

1 Original Research Article

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

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19 Short running head title: **Factors distinguishing dengue and COVID-19 in co-epidemics**

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25

26 **Abstract**

27 **Background.** As coronavirus 2019 (COVID-19) is spreading globally, several countries are handling
28 dengue epidemics. As both infections are deemed to share similarities at presentation, it would be
29 useful to distinguish COVID-19 from dengue in the context of co-epidemics. Hence, we performed a
30 retrospective cohort study to identify predictors of both infections.

31 **Methodology/Principal Findings.** All the subjects suspected of COVID-19 between March 23 and
32 May 10, 2020, were screened for COVID-19 within the testing center of the University hospital of
33 Saint-Pierre, Reunion island. The screening consisted in a questionnaire surveyed in face-to-face, a
34 nasopharyngeal swab specimen for the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-
35 CoV-2) reverse transcription polymerase chain-reaction and a rapid diagnostic orientation test for
36 dengue. Factors independently associated with COVID-19 or with dengue were sought using
37 multinomial logistic regression models, taking other febrile illnesses (OFIs) as controls. Adjusted Odds
38 ratios (OR) and 95% Confidence Intervals (95%CI) were assessed. Over a two-month study period, we
39 diagnosed 80 COVID-19, 60 non-severe dengue and 872 OFIs cases. Among these, we identified
40 delayed presentation (>3 days) since symptom onset (Odds ratio 1.91, 95% confidence interval 1.07-
41 3.39), contact with a COVID-19 positive case (OR 3.81, 95%CI 2.21-6.55) and anosmia (OR 7.80, 95%CI
42 4.20-14.49) as independent predictors of COVID-19, body ache (OR 6.17, 95%CI 2.69-14.14),
43 headache (OR 5.03, 95%CI 1.88-13.44) and retro-orbital pain (OR 5.55, 95%CI 2.51-12.28) as
44 independent predictors of dengue, while smoking was less likely observed with COVID-19 (OR 0.27,
45 95%CI 0.09-0.79) and upper respiratory tract infection symptoms were associated with OFIs.

46 **Conclusions/Significance.** Although prone to potential biases, these data suggest that non-severe
47 dengue may be more symptomatic than COVID-19 in a co-epidemic setting with higher dengue attack
48 rates. At clinical presentation, eight basic clinical and epidemiological indicators may help to
49 distinguish COVID-19 or dengue from each other and other febrile illnesses.

Keywords : coronavirus; COVID-19; severe acute respiratory syndrome; SARS-CoV-2; dengue; arbovirus; flavivirus; epidemics; pandemics; epidemiology; cohort study; risk factors; predictors; multivariate analysis; logistic regression; multinomial logistic regression

Author Summary

As coronavirus 2019 (COVID-19) is spreading globally, several countries are facing dengue epidemics with the fear the two plagues might overburden their healthcare systems. On Reunion island, southwestern Indian ocean: dengue virus is circulating since 2004 under an endemo-epidemic pattern with yearly outbreaks peaking between March and May since 2015, whereas Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the pathogen responsible of COVID-19, emerged in March 2020, imported from the Bahamas. COVID-19 and dengue are deemed two clinically similar entities, especially within the first two days from symptom onset. In this context, we conducted a cohort study between March 23 and May 10, 2020, within a SARS-CoV-2 testing center, aimed at identifying the factors discriminating both infections. Surprisingly, we found that non-severe dengue was more symptomatic than mild to moderate COVID-19. Indeed, we found body ache, headache and retro-orbital pain to be indicative of dengue, whereas contact with a COVID-19 positive case, anosmia, delayed presentation (>3 days post symptom onset) and absence of active smoking were indicative of COVID-19. These findings highlight the need for accurate diagnostic tools and not to jeopardize dengue control in areas wherever COVID-19 dengue co-epidemics have the potential to wrought havoc to the healthcare system.

71 Background

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

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

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

89 In this context, a new case of COVID-19 and dengue co-infection was reported [8].
90 Anticipating that the differential diagnosis between the two infections would be challenging,
91 we designated a retrospective cohort study aimed at identifying the clinical and
92 epidemiological profiles of SARS-CoV-2 and DENV infections to guide their management and
93 mitigate the impact of COVID-19 pandemic surge on the island.

