

1 **Myocarditis in naturally infected pets with the British variant of COVID-19**

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## 35 **Abstract**

36 Domestic pets can contract SARS-CoV-2 infection but, based on the limited information available to  
37 date, it is unknown whether the new British B.1.1.7 variant can more easily infect certain animal  
38 species or increase the possibility of human-to-animal transmission. In this study, we report the first  
39 cases of infection of domestic cats and dogs by the British B.1.1.7 variant of SARS-CoV-2 diagnosed  
40 at a specialist veterinary hospital in the South-East of England. Furthermore, we discovered that many  
41 owners and handlers of these pets had developed Covid-19 respiratory symptoms 3-6 weeks before  
42 their pets became ill and had also tested PCR positive for Covid-19. Interestingly, all these B.1.1.7  
43 infected pets developed atypical clinical manifestations, including severe cardiac abnormalities  
44 secondary to myocarditis and a profound impairment of the general health status of the patient but  
45 without any primary respiratory signs. Together, our findings demonstrate for the first time the ability  
46 for companion animals to be infected by the B.1.1.7 variant of SARS-CoV-2 and raise questions  
47 regarding its pathogenicity in these animals. Moreover, given the enhanced infectivity and  
48 transmissibility of B.1.1.7 variant for humans, these findings also highlights more than ever the risk  
49 that companion animals may potentially play a significant role in SARS-CoV-2 outbreak dynamics  
50 than previously appreciated.

## 51 **Introduction**

52 The COVID-19 pandemic secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-  
53 2) variant, carrying the Spike (S) protein amino acid change D614G (referred to as B.1 variant), has  
54 encompassed several millions of cases around the world. This global situation has favored the  
55 appearance of numerous genomic mutations, some of which have generated variants having selective  
56 advantages<sup>1</sup>. Three notable variants have emerged in late fall 2020 in several countries, which then  
57 spread rapidly across the world, including B.1.1.7 (also referred to as 20I/N501Y.V1) first detected in  
58 England<sup>2</sup>, B.1.351 (20J/N501Y.V2) first detected in South Africa and the recently identified “Brazil”

59 variant P.1 (20I/N501Y.V3). These three variants carry a constellation of genetic mutations, including  
60 those at the level of the S protein receptor-binding domain (RDB), which is essential for binding to the  
61 cell host ACE-2 receptor to facilitate virus entry.

62 The B.1.1.7 variant, also referred to as variant of concern (VOC) 202012/01 or 20I/501Y.V1, is  
63 estimated to have emerged in September 2020 in Kent, a county in the South-East of England, and has  
64 rapidly outcompeted pre-existing variants in England as the consequence of an increased  
65 transmissibility and infectivity <sup>2</sup>. Multiple lines of evidence indicate that its enhanced transmissibility  
66 is driven by the N501Y mutation and the amino acid  $\Delta 69/70$  deletion in RDB <sup>3</sup>. Consequently, the  
67 incidence of B.1.1.7 increased rapidly during a national lockdown implemented by the Government of  
68 the United Kingdom from 5 November to 2 December 2020, despite rigorous restrictions, causing an  
69 extraordinary surge of COVID-19 cases particularly affecting the Greater London area. As of 7  
70 February 2021, VOC 202012/01 comprised roughly 95% of new SARS-CoV-2 infections in the  
71 United Kingdom and has now been identified in at least 86 countries.

72 Several cases of SARS-CoV-2 infection have also been reported worldwide in domestic pets  
73 (especially cats and dogs) and it has been suggested that these animals became infected by their  
74 owners or handlers. Infections of domestic pets mostly resulted in unapparent to mild digestive and  
75 respiratory symptoms such as cough, runny nose, sneezing and conjunctivitis <sup>4-6</sup>.

76 Intriguingly, despite the uncontrolled surge of COVID-19 cases occurring in the UK since November  
77 2020, no infections by SARS-CoV-2 have been reported in companion animals so far. More  
78 surprisingly, to the best of the authors' knowledge, natural infection of any animal by the B.1.1.7  
79 variant has never been documented, neither in England nor anywhere else.

## 80 **Results**

81 We report a sudden increased number of domestic dogs and cats presented with myocarditis at the  
82 Cardiology Department of The Ralph Veterinary Referral Centre (RVRC), based on the outskirts of  
83 London (UK), between December 2020 and February 2021, with an unexpected rise in incidence from  
84 1.4% to 12.8% (8.5% in cats and 4.3% in dogs). This sudden surge of cases appeared to mimic the  
85 curve and timeline of the COVID-19 human pandemic in the UK due to the B.1.1.7 variant, starting in

86 mid-December 2020, peaking at the end of January 2021, before returning to the historical rate by  
87 mid-February 2021.

