

## COVID-19 prevention measures reduce dengue spread in Yunnan Province, China, but do not reduce established outbreak

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### ABSTRACT

The COVID-19 pandemic and measures against it provided a unique opportunity to understand the transmission of other infectious diseases and to evaluate the efficacy of COVID-19 prevention measures on them. Here we show a dengue epidemic in Yunnan, China, during the pandemic of COVID-19 was dramatically reduced compared to non-pandemic years and, importantly, spread was confined to only one city, Ruili. Three key features characterized this dengue outbreak: (i) the urban-to-suburban spread was efficiently blocked; (ii) the scale of epidemic in urban region was less affected; (iii) co-circulation of multiple strains was attenuated. These results suggested that countermeasures taken during COVID-19 pandemic are efficient to prevent dengue transmission between cities and from urban to suburban, as well to reduce the co-circulation of multiple serotypes or genotypes. Nevertheless, as revealed by the spatial analysis, once the dengue outbreak was established, its distribution was very stable and resistant to measures against COVID-19, implying the possibility to develop a precise prediction method.

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### Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in severe impacts on human health and the global economy [1,2]. To control the spread of COVID-19, various measures including wearing masks, body temperature checks, physical distancing, home quarantine and city-wide even national-wide lockdowns were implemented globally [3–10]. In addition to the positive effects to reduce COVID-19 transmission, these unprecedented measures also had potential influence on the circulation of other infectious diseases, including non-respiratory infectious diseases [11–13].

Dengue viruses (DENV) are mosquito-borne flaviviruses [14]. Primary infection with any of the four DENV serotypes usually causes dengue fever, however, secondary infection with different serotypes may result in much more severe and dangerous dengue hemorrhagic fever or dengue shock syndrome [15]. The four dengue viruses cause sustaining endemic in tropical and subtropical areas, with more than 100 countries affected and more than half worldwide population at risk [16,17]. Furthermore, regions where DENVs co-

circulate are increasing over time [18]. After the past several decades of vaccine development, of the dengue vaccines in development, live-attenuated vaccines (LAV) are the most advanced [19]. Among, CYD-TDV, a tetravalent live attenuated with a yellow fever 17D backbone, became the first licensed dengue vaccine in 2015, also known as “Dengvaxia”. However, its potential of increasing risks in seronegative subjects led to considerable controversy, making CYD-TDV limited to the seropositive persons as a public health recommendation by World Health Organization [20]. Though other two leading LAV candidates, TAK-003 (DENVax) and TV003/TV005 (U.S. National Institutes of Health [NIH]), are in phase 3 trials, no dengue vaccine is in widespread use to date [21]. Therefore, to prevent and control dengue epidemic, dengue surveillance is crucial to the strategy. Effective surveillance provides guidance for risk assessment and epidemic response [22].

Since the pandemic of COVID-19, the effects of COVID-19 countermeasures on DENV transmission attracted much attention [23,24]. However, the intensity of dengue epidemics reported during the pandemic in 2020 showed considerable variation with

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some countries experiencing historic low levels of transmission while others are seeing record outbreaks [25]. An evaluation in depth is therefore required to address the question of the impact of COVID-19 prevention measures on DENV transmission.

