Original Research Article

Distinguishing non severe cases of dengue from COVID-19 in the context of co-epidemics: a cohort study in a SARS-CoV-2 testing center on Reunion island

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Short running head title: Dengue and COVID-19 in co-epidemics

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40-word summary of the article’s main point

In the COVID-19 dengue co-epidemic setting of Reunion island, dengue was found more symptomatic than COVID-19 and associated with body ache, headache and retro-orbital pain, while COVID-19 was found associated with contact, anosmia, delayed presentation and absence of active smoking.

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
Abstract

Background. As coronavirus (COVID-19) is spreading globally, several countries are handling dengue epidemics. As both infections are deemed to share similarities at presentation, it would be useful to distinguish COVID-19 from dengue in the context of co-epidemics. In this aim, we performed a cohort study to identify predictors of both infections.

Methods. All the subjects suspected of COVID-19 between March 23 and May 10, 2020, were screened for COVID-19 within the testing center of the University hospital of Saint-Pierre, Reunion island. The screening consisted in a questionnaire surveyed in face-to-face, a nasopharyngeal swab specimen for the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) reverse transcription polymerase chain-reaction and a rapid diagnostic orientation test for dengue. Factors independently associated with COVID-19 or with dengue were sought using multinominal logistic regression models, taking other febrile illnesses (OFIs) as controls.

Results. Over a two-month study period, we identified among 80 COVID-19, 60 non-severe dengue and 872 OFIs cases, delayed presentation (>3 days) since symptom onset (Odds ratio 1.89, 95% confidence interval 1.4-3.40), contact with a COVID-19 positive case (OR 3.81, 95%CI 2.12-6.82) and anosmia (OR 8.27, 95%CI 4.39-15.54) as independent predictors of COVID-19, body ache (OR 6.83, 95%CI 2.84-16.41), headache (OR 5.38, 95%CI 1.81-15.94) and retro-orbital pain (OR 7.45, 95%CI 3.17-17.50) as independent predictors of dengue, while smoking was less likely observed with COVID-19 (OR 0.27, 95%CI 0.10-0.74).

Conclusions. Although prone to potential biases, these data suggest that non-severe dengue may be more symptomatic than COVID-19 in a co-epidemic setting with higher dengue attack rates.

Keywords: coronavirus, COVID-19, dengue, risk factors, cohort study
Background

During the past decades, there have been growing concerns about the risks of overlapping epidemics and co-infections with emergent viruses, especially with arboviruses that can share the same *Aedes* mosquito vector [1,2]. Yet, surprisingly, since the 2009 flu pandemic, the differential diagnosis between influenza and dengue has been scarcely investigated [3].

As Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is spreading globally, several countries are handling dengue epidemics, with fear for their healthcare systems and most vulnerable populations [4]. Thus, differentiate between the two diagnoses may be challenging and lead to misdiagnosis, which may occasion both delays in treatment and preventable deaths, but also inadequate isolation measures with the potential to trigger outbreaks, especially in the healthcare setting [4].

On Reunion island, a French overseas department located in the Indian ocean, best known to have host one of the largest chikungunya outbreaks and harbor a highly comorbid population [5,6], dengue virus (DENV) is circulating since 2004 under an endemo-epidemic pattern with outbreaks usually peaking between March and May, and increases with yearly upsurges since 2015 [7]. In 2020, the first cases of coronavirus 2019 (COVID-19) were detected on the island by March 11, six days before the French authorities decree the lockdown.

In this context, a new case of COVID-19 and dengue co-infection was reported [8]. Anticipating that the differential diagnosis between the two infections would be challenging, we designated a retrospective cohort study aimed at identifying the clinical and epidemiological profiles of SARS-CoV-2 and DENV infections to guide their management and mitigate the impact of COVID-19 pandemic surge on the island.
Methods
The full details of the methods can be found in the Supplementary Methodological appendix.