88 None of these patients with myocarditis had a previous history of heart disease and their clinical  
89 presentation was similar and characterized by acute onset of lethargy, inappetence, tachypnea/dyspnea  
90 (secondary to the presence of congestive heart failure), and, in some cases, syncopal events.

91 Diagnostic investigations revealed the presence of elevated cardiac troponin-I (median 6.8; range 0.68  
92 to 61.1 ng/mL [normal reference range 0.0-0.2 ng/mL]) accompanied by echocardiographic evidence  
93 of myocardial remodeling and/or signs of pleural effusion and/or pulmonary edema, often confirmed  
94 on thoracic radiographs and/or severe ventricular arrhythmias on electrocardiography (see  
95 Supplementary Figure S1). All affected animals made a remarkable improvement with cage rest,  
96 oxygen therapy, acute diuresis and, in some cases, anti-arrhythmic therapy with sotalol and fish oil  
97 supplementation before being discharged on oral medications after a few days of intensive care.

98 Notably, most owners and handlers of these pets with myocarditis had developed Covid-19 respiratory  
99 symptoms within 3-6 weeks before their pets became ill and many of these owners had tested PCR  
100 positive for Covid-19. Given this coincidence and the intriguing simultaneous evolution of  
101 myocarditis in these pets and the B.1.1.7 COVID-19 outbreak in UK, we decided to investigate SARS-  
102 CoV-2 infection in these animals. For this purpose, serum samples as well as oro/nasopharyngeal and  
103 rectal swabs were collected from seven animals (six cats and one dog) at initial presentation at the  
104 RVRC between January 22 and February 10, 2021 (Table 1 and Supplementary Table S1). During the  
105 same period, we collected blood samples from four other pets (two cats and two dogs) during their  
106 recovery, 2-6 weeks after they developed signs of myocarditis. None of the 11 animals with  
107 myocarditis developed any influenza-like symptoms and they all clinically improved within a few  
108 days of intensive care, although one cat (LL) represented one week after discharge with a relapse of  
109 her clinical signs, characterized by profound lethargy and uncontrolled ventricular tachycardia,  
110 prompting her owners to elect for euthanasia. All cats and dogs were neutered and aged between one  
111 to 12 years. Following collection, all samples were stored at -20°C until transportation in ice to  
112 MIVEGEC laboratory at Montpellier, France, for serological and virological investigations.

113 Oro/nasopharyngeal and rectal swabs were tested using the droplet digital RT-PCR (ddPCR) targeting  
 114 one region specific to the SARS-CoV-2 N gene and two regions of the Spike protein gene specific to  
 115 the three current predominant SARS-CoV-2 variants, namely 20I/N501Y.V1, 20J/N501Y.V2 and  
 116 20I/N501Y.V3. One target region, containing the N501Y mutation, is common to the three variants  
 117 and the other target region, containing the  $\Delta$ 69-70 deletion, is specific to the B.1.1.7 variant. Sera were  
 118 tested for SARS-CoV-2-specific IgG using three microsphere immunoassays (MIA) detecting IgG  
 119 binding to the N protein, the S1-RBD-protein or the S trimeric protein, as well as a retrovirus-based  
 120 pseudoparticle assay detecting SARS-CoV-2 neutralizing antibodies (see Materials and methods).

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122 **Table 1. Characteristics of dogs and cats diagnosed with myocarditis at The Ralph Veterinary**  
 123 **Referral Centre between January 22 and February 10, 2021**

	Species	Breed	Age	Sex	Days	General symptoms	Cardiac abnormalities	Troponin ng/mL	Covid-19+ contact	SARS-CoV-2 ddPCR	Serology
<b>BBK</b>	cat	DSH	9	M	2	Lethargy Inappetance	CHF	7.9	Yes	-	-
<b>HY</b>	cat	DSH	9	M	2	Lethargy Inappetance	CHF, VA	0.68	Yes	33 copies RNA/ $\mu$ L	-
<b>CH</b>	cat	Manx	12	F	2	Lethargy	CHF, VA	6.8	Unknown	-	-
<b>LL</b>	cat	Sphynx	10	F	3	Syncope	CHF, VA	45.6	Unknown	12 copies RNA/ $\mu$ L	-
<b>MR</b>	dog	Labrador	9	F	4	Lethargy, Inappetance Hemorrhagic diarrhea	VA	43.5	Yes	13 copies RNA/ $\mu$ L	-
<b>DB</b>	cat	DSH	9	M	8	Lethargy	CHF	1.31	Unknown	-	+
<b>FB</b>	cat	Scottish Fold	1	M	10	Lethargy Inappetance	CHF	12.1	Unknown	-	-
<b>DP</b>	dog	Mastiff	8	F	14	Syncope	CHF, VA	2.5	Unknown	NA	-
<b>SC</b>	cat	Siberian	1	F	28	Lethargy	CHF	4.92	Yes	NA	+
<b>KEO</b>	dog	Dalmatian	8	M	37	Syncope	VA	61.1	Yes	NA	+
<b>OR</b>	cat	Persian	1	M	64	Lethargy	CHF, VA	0.83	Unknown	NA	-

