

1 **CVnCoV protects human ACE2 transgenic mice from ancestral B BavPat1 and emerging**

2 **B.1.351 SARS-CoV-2**

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23

24 **Abstract**

25 The ongoing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic  
26 necessitates the fast development of vaccines as the primary control option. Recently, viral  
27 mutants termed “variants of concern” (VOC) have emerged with the potential to escape host  
28 immunity. VOC B.1.351 was first discovered in South Africa in late 2020, and causes global  
29 concern due to poor neutralization with propensity to evade preexisting immunity from  
30 ancestral strains. We tested the efficacy of a spike encoding mRNA vaccine (CVnCoV) against  
31 the ancestral strain BavPat1 and the novel VOC B.1.351 in a K18-hACE2 transgenic mouse  
32 model. Naive mice and mice immunized with formalin-inactivated SARS-CoV-2 preparation  
33 were used as controls. mRNA-immunized mice developed elevated SARS-CoV-2 RBD-  
34 specific antibody as well as neutralization titers against the ancestral strain BavPat1.  
35 Neutralization titers against VOC B.1.351 were readily detectable but significantly reduced  
36 compared to BavPat1. VOC B.1.351-infected control animals experienced a delayed course of  
37 disease, yet nearly all SARS-CoV-2 challenged naïve mice succumbed with virus dissemination  
38 and high viral loads. CVnCoV vaccine completely protected the animals from disease and  
39 mortality caused by either viral strain. Moreover, SARS-CoV-2 was not detected in oral swabs,  
40 lung, or brain in these groups. Only partial protection was observed in mice receiving the  
41 formalin-inactivated virus preparation. Despite lower neutralizing antibody titers compared to  
42 the ancestral strain BavPat1, CVnCoV shows complete disease protection against the novel  
43 VOC B.1.351 in our studies.

44 **Introduction**

45 Coronavirus disease 2019 (COVID-19) severely affects human health and societies worldwide.

46 It has accounted for more than 116 million morbidities and 2.5 million fatalities by early March

47 2021 (WHO, <https://covid19.who.int>). The responsible pathogen, severe acute respiratory

48 syndrome coronavirus type 2 (SARS-CoV-2), has rapidly spread globally despite stringent

49 intervention strategies (1). To control pandemic spread and disease, vaccination is considered

50 the most important and effective control measure (2). Several vaccines based on mRNA

51 technology or viral vectors are now authorized for emergency use and further products are in

52 final licensing phases (3). SARS-CoV-2 underwent adaptive mutations early during the

53 pandemic, with the D614G variant becoming globally dominant at the beginning of 2020 (4-6).

54 Viral evolution is a highly dynamic process that results in emergence of multiple,

55 geographically distinct new variants, first identified in the UK (B1.1.7), South Africa (B.1.351)

56 and Brazil (B.1.1.28; P1) (<https://www.ecdc.europa.eu/en/publications-data/covid-19-risk-assessment-variants-vaccine-fourteenth-update-february-2021>). These “variants of concern

57 (VOC)” acquired numerous mutations, particularly in the spike protein encoding gene (S), most

58 frequently within the S1 and the receptor binding domain (RBD) (7-9). These mutations confer

59 higher binding affinities and allow some VOC to evade pre-existing immunity (10), resulting

60 in increased transmissibility, including epidemiologic scenarios where “herd immunity” was

61 expected (11). Whereas variant B.1.1.7 might still be efficiently neutralized by vaccination-

62 elicited antibodies despite the RBD mutations (12-14), variant B.1.351 showed a remarkable

63 resistance to sera from vaccinated, as well as from convalescent individuals (15-18). VOCs that

64 evade from efficient cross-neutralization may evolve into dominant strains and necessitate

65 vaccine efficacy re-assessment. While indications for cross neutralization exist, e.g. by sera

66 from individuals vaccinated with SARS-CoV-2 mRNA vaccines (13, 19), *in vivo* data from

67 experimental immunization/challenge studies in standardized animal models are pending. In a

68 parallel approach, we investigated the efficacy of mRNA vaccine CVnCoV against SARS-

69

70 CoV-2 using an early B lineage 614G strain and the novel VOC B1.351 in a human ACE2  
71 transgenic mouse model of severe COVID-19 (20).