Study design and setting
We conducted a retrospective cohort study between March 23 and May 10, 2020, on all subjects screened for the CO-VID-19 within the UDACS (Unité de Dépistage Ambulatoire du COVID-19 Sud) of Saint-Pierre, one of the two SARS-CoV-2 testing centers of the Centre Hospitalier Universitaire Réunion (CHU). When SARS-CoV-2 emerged on the island, the dengue epidemic was already burgeoning, the UDACS was placed in the second line of the reception system for COVID-19 patients, the frontline being the emergency units and the dedicated hospital for COVID-19 patients, the CHU Félix Guyon, located in Saint-Denis, whereby are the prefecture and the international airport.

Ethics statement
Outpatients presenting consecutively at the SARS-CoV-2 testing center were informed of the study orally and by means of an information sheet. People who expressed no opposition were asked to answer a questionnaire and surveyed in face-to-face by a nurse, in accordance to the French legislation on bioethics for retrospective researches. Patient’s medical records were retrospectively reviewed, and de-identified data were collected in standardized forms according the MR-004 procedure of the Commission Nationale de l’Informatique et des Libertés (the French information protection commission). The ethical character of this study on previously collected data was approved by the Scientific Committee for COVID-19 research of the CHU Réunion and de-identified data were registered on the Health Data Hub.

Data collection
The items of the questionnaire included information on demographics, occupation, risk factors, comorbidities, intra-household and individual exposure to SARS-CoV-2, individual
symptoms and treatment. Temperature, pulse rate, respiratory rate and oxygen saturation (SpO₂) were measured upon the consultation, as well as the presence of cough and anxiety.

**Diagnostic procedures**

All the attendees were screened for SARS-CoV-2 using a nasopharyngeal swab inserted and held in one nostril for about twenty seconds [9]. The sample was processed for a SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) using the Allplex 2019-nCov™ assay (Seegene, Seoul, Republic of Korea) or an in-house kit (CNR Pasteur), targeting N, RdRP and E genes, or N and IP2/IP4 targets of RdRP, respectively. In addition, each patient suspected of dengue was tested for NS1 antigen using an OnSite™ Duo dengue Ag-IgG-IgM rapid diagnostic test (CTK Biotech, San Diego, CA, USA) and if negative further explored with a DENV RT-PCR or a dengue serology according to the timing of symptoms. People without symptoms were excluded from the study. Patients requiring hospitalization were transferred promptly from the UDACS to the COVID-19 units.

**Statistical analysis**

Given the research purpose, co-infections at clinical presentation were excluded from the analysis. Proportions between non COVID-19 and non-dengue other febrile illnesses (OFIs), COVID-19 and dengue subjects were compared using Chi square or Fisher exact tests, as appropriate. Univariable and multivariable multinomial logistic regression models were fitted within Stata14® (College Station, Texas, USA) to identify independent predictors of COVID-19 and dengue, taking OFIs as controls. For all these analyses, observations with missing data were ruled out and a P-value less than 0.05 was considered as statistically significant.
Results

Between March 23 and May 10, 2020, 1,715 subjects presented at the UDACS for screening or diagnosis purposes. Of these, 370 incoming patients were screened opportunistically for COVID-19 as part of an expanded screening week targeting admissions to our hospital (75% asymptomatic, all tested negative), and 332 were fully asymptomatic subjects (44% with the notion of a COVID-19 contact, of whom 6 tested positive; 53% healthcare workers, of whom 2 tested positive; 5 tested positive without notion of COVID-19 contact nor an occupational exposure). Both of these populations were excluded from the study, leaving 1,013 outpatients eligible to the analysis. The study population is shown in Figure 1.

The hospitalization rates for the COVID-19 and dengue patients were higher than those observed for the patients affected by OFIs (16.7% and 13.1%, respectively versus 1.8%, \( P < 0.001 \)). Among 40 inpatients, 2 patients out of 22 met the criteria for COVID-19 pneumonia and 6 out of 8 had dengue warning signs but none severe dengue at clinical presentation. No COVID-19 dengue co-infection was observed at clinical presentation.

COVID-19 patients presented later in their evolution compared to the subjects affected by dengue or OFIs (time elapsed since symptom onset, 7.5 days versus 4.2 days or 6.3 days, \( P < 0.001 \)). The average levels of temperature, pulse rate, respiratory rate and spO2 did not differ between the three groups of patients.