94 **Methods**

95 The full details of the methods can be found in the [Methodological appendix \(Supp-1 file\)](#).

96 **Study design, setting and population**

97 We conducted a retrospective cohort study using prospectively collected data between
 98 March 23 and May 10, 2020, on all subjects screened for the COVID-19 within the UDACS
 99 (*Unité de Dépistage Ambulatoire du COVID-19 Sud*) of Saint-Pierre, one of the two SARS-CoV-
 100 2 testing centers of the *Centre Hospitalier Universitaire (CHU) Réunion*. When SARS-CoV-2
 101 emerged on the island, the dengue epidemic was already burgeoning, the UDACS was placed
 102 in the second line of the reception system for COVID-19 patients, the frontline being the
 103 emergency units and the dedicated hospital for COVID-19 patients, the CHU Félix Guyon,
 104 located in Saint-Denis, whereby are the prefecture and the international airport. People
 105 without symptoms were excluded from the study.

106 **Ethics statement**

107 Outpatients presenting consecutively at the SARS-CoV-2 testing center were informed of the
 108 study orally and by means of an information sheet. Adult people, like the children under 18
 109 years (with the additional verbal consent of their parent or legal guardian) who expressed no
 110 opposition, were asked to answer a questionnaire and surveyed in face-to-face by a nurse, in
 111 accordance to the French legislation on bioethics for retrospective researches. Patient's
 112 medical records were retrospectively reviewed, and de-identified data were collected in
 113 standardized forms according to the MR-004 procedure of the *Commission Nationale de*
 114 *l'Informatique et des Libertés* (the French information protection commission). The ethical
 115 character of this study on previously collected data was approved by the Scientific
 116 Committee for COVID-19 research of the CHU Réunion and de-identified data were
 117 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 peripheral oxygen saturation (SpO₂) were measured upon the consultation, as well as clinical symptoms, including verification of the presence of cough and anxiety.

Diagnostic procedures

All the attendees were screened by a skilled nurse for SARS-CoV-2 using a nasopharyngeal swab inserted and held in one nostril until reaching the posterior wall of the nasopharynx 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 depending on the date of symptom onset.

Statistical analysis

Given the research purpose, COVID-19-dengue co-infections at clinical presentation were excluded from the analysis. Other febrile illnesses (OFIs) were defined as patients tested negative for SARS-CoV-2 and further considered as unrelated to dengue, either clinically, virologically, or serologically. COVID-19, dengue and OFI subjects were compared using Chi square or Fisher exact tests, as appropriate. Univariable and multivariable multinomial logistic regression models were fitted within Stata14® (StataCorp, College Station, Texas, USA) to identify both the independent predictors of COVID-19 and dengue, taking OFIs as

142 controls. Crude and adjusted odds ratios (OR) and 95% confidence intervals (95%CI) were
143 assessed using the binomial and Cornfield methods, respectively.

144 For all these analyses, observations with missing data were ruled out and a *P*-value
145 less than 0.05 considered 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 these populations were excluded from the study, leaving 1,013 outpatients eligible to the analysis. The study population is shown in Figure 1.