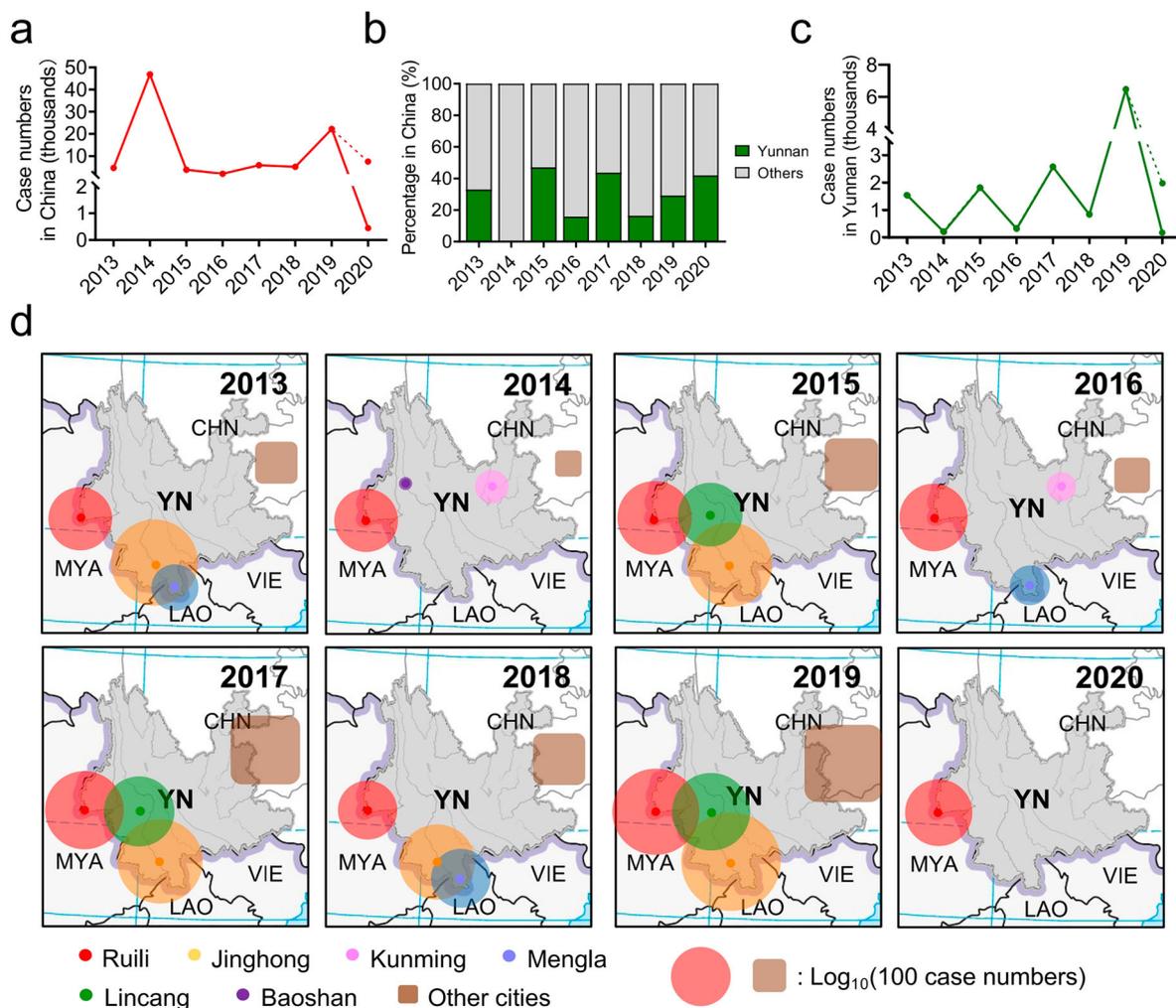
In the past two decades, China identified sharp increases in dengue cases, primarily in the southern provinces of Yunnan and Guangdong [26–28]. Yunnan province is located in southwestern China and has a suitable climate for the maintenance of DENV vectors. It shares a 4060-km border with Vietnam, Laos, and Myanmar where dengue is endemic. It is therefore one of the worst-hit dengue areas in China, with all four serotypes having been detected [29]. In addition to dengue, Yunnan province is also the worst-hit COVID-19 area in China, with three outbreaks of COVID-19 traced to imported cases in once city, Ruili.

Here, we report on the impacts of COVID-19 control measures on dengue epidemics and distribution in

Yunnan province of China. Specifically, we use spatial analyses to describe the 2020 dengue outbreak in Ruili city in Yunnan Province, and we report on seroprevalence studies from 81 patients to understand how COVID-19 restrictions influenced the inter- and intracity dengue transmission. We provide suggestions on how COVID-19 control might be adapted for dengue control in the future.

## Results

In 2020, China recorded only 778 cases of dengue, 95% lower than the average annual number from 2013 to 2019 (11,356 per year) (Figure 1a). Despite this dramatic decrease in the number of cases, proportionally, the months in which cases occurred did not change (S Figure 1). Other factors critical for DENV circulation, such as the temperature, precipitation did not exhibit changes that would explain the observed changes in cases (S Figure 2A, B). Thus the dramatic reduction



**Figure 1.** The 2020 dengue epidemic in Yunnan, China, was reduced and confined to Ruili. (A) Annual case numbers in China since 2013. A predicted case number in 2020 by ARIMA model is shown as the dotted line. (B) The proportion of dengue cases in Yunnan to total numbers in China. (C) Annual case numbers in Yunnan since 2013. A predicted case number in 2020 by ARIMA model is shown as the dotted line. (D) The geographical distribution of dengue cases in Yunnan since 2013. Only top three affected cities were shown on the map, and the area of colour circles represent the logarithm of annual case numbers in the cities. The cases in the other cities were displayed together as brown square.

