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M2 bio-informatics - Université de Paris

Course : Writing and designing a research project

Unleashing the beast within, unleashing the beast outside

Comparative study of the spreading of a forest arbovirus to anthropized areas and the introduction of a cosmopolitan virus into remote human amazonian populations

Research type	**Experimental design**		
Key words	Dengue virus, Mayaro virus, population dynamics, immuno-genetics, vector skills		
Grant requested	366 845 €	Duration	24 months

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Executif summary

Public health concerns often focus on the emergence of tropical diseases in highly anthropized areas but rarely on the opposite mechanism: the introduction of urban-environment diseases in remote locations where the population is naive. The SARS-CoV-2 epidemic shed light on the vulnerability of isolated Amazonian populations, weakened by their immunological naivity, the lack of infrastructure, the constant risk of emergence of new diseases, as well as the problems inherent to their remoteness. Moreover, for these communities, each death threatens the tribe to fall below a critical size, putting their very existence at risk. Investigating the spatio-temporal expansion of diseases can be complicated in case of vectorial and/or zoonotic diseases, where disease spreading need not only susceptible population, but also spreading of the animals reservoirs and/or spillover to indigenous species. To adress this topic, we propose to develop a framework for understanding the diffusion of cosmopolitan virus and its impact in isolated human populations, and the process of peridomestication of forest virus. For this, our study will be implemented in French Guiana, with two viral disease models : Dengue, and Mayaro fever.

Dengue virus is a RNA Flavivirus that is transmitted by mosquitoes of the genus *Aedes* a*n*d *respo*nsible for the eponym condition. Dengue is considered by the World Health Organization as the most widespread mosquito-borne disease, with an official number of cases ranging from 50 million to 200 million, and closer to 400 million according to recent estimates. Mayaro virus was first described in Trinidad and has since been responsible for several epidemics in South America where it is mainly transmitted by *Haemogogus* mosquitoes. Its rapid expansion in tropical and Caribbean regions, as well as its biological similarities with the chinkungunya virus, may cause it to fly under the radar and allow its spread into new territories.

In the project, we will describe the mechanisms of introduction and spread in remote areas of Dengue Virus, and the potential for dispersion of a forest virus, Mayaro. For this, the project will be organized in three workpackages. The first one will be dedicated to the spread of the Dengue vector and Dengue Virus along two main inhabited rivers of the country. We will explore the current distribution of the main vector *Aedes aegypti*, decipher populations dynamics, and virus carriage. In the second workpackage, we will describe the mosquitoes communities with metabarcoding, and conduct metatranscriptomics studies all along the rivers and in the coastal areas, and we will reconstruct relations between viruses and putative hosts using ecological network theory. In the last workpackage, we will expect to identify the genetic determinants of anti-dengue innate immune response of amerindians, bushnegroes and caucasian populations to an ubiquist (Dengue) and a Forest (Mayaro) viruses, and to define the human genetics determinants of variation in anti-dengue and anti-Mayaro immune responses.

State of the art

The acceleration of environmental changes are responsible for major changes on vector-host-pathogens interactions[1,2]. Arboviral diseases thought to be under control resurgence and threatens the public health at large scales[3].

Present for hundreds of years, Dengue virus experienced its first major expansions in the nineteenth century among merchant ships, then during the world wars. In the 1970s, 9 countries reported severe cases of dengue fever, and today it is estimated that 50% of the world's population is exposed to it. The conditions predicted by the Intergovernmental Panel on Climate Change, i.e. a general increase in temperature and humidity on land, coupled with the continued increase in trade flows, will most certainly favor the expansion of the disease in areas previously spared[4]. Dengue fever, sometimes also called “break-bone fever”, is manifested in a wide range of symptoms. The pathogen has four serotypes: DENV-1, DENV-2, DENV3, and DENV-4. Infection with one serotype leads to lifelong immunity to that one but does not protect against the others and may even increase the severity of subsequent infections with other serotypes[5]. In few cases, people undergoing a second infection suffer a life-threatening shock-syndrom[5–8].

Mosquitoes communities, abundances and diversity, are significantly different in wild and anthropized environments (deforestation or urbanization), human habitations being associated by a higher number of disease-vectoring species[9]. Modified habitats may indeed provide new favorable niches, or different microclimatic conditions that favor the most opportunistic and generalist species.

Anyway, the main recognized vector are often not entirely responsibly for the circulation of a pathogen[10], indeed, some pathogens may be found in locations where it is unknown whether the vector is present, or even where the vector is known to be absent. Some species may indeed serve as bridge, and even if they could act as less efficient viral spreaders, they could host virus, allow replication, and transmit to people living at the forest borders, that in turn could infect anthrophilic species that would then amplify the cycle : this is the so-call peridomestication of the cycle.