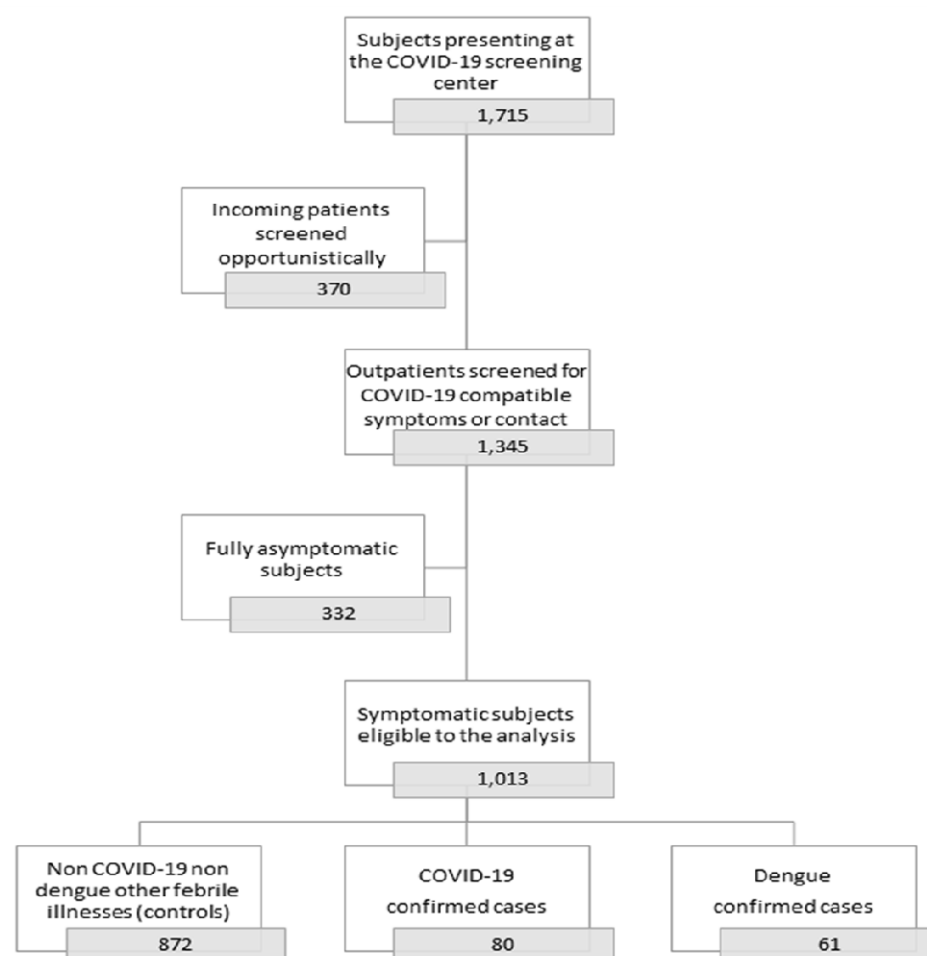


Figure 1. Study population

The characteristics of the 1,013 symptomatic subjects eligible to analysis are presented in [Table 1](#).

The hospitalization rates (at least one night) for the COVID-19 and dengue patients were higher than those observed for the patients affected by OFIs (17.5% and 8.2%, respectively *versus* 1.5%, $P < 0.001$). Among 32 patients that were hospitalized, 2 COVID-19 patients out of 14 met the criteria for COVID-19 pneumonia and 5 dengue patients out of 5 had dengue warning signs but none had 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 were identified as candidate predictors for dengue whereas recent return from travel abroad and cough, as candidate protective factors against dengue. Interestingly, upper respiratory tract infection (URTI) symptoms (*i.e.*, sore throat, runny nose, nasal congestion or sneezing) were identified as candidate protective factors against both diagnoses, which made these rather predictors of OFIs ([S1 Table](#), [Supp-2](#)).

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 2](#)).

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 ([S2 Table](#), [Supp-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. 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. Among the epidemiological variables, the contact with a COVID-19+ 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 [S1 Figure](#).

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 instances, 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 southern part of the island, 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 both from the poor sensitivity of SARS-CoV-2 RT-PCR and rapid NS1 antigen, rather than from the false positive rates.

Third, given the fear of COVID-19 at that time, we cannot rule out the possibility of a reporting bias, as some patients may have declared URTI symptoms or cough in excess just to be tested for SARS-CoV-2. Consistent with this, are the relatively high percentages of cough and URTI symptoms among dengue cases, as well as the totality of anxiety cases upon testing observed within the OFI group (data not shown), for instances.

Together with the abovementioned sources of bias, a lack of power might have reduced the capability to shed light on other discriminating factors. However, we believe that this study faithfully reflects the real epidemiological situation on Reunion island at that time, given diagnostic practices and means that were commonly used in this era of uncertainty, which is unlikely to have biased the overall sense of our results.

