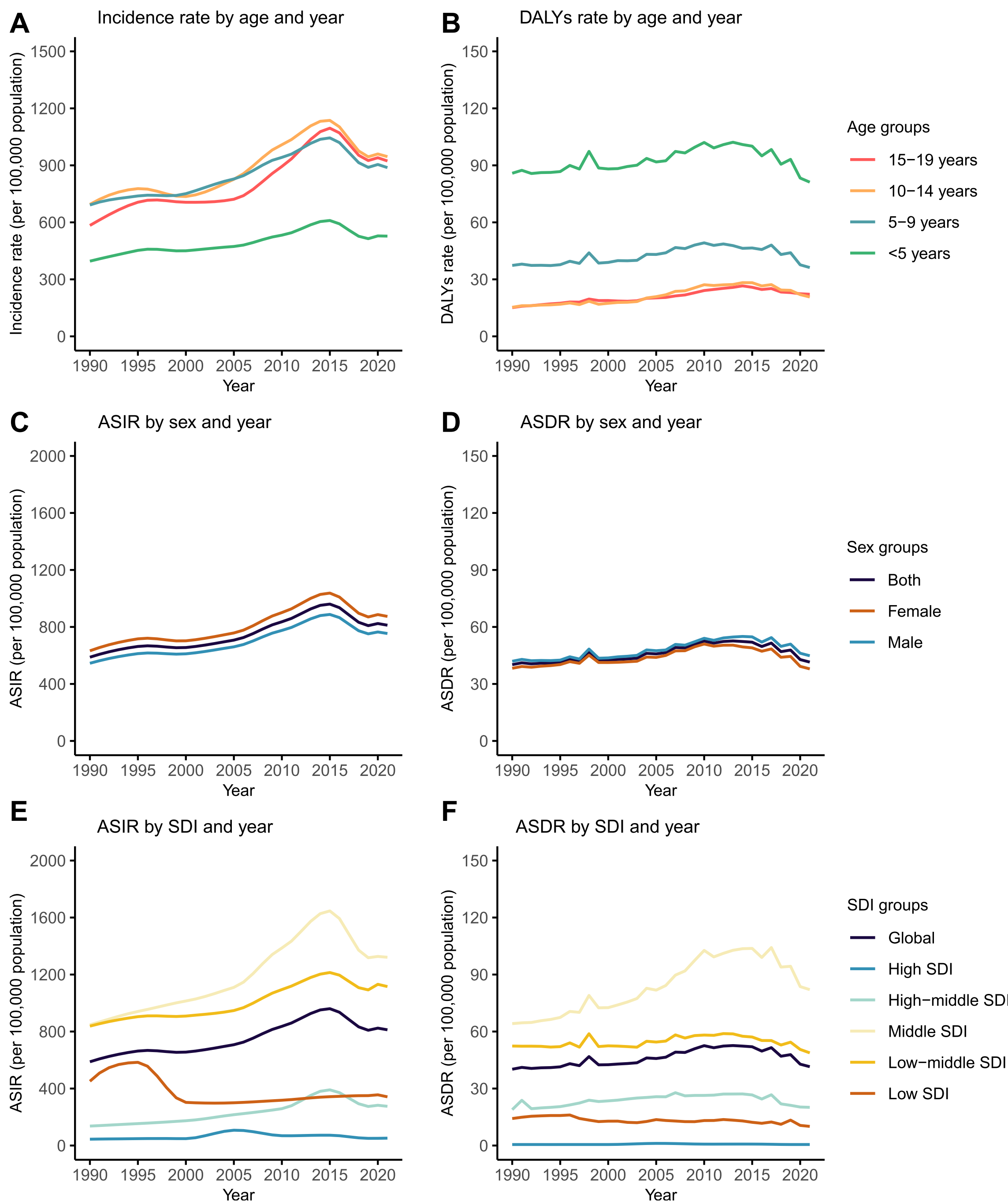

***Fig. 2:* Age-standardised incidence rate and age-standardised DALYs rate per 100,000 population of dengue among children and adolescents grouped by age, sex, and SDI quintiles from 1990 to 2021. Incidence rate (A) and DALYs rate (B) by age group and year. ASIR (C) and ASDR (D) by sex group and year. ASIR (E) and ASDR (F) by SDI group and year**. ASIR, age-standardised incidence rate; ASDR, age-standardised DALYs rate; SDI, socio-demographic index; DALYs, disability-adjusted life-years.