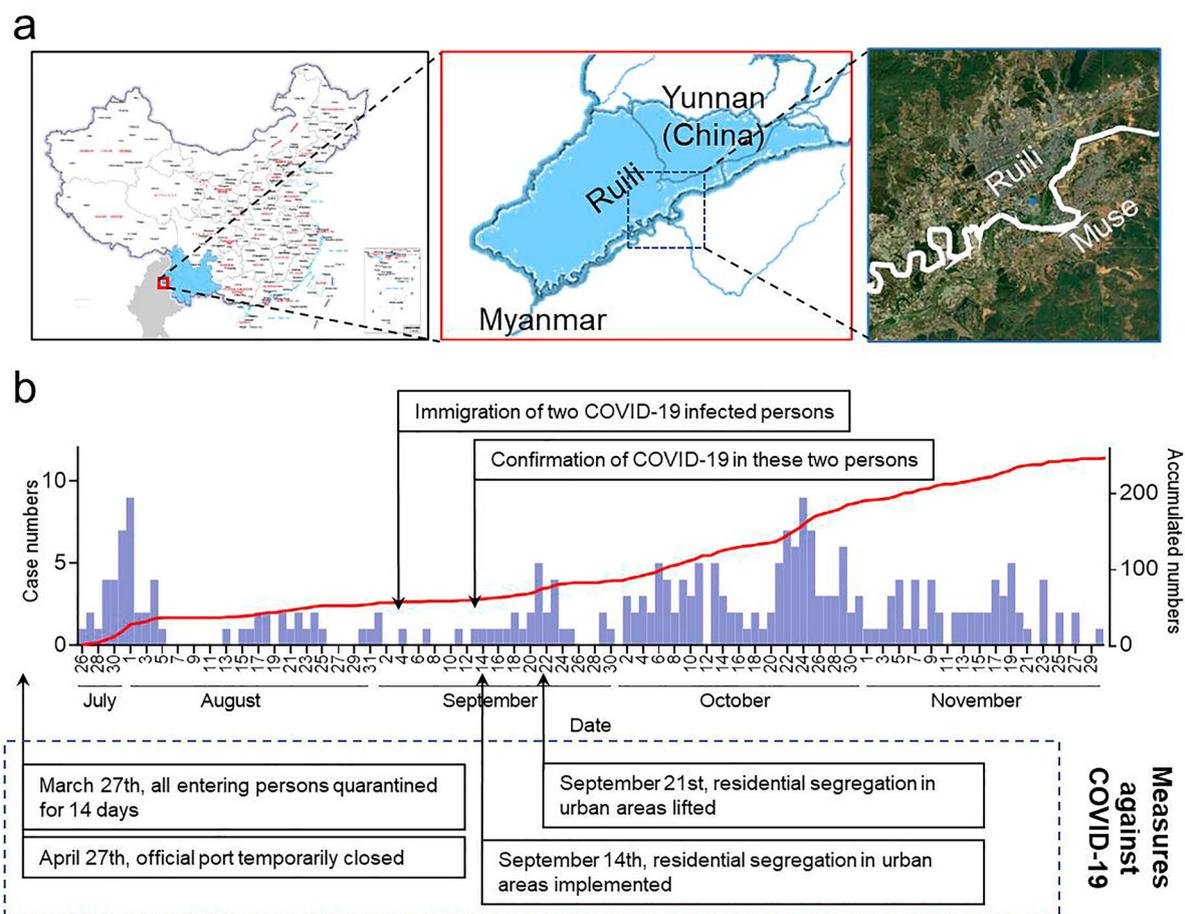
in dengue cases this year can most likely be attributed to the COVID-19 pandemic and the resultant prevention and containment measures.

The dengue cases in Yunnan province usually accounted for 20–40% of the total cases reported in mainland China (Figure 1b). In 2020, Yunnan province reported 249 dengue cases, about one-third of the total cases in China. Because mosquito control efforts are typically stepped up after each dengue outbreak, the annual number of dengue cases fluctuates in Yunnan: with trough years regularly followed by peaks with both gradually increasing since 2008, when locally acquired dengue was first reported (Figure 1c). Based on this pattern, 2020 should have been a trough year, however, dengue cases this year were lower than any previous trough year, and only accounted for 10% of number predicted by autoregressive integrated moving average (ARIMA) model (Figure 1c). Dengue cases in Yunnan province were unprecedentedly reduced, as they were across China.