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 of infection" and the trade-off model according to which, the time spent in

the susceptible group to an infectious disease is inversely correlated to its incidence [11], and the virulence (*i.e.*, 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 ("paucisymptomatic") character of COVID-19 illness during the first pandemic surge on Reunion island, as well as some consecutive lags in contact tracing. Overall, the individuals who did not feel or only slightly sick with COVID-19 might not have felt 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, which was observed upstream to the analysis (*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 to be observed with COVID-19 as compared to OFIs or dengue, but this apparent protective effect was not robust as suggested above. Moreover, it was not replicated for asymptomatic SARS-CoV-2 infections, nor was it shown to protect from contracting illness with COVID-19 (data not shown). This finding seems paradoxical given recent evidence shows that Angiotensin-converting enzyme 2 (ACE2), the SARS-CoV-2 entry receptor, is overexpressed in smoker's bronchial and alveolar epithelia, which should increase the risk of infection [16-18]. Whether this finding results from abovementioned misclassification or reporting bias deserves further studies. Notwithstanding, this fuels the smoker's paradox according to which active smokers were first underreported among the patients hospitalized for COVID-19 in several countries [19], then less likely to be infected, as shown from a recent meta-analysis [20].

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 at presentation 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. These findings highlight also

284 the need not to jeopardize dengue control wherever COVID-19 dengue co-epidemics have
285 the potential to wrought havoc to the healthcare system [21].

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Supporting information

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. STROBE checklist.

Notes

Author's contributions. F.A and C.L 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 disease of 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: Saturation of peripheral oxygen; UDACS: unite de dépistage ambulatoire du coronavirus sud; URTI : upper respiratory tract infection; 95% CI: 95% confidence intervals.

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Data availability statement. The data will be fully accessible within a data repository once the article is accepted for publication.

References

1. Caron M, Paupy C, Grard G, Becquart P, Mombo I, Nso BB, et al. Recent introduction and rapid dissemination of Chikungunya virus and Dengue virus serotype 2 associated with human and mosquito coinfections in Gabon, central Africa. *Clin Infect Dis* 2012; 55: e45-53. <http://dx.doi:10.1093/cid/cis530>. Epub 2012 Jun 5.
2. Waggoner JJ, Gresh L, Vargas MJ, Ballesteros G, Tellez Y, Soda J, et al. Viremia and clinical presentation in Nicaraguan patients infected with Zika virus, Chikungunya virus and Dengue virus. *Clin Infect Dis* 2016; 63:1584-1590. <http://dx.doi:10.1093/cid/ciw589>.
3. Huang SY, Lee IK, Wang L, Liu JW, Hung SC, Chen CC, et al. Use of simple clinical and laboratory predictors to differentiate influenza from dengue and other febrile illnesses in the emergency room. *BMC Infect Dis* 2014; 14: 623. <http://dx.doi:10.1186/s12879-014-0623-z>.
4. Wilder-Smith A, Tissera H, Ooi EE, Coloma J, Scott TW, Gubler DJ. Preventing dengue epidemics during COVID-19 pandemic. *Am J Trop Med Hyg* 2020; 103: 570-571. <http://dx.doi:10.4269/ajtmh.20-0480>.
5. Gérardin P, Guernier V, Perrau J, Fianu A, Le Roux K, Grivard P, et al. Estimating Chikungunya prevalence in La Réunion island outbreak by serosurveys: two methods for two critical times of the epidemic *BMC Infect Dis* 2008; 8: 99. <http://dx.doi:10.1186/1471-2334-8-99>.
6. Cournot M, Lenclume M, Le Moullec N, Debussche C, Doussiet E, Fagot-Campagna A, et al. Prevalence, treatment and control of hypertension in La Réunion: the RÉDIA population-based cohort study. *Blood Press* 2017; 26(1):39-47. <http://dx.doi:10.1080/08037051.2016.1182854>. Epub 2016 May 19.
7. Vincent M, Larrieu S, Vilain P, Etienne A, Solet JL, François C, et al. From the threat to the large outbreak: dengue on Reunion island. *Euro Surveill* 2019; 24: 1900346. <http://dx.doi:10.2807/1560-7917.ES.2019.24.47.1900346>.