Fig. 4 presents the GBD regional-level observed ASIRs and ASDRs among children and adolescents from 1990 to 2021 and their association with the SDI. ASIR and ASDR peak at SDI values between 0.55 and 0.60, then decline with increasing SDI values, and are lowest when the SDI is between 0.75 and 0.85. Based on the SDI from 1990 to 2021, Tropical Latin America has a much higher ASIR than expected (Fig. 4A), while

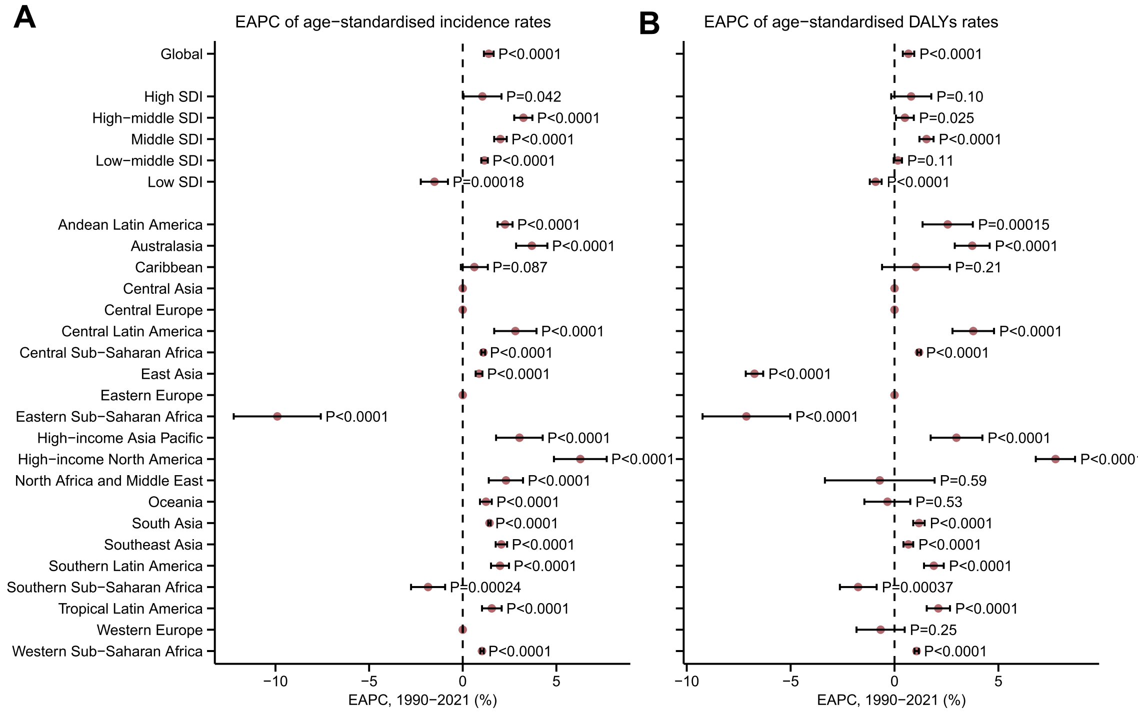

Fig. 3: **Estimated annual percentage changes of age-standardised incidence rates (A) and age-standardised DALYs rates (B) for dengue infection among children and adolescents from 1990 to 2021, by SDI region and GBD region. The circle represents the point estimate of EAPC of the age-standardised incidence rate or age-standardised DALYs rate, and the error bar represents the corresponding 95% confidence intervals**. EAPC, estimated annual percentage change; SDI, socio-demographic index; DALYs, disability-adjusted life-years.

Southeast Asia has a much higher ASDR than expected (Fig. 4B) during every year of the study period.

Dengue in children and adolescents among different countries and territories

According to GBD 2021, a total of 126 countries or territories worldwide have recorded dengue infections in children and adolescents, causing dengue-associated DALYs in 134 countries or territories (Fig. 5).

In 2021, the number of dengue incidence was highest in India, which accounted for almost half of the total number of dengue incidence in children and adolescents globally (10,468,633/21,641,016 = 48.37%), followed by Brazil (3,968,258) and Pakistan (1,258,413).