124 Days: days between disease onset and the medical consultation at the clinics, including sampling.

125 DSH: Domestic shorthair cat. CHF: Congestive heart failure. VA: Ventricular arrhythmia. NA: Not  
 126 available.

127 All oro/nasopharyngeal swabs were found SARS-CoV-2 ddPCR negative. However, ddPCR positive  
 128 signals were obtained for the three regions from the rectal swabs from three of seven animals (two cats  
 129 and one dog), indicating infection with the British B.1.1.7 variant. The RNA concentration ranged  
 130 from 12 to 33 copies/ $\mu$ L of specimen, indicating low viral load (Table 1). In addition, one animal

131 sampled during the acute phase of the disease which tested ddPCR negative, as well as two of four  
132 animals sampled during the recovery period, were found to have SARS-CoV-2 antibodies. Therefore,  
133 in total, six of our 11 investigated animals were shown SARS-CoV-2 positive, either by ddPCR or by  
134 serology. More interestingly, considering only the five animals from which owners or handlers were  
135 laboratory confirmed Covid-19 positive, four were shown SARS-CoV-2 positive (Table 1).

## 136 **Discussion**

137 To our knowledge, this is the first report of infection of both cats and dogs by the British B.1.1.7  
138 variant of SARS-CoV-2. Given the enhanced infectivity and transmissibility of B.1.1.7 variant for  
139 humans, the discovery of B.1.1.7 infected cats and dogs highlights more than ever the risk that  
140 companion animals may potentially play a significant role in SARS-CoV-2 outbreak dynamics than  
141 previously appreciated. Further studies are therefore urgently required to investigate the likelihood of  
142 pet-to-pet transmission, as well as pet-to-human transmission of the B.1.1.7 variant and to show  
143 whether the N501Y mutation and the  $\Delta 69-70$  deletion render the virus more infectious for these  
144 animals.

145 The other remarkable and unexpected finding of our study is the development of unusual clinical  
146 manifestations in B.1.1.7 infected cats and dogs, including severe cardiac abnormalities secondary to  
147 myocarditis and a profound impairment of the general health status of the patient but without any  
148 primary respiratory signs. With the exception of only one cat from Spain, which developed  
149 cardiorespiratory failure resulting in severe respiratory distress <sup>7</sup>, both natural and experimental SARS-  
150 CoV-2 infections of cats and dogs have so far been reported to be either asymptomatic or display mild  
151 upper respiratory disease. Although that the B.1.1.7 infection in humans seems to be associated with  
152 higher COVID-19 mortality or clinical severity, the association between myocarditis and B.1.1.7  
153 infection in domestic pets has to be acknowledged and addressed <sup>8</sup>. In this context, it is important to  
154 highlight the fact that myocarditis associated with multisystem inflammatory syndrome is also a well-  
155 recognized complication of COVID-19 in people (both adults and children) probably from  
156 exaggerated immune response of the host <sup>9,10</sup>.

157 Together, our findings demonstrate the ability for companion animals to be infected by the B.1.1.7  
158 variant of SARS-CoV-2 and raise questions regarding its pathogenicity in these animals. Therefore,  
159 there is an urgent need to greatly accelerate and strengthen the investigations and surveillance of  
160 animal infections by highly-transmissible variants such as British B.1.1.7, South-African B1.351 and  
161 Brazilian P.1 variants as part of the global response to the ongoing multi-species COVID-19  
162 pandemic.

## 163 **Materials and methods**

### 164 **RNA extraction**

165 Rectal and oro/naso-pharyngeal swabs were resuspended by vortexing in 300  $\mu$ L of PBS. Total RNA  
166 was extracted from 200  $\mu$ L of supernatant of rectal swab and from 200  $\mu$ L of viral transport medium of  
167 nasopharyngeal swabs. Extraction was performed on the extraction system IndiMag 48 (Indical  
168 Bioscience), using magnetic bead technology, with the IndiMag Pathogen kit according to the  
169 manufacturer's instructions. The elution volume was 100  $\mu$ L.

### 170 **One step dRT-PCR**

171 The RT-dPCR procedure was performed following the manufacturer's instructions using the QIAcuity  
172 8, 5-plex (Qiagen, Germany), the QIAcuity One-Step Viral RT-PCR Kit (Cat No. 1123145, Qiagen,  
173 Germany) and the 24-well 26K Nanoplates (Cat No. 250001, Qiagen, Germany). The ddRT-PCR  
174 technique showed higher sensitivity and specificity compared to RT-qPCR for diagnosis of COVID-19  
175 <sup>11</sup>.