8. Verduyn M, Allou N, Gazaille V, Andre M, Desroche T, Jaffar M-C, et al. Co-infection of dengue and COVID-19: A case report. *PLoS Negl Trop Dis* 2020; 14: e0008476. <https://dx.doi.org/10.1371/journal.pntd.0008476>.
9. Marty FM, Chen K, Verrill KA. How to obtain a nasopharyngeal swab specimen. *New Engl J Med* 2020; 382; e76. <https://dx.doi.org/10.1056/NEJMvcm2010260>.
10. Nacher M, Douine M, Gaillet M, Flamand C, Rousset D, Rousseau C, et al. Simultaneous dengue and COVID-19 epidemics: difficult days ahead? *PLoS Negl Trop Dis* 2020; 14: e0008426. <https://dx.doi.org/10.1371/journal.pntd.0008426>.
11. Katzelnick LC, Ben-Shachar R, Mercado JC, Rodriguez-Barraquer I, Elizondo D, Arguello S, et al. Dynamics and determinants of the force of infection of dengue virus from 1994 to 2015 in Managua, Nicaragua. *Proc Natl Acad Sci U S A* 2018; 115: 10762-10767. <https://dx.doi.org/10.1073/pnas.1809253115>.
12. Ebert D, Bull JJ. Challenging the trade-off model for the evolution of virulence: is virulence management feasible? *Trends Microbiol* 2013; 11: 15-20. [https://dx.doi.org/10.1016/s0966-842x\(02\)00003-3](https://dx.doi.org/10.1016/s0966-842x(02)00003-3).
13. Ruy W, Hsu SY, Tsai HL, CT Chen. COVID-19 mimicking dengue fever with the initial manifestation of retro-orbital pain – a rare case. *J Formos Med Assoc* 2020 Jun 4; S0929-6646(20)30229-1. <https://dx.doi.org/10.1016/j.jfma.2020.05.039>. Online ahead of print.
14. Ng MY, Wan EYF, Wong HYF, Leung ST, Lee JCY, Chin TW, et al. Development and validation of risk prediction models for COVID-19 positivity in a hospital setting. *Int J Infect Dis* 2020 Sep 15; S1201-9712(20)30738-4. <https://dx.doi.org/10.1016/j.ijid.2020.09.022>. Online ahead of print.
15. Salmeron Ceron D, Bartier S, Hautefort C, Nguyen Y, Nevoux J, Hamel AL, et al. Self-reported loss of smell with nasal obstruction to identify COVID-19. The multicenter Coranosmia cohort study. *J Infect* 2020; 81: 614-620. <https://dx.doi.org/10.1016/j.jinf.2020.07.005>.

16. Zhang H, Rostami MR, Leopold PL, Mezey JG, O'Beime SL, Strulovici-Barel Y, et al. Expression of the SARS-CoV-2 ACE2 receptor in the human airway epithelium. *Am J Resp Crit Care Med* 2020; 202; 219-229. <https://dx.doi.org/10.1164/rccm.202003-0541OC>.
17. Jacobs M, Van Eeckhoutte HP, Wijnant SRA, Janssens W, Joos GF, Brusselle GG, et al. Increased expression of ACE2, the SARS-CoV-2 entry receptor, in alveolar and bronchial epithelium of smokers and COPD subjects. *Eur Respir J* 2020; 56: 2002378. <https://dx.doi.org/10.1183/13993003.02378-2020>.
18. Liu A, Zhang X, Li R, Zheng M, Yang S, Dai L, et al. Overexpression of the SARS-CoV-2 receptor ACE2 is induced by cigarette smoke in bronchial and alveolar epithelia. *J Pathol* 2021; 253: 17-30. <https://dx.doi.org/10.1002/path.5555>. Epub 2020 Oct 27.
19. Usman MS, Siddiqi TJ, Khan MS, Patel UK, Shahid I, Ahmed J, et al. Is there a smoker's paradox in COVID-19? *BMJ Evid Based Med*. 2020 Aug 11;bmjebm-2020-111492. <https://dx.doi.org/10.1136/bmjebm-2020-111492>. Online ahead of print.
20. Simons D, Shahab L, Brown J, Perski O. The association of smoking status with SARS-CoV-2 infection, hospitalization and mortality from COVID-19: a living rapid evidence review with Bayesian analyses (version 7). *Addiction* 2020; 10.1111/add.15276. <https://dx.doi.org/10.1111/add.15276>.
21. Olive MM, Baldet T, Devillers J, Fite J, Paty MC, Paupy C, et al. The COVID-19 pandemic should not jeopardize dengue control. *PLoS Negl Trop Dis* 2020; 14: e0008716. <https://dx.doi.org/10.1371/journal.pntd.0008716>.