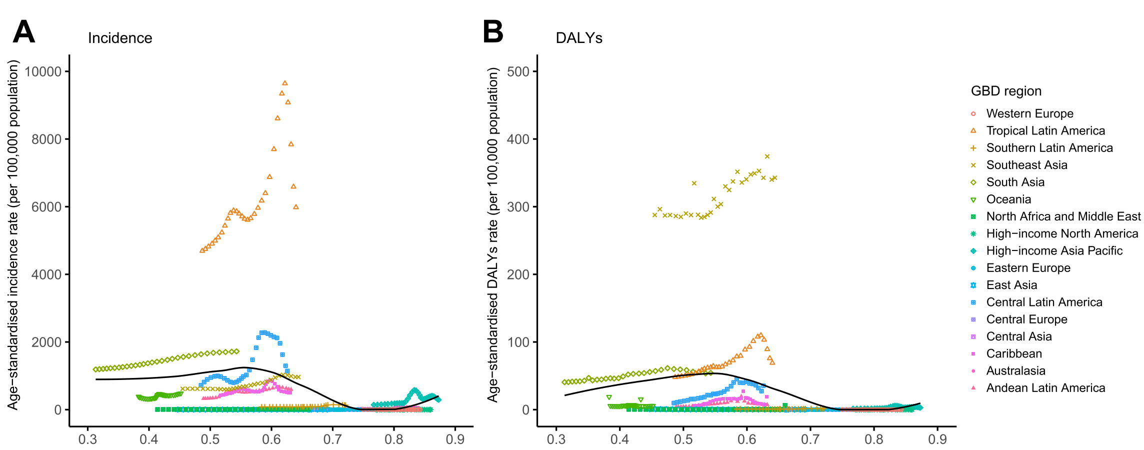

Fig. 4: **Age-standardised incidence rates (A) and age-standardised DALYs rates (B) per 100,000 population of dengue among children and adolescents for 17 GBD regions by SDI, 1990–2021**. SDI, socio-demographic index; DALYs, disability-adjusted life-years; GBD, Global Burden of Diseases, Injuries, and Risk Factors Study.