Last, human population have different clinical responses to pathogens[11,] that could be investigated with variation of the ranscriptional responses. There is a strong genetic predisposition to dengue hemohrragic fever (previsouly studied using GWAS)[12]: computed a weighted polygenic risk score (PRS) for each individual. For example, It has recently been found that seven single nucleotide polymorphisms (SNPs) are associated with severe dengue outcome[13].

Severe dengue infection usually results from an overreacting immune response. Peripheral Blood Mononuclear Cells (PBMCs) from severe dengue and influenza patients exhibit specific transcriptomic responses to viral infection. Cytokines and inflammatory response genes are overexpressed by and specifically discriminate PBMCs from severe dengue patients[14] Differences in antiviral immune responses between populations from different geographic origins have been shown to rely on population-specific immune-responsive regulatory variants**[11].** Although crucial to the understanding of their susceptibility to dengue, the genetic determinants of anti-dengue innate immune response of worldwide population have not been characterized so far. A recent meta-

analysis of genome-wide association studies (GWAS) has identified at least seven SNPs located in five distinct genes that are associated with the risk of severe outcomes (dengue hemorrhagic fever/dengue showk syndrome) in Southeast and Northeast Asians during dengue infection[13].

In French Guiana, Bushinenge (Noirs marrons) represent around 35% of the population, Guianese creole represent around 40% of the population and Europeans are 12% of the population. French Guiana population also belongs to Amerindian community (around 3% of the population) and other communities including Asians, Brazilians. The focus will be on four of targeted populations with very different pasts :

- The Bushi-Nengue community is originating from various regions of Africa and arrived in South America during the first period of the slave trade. They then escaped from the Dutch plantations following violent uprisings in the late 17th - early 18th centuries and recreated communitues in the forest, particularly around the Maroni River, the current border with Suriname.
- The Wayanas are an Amerindian tribe from western Guiana where they arrived relatively recently, from the congervernce of various cariban-speaking tribes (northeasterns South America). Living on middle to high-Maroni river, their population is estimated to 1500.
- The Wayampi Amerindian tribe belongs, by culture and language, to the ethnic group of the tupi-guarani, the first and historical inhabitants of the deep Amazonian forest. Their 1800 representatives occupy the middle and upper part of the Oyapock river, border with Brazil.
- The caucasian of the coast, who may be exposed to indigenous virus if a peridomestic cycle of the Mayaro virus is likely to occur, as the Yellow Fever virus escaped from Amazonian forest decades ago, and now occur in rural areas thanks to bridge species [15].

Remote populations may pay a heavy toll to severe dengue infections. In French Guiana, highest dengue infection risks are found in the Low Maroni area (80%), the Low Oyapock area, (76%) and the coastal area (70%)[16] where human densities are the highest. French Guiana territories thus represent an ideal observatory of the diversity of populations' genetic uniqueness regulates their immunity to arbovirus infection, with a final objective to adjust public health measures and surveillance efforts of a health community approach[17,18].

Objectives

- To describe the mechanisms of introduction and spread of two arboviruses in remote areas and from urban areas
- To gain an insight of genetic determinants, opening the door to a better understanding of fundamental biological disease mechanisms and paving the way to adjustments of public health measures and surveillance efforts
- To stress the vunerability of left behind populations, identify the genetic determinants of anti-dengue innate immune response of amerindians, bushnegroes and caucasian populations to a ubiquist (Dengue) and a Forest (Mayaro) viruses, and to define the human genetics determinants of variation in anti-dengue immune responses.

Workpackages

WP1. From coast to forest: Ecology and population dynamics of an invader, *Aedes aegypti* mosquitoes

The first work package will investigate the distribution of the main vector of Dengue virus (*Aedes aegypti*) along the border rivers and how the population spatially expanded southward from the northern urbanized parts of the country to more remote areas.

Task 1. Sampling methods

Captures of mosquitoes will be conducted in the settlements along the rivers, using baited passive box traps. At each site, 10 traps will be activated during 24 hours consecutively, in order to sample all the richness of the mosquitoes communities. The first 25 *Aedes agypti* will be stored in individuals tube, the remaining mosquitoes will be randomly pooled by 20.

The disturbance gradient can be estimated thanks to a rigorous follow-up of population density and the ground occupation since 20 years by the Office national des Forêts and the Parc Amazonien (National Park) de Guyane.