Table 1. Characteristics of 1,013 subjects consulting a COVID-19 screening center during the COVID-19 dengue co-epidemics, Reunion island, Saint-Pierre, March 23-May 10, 2020

Outcomes	Other febrile illnesses (n = 872)		COVID-19 (n = 80)		Dengue (n = 61)		
Variables	n	(%)	N	(%)	N	(%)	P value
Male gender	343	39.3	33	41.2	31	50.8	0.205
Age (years), $\mu \pm$ sd	38.7	16.2	39.2	18.4	42.0	13.4	0.280
0-30 (Q1)	253	29.0	28	35.0	8	13.1	0.002
31-41 (Q2)	247	28.3	10	12.5	26	42.6	
42-54 (Q3)	221	25.3	27	33.7	13	21.3	
55-94 (Q4)	151	17.3	15	18.7	14	22.9	
Contact with a COVID-19 positive case	231	26.5	42	52.5	6	9.8	< 0.001
Return from travel abroad < 15 days	202	23.2	42	53.2	6	9.8	< 0.001
Previous dengue episode	32	3.7	6	7.6	9	14.7	0.001
Comorbidities [§]	435	49.9	34	42.5	31	50.8	0.437
Morbid obesity (body mass index $\geq$ 40 kg/m ²)	19	2.2	0	0.0	2	3.3	0.359
Active smoking [†]	146	16.8	4	5.2	12	19.7	0.022
Fever	374	42.9	45	56.2	59	96.7	< 0.001
Duration of fever (days), $\mu \pm$ sd	3.34	3.15	3.43	3.35	3.03	2.88	0.799
Cough	435	49.9	36	45.0	17	27.9	0.003
Duration of cough (days), $\mu \pm$ sd	5.44	5.71	2.14	12.84	5.79	7.98	0.099
Dyspnea/Shortness of breath	204	23.4	13	16.3	13	21.3	0.332
Duration of dyspnea (days), $\mu \pm$ sd	4.14	4.50	5.44	8.43	7.75	5.25	0.376
Body ache [‡]	339	38.9	32	40.0	52	85.2	< 0.001
Duration of pain (days), $\mu \pm$ sd	3.89	3.69	4.34	5.49	2.90	2.72	0.088
Diarrhea	179	20.2	19	23.7	13	21.3	0.746
Duration of liquid stools (days), $\mu \pm$ sd	2.70	2.62	4.50	3.79	2.25	3.14	0.099
Gut symptoms [¶]	44	5.0	4	5.0	13	21.3	< 0.001
Ageusia	84	9.6	25	31.2	11	18.0	< 0.001
Duration of ageusia (days), $\mu \pm$ sd	3.93	4.16	4.73	3.32	3.25	2.01	0.263
Metallic taste (dysgeusia)	4	0.5	0	0.0	2	3.3	0.068
Anosmia	67	7.7	28	35.0	3	4.9	< 0.001
Duration of anosmia (days), $\mu \pm$ sd	4.35	4.45	4.22	3.59	1.00	1.00	0.199
Fatigue	370	42.4	38	47.5	49	80.3	< 0.001
Duration of fatigue (days), $\mu \pm$ sd	4.29	4.20	6.48	5.75	3.44	3.00	0.027
Headache	410	47.1	31	38.7	56	91.8	< 0.001
Duration of headache (days), $\mu \pm$ sd	3.95	3.94	4.69	5.61	3.02	2.74	0.324
Retro-orbital pain	26	3.0	1	1.2	17	27.9	< 0.001
URTI symptoms [#]	459	52.6	31	38.7	20	32.8	0.001
Duration of rhinorrhea (days), $\mu \pm$ sd	4.45	4.47	5.33	3.69	2.10	0.91	0.036
Duration of sore throat (days), $\mu \pm$ sd	4.17	3.98	4.00	3.27	6.20	8.22	0.995
Presentation > 3 days after symptom onset	481	57.2	54	70.1	24	40.0	0.002
Time elapsed since symptom onset (days), $\mu \pm$ sd	6.27	6.25	7.54	6.50	4.18	4.57	< 0.001
Need for physical examination at presentation	131	15.0	8	10.1	19	31.1	0.001
Dry cough at presentation	10	1.1	2	2.6	1	1.6	0.315
Anxiety at presentation	17	1.9	0	0.0	0	0.0	0.459
Frontal temperature (°C), $\mu \pm$ sd	37.11	0.92	36.98	0.99	37.33	1.27	0.337
Cardiac rate (pulses per minute), $\mu \pm$ sd	86.84	16.46	86.38	16.80	89.89	18.60	0.520
Respiratory rate (cycles per minute), $\mu \pm$ sd	17.56	4.88	17.39	5.69	18.09	4.98	0.479
SpO ₂ (%), $\mu \pm$ sd	97.85	1.08	97.23	1.47	97.72	1.11	0.002
Hospitalization	13	1.5	14	17.5	5	8.2	< 0.001
Length of Stay (days), $\mu \pm$ sd	1.4	0.7	9.9	7.1	1.0	0.7	< 0.001