Besides this observed reduction in the magnitude of the dengue cases, the geographic distribution was also remarkably confined. Dengue epidemics in Yunnan, regardless of the scale, usually involved more than one city, commonly including Jinghong, Ruili,

Baoshan, Mengla, Lincang, and the provincial capital, Kunming (Figure 1d). The outbreak in 2020, however, was restricted to Ruili only with no local cases reported in other cities where dengue is typically reported annually. Interestingly, the number of dengue cases in Ruili was similar in magnitude to prior years (Figure 1d, red circle). Factors that have shown to be important for dengue transmission such as temperature, rainfall and vector index showed no significant difference in Ruili in the past 2 years (S Figure 3A-C). Furthermore, compared with previous years, the dengue epidemic in Ruili this year showed no significant change in age composition or gender ratio (S Figure 4). Taken together, measures to prevent the spread of COVID-19 seem to have also blocked dengue transmission in Yunnan cities except Ruili, in which even the magnitude was similar as before, suggesting that effects of these measures on dengue transmission in Ruili were different from other cities.

Ruili is surrounded by Myanmar on three sides and its urban area is highly integrated with Muse, the neighbouring Myanmar city (Figure 2a). In some parts, the cities are separated only by a narrow river (S Figure 5). The Ruili and Muse ports comprise the busiest gateway between Yunnan and Myanmar,



**Figure 2.** The geographical feature of Ruili facilitated the epidemics of dengue and COVID-19. (A) The study area. (B) The daily case number (columns in purple) and the accumulated numbers (line in red) in 2020 dengue epidemic in Ruili. The COVID-19 cases and measures taken against it were shown in boxes.

through which more than 8 million people passed in 2019. Since 31st March 2020, the ports were closed as a part of the COVID-19 pandemic restrictions. Travel out of Ruili to other cities in China was not restricted, though tourists had to undergo body temperature checks and show their health QR code to document their chance of exposure at all transportation stations. Domestic tourists to Ruili decreased by 60% but still reached 2.5 million (S Figure 6), with most from other cities in Yunnan Province. Ruili did not have any COVID-19 cases until 13 September, when two individuals entered Ruili illegally (i.e. did not pass the border health screens) from Muse on 3 September were confirmed to be COVID-19 positive on 13 September. In response, Ruili city officials instituted a 1-week lockdown (Figure 2b).

These two COVID-19 imported cases are indicative of the porous border between Ruili and Muse, which makes it difficult to prevent the cross-border transmission of infectious diseases. Because Muse experienced a dengue epidemic in 2020, it is likely that similar unchecked crossings or asymptomatic infections may explain the source of dengue in Ruili.