Task 2. Population genomics

Using double-digest Restriction site-Associated DNA (ddRAD) sequencing protocol for Aedes[19], we will develop a panel of single nucleotide polymorphisms (SNPs) based on several coastal populations representing the expected core of the populations, and riverine populations. Small sample sizes (ie, 20 - 30 per site, expected to be captured in a single night) can be enough informative for studying the genetic differentiation and the evolutionary relationships of populations[20]. Sequence reads will be processed in Stacks and BOWTIE 2.0. The geographical structuring of genetic variation will be explored with distance-based redundancy analysis (dbRDA) and evolutionary relationships among populations, with a maximum likelihood approach as implemented in RaxML.[21]

Demographics history, expected to quantifying changes in effective population sizes and migration rates, will be explored with pairwise sequentially Markovian coalescent method[22] and will be useful to evidence for multiple size changes (in case, for instance, of non continuous invasions due to ecological constraints, as urbanisation has not been continuous in time and space, and could then be seen as stocastic events for mosquitoes) population splits, multiple population (resulting from several invasions), gene-flow, admixture events, bottleneck and growth.

Task 3. Dengue vector spreading

The classical methods used to detect molecular trace of infection by Dengue virus [23] will be used on *Aedes aegypti*, and interpreted according to season and capture location, and habitat patterns.

WP2. Escaping from forests : searching for cryptic vectors, carrying cryptic viruses

We then aim to find out whether other mosquitoes are capable of hosting and transmitting the dengue virus, and if "bridge vectors" are likely to be observed[10], thus complicating the Dengue epidemiology and risks at the forest borders. In this step, we will also investigate the presence of other viruses, with an interest on forest arbovirus (eg, Mayaro virus, among others).

Task 1. Identification of mosquitoes communities with metabarcoding

To this purpose, we will use first a mosquitoes communities screening on the previously mentionned pools, using metabarcoding to caracterize the diversity of the communities, following previously proposed workflow[24] and relying on reference librairies of Guiana mosquitoes[25].

Task 2. Identification of viral diversities with metatranscriptomics

Metatranscriptomics (total RNA sequencing) enables nontargeted, high-throughput detection and characterisation of viruses in a sample. As virus load and prevalence may be low, the pipeline optimized for detection of arboviruses in large pools of mosquitoes, essential for the incorporation of this technique into arbovirus surveillance programs, will be used [26].

High-throughput shotgun sequencing will be carried using Illumina MiSeq, reads being cleaned using FaQCs. MEGAHT will be used to create contigs by a de bruijn graph based de novo assembly process. BWA-MEM and Samtools will be used to obtain the number of reads aligning to each contig. Taxonomic assignment will be performed using a homology search against the nucleotide and protein databases.

The viral genomes' completeness of assigned contigs will be tested using CHECKV[27]. Finally, a matrix corresponding to the number of viral reads at the genus/subfamily level for each species-habitat couple was built for statistical analysis : rarefaction curves to assess completedess, alphadiversity explored according to communities and habitats, and betadiversity along the two gradients.

Task 3. Network analysis.

Comparative analysis of metatranscriptomics and metacommunies of vectors could allow identifying putative hosts. For this purpose, we propose to use the ecological network tools[28,29] that could be applied here, on a very innovative purpose, to identify most likely vectors of any virus of interest.

WP3. Immuno-genetics for severe infections : an ethnic approach of the risk

Here the aim is to evalute how ethnicity drive innate immune response to arbovirus. Dengue virus may invade remote amerindian populations, and some forest virus may escape and reach urbanized areas. What are the expected replies of such naive populations ? The experiment will be run on three ethnical groups living on the border rivers of French Guiana : the Bushi-Nengue community, the Wayana and the Wayampi communities (amerindians), and on the caucasian group living in coastal and industrialized areas. Theses communities have very distinct histories, issued from slave-trade (bush negroes), arrived from Carribean ca 10,000 years ago (Wayana), or mograting from the core of the Amazon (tupi-guarani Wayapi). In contrast, the caucasian population will serve as reference for the transcriptomics as their metabolic reactions are well-known, and as they are naive from any amazonian arbovirus.

Task 1. Sampling (blood and saliva)

We expect to collect 50 people from each group (50 healthy adults per ethny) : a set of saliva samples for SNPs typing used for ethnic characterization and (ii) a set of 30mL-blood sample (collection of PBMCs in CPT™ tubes).

Task 2. Genotyping and serology

The individuals included in WP1 will be whole-genome genotyped using the Illumina HumanOmni5-Quad BeadChip array. Haplotypes will be analyzed. SNPs and allelic states will be aligned with the 1,000 Genomes Project imputation reference panel. Individual ancestry will be estimated (ADMIXTURE bioinformatic tool).