Univariable analysis proposed contact with a COVID-19+ case, recent return from travel abroad (<15 d), fever, ageusia, anosmia (loss of smell) and delayed presentation (>3 d) since symptom onset as candidate predictors for COVID-19, active smoking as candidate protective factor against COVID-19, previous episode of dengue, fever, body ache (\( i.e. \), muscle pain, backache with tightness/stiffness), ageusia, gut symptoms (\( i.e. \), nausea, vomiting, dyspepsia, eructation or abdominal pain), metallic taste, fatigue, headache and...
retro-orbital pain as candidate predictors for dengue, and upper respiratory tract infection (URTI) symptoms (i.e., sore throat, runny nose, nasal congestion or sneezing) as a candidate protective factor for both diagnoses referring to another cause of febrile illness (Supplementary Table 1).

Multivariable analysis identified delayed presentation (>3 d) since symptoms onset, contact with a COVID-19 positive case and anosmia as independent predictors of COVID-19, body ache, headache and retro-orbital pain as independent predictors of dengue, while active smoking was less likely observed with COVID-19 and URTI symptoms were indicative of OFIs (Table 1).

A sensitivity analysis restricted to the patients with COVID-19 or with dengue confirmed anosmia, URTI symptoms and delayed presentation (>3 d) on the one hand, body ache, fatigue, headache, retro-orbital pain and rapid presentation (≤ 3 d) on the other hand, as discriminating factors between the two infections (Supplementary Table 2).
Discussion

COVID-19 and dengue are two clinically similar entities, especially within the first 24 to 48 hours from symptom onset [10]. In a context of co-epidemics, our cohort study, conducted within a SARS-CoV-2 testing center upon mild to moderate cases of COVID-19 and non-severe cases of dengue identified several key distinctive features for both infections. Thus, among the clinically discriminant variables at presentation, retro-orbital pain, body ache and headache were strong predictors of dengue while anosmia was the only predictor of COVID-19 and URTI symptoms were indicative of OFIs. To a lesser extent, gut symptoms other than diarrhea, dysgeusia and fatigue were suggestive of dengue whereas cough referred to another diagnosis (OFIs or COVID-19), albeit found in nearly a third of dengue. Thus, among the epidemiological variables, the contact with a COVID+ case and a delayed presentation beyond three days of symptom onset were predictive of COVID-19, a rapid presentation within three days was suggestive of dengue, while active smoking was less likely observed with COVID-19 or associated with OFIs. These elements are summarized in the Supplemental Figure 1.

Our findings reveal several unexpected differences at the presentation to hospital between COVID-19 or dengue as compared to OFIs, and between COVID-19 and dengue, dengue appearing at first glance more symptomatic and with a more abrupt onset than COVID-19 or OFIs in the setting of a SARS-CoV-2 testing center.

These discrepancies might reflect first a selection bias, the more symptomatic cases of both infections having been referred primarily to the emergency units, these redirecting the COVID-19 cases towards the Saint-Denis referral hospital for quarantine purpose. This could be arguably deduced from weighing on the inverse probability of hospitalization, which was on average 2.5-fold higher than from the UDACS, all through the study period.
Doing so abrogates, for instance, the effects of a delayed presentation and the protection of active smoking for the prediction of COVID-19 (data not shown). Together with the fact that the dengue epidemic was more active in the south, this fuels the idea that time to presentation in our study partly stemmed from differences in recruitment driven both by the organization and access to care. Importantly, weighing the analysis strengthened also the odds ratios of a contact with a COVID-19+ case for the same, as well as those of headache and retro-orbital pain for the prediction of dengue. These elements suggest that this putative selection bias was more pronounced on epidemiological than on clinical variables.

Second, our results might also be affected by a misclassification bias, which may arise from the poor sensitivity of both rapid NS1 antigen and SARS-CoV-2 RT-PCR. Consistent with this, are the high percentages of cough and URTI symptoms in dengue cases, for instances.