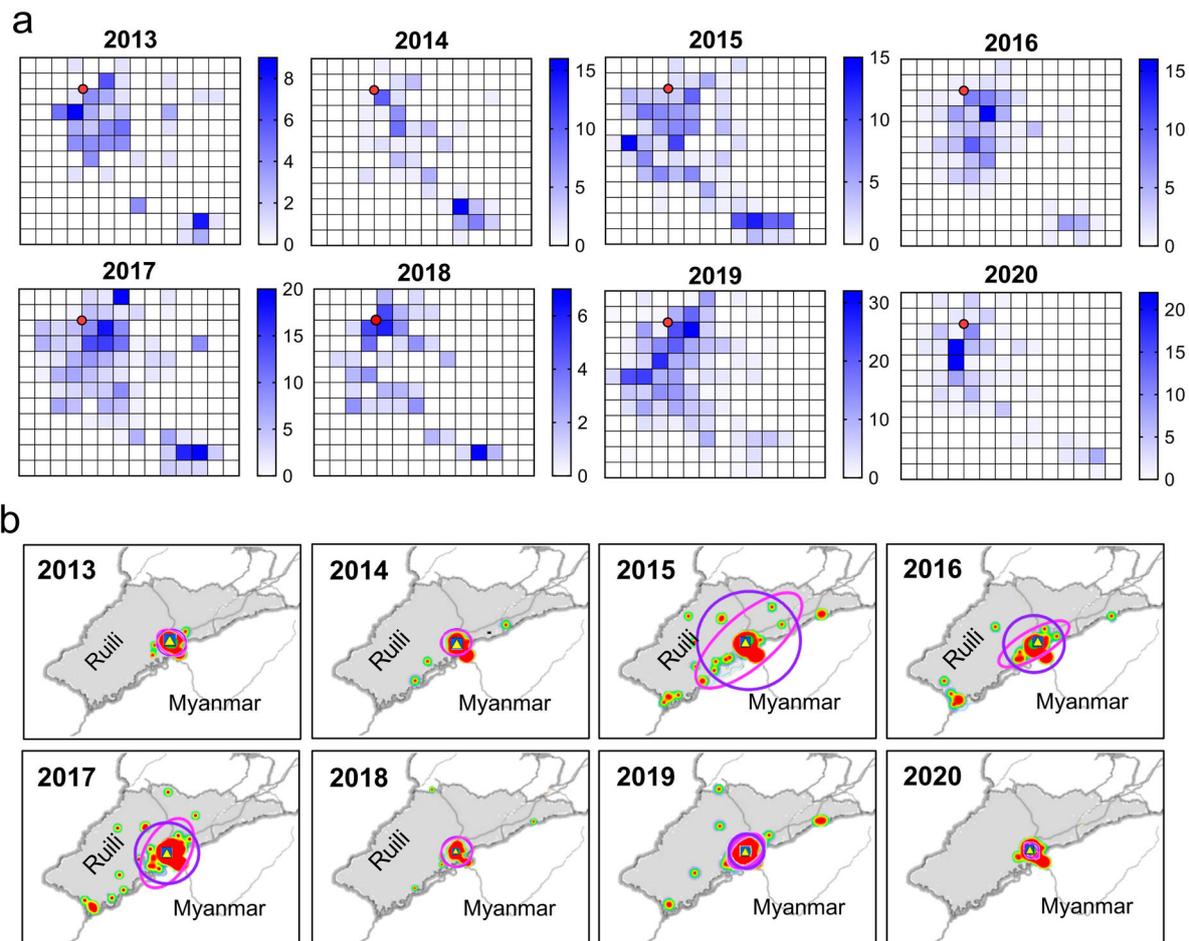
Except for an additional three imported cases in January, the dengue outbreak in Ruili started on July 27th, 2–months later than usual. Using the emergence of COVID-19 cases and resultant prevention measures, the dengue epidemic can be characterized into early and late phases (Figure 2b). The early phase (27th July to 14th September) consisted of 60 patients with a daily average of 1.2 new patients, while the late phase (15th September to 30th November) consisted of 186 dengue cases with a daily average of 2.6 new cases (Figure 2b). It was surprising that the late phase, which occurred when control measures were enhanced due to COVID-19 cases, was larger than the early phase. All of the prevention measures including the city-wide lockdown did not reduce dengue scale in this phase, although they immediately prevented the spread of COVID-19. This indicates that measures against COVID-19 had no effect on containing the dengue epidemic once it was established.

To validate the inefficacy of these measures on containing the dengue epidemic within Ruili, we used spatial analysis to compare the geographical characteristics of previous and the current dengue outbreaks in Ruili (S Figure 7A). Among outbreaks from 2013 to 2020, no significant difference was found with respect to the average nearest neighbour analysis (S Figure 7B), the standard distance of dengue cases (S Figure 7C), nor among parameters of the standard deviation ellipse (S Figure 7D, E). These results suggest the case distribution in urban Ruili is relatively stable and is not affected by measures taken to control COVID-19. To further test the stability of dengue in Ruili, we performed a cluster analysis by counting cases within fishnet polygons (grid incidents). Urban Ruili

was divided into 500-m square grids (S Figure 8A), the maximum distance that *Aedes aegypti* typically fly (16). Although the dengue-affected grids accounted for 2–48% of the urban region (S Figure 8B) in a scale-dependent manner (S Figure 8C), the grid incidence (case number per grid) demonstrated a skewed rather than normal distribution (S Figure 8D), and obeyed a power-law distribution with exponents very close to -1 (S Figure 8E). This indicates that most of the cases each year are concentrated in a small fraction of the grids. Moreover, these hot grids are fairly consistent or at least proximal every year, even in 2020 (Figure 3a). This further suggests that the spatial distribution of dengue within Ruili is dictated by inherent factors of the underlying urban pattern and that these factors are resistant to measures against COVID-19.

In addition to those urban cases, a small but substantial fraction of dengue cases was scattered in the surrounding suburban areas. In each dengue outbreak, urban cases preceded suburban cases. Moreover, the central feature (green circle), mean center (blue square) and median centre (yellow triangle) of the geographical analysis were highly correlated and collocated in the urban area (Figure 3b), suggesting that the epidemic spread from the urban centre to the surrounding suburban areas. The direction of spread from urban to suburban did not change during COVID-19, however, the percentage of suburban cases was significantly reduced compared with prior outbreaks (Figure 3(b), S Figure 9A). In line with this, the average nearest neighbour distance between cases (S Figure 9B) and the standard distance of between cases (S Figure 9C) were much smaller in 2020 than as observed from 2013 to 2019, providing further support that suburban transmission of dengue was reduced concomitant with the COVID-19 pandemic.

