Measuring mosquito-borne viral suitability and its implications for Zika virus transmission in Myanmar

Perez PN [a,b], Alcantara LCJ [c], Obolski U [d], Maia de Lima M [c], Ashley EA [e,f,g], Smithuis F [e,f,g], Horby P [f], Maude RJ [f,g,h,i], Lourenço J [d]

Affiliations:

[a] *Department of Global Health and Tropical Medicine, University of Oxford, UK*

[b] *Department of Infectious Disease Epidemiology, Imperial College, London, UK*

[c] *Laboratory of Haematology, Genetics and Computational Biology, FIOCRUZ, Brazil*

[d] *Department of Zoology, University of Oxford, UK*

[e] *Myanmar-Oxford Clinical Research Unit, Yangon*

[f] *Nuffield Department of Medicine, University of Oxford, UK*

[g] *Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, UK*

[h] *Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University,Thailand*

[i] *Harvard TH Chan School of Public Health, Harvard University, Boston, USA*

Correspondence to:

Pablo N Perez-Guzman (p.perez-guzman@imperial.ac.uk)

Abstract

In South East Asia, mosquito-borne viruses have long been recognised as a cause of high disease burden and significant economic costs. While certain countries in the region often serve as robust references for epidemiological data on particular mosquito-borne viruses, our current understanding of the epidemiological situation and transmission potential in Myanmar is still incomplete. Here, we use a simple mathematical approach to estimate a mosquito-borne viral suitability index aiming to better characterise the intrinsic potential of Zika virus (ZIKV) in Myanmar to inform national surveillance and control efforts. Results suggest that many districts of Myanmar are suited for ZIKV transmission, with peak transmission season between June and October, with high potential in districts containing two major urban centres and sharing international borders with countries which have previously reported ZIKV trasnmission. Our research identifies spatial heterogeneities and a temporal window of importance for surveillance and control in Myanmar with implications for public health in the region.

Introduction

Zika is a mosquito-borne virus (MBV) transmitted to humans by the peridomestic *Aedes aegypti* and *albopictus* mosquito species. The global attention Zika virus (ZIKV) has received in recent years comes from an ongoing epidemic in the Americas with significant human morbidity and its potential link with neurological pathologies in neonates [1, 2, 3]. The virus' potential for causing outbreaks of great magnitude was first recognised in 2007 on Yap Island (Micronesia) and later in 2013-2014 in the French Polynesia [4, 5]. In May 2015 autochthonous transmission was confirmed in the Northeast region of Brazil

[6], although analysis of genetic data suggests undetected circulation in the Americas at least since early 2014 [1]. Spread was later reported in the Caribbean and North America [6]. According to the last report by the World Health Organisation (WHO) by March 2017 there was evidence of ongoing ZIKV transmission in 84 countries / territories, with warnings of potential introduction and establishment of the virus into 64 other countries [6].

Preparation and response to the public health threat of ZIKV presents several challenges, such as the ongoing co-circulation of other MBVs [7, 8, 9, 10, 11, 12]. Infection with ZIKV is mostly asymptomatic [4] and classification of Zika based on clinical symptoms alone is complicated by similar pathologies induced by dengue (DENV1-4) and chikungunya (CHIKV) viruses. Common viral diagnostic tests based on antibody detection also show strong ZIKV cross-reactivity with viruses of the same genus (*Flavivirus*) such as West Nile virus, DENV, tick-borne encephalitis virus and yellow fever virus. Concurrently, access to viral diagnostics and surveillance tools across the globe is highly variable [11, 14, 15] and even within countries with sufficient resources it is rarely the case that reported case data is representative of the true burden of transmission [10, 15, 16].

South East Asia (SEA) is the most densely populated region of the world and has experienced rapid urbanization in the past century. Such demographic factors and tropical climate are believed be the main drivers of the success of *Aedes* mosquitoes in the region. However, surveillance of MBVs such as DENV has been heterogeneous with a few countries such as Vietnam, Thailand and Singapore reporting epidemiological data spanning several decades and serving as global references [17, 18]. Other countries such as Myanmar have also reported robust data [19, 20, 21]. For ZIKV the general picture is more incomplete, albeit evidence of continued transmission in the region from serosurveys and occasional viral isolation in residents and travelers to the region [22, 23, 24, 25]. Evidence supports the notion that ZIKV transmission in SEA preceded that of the Americas even with an apparently low number of cases and no major epidemics reported. To date, only one imported ZIKV case has been notified by the Myanmar Ministry of Health and Sports (MOHS) [26] and the virus' spatio-temporal potential for transmission in the country is largely unknown.