This being said, our findings are also in agreement with the literature. First, the fact that dengue was more symptomatic than COVID-19 fulfills both the concept of "force infection" and the trade-off model according to which, the time spent in the susceptible group of an infectious disease is inversely correlated to its incidence [11], and the virulence (e.g., ability to cause illness, lethality) grows with the transmission rate until it reaches a plateau [12]. Consistent with these assumptions, according to Santé Publique France reports, the attack rate observed over the study period was 22-fold higher for dengue (≈905 per 100.000 inhabitants) than for COVID-19 (≈41 per 100.000 inhabitants). This was explained by the recent introduction of DENV-1 serotype (March 2019) complicating five years of DENV-2 circulation [7], cases of secondary dengue, the effectiveness of the lockdown to slow the progression of COVID-19 and the fact that SARS-CoV-2 impacted at that time mainly "healthy" individuals (travelers and their relatives). In this framework, the relevance of body ache, headache and retro-orbital pain at presentation
for the differential diagnosis between COVID-19 and dengue accounts for the involvement of
dengue in the general and digestive spheres, as proposed by Nacher et al. in a recent
opinion paper, COVID-19 being more pronounced in the respiratory sphere [10].
Interestingly, we also found one COVID-19+ case who was tested negative for dengue
suffering retro-orbital pain, as previously reported in Taiwan [13].
Second, our cohort study supports the high positive predictive values and specificities
of the contact with a COVID-19+ case and anosmia for the diagnostic of COVID-19, which is
congruent with risk prediction models developed for healthcare workers in Italy [14] and
findings from the Coranosmia cohort study in France [15], respectively.
Together with the abovementioned putative selection bias, the delayed presentation
to hospital of COVID-19 cases, as compared to dengue, might also illustrate the mild ("pauci-
symptomatic") character of COVID-19 illness during the first pandemic surge on Reunion
island, as well as some consecutive lags in contact tracing. Overall, individuals who did not
feel or only slightly sick with COVID-19 might have not feel the need to be tested. However,
this hypothesis does not stand the absence of clear association between the proportions of
asymptomatic infections and time to presentation (i.e., with 3-fold more asymptomatic
cases, OFIs cases presented faster than COVID-19 cases; data not shown).
Interestingly, active smoking was less likely observed with COVID-19 as compared to
OFIs or dengue, but this effect was not robust as suggested above. Moreover, it was not
replicated for asymptomatic SARS-CoV-2 infections, nor it was among COVID-19+ cases for
the protection against illness (data not shown). Notwithstanding, this result fuels the
smoker's paradox according to which active smokers were underreported among the
patients hospitalized for COVID-19 in several countries [16].
In conclusion, our cohort study identified several factors distinguishing non severe dengue from COVID-19 at clinical presentation in a context of recent dengue endemicity and first introduction of SARS-CoV-2. Although prone to potential biases, these data suggest that non severe dengue may be more symptomatic than COVID-19 in a co-epidemic setting with higher dengue attack rates, a pattern that might also result from different forces of infection (lesser exposure to SARS-CoV-2 than to DENV). Whether these findings may serve other regions facing co-epidemics, deserves more investigations, development and validation of more accurate diagnostic tools.

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Supplementary data

Supplementary materials are available online. While the supplementary tables have been copyedited, the Methodological appendix and the Venn diagram have not been copyedited and are the sole responsibility of the authors. Questions and comments about these should be addressed to the corresponding author.
Notes

Author’s contributions. F.A and CL conceived and designed the study. A.J, F.A, A.B, F.A, Y.K, F.L, P.P, R.M contributed to the data acquisition. P.G designed and performed the statistical analyses and is the data curator. F.A, C.L., A.B., and PG interpreted the data. A.J. and C.L drafted the paper with the help of P.G. All authors contributed to critical examination of the paper for intellectual content and approved the final manuscript.

List of abbreviations. CIR: cumulative incidence rate (= attack rate); CNR: centre national de reference; COVID-19: coronavirus 2019; DENV: dengue virus; OFIs: other febrile illnesses; aOR: adjusted odds ratio; RT-PCR: reverse transcription – polymerase chain reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; spO2: partial saturation of oxygen; UDACS: unite de dépistage ambulatoire du coronavirus sud; URTI: upper respiratory tract infection; 95% CI: 95% confidence intervals.