Because of the urbanization occurring in Yunnan Province, the suburban population is gradually decreasing as more people move to the cities. It is thus possible that the observed decrease in suburban cases is a consequence of the decreased suburban population. To address this question, we used standard deviation ellipses to analyse the distribution of dengue cases along the Ruili-Muse border where many of the new urban communities are forming. As expected, the oblateness (major axis/minor axis) of the ellipse, which was close to 1 in 2013 and 2014, increased to greater than 1 since 2015, and the major axis displayed a parallel trend to the Ruili-Muse border, consistent with the population (S Figure 9D). In contrast, the oblateness radically changed in 2020, with the major axis perpendicular to the border (S Figure 9E). These results indicate the reduction of suburban cases can be attributed to the inhibition of dengue spread from urban to suburban, and not because of a decreasing suburban population.



**Figure 3.** The distribution of dengue cases remained stable in Ruili urban area but reduced in the suburban area in 2020. (A) The clustering analysis of dengue cases by fishnet polygons in the urban region of Ruili from 2013 to 2020. Red spot indicates the location of the municipal government for reference. The spatial resolution of a grid is 0.5 km. Dengue case counts in each grid were counted and displayed in thermodynamic diagram. (B) The distribution of dengue cases in suburban area from 2013 to 2020. Standard distance (1 standard deviation) and standard deviation ellipse (1 standard deviation) are displayed as a blue circle and purple ellipse, respectively. The central feature (green circle), mean centre (blue square) and median centre (yellow triangle) were calculated by Euclidean distance to display the spatial distribution characteristics.

During dengue epidemic in Ruili this year, we collected serum from one-third of the patients ( $N = 81$ ). To investigate the origin of DENV in 2020, the capsid and pre-membrane genes (CprM) were amplified and sequenced from 81 serum samples and compared to samples collected between 2014 and 2017. Sequencing analysis showed that 73 patients were infected with DENV-3 and 8 patients were infected with DENV-1 (Figure 4a). The DENV-1 cases emerged during the late phase and formed a small cluster. All of the DENV-3 formed two clusters, either by time (serial number) or by homology. The first DENV-3 cluster consisted mostly of cases from the early phase while the second DENV-3 cluster consisted primarily of cases occurring during the late phase (Figure 4a). This implies two different introductions.

Comparing the 2020 samples to those collected between 2014 and 2017, the DENV-3 strain from the early phase was detected in six patients in 2016 and 2017, suggesting it had been circulating in Ruili and Muse before and re-emerged (Figure 4b). Similarly,

sequencing analysis indicates the DENV-1 strain had been circulating before in the area (Figure 4c). In contrast, the DENV-3 strains from the late phase, which occurred after the imported COVID-19 cases, had not been detected before 2020, rather was consisted with the two January dengue cases imported from Muse (No. 2020\_02 and 2020\_03) (Figure 4b), suggesting it was a strain circulating in Muse that was re-imported into Ruili during the COVID-19 pandemic. These results indicate Ruili not only had DENV strains circulating locally, but also experienced imported strains that are geographically very hard to prevent, resulting in dengue outbreaks in Ruili despite the presence of countermeasures against COVID-19.

In addition to elucidating the origin of DENV this year, sequence analysis also revealed the co-circulation of various serotypes. Of 429 samples collected in Ruili between 2014 and 2017, all four serotypes of DENV, have been previously detected. DENV-1 (305/429) was the predominant serotype, followed by DENV-2 (77/429), DENV-3 (28/429) and DENV-4 (19/429)



## Discussion

COVID-19 pandemic and the various measures taken to prevent its spread provided a unique opportunity to understand infectious disease transmission and to evaluate the efficacy of each countermeasure. We show that the dengue epidemic in Yunnan Province during the COVID-19 pandemic was dramatically reduced and confined to only once city, Ruili. Although dengue did occur in Ruili, the urban-to-suburban spread was efficiently blocked and co-circulation of multiple strains was attenuated to just DENV-3 and DENV-1. The measures that blocked COVID-19 spread also effectively blocked the urban-to-suburban spread and likely prevented intercity spread from Ruili to other cities. The inhibition of intercity transmission is of great significance, because it could not only decelerate the spread of dengue virus but also reduce the co-circulation of multiple strains in same places, which is critical for the occurrence of severe dengue infection [30,31].