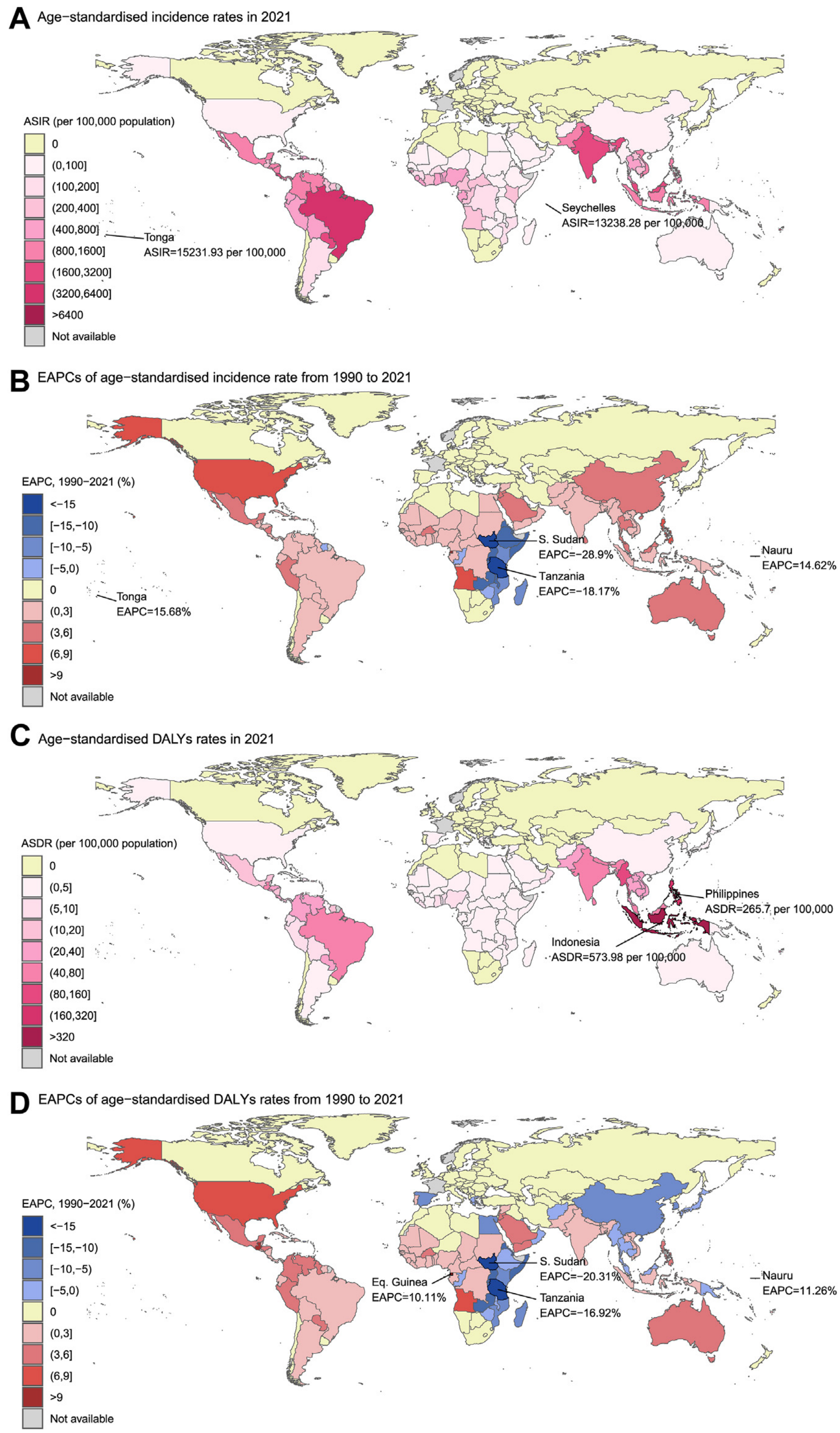

Fig. 5: **Global trends in the incidence and DALYs of dengue infection among children and adolescents in 204 countries and territories, from 1990 to 2021. Age-standardised incidence rates in 2021 (A), EAPCs of age-standardised incidence rates from 1990 to 2021 (B), age-standardised DALYs rates in 2021 (C), and EAPCs of age-standardised DALYs rates from 1990 to 2021 (D)**. ASIR, age-standardised incidence rate; EAPC, estimated annual percentage change; ASDR, age-standardised DALYs rate; DALYs, disability-adjusted life-years.

These three countries accounted for 72.53% of the total number of dengue incidence among children and adolescents worldwide (Table S4). The number of dengue incidence increased in most of the countries or territories (98 out of 126), while the most significant increase was in Equatorial Guinea with an increase of 3840.49% from 1990 to 2021, followed by Nauru (2830.55%) and Angola (2043.98%) (Table S4). In 2021, the highest ASIR of dengue among children and adolescents was in Tonga (15,231.93 per 100,000), followed by Seychelles (13,238.28 per 100,000), Comoros (12,469.83 per 100,000), and Marshall Islands (10,940.93 per 100,000) (Table S4 and Fig. 5A). Between 1990 and 2021, a total of 80 countries or territories show an increasing trend in ASIR, with Tonga (EAPC = 15.68%, 95% CI, 11.81%–19.56%) showing the greatest increase, followed by Nauru (EAPC = 14.62%, 95% CI, 9.57%–19.68%) and Equatorial Guinea (EAPC = 10.38%, 95% CI, 8.72%–12.04%) (Table S4 and Fig. 5B). Only 20 countries or territories showed a decreasing trend in ASIR in children and adolescents, mainly in eastern Africa, such as South Sudan, United Republic of Tanzania, Rwanda, etc (Table S4 and Fig. 5B).

In 2021, the number of dengue-associated DALYs was highest in Indonesia (479,293.90), followed by India (281,443.34) and Philippines (115,330.58), which cumulatively accounted for 83.22% of the global burden of dengue-associated DALYs in children and adolescents (Table S5). The country with the highest burden of DALYs due to dengue in 2021 was Indonesia, with an ASDR of 573.98 per 100,000 population in 2021, followed by Philippines with an ASDR of 265.70 per 100,000 population. The remaining countries or territories had ASDRs of less than 200 per 100,000 population (Table S5 and Fig. 5C). From 1990 to 2021, more than half of the countries or territories with recorded dengue-induced DALYs showed an increasing trend in ASDR (69 of 134), with the greatest increase in Nauru (EAPC = 11.26%, 95% CI, 7.86%–14.66%), followed by Equatorial Guinea (EAPC = 10.11%, 95% CI, 8.43%–11.80%) and Guatemala (EAPC = 10.08%, 95% CI, 8.68%–11.49%) (Table S5 and Fig. 5D). A total of 35 countries or territories showed a decreasing trend in ASDR, mainly in eastern sub-Saharan Africa, eastern and south-eastern Asia, such as South Sudan, United Republic of Tanzania, Rwanda, China, etc (Fig. 5D). ASIR and ASDR both decreased the most in South Sudan.