Given that mainland countries of SEA share many of the climatic and eco-demographic factors that dictate positive suitability for *Aedes* mosquitoes, it is reasonable to assume that districts within Myanmar have the potential for epidemic or endemic transmission of ZIKV. In this study, we introduce a simple mathematical framework to characterize for the first time a mosquito-borne viral suitability index in the context of Myanmar. We validate this approach using historical DENV data from the country and discuss its present and future implications for public health and control for ZIKV.

Methods

Our approach develops from a climate-driven, mosquito-borne mathematical model of viral transmission that has been successfully applied for the 2012 dengue serotype 1 outbreak in the island of Madeira (Portugal) [27], the 2014 dengue serotype 4 outbreak in Rio de Janeiro (Brazil) [28] and the 2015-2016 ZIKV outbreak in Feira de Santana (Brazil) [10]. In these case studies, given availability of reported epidemic curves, deterministic simulations were used with a Markov-chain Monte Carlo fitting approach to derive key eco-epidemiological parameters [10, 27, 28]. In the context of Myanmar and the lack of

reported case counts, we addressed the potential for ZIKV transmission by focusing on the model's equation for the basic reproductive number (R0) [10]. R0 can be summarized as (NV/NH)*P, in which NV/NH is the number of adult female mosquitoes per human (with NH equal to the human population size and NV the adult female vector population size), and P is a complex expression containing demographic and epidemiological parameters that influence viral transmission (Figure 1A). Since the expression for P includes human, entomological and viral factors, while it ignores host-population size, it can be defined as a *mosquito-borne viral suitability index*, in contrast with existing *vector suitability* indices, which generally consider entomological factors and / or vector-population sizes only. The index P is a positive number and can be interpreted as the transmission potential of a single, infected adult female mosquito per human. Values of P>1 indicate positive viral suitability (i.e. capacity of a single female to contribute to epidemic expansion), while P<1 implies unsuitability.

While some parameters used to calculate P can be quantified through known constant values, others follow mathematical expressions that depend on climatic variables and three scaling factors, α, ρ and η (Figure 1A). The expressions have been obtained and validated in a range of laboratory experiments on live mosquito populations under climatic-variable manipulation (see [10] for expressions) and represent how such parameters vary with temperature and humidity levels [10, 27, 28]. The scaling factors are used to fine-tune (up- or down-regulate) the strength of the climate variables on the parameters, as it is widely accepted that the original mathematical expressions fit particular ideal laboratory conditions of the experiments and may not directly represent natural conditions [29]. Fitting exercises to ZIKV epidemic curves that would allow for quantitative estimations of scaling factors α, ρ and η were not possible for Myanmar because no cases have been reported so far. To overcome this limitation, we ran a parameter sweep on the three factors in the range 0-10, and drew the combination of three values that would derive a yearly mean life-span of adult mosquitoes of ~9 days and an extrinsic incubation period of ~5 days. These heuristics were based on prior knowledge for ZIKV and DENV transmission estimations with the same model [10, 27, 28] and on reported biological ranges for *Aedes* mosquitoes [10, 29, 30, 31].

Previous work from our group and others have reported that under an endemic scenario, MBVs such as DENV, ZIKV and CHIKV tend to present local transmission seasons synchronized in time [32, 33]. The consensus is that local transmission potential is driven by climate temporal-changes which affect mosquitoes and therefore the pathogens in similar ways. Hence, to validate our index P approach and given the absence of case counts on ZIKV in Myanmar, we reverted to country-level DENV time series reported between 1996 and 2001 [21].

Please refer to the *Data* section for a description on the epidemiological and climate time series used in this study and the section *Parameters specific to Myanmar* for all subnational values found and used for the scaling factors α, ρ and η.