In order to know serological status of population, and control of immunity of persons included in task 3, serologies will be done according to Hozé et al.[30]. Before all subsequent analyis, previous exposures to other arboviruses of public health interest (chikungunya, zika) will be considered by a serology of all people, interactions between DENV, MAYV, and these potential effect-modifiers will be tested and subgroup analyses conducted accordingly.

Task 3. BMC simulation and severe Dengue

PBMCs collected in task 1 will be left untreated as a baseline control or exposed to a contemporary DENV and MAYV strains having recently circulated in French Guiana. Expression of I IFNs, ISGs and cytokine using RT-qPCR will help eliciting the strongest response, best time-point of analysis and most immunogenic DENV and MAYV strain, according to ethnic group. Following stimulation, RNA will be sequenced on an Illumina HiSeq2000. Differential expression levels between DENV

and MAY -stimulated and unstimulated conditions will be assessed. Associations between SNPs and gene expression will be tested: expression Quantitative Trait Loci (eQTLs) mapping will be performed. Response eQTLs will be defined as stimulated eQTLs associated to a significant difference in response to DENV and MAYV stimulation. A specific attention will be brought to “archaic eQTLs” introduced into NC genomes through introgression from archaic hominins[11].

Individuals experiencing severe dengue will be whole-genome genotyped (saliva sample set 3, Task 1). Immune correlates will be produced by searching whether reQTLs defined in previous steps specifically discriminate individuals experiencing severe dengue from non-severe patients.

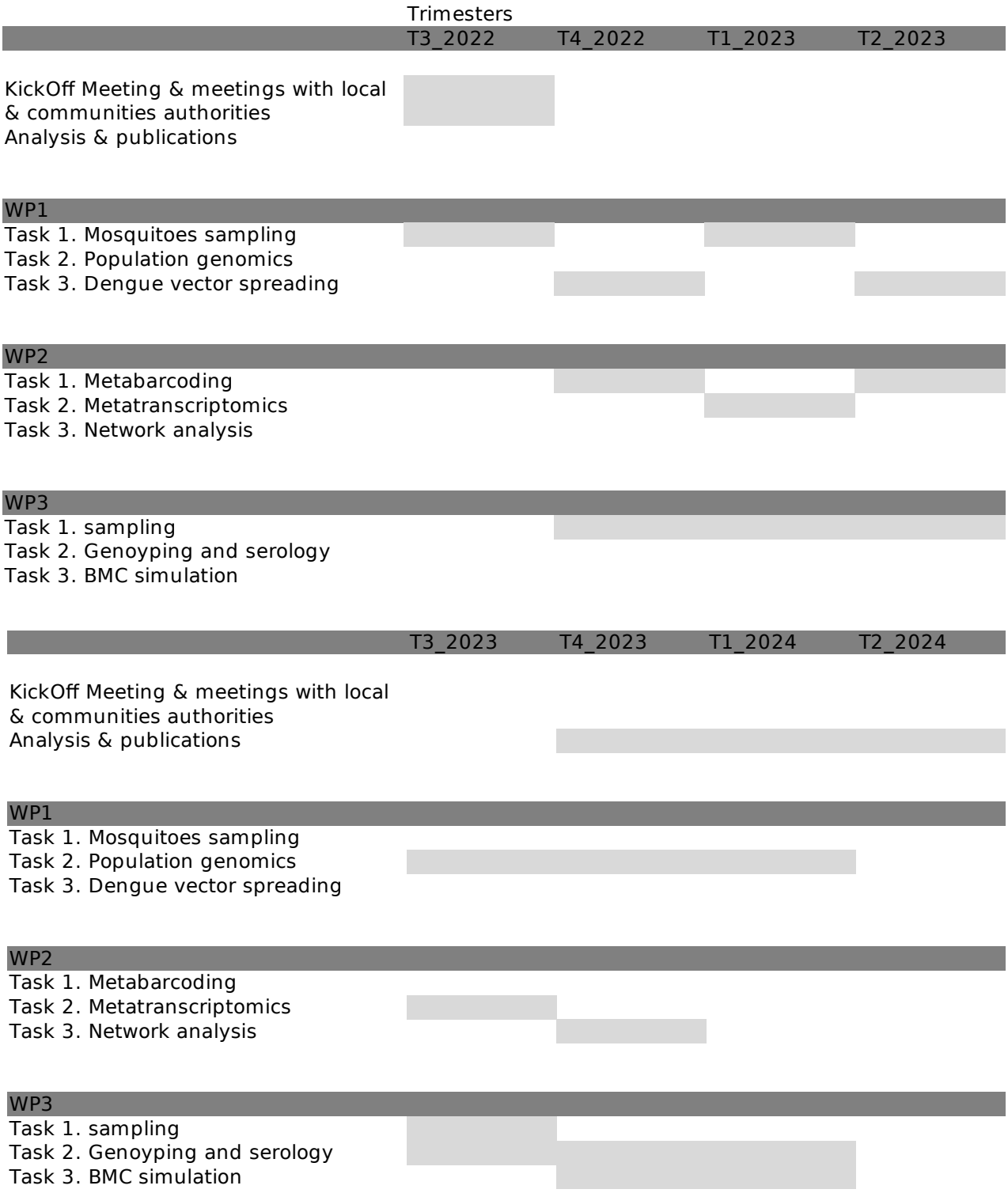
Expected difficulties and fall-back solutions