Discussion

To our knowledge, this is the first study reporting the global disease burden, temporal trends, and regional differences of dengue for the population of children and adolescents that have often been neglected in previous dengue-related studies. Our study found that the disease burden caused by dengue was consistently higher in children and adolescents globally than in the entire population. From 1990 to 2021, the number and rate of dengue incidence and DALYs among children and adolescents showed increasing trends, but the increase was more pronounced in incidence than in DALYs. In 2021, it is estimated that 21.64 million children and adolescents were infected with dengue globally, increasing by 63.43% from 1990, with an ASIR of 812.16 per 100,000 population and an EAPC of 1.39%. The incidence and resulting DALYs burden of dengue in children and adolescents were higher in middle SDI regions, as well as Central Latin America, South Asia, Southeast Asia, and Tropical Latin America. Our results suggest that the global disease burden of dengue in children and adolescents should be emphasised, and clarifying the disease burden and dynamics of dengue in children and adolescents could provide an important reference value for global public health officials and policymakers to develop vaccine programmes and implement interventions to mitigate the growing global dengue burden.

Globally, the ASIR of dengue infections in children and adolescents has increased gradually since 1990, reaching a peak in 2015, followed by a slow decreasing trend, but with a slight increase in 2020 and 2021, and an overall increasing trend. This trend was consistent with the trend observed in the entire population by GBD 2021.[23] The increase in ASIR of dengue in 2020 and 2021 might be attributed to the use of new data sources and updated estimation methods in GBD 2021, which also led to inconsistencies in the estimated timing of the peak in different studies.[23,24] Du et al. analysed the dengue burden for the entire population from 1990 to 2019 based on GBD 2019 and found that there was an increasing trend in the global ASIR of dengue infection from 1990 to 2011, but a decreasing trend from 2011 to 2019.[16] WHO has proposed a global strategy for dengue prevention and control 2012–2020 to achieve a dengue mortality rate of <0.1% and a reduction in incidence by 50% in 2020, but the strategy did not set specific targets for children and adolescents.[20] In most countries, the major burden of dengue incidence and mortality is in children.[34–37] We found that the ASIR and ASDR of dengue were higher in children and adolescents globally than in the entire population, which further indicates that the burden of dengue in children and adolescents is substantial and requires more attention.

Among children and adolescents of different ages, children under 5 years of age have the lowest prevalence but do result in the highest DALYs. In other studies not limited to children and adolescents, children under 5 years of age also tended to have the heaviest DALYs burden.[21] Further analyses found that among children under five years of age, the lower the age, the more severe the DALYs burden due to dengue, even reaching 333.46 per 100,000 population in infants <28 days old, although their incidence was the lowest. Younger infants might have a protective level of anti-DENV antibodies from the maternal body and therefore have a lower risk of dengue infection compared to older infants.[38] However, primary dengue infection in infants may have unique clinical features and develop into severe forms more quickly and be more likely to lead to dengue hemorrhagic fever (DHF) and life-threatening illnesses than in older children and adults.[39,40] Malaria, a widely publicised tropical infectious disease, also affects children under 5 years of age most severely, with the highest incidence rate and the highest DALYs rate in all age groups.[41,42] In high transmission areas, the main burden of malaria, including nearly all malaria-related deaths, is borne by young children.[43] Although there is no study reporting gender-related transmission of dengue for the time being, we still observed that among children and adolescents globally, the ASIR of dengue is higher in females than males, while the ASDR is higher in males than females, which is consistent with the results observed in GBD 2017.[21]