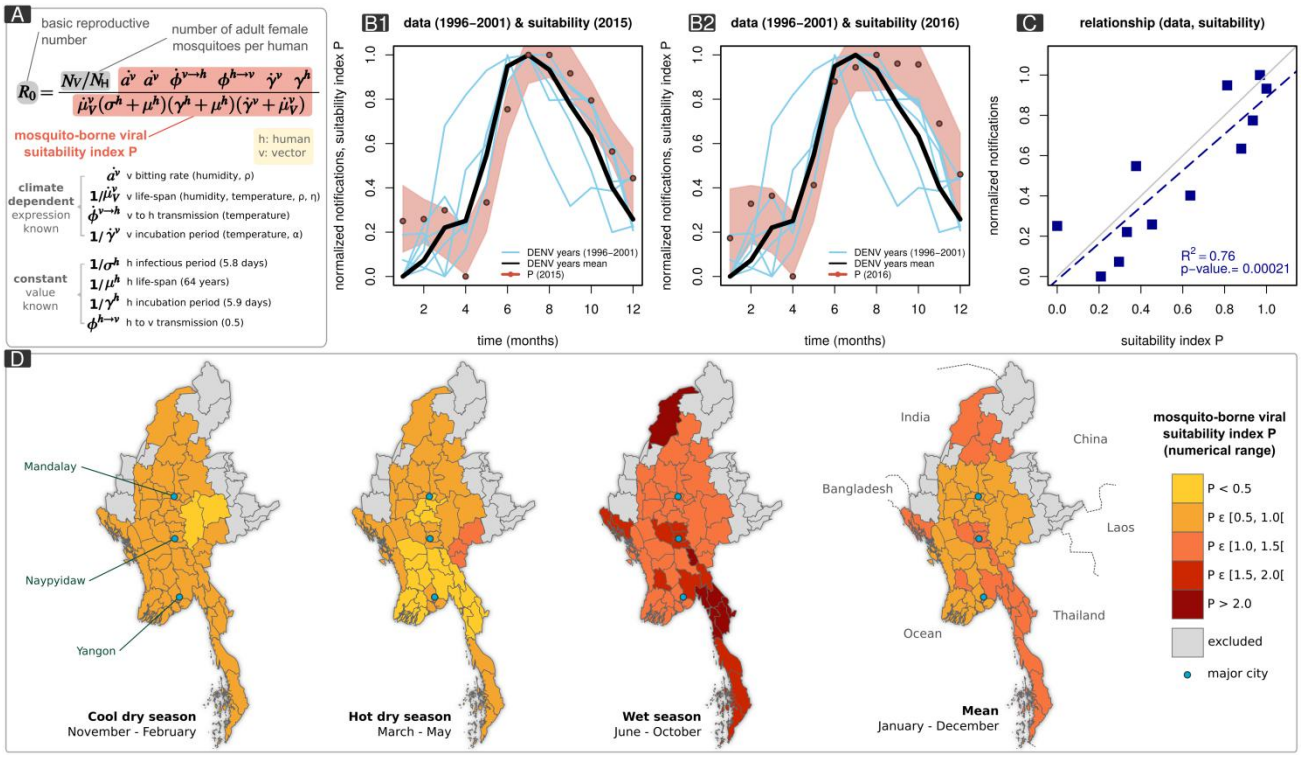

***Figure 1 - Results*. Panel A** presents the expression of the basic reproductive number R0 and mosquito-borne viral suitability index P. **Panel B1** presents the mean estimated index P across Myanmar for 2015 (red dots, locally weighted smoothing bounds within red area) superimposed on monthly case counts of DENV for several transmission seasons (1996-2001, blue lines) in Myanmar. The black line is the mean DENV case counts 1996-2001. **Panel B2** is the same as B1 but with P estimated for 2016. **Panel C** is a linear regression of mean DENV case counts (1996-2001) versus the mean index P (2015-2016) as displayed in panels B1-2. **Panel D** shows maps of Myanmar coloured according to mean index P in different seasons of the year (as labelled in each map). Grey districts were excluded (see *Data* section for exclusion criteria). Light blue points mark 3 major urban centres of Myanmar. Borders with key neighboring countries are shown on the map to the right. For panels B-D, all model parameters are as in figure A, except for α, ρ and η as described in section *Parameters specific to Myanmar*. In panels B1-2, case counts and index P time series are normalized to 0-1 by the maximum value for visualization purposes (with case counts under log 10).