Data are numbers, column percentages, and P values for Chi2 or Fisher's exact tests, unless specified as means, standard deviations, and P values for Kruskal-Wallis tests. [§] 15: Urgent Medical Aid Service (SAMU); [§] diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease, asthma, or cancer; [†] Current smoker, as compared to never smoker and past smoker; [‡] muscle pain or backache with tightness and/or stiffness; [¶] nausea, vomiting, dyspepsia, eructation or abdominal pain [#] sore throat, runny nose, nasal congestion, or sneezing.

Table 2. 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)				
Predictors	n	CIR, %	aOR	95% CI	P value	n	CIR, %	aOR	95% CI	P value
Contact with a COVID-19 positive case	40	15.33	3.81	2.21 - 6.55	< 0.001	6	2.30	0.8	0.31 - 2.09	0.663
Active smoking †	4	2.53	0.27	0.09 - 0.79	0.017	12	7.59	1.39	0.65 - 2.94	0.391
Cough	32	6.82	0.82	0.47 - 1.42	0.474	17	3.62	0.38	0.19 - 0.73	0.003
Body ache ‡	29	7.09	1.12	0.66 - 2.14	0.564	52	12.71	6.17	2.69 - 14.14	< 0.001
Anosmia	26	27.96	7.80	4.20 - 14.49	< 0.001	3	3.23	0.47	0.12 - 1.75	0.258
Headache	28	5.69	0.79	0.45 - 1.38	0.403	55	11.18	5.03	1.88 - 13.44	0.001
Retro-orbital pain	1	2.27	0.45	0.05 - 3.74	0.458	17	38.64	5.55	2.51 - 12.28	< 0.001
URTI symptoms #	28	5.63	0.52	0.30 - 0.91	0.021	20	4.02	0.49	0.26 - 0.93	0.028
Presentation > 3 days after symptom onset	54	9.69	1.91	1.07 - 3.39	0.027	24	4.31	0.74	0.40 - 1.36	0.339

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 -5733, Goodness of fit chi-2 test's probability 0.823, areas under the receiver operating characteristic curves 0.783 and 0.877, respectively.

34 **Figures**

35 **Fig 1. Study population**

36

37 **S1 Fig. Predictors associated with COVID-19, dengue, and other non-febrile illnesses**

38 Predictors for COVID-19 are displayed in the bottom left circle of the Venn diagram, predictors for dengue
 39 in the top circle, and predictors for non COVID-19 non dengue other febrile illnesses in the bottom right
 40 circle. Independent predictors are in bold characters, crude predictors that do not resist to multiple
 41 adjustments are in thin characters.