176 Briefly, the RT-dPCR reaction mixture was assembled as follows: 4x One-Step Viral RT-PCR Master  
177 Mix 10 $\mu$ l, 100x Multiplex Reverse Transcription Mix 0.4 $\mu$ l, 20x of set of primers and probes 0149,  
178 0130, 0150 (ref IAGE) 2 $\mu$ l x3 (6 $\mu$ L), RNase free water 22.6 $\mu$ l, and RNA template 1  $\mu$ l, in a final  
179 volume of 40  $\mu$ l. 0130 target 2019-nCoV\_N2 region NC\_045512v2 fluorophore HEX, amplicon  
180 length 67bp. 0149 target S region: mutation deletion 69-70, lineage B1.1 & B1.258, fluorophore HEX,  
181 amplicon length 100bp. 0150 target S region: mutation N501Y, lineage B1.1.7, fluorophore Cy5,  
182 amplicon length 133bp. The sequences are confidential and are filed under the number EP20306715.2

183 The mixture was prepared in a pre-plate and then transferred into the 24-well 26K Nanoplate. The later  
184 was then loaded to the QIAcuity 8 instrument, which is a fully automated system. The workflow  
185 included i) priming and rolling step in order to generate and isolate the chamber partitions, ii) the  
186 amplification step under the following cycling protocol: 50 °C for 40 min for reverse transcription, 95  
187 °C for 2 min for enzyme activation, 95 °C for 5 s for denaturation and 60 °C for 30 s for  
188 annealing/extension for 40 cycles, and iii) the imaging step was done by reading in the following  
189 channels FAM, HEX, and CY5. The full workflow time was around 2 hours for the three steps. The  
190 experiments were performed using a negative control (no template control, NTC) and a positive  
191 control (a patient's sample confirmed positive by RT-PCR with our routine diagnostic testing). All  
192 reactions had at least 25,400 partitions. Data were analysed using the QIAcuity Suite Software V1.1.3  
193 (Qiagen, Germany) and expressed as copies/ $\mu$ l.

#### 194 **Microsphere immunoassay**

195 Cat and dog serum samples were tested using a multiplex Microsphere immunoassay (MIA). 10 $\mu$ g of  
196 three recombinant SARS-CoV-2 antigens: nucleoprotein (N), receptor binding domain (RBD) and  
197 trimeric spike (tri-S) were used to capture specific serum antibodies. Distinct MagPlex microsphere  
198 sets (Luminex Corp) were respectively coupled to viral antigens using the amine coupling kit (Bio-  
199 Rad Laboratories) according to manufacturers' instructions, whereas a microsphere set coupled with  
200 recombinant human protein (O6-methylguanine DNA methyltransferase) was used as control in the  
201 assay. The MIA procedure was performed as described previously<sup>12</sup>. Briefly, microsphere mixtures  
202 were successively incubated protected from the light on an orbital shaker with serum samples (1:400),  
203 biotinylated protein A and biotinylated protein G (4  $\mu$ g/ml each) (Thermo Fisher Scientific) and  
204 Streptavidin-R-Phycoerythrin (4  $\mu$ g/ml) (Life technologies). Measurements were performed using a  
205 Magpix instrument (Luminex). Relative Fluorescence Intensities (RFI) were calculated for each  
206 sample by dividing the MFI signal measured for the antigen-coated microsphere sets by the MFI  
207 signal obtained for the control microsphere set, to account for nonspecific binding of antibodies to  
208 beads. Specific seropositivity cut-off values for each antigen were set at three standard deviations  
209 above the mean RFI of the 29 dogs and 30 cats serum samples sampled before 2019. Based on the pre-



210 pandemic population, MIA specificity was set at 96.6% for N protein for dogs and cats, at 96.6% for  
211 RBD for cats and 100% for dogs and 100% for tri-S for cats and 96.6% for dogs.

## 212 **Neutralization activity measurement**

213 To measure the neutralizing activity in cat and dog sera, a MLV-based pseudoparticle carrying a GFP  
214 reporter pseudotyped with SARS-CoV2 spike (SARS-CoV-2pp) was used. Each SARS-CoV2 positive  
215 sample detected by MIA was processed according to neutralization procedure as previously described  
216 <sup>13</sup>. The level of infectivity was expressed as % of GFP positive cells and compared to cells infected  
217 with SARS-CoV-2pp incubated without serum. Pre-pandemic sera from France was used as negative  
218 controls, and anti-SARS-CoV-2 RBD antibody was used as positive control.

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230 None of the authors have any conflict of interest (financial or personal) in this study.

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