Results

The index P was first tested in the context of DENV case count data at the national-level publicly available for the period between 1996 and 2001 [21]. For this, we estimated P for each district using available local climatic data (2015-2016), aggregating and averaging P across all districts of the country and per month (Figures 1 B1-2). While the epidemiological and climatic data available for the analysis were from different time periods, we found that both the 2015 and 2016 estimated indices presented seasonal fluctuations in sync with case counts from multiple years. A linear correlation between mean DENV counts (1996-2001) and mean index P (2015-2016) showed that 76% of the case count dynamics could be explained by the index P with statistical significance (*p-value*=2x10^{-4}, Figure 1C). The dynamics of the index P at the country level further presented key signatures in accordance to Myanmar's climatic seasons. Namely, (i) a sharp increase in transmission potential during May and June, coincident with the onset of the rainy season (Jun - Oct), and (ii) a trough in potential in the middle of the hot and dry season (Mar - May).

We then looked at the spatial variation of the index P (2015-2016) across Myanmar, focusing on average estimations within the cool dry (Nov - Feb), hot dry (Mar - May) and wet seasons (Jun - Oct), as well as averaged over the entire year (Jan - Dec). As seen in Figure 1D, the cool dry season presented a generally homogeneous index P of less than 1 across space, at a time when climatic conditions are expected to be less favorable for the mosquito and therefore for viral suitability. In contrast, the hot and wet seasons presented varying degrees of index P in space. On the one hand, in the hot dry season 53 out of 56 districts had P<1 and only 3 had P>1. While temperature during this season was generally above the acknowledged threshold of 15º Celsius for *Aedes*-borne transmission [27, 34], low transmission potential could be explained by incompatible humidity conditions. The wet season, on the other hand, was found to have highest estimated potential, characterized by P>1 across the entire country, with 7 districts having an index above 2.

When the index P of each district was averaged for a full year (Jan - Dec), 22 districts had an index P>1, suggesting a yearly positive potential for transmission (Figure 1D, right). Critically, the locations of 16 out of those 22 districts highlighted important geographical features. For instance, 11 districts shared direct international borders with Thailand, China, India and Bangladesh, which are known to have transmission of MBVs including Flaviviruses. This observation was statistically significant against a null hypothesis that indexes P>1 and P<1 were equally distributed between districts with and without international borders (p-value=0.001, Fisher's exact test). Five districts with P>1 were found to adjoin the cities of Nay Pyi Taw and Yangon (the country's two major urban and economic centres), although this pattern was not statistically significant (p-value>0.05, Fisher's exact test).

Discussion

We were able to validate the index P as a measure for mosquito-borne viral suitability by demonstrating that our temporal estimates of P were virtually synced with the dynamics of historical DENV case counts in Myanmar. Exploiting the fact that transmission seasons of different *Aedes*-born viruses (e.g. DENV, CHIKV, ZIKV) tend to be locally synced in time in other regions of the world [32], we here discuss and speculate on the ZIKV public health implications of the index P's spatio-temporal patterns found both at the national and subnational levels.

At the national level the wet season (Jun - Oct) was estimated to present the highest potential for ZIKV transmission, while the hot and dry season (Mar - May) presented the lowest potential. We therefore argue that in Myanmar, adequate surveillance and health care delivery resources should be fully operational by the end of the hot and dry season (May), in anticipation for the first ZIKV epidemic that is likely to occur in the following period of high transmission potential.

On the other hand, we identified important spatial variations in ZIKV transmission potential across Myanmar. The highest potential was found in the primarily rural districts bordering with Thailand, China, India and Bangladesh. If confirmed, these estimates have significant epidemiological and public health consequences. For example, there are reports of possible ZIKV transmission within those neighbouring countries and it is also known that such international borders are home to sizeable mobile populations with limited access to healthcare [35]. Introduction of ZIKV into Myanmar through such borders would therefore carry a significant public health burden but would also likely be difficult to detect with a passive

surveillance system.