72

73 **Results**

74 **Strong antibody responses in mRNA-vaccinated mice**

75 We used the K18-hACE2 transgenic mouse model (21) to determine the protective efficacy of  
76 a spike-protein encoding mRNA vaccine (CVnCoV) against the ancestral SARS-CoV-2 B-  
77 lineage strain BavPat1 that closely matches the mRNA encoded S protein, and the heterologous  
78 VOC B.1.351 NW-RKI-I-0028. For immunization, either 8 $\mu$ g of the CVnCoV vaccine (22) or  
79 20 $\mu$ L of a formalin-inactivated and adjuvanted SARS-CoV-2-preparation (FI-Virus) was  
80 administered on days 0 and 28. Mice were challenged 4 weeks after boost vaccination with  
81 more than 10<sup>5</sup> TCID<sub>50</sub> of SARS-CoV-2 BavPat1 or B.1.351 NW-RKI-I-0028. A sham (NaCl)  
82 group served as non-vaccinated control (Fig. S1). Sera from CVnCoV-vaccinated mice  
83 collected on days 28 and 55 showed a strong induction of anti-RBD total immunoglobulin (Ig)  
84 with a significant increase on day 55 (4 weeks after boost) compared to day 28 (4 weeks after  
85 prime). CVnCoV-induced anti-RBD total Ig levels were significantly higher than levels  
86 induced by the FI-Virus preparation. There was no significant boost effect with the FI-Virus  
87 preparation when comparing anti-RBD levels at day 55 versus day 28 (Fig. 1A). The strong  
88 induction of anti-RBD antibodies in the CVnCoV group was reflected by high virus  
89 neutralization titers (VNT). Sera from day 55 after immunization with CVnCoV showed a  
90 significantly higher neutralizing capacity compared to sera from animals that had received the  
91 FI-Virus preparation. Importantly, neutralization of VOC B.1.351 (mean = 525) was less  
92 effective compared to BavPat1 (mean = 10,151) for the CVnCoV group, but far exceeded the  
93 values recorded for the FI-Virus group (mean  $\leq$  32) (Fig. 1B). Overall, CVnCoV induced robust

94 antibody responses in a prime-boost regime, capable of efficiently neutralizing both BavPat1  
95 and VOC B.1.351 NW-RKI-I-0028 *in vitro*.

96

97 Complete protection of mRNA-immunized mice from disease and mortality

98 Subsequently, the potential of CVnCoV to protect from SARS-CoV-2 challenge infection was  
99 analyzed. Stocks of both challenge viruses were characterized by deep-sequencing  
100 demonstrating the characteristic mutations of VOC B.1.351, but no other relevant alterations  
101 (Fig. S2, table S2). Immunized K18-hACE2 mice were studied using a high dose-challenge  
102 model which induces severe clinical disease resembling COVID-19 in humans (23). In addition,  
103 mice develop severe encephalitis specific to this animal model (20). On day 4, animals in the  
104 sham group started succumbing to the BavPat1 infection (Fig. 1C). B.1.351 infection led to a  
105 delayed onset of severe disease compared to BavPat1, with 20% survival on day 10 after  
106 inoculation (Fig. 1D). Thus, K18-hACE2 mice were highly susceptible to both SARS-CoV-2  
107 variants. Importantly, vaccination with CVnCoV resulted in complete protection (100%  
108 survival) against BavPat1 and B.1.351 with no significant weight loss or disease symptoms  
109 throughout the course of the challenge infection (Fig. 1C-D and Fig. S3). In contrast, prior  
110 administration of the FI-Virus preparation provided sub-optimal protection against either  
111 BavPat1 or B.1.351, resulting in weight loss and signs of distress (Fig. 1 and Fig. S3). Some of  
112 the FI-virus-immunized animals experienced very early weight loss and disease signs after  
113 VOC B.1.351 challenge infection, earlier than sham-groups. In conclusion, survival rates, body  
114 weight changes and disease scores revealed complete protection by the CVnCoV vaccine in  
115 K18-hACE2 mice against lethal SARS-CoV-2 challenge, including against VOC B.1.351.

116

117

118 mRNA-immunization significantly decreased viral RNA loads in selected tissues