- All considerations will be taken regarding the use of ethnical information, according to the recommandations of the Comité Consultatif National d’Éthique.
- Parts of the work will be implemented in the National Park, sampling mosquitoes will require adhoc authorizations.
- The study will be conducted in part in communities with strong traditions and little French speaking. The presence in the villages as well as the sampling will be preceded by an agreement with the chief of the community as well as a discussion with the representatives. Interpreters will serve as intermediaries to ensure that the customs of each ethnic group are respected. Interventions will be made in schools to present the project and the reason for our presence to the children. The conclusions will be the object of presentations and playful activities for the communities concerned.

Conclusion and perspectives

Expanding from cities to most remote areas, from the most worldwide widespread arbovirus vector to cryptic and likely undescribed amazonian mosquitoes species, from traps in the rain forest to latest benchmark innovative genomics technics, from "les Abandonnés de la République"[31] to the European citizens working af the Kourou European spaceport, project will be a major "One Health" initiative, paving uncovered issues on medical care.

Schedule


Trimesters
T3_2022
T4_2022
T1_2023
T2_2023
KickOff Meeting & meetings with local & communities authorities
Analysis & publications
WP1
Task 1. Mosquitoes sampling
Task 2. Population genomics
Task 3. Dengue vector spreading
WP2
Task 1. Metabarcoding
Task 2. Metatranscriptomics
Task 3. Network analysis
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Task 2. Genoyping and serology
Task 3. BMC simulation
T3_2023
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WP2
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WP3
Task 1. sampling
Task 2. Genoyping and serology
Task 3. BMC simulation

Budget

WP1	Task 1. mosquitoes sampling	42200
	2 persons, 3 months (1 month on river 1, 1 month on river 2, 1 month on Coast)	18000
	matérial (traps, batteries, misceallenous)	6000
	external services (car rental for work on the coast, boat + pilot renting for each river)	8000
	Dry ice	3000
	feeding, lodging (40€ / pers/day)	7200
WP1	Task 2. population genomics	
	4 months (extraction + sampling preparation 1 month; analysis 3 months)	12000
	external service (SNP array design and screening)	12000
WP1	Task 3. Dengue screening	
	lab reagents (extraction, PCR)	1000
	external services (Sanger sequencing)	1500
	2 months lab work	6000

WP2	Task 1. metabarcoding	38000
(field work done in WP1/task1)	sample preparation (extraction, PCR)	3000
	external services (sequencing)	5000
	lab work (sampling preparation) and analysis (ingénieur, 1 month)	6000
WP2	Task 2. metatranscriptomics	
	samples preparation (1 month)	3000
	external services	9000
	bioinfo analysis (3 months)	9000
WP2	Task 3. network analysis	
	analysis (2 months)	3000

WP3	Task 1. Sampling (blood and saliva)	107500
travelling expenses (boat, car) with WP1	nurse 3 months	9000
	material (tubes, syringes, ...)	3000
	dry ice	3000
WP3	Task 2. Genotyping and serology	
	expected : 250 pers. 170€ /pers	42500
WP3	Task 3. PBMC stimulation & severe Dengue	
	RNAseq (DENV stimulated+unstimulated): 200 €/sample	50000

transversal costs	486345
international travels (France <------> French Guiana) x 6	6000
3 Intl congress	9000
publications (open access options)	6000
3 "Master 2" stipends (1 / WP)	9300
24 months postdoc	120000
2 researchers dedicated to the project, charged by their institution	307200
General costs (15% of the salaries)	28845
TOTALS	
TOTAL PROJECT	674045
TOTAL REQUESTED	366845

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