# Title Page

# Manuscript Title:

# Dengue climbing on top of the world- 2019’s big jump broke the record

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# Dengue climbing on top of the world- 2019’s big jump broke the record

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# Accounting for nearly one hundred million symptomatic cases worldwide annually, dengue continues to expand to newer territories.[1](#_ENREF_1),[2](#_ENREF_2) Nepal, a Himalayan country sandwiched between the world’s two most populous nations, India and China, experienced its largest dengue outbreak in 2019 with >14,600 cases and at least six deaths.[3](#_ENREF_3) With altitudes from 70 meters to the “Top of the World” and with climate types from desserts to rainforests, Nepal is a unique environment to study the changing distribution of infectious diseases.

# Although circulation of all four dengue virus serotypes was confirmed as early as 2006,[4](#_ENREF_4) dengue remained only a minor public health issue causing <100 cases annually before 2010.[3](#_ENREF_3),[5](#_ENREF_5),[6](#_ENREF_6) In 2010, >1,000 cases were reported mainly from the southern lowlands (altitude <800 meters).[3](#_ENREF_3),[5-7](#_ENREF_5) Since then, major dengue outbreaks have occurred in the country every two-to-three years, causing up to 2,100 cases (figure 1a) and a time-series analysis over the past 15 years[3](#_ENREF_3),[5](#_ENREF_5),[6](#_ENREF_6) shows an exponentially increasing trend (p = < 0·0001). The 2019 outbreak, however was truly unprecedented and catastrophic, causing over three-times the number of cases reported in all previous years combined (2005-2018, figure 1a). In 2019, cases began to appear in May, following early arrival of the rainy season, and eventually spread to 67 (out of 77) districts covering all seven provinces, with sixteen districts reporting >100 cases (figure 1b). The country’s capital, Kathmandu (altitude 1400 meters), alone reported > 2,500 cases, while another hill district Kaski (mean altitude 1400 meters), a popular tourist destination, experienced its first major dengue outbreak with > 2,800 cases.[3](#_ENREF_3) Plotting districts from highest to lowest mean elevation (figure 1b) and the cases they report clearly shows spread to higher elevations and the unprecedented jump made in 2019. Although dengue-transmitting mosquitoes have been found at elevations up to 2100 meters in Nepal,[8](#_ENREF_8) patient travel histories are not always collected making the exact altitude reached by dengue difficult to estimate. While we do not yet know the cause of the 2019 outbreak, a serotype switch from serotype 1 to serotype 2 or 3 is suspected, given both were confirmed in travellers visiting Nepal during 2019 outbreak.7,[9](#_ENREF_9) This outbreak also coincided with contemporaneous larger dengue outbreaks in Pakistan and Bangladesh, as well as other parts of Asia and South America. Once official statistics become available, 2019 is likely to be the biggest year on record for dengue globally.

# Since a devastating earthquake hit the country in 2015, dengue control has become one of the country’s fastest growing public health challenges. The Epidemiology and Disease Control Division (EDCD) is the national body responsible for epidemic preparedness and disease control and coordinated the response to the 2019 dengue outbreak. EDCD’s strategy involved rapid response teams to ‘search-and-destroy’ mosquitos, rapid supply of point-of-care diagnostics, and broad public awareness campaigns. But the size of the 2019 outbreak sometimes overwhelmed capacity, particularly for diagnostics and patient management. As planned[10](#_ENREF_10), reducing disease severity and mortality through careful monitoring by basic blood tests was prioritised over accurate diagnosis and reporting. The actual size of this outbreak is still unknown and the number could be beyond reported figures. Moreover, the dengue control programmes were partly affected by the transition of responsibility from federal to provincial and local governments creating ambiguity over the roles of different government levels for different actions.

# After the 2010 outbreak, with the expanding range of all dengue virus serotypes[4](#_ENREF_4),[7](#_ENREF_7) and the spread of mosquito vectors to higher altitudes 8, many suggested it was merely a matter of time before Nepal experienced its first nationwide outbreak[5](#_ENREF_5),[7](#_ENREF_7). Despite this, capacity for research, surveillance and control has not kept pace with this growing threat. In particular, molecular surveillance for dengue virus serotyping should now be prioritized given the higher risk of severe disease in high altitude districts that have, so far, only experienced one serotype. Collecting patient travel histories can also play in important role in tracking the true location of infection. Nonetheless, there are also opportunities. Nepal is endemic for Japanese encephalitis (JE), a dengue-related mosquito-borne disease, for which a well-maintained nationwide surveillance system exists.[5](#_ENREF_5) Now is the time to consider an integrated surveillance system for dengue and other arboviral diseases, such as zika and chikungunya, utilizing and upgrading the existing laboratory-based JE surveillance platform. The 2019 Nepal dengue outbreak should be a wakeup call to strengthen the country’s health system against new arboviral threats and should emphasize the opportunity for researching mosquito-borne diseases in such a unique climate-sensitive setting.

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**Figure legend:**

**Figure 1. The increasing trend of dengue cases and its expansion towards higher altitude in Nepal, 2005-2019.** The data were archived from the publicly available government’s annual reports and disease control division’s outbreak reports, or confirmed infection in the archived serum samples collected from febrile patients[3](#_ENREF_3),[5](#_ENREF_5),[6](#_ENREF_6). **(A)** Time series graph with fitted exponential slope, 2005-2019 (natural and log10-scale). Time series analysis with continuity correction was performed for annual dengue cases reported in Nepal and Mann-Kendall trend tests was employed for statistical significance of the trend p = < 0·0001). **(B)** Bubble plot of dengue cases with size proportional to the number of cases reported per year in each district organized by highest mean altitude (top) to lowest mean altitude (bottom). Some districts have wide range of elevation from lower to higher. Travel history data was not available from the database.