Additionally, we found high potential for ZIKV transmission in districts adjacent to the largest urban centres of Myanmar. Due to the domestic nature of the mosquito species involved, urban centres are a hallmark for ZIKV transmission and establishment, with attack rates above 60% reported elsewhere [9, 10, 16]. For the city of Yangon, for example, a similar attack rate would result in +3 million cases, and would incur significant health and economic consequences. The estimated higher ZIKV potential around Myanmar's urban centres therefore calls for active surveillance initiatives, to detect early epidemic transmission chains in time for mosquito-control interventions which may effectively hamper the full potential of ZIKV and prevent such high attack rates.

Exposure to ZIKV infection during gestation is a major risk factor for development of a variety of neonate neurological complications including microcephaly (MC) [1, 2, 3]. Recent studies have further suggested that the risk of MC is highest for exposure around week 17 of gestation, resulting in a lag of approximately 5 months between ZIKV and MC epidemic peaks [2, 3, 5, 10]. Based on the estimated time window of peak ZIKV transmission potential in Myanmar between June and October, we therefore predict that epidemics of MC in the country would occur between November and March. This time window is therefore critical for active MC surveillance to be established in Myanmar. To date there has been no report of significant increases in MC cases in Myanmar. Caution should be taken in assuming this as evidence for no ZIKV circulation, since other epidemics have not reported ZIKV-associated MC cases [4] and it is possible that only one of two existing lineages of the virus is responsible or such clinical manifestations [1, 2, 3, 38].

Put together, the estimated spatio-temporal variations in ZIKV transmission potential obtained in this study suggest that in order to mitigate mosquito populations before the onset of ZIKV epidemics or prevent potential ZIKV introduction events from neighbouring countries, control initiatives should take place just before, and at the beginning of, the wet season. Special attention could also potentially be stratified across the identified country borders and major urban centres as these may have higher transmission potential.

Epidemiological models are useful tools to gauge the burden of a disease of interest, assess transmission potential, mosquito suitability, prompt surveillance efforts, inform better public health policies and highlight areas for pressing research. Such approaches are even more critical in epidemiological settings characterized by the absence of sustained surveillance or for pathogens which tend to have mild or asymptomatic pathology. The method here introduced requires solely climatic data and basic ento-epidemiological assumptions for which literature support is available. While the main goal of this research was to raise awareness and ease preparedness for ZIKV transmission in Myanmar, we foresee the usefulness and applicability of the index P for other regions of the world for which surveillance data is still missing, either due to lack of resources or absence of the pathogen.

Data

We used DENV case counts for Myanmar between 1996 and 2001 as published by Naing et al. [21]. These epidemiological time series were aggregated at the level of the country and by month. The original

source of the case counts was the official annual reports of the Myanmar National Vector-Borne Disease Control programme (VBDC). Cases included total reports of dengue fever (DF) and dengue haemorrhagic fever (DHF).

The administrative distribution of Myanmar into districts was suitable for our analysis, since it was possible to classify them by predominant weather conditions, using the Köppen-Geiger classification [36]: equatorial monsoonal (Am), equatorial winter dry (Aw), warm temperate-winter dry-hot summer (Cwa), warm temperate-winter dry-warm summer (Cwb) and arid steppe-hot arid (BSh). We obtained climate data from the United States National Oceanic and Atmospheric Administration webpage [37], which had incomplete observations that we then complemented with information from the Department of Meteorology and Hydrology, Yangon, for the period 2015-2016. Time and resource constrains for this process of data collection allowed for retrieving data from 14 weather stations, which were representative of the following districts: Pathein station, for the districts of Pathein, Pyapon, Maubin, Myaungmya and Labutta; Hpa An station, for Hpa An, Myawaddy, Kawkareik, Mawlamyine and Thaton; Sittwe station, for Sittwe, Marauk-U and Maungdaw; Dawei station, for Dawei, Myeik, and Kawthoung; Yangon Airport station, for North, South, East and West Yangon; Bago station for Bago, Hpapun and Hinthada; Nay Pyi Taw Airport station for North and South Nay Pyi Taw, Yamethin and Magway; Loikaw station for Loikaw, Bawlake and Langkho; Katha station for Katha, Bhamo and Mohnyin; Hkamti station for Hkamti district only; Taunggyi station for Taunggyi and Loilen; Mandalay Airport station for Mandalay, Kyaukse, Miyngyan, Nyaung-U and Meiktila; an average of the weather conditions in the Am region, for the districts of Kyaukpyu and Thandwe); and an average of the weather conditions in the Aw region, for the districts of Minbu, Pakokku, Gangaw, Pyinoolwin, Sagaing, Shwebo, Monywa, Kale, Yinmabin and Kyaukme.