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Table 1. Independent predictors in multivariate analysis distinguishing COVID-19 and dengue from other febrile illnesses among 972 subjects consulting a COVID-19 screening center during the COVID-19 dengue co-epidemics, Reunion Island, Saint-Pierre, March 23-May 10, 2020

| Outcomes (versus other febrile illnesses as controls*) | COVID-19 (n = 74) | Dengue (n = 60) |
|------------------------------------------------------|------------------|----------------|
| Predicators                                          | n    | CIR, %  | aOR  | 95% CI | P value | n    | CIR, %  | aOR  | 95% CI | P value |
| Age, years                                           |      |         |      |        |         |      |         |      |        |         |
| 0-30 (Q1)                                            | 24   | 8.63    | 0.90 | 0.41 - 1.93 | 0.782 | 8    | 2.88   | 0.21 | 0.06 - 0.68 | 0.009 |
| 31-41 (Q2)                                           | 10   | 3.68    | 0.41 | 0.17 - 1.00 | 0.050 | 25   | 9.19   | 1.03 | 0.43 - 2.44 | 0.947 |
| 42-54 (Q3)                                           | 26   | 10.20   | 1.24 | 0.60 - 2.53 | 0.554 | 13   | 5.10   | 0.38 | 0.14 - 0.99 | 0.048 |
| 55-94 (Q4)                                           | 14   | 8.38    | 1    |         |         | 14   | 8.38   | 1    |         |         |
| Contact with a COVID-19 positive case                | 40   | 15.33   | 3.81 | 2.12 - 6.82 | <0.001 | 6    | 2.30   | 0.88 | 0.34 - 2.24 | 0.778 |
| Active smoking†                                      | 4    | 2.53    | 0.27 | 0.10 - 0.74 | 0.011 | 12   | 7.59   | 1.72 | 0.34 - 2.24 | 0.182 |
| Cough                                                | 32   | 6.82    | 0.81 | 0.45 - 1.44 | 0.471 | 17   | 3.62   | 0.38 | 0.20 - 0.74 | 0.004 |
| Body ache‡                                           | 29   | 7.09    | 1.12 | 0.62 - 2.01 | 0.705 | 52   | 12.71  | 6.83 | 2.84 - 16.41 | <0.001 |
| Anosmia                                              | 26   | 27.96   | 8.27 | 4.39 - 15.54 | <0.001 | 3    | 3.23   | 0.43 | 0.09 - 2.07 | 0.296 |
| Headache                                             | 28   | 5.69    | 0.84 | 0.50 - 1.41 | 0.508 | 55   | 11.18  | 5.38 | 1.81 - 15.94 | 0.002 |
| Retro-orbital pain†                                   | 1    | 2.27    | 0.39 | 0.03 - 4.19 | 0.437 | 17   | 38.64  | 7.45 | 3.17 - 17.50 | <0.001 |
| URTI symptoms#                                       | 28   | 5.63    | 0.53 | 0.31 - 0.89 | 0.017 | 20   | 4.02   | 0.46 | 0.23 - 0.91 | 0.027 |
| Presentation > 3 days after symptom onset            | 54   | 9.69    | 1.89 | 1.04 - 3.40 | 0.035 | 24   | 4.31   | 0.76 | 0.40 - 1.44 | 0.402 |

Multinomial logistic regression model with other non COVID-19 non dengue febrile illnesses*, taken as controls. Data are numbers, cumulative incidence rates (CIR) expressed as percentages, adjusted odd ratios (aOR), 95% confidence intervals (95% CI) and P values for Wald tests. † Current smokers, as compared to never smokers and past smokers ‡ muscle pain or backache with tightness and/or stiffness; # sore throat, runny nose, nasal congestion, or sneezing. The indicators of performance of the model are as follows: Bayesian information criterion -5696, Goodness of fit chi-2 test’s probability 0.605, areas under the receiver operating curves 0.795 and 0.892.
respectively.
Figures

Figure 1. Study population