119 To investigate whether CVnCoV vaccination prevented productive infection or dissemination  
120 of replicating SARS-CoV-2, we took oral swabs on 4 dpi to monitor viral RNA load in saliva.  
121 In the sham group, 4/4 and 4/5 samples were positive for viral genome after infection with  
122 BavPat1 or VOC B.1.351, respectively (Fig. 2A). FI-Virus administration prior to challenge  
123 did not significantly reduce viral genome load in saliva with 40 to 60% of animals showing  
124 positive RT-qPCR results on 4 dpi (Fig. 2A). In contrast, after CVnCoV vaccination, no viral  
125 genomes were detected in oral swabs of either challenge group. To further explore the  
126 prevention of viral replication following challenge, we determined viral load in the upper  
127 respiratory tract (URT) (conchae) and the lower respiratory tract (LRT) (trachea, caudal lung  
128 and cranial lung), as well as in the central nervous system (brain, cerebellum/cerebrum) (Fig.  
129 2B-F) in animals reaching the humane endpoint or at the day of termination (10dpi). Similar to  
130 the quantitative RNA load results obtained from the oral swabs, the URT provided a niche for  
131 replication in both sham and FI-Virus groups (Fig. 2B). In the CVnCoV-vaccinated group  
132 challenged with BavPat1, only 3/10 animals showed low genome copy numbers in the conchae.  
133 No animal was positive in the LRT or the brain, indicating complete protection from infection  
134 by BavPat1 (Fig. 2C-F). For VOC B.1.351, 6/10 CVnCoV-vaccinated animals exhibited  
135 residual viral replication in the conchae, but viral levels were reduced without reaching  
136 statistical significance (Fig. 2B). In contrast, CVnCoV prevented any detectable replication of  
137 this VOC in the LRT and the brain, with low viral copy numbers close to the limit of detection  
138 in the lung of only 2/10 animals, and in the cerebrum for only 1/10 animals (Fig. 2C-F). FI-  
139 Virus administration provided partial protection in the LRT in animals challenged with  
140 BavPat1, but not with VOC B.1.351, and did not significantly protect against viral replication  
141 in the cerebellum or cerebrum regardless of SARS-CoV-2 variant (Fig. 2). Of note, some of the  
142 animals receiving the FI-Virus preparation showed viral loads at the level of the sham group in  
143 the LRT (Fig. 2).

144 In summary, vaccination with CVnCoV conferred complete protection against lethal challenge  
145 with SARS-CoV-2 lineage B BavPat1 and VOC B.1.351 strain NW-RKI-I-0028 in the  
146 transgenic K18-hACE2 mouse model. CVnCoV induced robust anti-RBD antibody responses  
147 with high neutralizing capacity against both BavPat1 and VOC B.1.351. Furthermore, CVnCoV  
148 prevented dissemination of SARS-CoV-2 from the inoculation site into other organs and  
149 provided a solid protection against an ancestral SARS-CoV-2 and a VOC B.1.351 strain.

150

## 151 **Discussion**

152 The emergence of new strains with immune escape potential, such as the VOC of the B.1.351  
153 lineage that appeared first in South Africa, are of great concern, since all available COVID-19  
154 vaccines are based on the ancestral SARS-CoV-2 strains. The B.1.351 variant is of particular  
155 interest due to the observed immune-escape features with a reduced neutralization efficacy (10)  
156 and reduced protective efficacy reported for a licensed vaccine (24). We therefore tested an  
157 mRNA vaccine (CVnCoV) against a standard ancestral SARS-CoV-2 B lineage strain  
158 (BavPat1) in comparison to a VOC B.1.351 isolate in a transgenic mouse model.

159 Our data demonstrate that CVnCoV fully protects mice against disease caused by two different  
160 SARS-CoV-2 variants. CVnCoV vaccination, but not immunization with FI-Virus, rescued all  
161 transgenic mice from lethal infection caused by BavPat1 and VOC B.1.351 isolate NW-RKI-I-  
162 0028. The sub-optimal FI-Virus preparation reduced viral replication in the LRT solely after  
163 challenge with BavPat1, but showed no significant effect on viral dissemination as well as the  
164 viral genome loads in the URT. In contrast, CVnCoV immunization resulted in abundant RBD-  
165 specific and neutralizing antibodies, and conferred a complete and robust protection, including  
166 from viral replication in the lung and the brain. Only very limited viral replication was observed  
167 in the URT of mRNA-vaccinated animals challenged with VOC B.1.351. The relevance to  
168 disease transmission of this minimal viral replication in the conchae remains to be established.

169 The reduced neutralizing capacity of sera from CVnCoV-vaccinated transgenic mice against  
170 VOC B.1.351, and the insufficient prevention of replication in the conchae, might reflect the  
171 currently detected transmission rates of this VOC in human populations previously exposed to  
172 the ancestral strain. Nevertheless, our study provides the first evidence for the efficacy of a  
173 vaccine to prevent disease and viral dissemination from the site of infection against an emerging  
174 SARS-CoV-2 variant in a sensitive, well-established and accepted *in vivo* model. The very high  
175 neutralizing titers against BavPat1 elicited by the mRNA immunization as well as the fold  
176 reduction recorded for VOC B.1.351 may be unique to the mouse model employed in this study  
177 and require validation in other experimental models.