Intriguingly, measures against COVID-19 did not reduce the scale of dengue outbreak within Ruili. This unexpected discovery led us to spatially analyse and compare the distribution of dengue cases in previous and current outbreak. We found that the dengue transmission foci in Ruili are very stable between years and are not easily changed, even in face of the extreme measures taken during the pandemic of COVID-19. This speaks to characteristics of the urban landscape conducive to DEN transmission and that, once established in the mosquito population, restricting human behavior may have less impact. Further analysis should investigate whether there are modifiable characteristics that define these foci which can be targeted for traditional dengue control measures.

The effects of measures against COVID-19 on intra- and intercity DENV transmission were interesting. Since the pandemic, the influence of COVID-19 on dengue epidemics was reported from several countries, but their findings were inconsistent [24,25,32]. As reviewed by Brady and Wilder-Smith, the dengue magnitude was larger in 2020 than their historical average in countries such as Pakistan, Peru, Singapore, Thailand, Ecuador, Paraguay, Bolivia, French Guiana, Suriname, Colombia, Mexico, Guatemala, Honduras, Nicaragua and Panama [1,25,32–34]. Notably, dengue has been endemic in these countries for many years. In contrast, in regions or countries including Taiwan, Bhutan, and Sri Lanka where the imported cases are easy to prevent because of their geographic features, dengue in 2020 was significantly lower than before [35,36]. Our results may shed new light on understanding the discrepancy between these reports. In cities where dengue outbreaks are associated with imported cases or where imported cases are easy to prevent, the

countermeasures will be an economic and efficient approach to prevent dengue outbreak. However, in areas where dengue is endemic or in cities like Ruili where it is very difficult to prevent the importation of dengue cases, the measures tend to be ineffective, and other approaches, such as mosquito control should continue to be considered a priority.

## Methods

### *Ethical considerations*

This study was approved by the Research Ethics Committee of Capital Medical University and Yunnan Institute of Parasitic Diseases. Written informed consent was obtained from all patients and/or legal guardians of children.

### *Study area*

Yunnan Province is a south-western province in China, with an area of 0.39 million km<sup>2</sup> and about 48.58 million permanent residents. Yunnan is located in low latitude inland areas with a tropical and subtropical monsoon climate. It shares a 4060 km boundary with Myanmar, Laos, and Vietnam.

Ruili is an important port city located at the border of Yunnan and Myanmar, making up an area of 1020 km<sup>2</sup> with an average elevation of 780 m and a population of 0.2 million. As the second largest city of Yunnan, Ruili is an important land route connecting Southeast Asia and South Asia with China. The adjacent city of Muse is the fourth largest city in Myanmar, with significant economic and trade contact to Ruili. The urban areas of the two cities are highly integrated.

### *Dengue cases confirmation*

Febrile patients whose IgM antibodies for dengue NS1 were positive were considered suspected dengue cases. Their blood samples were sent to local Centers for Disease Control to test for dengue viral nuclear acids test by polymerase chain reaction (PCR). PCR positive samples were considered as confirmed dengue cases. Geographic and relevant clinical information for the patients were recorded. Samples were collected from all dengue cases in Ruili during the entire year. The age and gender of confirmed cases were recorded, and the epidemic curve was plotted.

### *Data collection*

Monthly dengue epidemic data in mainland China from 2013 to 2020 was provided by the Chinese Center for Disease Control and Prevention, Beijing, China. Dengue epidemic data in cities in Yunnan Province from 2013 to 2020 was provided by the Yunnan Center

for Disease Control and Prevention. The annual mean air temperature and the mean of annual total precipitation were extracted from the China Climate Bulletin (available at <http://www.cma.gov.cn/>). The annual mean air temperature and the mean of annual total precipitation in Yunnan province were reported by local meteorological bureau (available at <http://yn.cma.gov.cn/>).

### Epidemic prediction

ARIMA (Auto Regressive Integrated Moving Average) was used to build forecasting models.