To include a district in the present analysis, we used the criteria that its main population settlements were below 1500 meters above sea level, since the entomological modelling system we employed does not account for the effect of elevation on vector ecology and higher altitudes are less favourable to mosquito survival, plus either of the following: having access to climate variables from its weather station; or that its central point was within 100 Km of a station from which climate information was available; or being situated within a weather region were climate could be extrapolated from other districts' stations. The latter was done since an analysis of variance showed no difference in mean temperature across weather stations in the Am ($F=0.391$, p-value=0.53; Dawei, Hpa An, Yangon, Pathein and Sittwe, and Bago stations) and Aw regions ($F=2.793$, p-value=0.09; Taungoo, Loikaw and Nay Pyi Taw stations). Extrapolation was not done for districts within the Cwa region, as there was a statistically significant difference in weather observations from individual stations ($F=12.03$, p-value<0.05; Hkamti, Katha nad Taunggyi stations). Lastly, Mandalay was a single station within the BSh region and Hakha station from the Cwb region was removed from analysis, due to elevation criteria.

The three weather seasons defined in this study for the context of Myanmar were: cool dry season, from November to February, hot dry season, from March to May, and wet (monsoon) season, from June to October. National means (standard deviations) of yearly and cool, hot and wet season were, correspondingly: temperature in degrees Celsius 27.1 (2.8), 26.7 (1.5), 28.8 (1.3), and 27.7 (1.4); percent humidity 77.9 (11.1), 79.9 (5.3), 64.5 (5.8), 85.3 (6.7); and inches of rainfall 0.17 (0.43), 0.03 (0.13), 0.01 (0.05) and 0.47 (0.62).

Limitations and future work

There are certain limitations to our approach, although these can be revisited when ZIKV and / or entomological data becomes available for Myanmar. We note unavailability of high resolution climatic data meant that (1) it was impossible to estimate suitability in the border with China and Laos, two countries in which DENV transmission is reported to be endemic, and (2) that weather stations had to be used for vast geographical ranges limiting our capacity to explore potentially relevant spatial heterogeneities within the larger districts. The climatic data used was also limited to 2 years, and although we show that the index P in that period explains much of DENV's epidemiology in 1996-2001, it is uncertain to what degree our estimations explain the post 2002 period. It should also be noted that we interpret P>1 as potential for transmission, but the real epidemic threshold (R0>1) is still dependent on the total number of female mosquitoes per human (NV/NH). Without empirical support for the size and distribution of the vector population, however, this could not be fully evaluated.

Parameters specific to Myanmar

As detailed in the main text, unknown parameters α, ρ and η were obtained for each weather station using a parameter sweep with heuristics of adult mosquito life-span of ~9 days and extrinsic incubation period of ~ 5 days (over the period 2015-2016). See main text for details. The obtained values for α, ρ and η per weather station were (in order): Pathein 1.414, 0.78, 2.241; Hpa An 1.414, 0.78, 2.241; Sittwe 1.552, 0.45, 2.517; Dawei 1.414, 0.56, 2.517; Yangon 1.552, 0.78, 2.241; Am 1.414, 0.78, 2.379; Bago 1.414, 0.67, 2.379; Nay Pyi Taw 1.552, 0.45, 2.517; Loikaw 1.966, 0.45, 2.379; Aw 1.552, 0.78, 2.241; Katha 1.689, 0.56, 2.379; Hkamti 1.828, 1.00, 1.828; Taunggyi 1.828, 0.78, 1.828; Mandalay 1.552, 0.23, 2.655.

The districts found to have yearly mean index P>1 were: Magway, Nay Pyi Taw north, Nay Pyi Taw south, Yamethin, Bhamo, Katha, Mohnyin, Dawei, Kawthoung, Myeik, Maungdaw, Mrauk-U, Sittwe, Bago, Hinthada, Hpapun, Hkamti, Hpa-An, Kawkareik, Mawlamyine, Myawaddy, Thaton (with no particular order).

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Competing Interest Statement

Authors declare no competing interests.

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