178 The pathophysiology of SARS-CoV-2 VOC infections remains largely unknown and detailed  
179 animal model data are missing. In our study, we observed a delayed course of disease in K18-  
180 hACE2 mice infected with a VOC B.1.351 strain, and hypothesize that mutation accumulation  
181 might result in a changed *in vivo* phenotype. Short-term infections performed in hamsters have  
182 failed to detect diverging phenotypes in ancestral versus VOC lineages (25), but comparable  
183 data sets about the complete course and replication in the upper respiratory tract are still pending  
184 for all VOCs in other animal models. These apparently discordant findings call for further  
185 pathological and immunological assessments of pathogenicity of emerging lineages.

186 Here we report full protection against a VOC by CVnCoV immunization, associated with high  
187 anti-RBD and neutralizing antibodies. Whether antibodies alone were sufficient for the  
188 beneficial outcome remains to be further validated. Broad immune responses elicited by  
189 vaccines, including cellular responses in addition to neutralizing antibodies, antibody  
190 dependent cytotoxicity (ADCC), or antibody-mediated innate immune effector functions, could  
191 help explain the protection. Potent T cell immunity could ensure the success of an immunization  
192 when antibodies decline. CVnCoV vaccination was previously shown to induce Th1 immunity  
193 and trigger S-specific CD8<sup>+</sup> T cell responses in mice (22). Re-challenge studies in non-human

194 primates confirmed a role for CD8<sup>+</sup> T cells in protection (26). Although point mutations in the  
195 MHC-I-restricted viral epitopes could subvert CD8<sup>+</sup> T cell surveillance (27), the majority of  
196 SARS-CoV-2 T cell epitopes recognized by convalescent individuals or vaccinees immunized  
197 with licensed mRNA vaccines, appear unaffected by unique VOC mutations (28). These  
198 findings indicate a role of cellular immunity in defense against SARS-CoV-2. Here, we  
199 observed protection against disease upon challenge infection with VOC B.1.351 after CVnCoV  
200 vaccination, despite reduced virus neutralizing titers. These observations suggest that either  
201 complementary immune mechanisms are effective or that residual virus neutralizing titers  
202 against B.1.351 are sufficient for *in vivo* neutralization in this model. In line with this, it has  
203 recently been demonstrated in a non-human primate infection model that relatively low  
204 neutralizing antibody titers can protect from SARS-CoV-2-related clinical signs (26). The  
205 precise contribution of various immune compartments to CVnCoV efficacy requires further  
206 evaluation.

207 Our proof-of-principle study demonstrates that an mRNA vaccine can protect hACE2 mice  
208 against disease caused by SARS-CoV-2 independent from the lineages or variant SARS-CoV-  
209 2.

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216

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221

222 **Author’s contribution**

223 Conceptualization: DH, BC, SR, JM, SOM, TCM, BP, AD, MB. Methodology: DH, BC, SR,  
224 NR, JM, SOM, CW, AB, KW, BP, AD, MB. Formal analysis: DH, BC, NJH, LU, JS, AK, AB,  
225 CW. Investigation: DH, BC, NJH, LU, CF, JS, AK, AB, AM, FS, CW. Resources: SR, NR,  
226 JM, TCM, SOM, BP, AD, MB. Data Curation: DH, BC, NJH, LU, JS, CW, AD, MB. Writing  
227 – original draft preparation: DH, BC, NJH, LU, CW, AD, MB. Writing – review and editing:  
228 DH, BC, SR, NR, AB, KW, CW, SOM, TCM, BP, AD, MB. Visualization: DH, BC, NJH, LU,  
229 CF, CW. Supervision: DH, BC, AB, KW, SOM, TCM, BP, AD, MB. Project administration:  
230 DH, BC, SR, NR, JM, SOM, TCM, BP, AD, MB. Funding acquisition: SR, SOM, BP, AD,  
231 MB, TCM.

232

233 **Competing interest**

234 S.R., B.P., N.R., J.M. and S.O.M. are employees of CureVac AG, Tuebingen Germany, a  
235 publically listed company developing mRNA-based vaccines and immunotherapeutics. All  
236 authors may hold shares in the company. S.R., B.P., N.R., are inventors on several patents on  
237 mRNA vaccination and use thereof.