The ARIMA model, a frequently used time-series forecasting model, is a generic linear stochastic model that combines autoregressive (AR), integrated (I), moving-average (MA) models to analyse time series. A typical autoregressive model takes previous values and uses a linear combination of those values to forecast the future values of the variable of interest. The moving-average model employs the previous forecasts' errors in a manner similar to that of a regression model. The general notation is ARIMA (p,d,q), where p is used to calculate AR using p preceding periods from the time series, d represents the degree of differencing that is used to transform the data into a stationary series, and q is the order of the moving average. Forecasting using ARIMA is calculated as follows:

$$y_t = c + \varphi_1 y_{t-1} + \dots + \varphi_p y_{t-p} + \theta_1 \varepsilon_{t-1} + \dots + \theta_q \varepsilon_{t-q} + \varepsilon_t$$

where  $y_t$  is the difference at degree d of the original series of time series,  $\varphi$  represents autoregressive model parameters,  $\theta$  represents moving-average model parameters, and  $\varepsilon_t$  is white noise.

To determine the incidence of dengue in mainland China, ARIMA (0,0,1) was selected as the best model, while ARIMA (0, 0, 0) was selected as the best model for determining dengue incidence in Yunnan Province.

### Geospatial analysis

All the point locations of dengue cases were geocoded from their residence for geospatial analysis. The point shapefile was prepared using ArcGIS 10.5 (Esri, USA). Spatial autocorrelation was tested using average nearest neighbour, spatial autocorrelation (global Moran's I) to assess spatial aggregation characteristics. Standard distance (1 standard deviation) and standard deviation ellipse (1 standard deviation) were analysed to describe the spatial patterns of dengue cases. The central feature, mean center and median center were unweighted and calculated by Euclidean distance to display the spatial distribution characteristics.

### Cluster analysis

To analyse the annual distribution pattern of dengue cases in Ruili, clusters were identified using the rectangular area covering all urban areas. To construct a stable study area over the years, the municipal government was selected as a reference point. The region was divided into grids with a spatial resolution of 0.5 km yielding 168 grid cells. The annual incidence of dengue cases within fishnet polygons was obtained using the Data Management Tools and Spatial Statistics Tools of ArcMap 10.1 software. The output data was imported into and analysed using SPSS 20.0 to explore the stability and their potential relationship with the epidemic data over the years.

### Viral extraction and sequencing

DENV in the samples was isolated and proliferated by Vero cell cultivation. Viral RNA was extracted from the supernatant using a QIAamp Viral RNA Mini Kit (QIAGEN, CA, USA) according to the manufacturer's instructions. cDNA was synthesized by reverse transcription with GoScript Reverse transcription kit (Promega) at 25°C, 5 min; 42°C, 60 min; 70°C, 15 min. PCR was performed with modified PCR primer sets targeting the C/PrM and E genome sequences of DENVs. Sense, 5'-TCAA-TATGCTGAAACGCGGAGAAACCG-3', Anti-sense, 5'-TTGCACCAACAGTCAATGTCTTCAGG-TTC-3'. The PCR conditions as follows: denaturation at 94°C for 3 min, followed by 40 cycles of amplification (94°C for 30 s, 55°C for 30 s, and 72°C for 2 min), and then a final elongation step at 72°C for 10 min. The final amplicons, stained with SYBR® Safe DNA Gel Stain (Invitrogen, USA), were visualized on 1.6% agarose gels with UV transillumination and purified by EasyPure® Quick Gel Extraction Kit (Transgen, China). The PCR products were then subjected to the Huada Gene Technology Co. Ltd (Shenzhen, China) and sequenced. All procedures were conducted in a Biosafety Level 2 laboratory.

### Phylogenetic analysis

The nucleotide sequences similarities were compared and analysed by Molecular Evolutionary Genetics Analysis (MEGA), version 7.0. Multiple alignments of the complete coding regions were performed using the CLUSTAL W method. Maximum-likelihood phylogenetic analysis was performed using the Tamura Nei model with gamma distributed rates and 1000 bootstrap replicates in MEGA 7.0 [20].

## Statistical analysis

Correlations analysis, autoregressive integrated moving average model analysis were performed by SPSS 20.0. Scientific graphs were designed by GraphPad Prism 8.0.

## Author contributions

**Z. Y. Sheng:** Methodology, Formal analysis, Visualization, Writing - Original Draft, Funding acquisition

**M. Li:** Investigation, Data Curation, Validation,

**L. Xie:** Investigation, Data Curation

**J. R. Mao:** Resources, Investigation

**Y.H. Liu:** Resources, Investigation

**H.E. Brown:** Discussion, Revision of the manuscript

**H.N. Zhou:** Resources, Project administration

**P.G. Wang:** Conceptualization, Project administration, Writing - Original Draft, Funding acquisition

**J. An:** Supervision, Project administration, Funding acquisition

## Data and materials availability

All data is available in the main text or supplementary materials.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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