Our study showed that children and adolescents in Tropical Latin America experienced the most severe threat of dengue infection, with the highest ASIR. The dengue outbreak in Brazil in 2007 demonstrated a change in the age group characteristics of dengue, with an increasing number of children suffering from severe dengue.[44] In the past decades, Latin America has experienced the eradication of *Ae. aegypti*, re-infection and the re-emergence of dengue, until now it is a serious and escalating public health problem in the Latin American region.[45] The occurrence of this phenomenon is mainly caused by the lack of political willingness, the dramatic growth of the urban population, migratory flows and insufficient financial resources.[45] In some less developed countries in Latin America, with less infrastructure to cope with expanding populations, outbreaks may be more likely to become common.[46,47] Besides, climate change, poor sanitation and extreme poverty have led to an expansion of breeding sites for *Ae. aegypti*, exacerbating the increase in dengue incidence.[46,48] Furthermore, the DALYs burden of dengue infection on children and adolescents was highest in Southeast Asia, especially in Indonesia and Philippines, where the ASDR of dengue was significantly higher than in other countries. Southeast Asia is one of the most threatened regions by dengue.[21,49] Colón et al. predicted that in Southeast Asia the incidence of dengue will peak this century and then decline to lower levels, with the largest decreases in northern Thailand and Cambodia, and the largest increases in equatorial regions.[49] From 1990 to 2021, the ASDR and ASIR of dengue among children and adolescents showed decreasing trends in some countries or territories, mainly in Southern Sub-Saharan Africa and Eastern Sub-Saharan Africa, with the most significant decreases in South Sudan and the United Republic of Tanzania. Also, there is a pronounced decline in dengue-associated ASDR among children and adolescents in the East Asia regions.

We found that the distribution pattern of dengue burden in children and adolescents across SDI regions differed from that of the entire population. In our study, the dengue burden in children and adolescents was highest in middle SDI regions, followed by low-middle SDI regions, but was lowest in high SDI regions. Whereas in previous studies of entire population, the dengue burden tended to be highest in low-middle SDI regions.[21,50] Furthermore, in the study of GBD 2017, the dengue burden in low SDI regions was relatively high,[21] whereas in our study, the dengue burden of children and adolescents in low SDI regions was lower than the global level, especially the burden of dengue-induced DALYs. This discrepancy might be attributed, on the one hand, to the different allocation of health resources to different populations in different regions and, on the other hand, to the fact that GBD 2021 used some new data sources and updated methodologies.[24–26] Dengue is primarily an urban and suburban disease, but also occurs in rural areas.[51] Urbanization has led to rapid population growth and has dramatically increased the density, larval development rate and adult survival time of *Ae. aegypti*, in addition to the fact that *Ae. aegypti* is highly adapted to urban life, thus increasing the feasibility of dengue transmission.[52,53]

While dengue has historically been prevalent in tropical and subtropical regions, recent evidence points to its expansion beyond these areas. New detections of local dengue transmission in areas without previous transmission and increased cases in areas with sporadic transmission have been documented in southern Europe and the United States,[54,55] as well as unprecedented outbreaks at high altitudes as seen in Nepal.[56,57] Travelers with the virus to non-endemic areas are the main source of triggering local transmission.[4] Besides, international travelers are increasingly at risk of dengue, sentinel travelers have uncovered dengue outbreaks in regions like Sharm El-Sheikh, Egypt.[58] Dengue is now the leading cause of fever among returning travelers, surpassing malaria among travelers to South-East Asia.[4] This expanding geographic footprint of dengue, coupled with the disease burden emphasised in children and adolescents, highlights the urgent need for enhanced global control measures and vaccination efforts, particularly in areas that may not have the infrastructure or historical experience with managing dengue outbreaks.

There is no specific treatment for dengue infection now. Vaccination is seen as an important part of a comprehensive strategy to control the disease burden of dengue, which also includes vector control, appropriate case management, community education and community participation.[8] Currently, two dengue vaccines have been licensed, CYD-TDV (Dengvaxia®) and TAK-003 (Qdenga®).[59] CYD-TDV is a recombinant tetravalent live dengue vaccine that can be used in individuals aged 9–45 years or 9–60 years (depending on country-specific regulatory approvals) residing in dengue-endemic countries or regions.[59] However, it requires individuals who have been previously infected with the DENV to be able to receive the vaccine, as the vaccine might cause severe disease in people who have not been previously infected with dengue.[59] The limitations of CYD-TDV are increased testing costs and limited use. TAK-003 is a live-attenuated vaccine using the DENV2 strain as the genomic backbone to protect against any serotype of the virus.[60] Previous studies showed the advantage of TAK-003 as a new tool to mitigate dengue in countries with a high disease burden, with a cumulative vaccine efficacy over 5 years against virologically confirmed dengue of 61.2% and against dengue-related hospitalizations of 84.1%.[61] WHO recommends the use of TAK-003 (available vaccine only) for children aged 6–16 years in settings with high dengue transmission intensity.[60] This makes TAK-003 especially valuable in settings like the ones highlighted in our study, where the burden of dengue remains substantial. However, dengue incidence in children and adolescents tends to be higher in low- and middle-income countries, as well as in some resource-limited countries, where health budgets are often constrained between control and treatment.[62] Furthermore, the effectiveness of existing vaccines is unsatisfactory for younger children, as well as for older adults.[60] Therefore, the development of highly effective, low-cost dengue vaccines for a wide range of populations remains a major challenge for current and future dengue prevention and control strategies.[63,64]

However, there are also some limitations of this study. First, our study relied on the availability and quality of primary data in GBD 2021, and like all GBD studies, limitations of the GBD methodology might cause bias in our estimates.[16,21,24] Data collected from different regions and countries might differ in terms of quality, comparability, accuracy and the extent of missing data.[65] For one thing, in many countries affected by dengue epidemics, there are limitations in surveillance systems and reporting mechanisms, and the accuracy and comprehensiveness of the data have yet to be improved. For another, previous studies suggested that there were discrepancies between GBD estimates and reported dengue cases,[66,67] underscoring the imperative for comprehensive analysis in areas with pronounced disparities. Second, we could not obtain information related to dengue serology, which is a key factor in the global transmission and epidemiology of dengue and an extremely important reference for the development of vaccine policies.[68–70] Third, referring to the estimation methods usually used in previous studies,[16,30,32] we chose linear regression to evaluate the long-term and average trends in dengue burden among children and adolescents from 1990 to 2021. However, no matter what model is chosen, there may be a risk of model misspecification. The assumption that the relationship between the natural logarithm of ASR and the calendar year is linear may not fully capture the underlying complexities in dengue burden trends, such as the potential inflection points or sudden trend shifts that could be identified using other methods such as joinpoint regression. Therefore, future analyses need to explore more flexible modeling approaches to provide a more nuanced understanding of temporal trends in dengue burden. Besides, consistent with previous studies,[16,30,32] our estimation for trends in disease burden relies on the EAPC and its 95% CIs. However, interpretation should be cautious to avoid over-reliance on significance testing, as even if the 95% CIs for some changes cross zero or the P value is close to 0.05 (or other cutoff values),[71,72] the actual magnitude of change might still be important in the public health or clinical practice sense. Finally, although our study was subdivided by age, these categorizations relied on GBD-defined age groups, and therefore might still be insufficient to capture the complex differences in dengue among children and adolescents of different ages and preclude estimation of burdens in more refined age categories that might inform vaccine policy.[21,69] Therefore, future research should focus on improving global dengue surveillance capacity, standardizing reporting mechanisms, and refining age-group analyses to more accurately quantify the burden of dengue in children and adolescents and to inform the development of more effective vaccination and prevention and control policies.

In conclusion, the disease burden of dengue in children and adolescents globally is enormous and has been increasing from 1990 to 2021, with a particularly great DALYs burden among children under 5 years of age. The incidence and DALYs burden of dengue in children and adolescents was higher in middle SDI regions, as well as Central Latin America, South Asia, Southeast Asia and Tropical Latin America. From 1990 to 2021, the number and rate of incidence and DALYs of dengue in children and adolescents showed increasing trends, especially in High-income North America. The distribution patterns of dengue incidence and its resulting DALYs distribution vary across different countries and territories among children and adolescents. Importantly, this is the first study to focus exclusively on the population of children and adolescents, offering new insights into the disease burden of dengue in this vulnerable age group, which has significant implications for policymakers and public health officials, as it underscores the need for age- and region-specific strategies to mitigate the growing global burden of dengue.

Contributors

JL and BN conceptualised and supervised the study. JD did data acquisition, data cleaning, formal analysis, and visualization. JD drafted the original manuscript. JD, HZ, YW, QL, MD, WY, CQ, SZ, WC, LZ, ML, BN, and JL did critical review, interpreted the findings, and revised the manuscript. JD, BN, and JL have access to and verify the underlying study data. All authors reviewed and approved the submitted version of this manuscript. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

The datasets generated during and/or analysed during the current study are available in the GBD repository [http://ghdx.healthdata.org/gbd-results-tool].

Editor note

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Declaration of interests

All authors declare no conflict of interest with the content of this article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102943.

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