238

239 **Fig. 1. CVnCoV protects K18-hACE2 mice against SARS-CoV-2 variants BavPat1 and**  
240 **B1.351.** K18-hACE2 mice were vaccinated with 8 $\mu$ g CVnCoV, received 10<sup>6</sup> FI-Virus or NaCl  
241 (SHAM) on day 0 and day 28 followed by i.n. challenge with 10<sup>5,875</sup> TCID<sub>50</sub> of SARS-CoV-2  
242 variants BavPat1 or 10<sup>5,5</sup> TCID<sub>50</sub> B1.351. **(A)** RBD-Elisa with sera from K18-hACE2 mice on  
243 day 0, 28 and 55 of respective groups: median and interquartile range are presented. Dashed  
244 line indicates threshold for positive anti-RBD antibody level. **(B)** Virus neutralization assay  
245 using day 55 sera from all three groups. Bars indicate mean with SD. **(C and D)** Survival curves  
246 (Kaplan-Meyer) for K18-hACE2 mice from all three groups challenged either with BavPat1  
247 (C) or B.1.351 (D) and followed up for 10 days post infection (DPI). P-values were determined  
248 by nonparametric one-way ANOVA and Dunn's multiple comparisons test (A and B) or log-  
249 rank (Mantel-Cox) test (C and D).

250

251 **Fig. 2. CVnCoV prevents replication of SARS-CoV-2 variants BavPat1 and B.1.351 in**  
252 **K18-hACE2 mice.** RT-qPCR for genomic RNA of SARS-CoV-2 was performed with either  
253 (A) oral swab samples at day 4 or (B) from organ samples of the upper respiratory tract, (C -  
254 E) the lower respiratory tract, and (F and G) the brain at day 10 or at the humane endpoint. P-  
255 values were determined by nonparametric one-way ANOVA and Dunn's multiple comparisons  
256 test. Scatter plots are labeled with median (height of the bar) and interquartile range.

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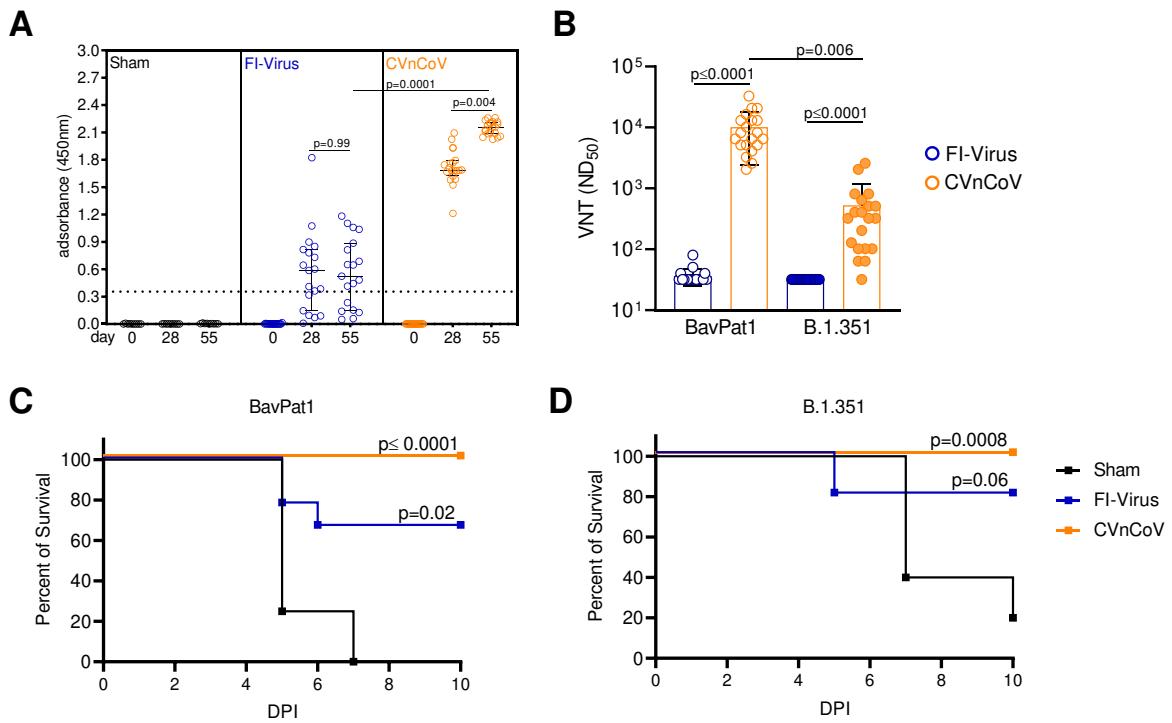
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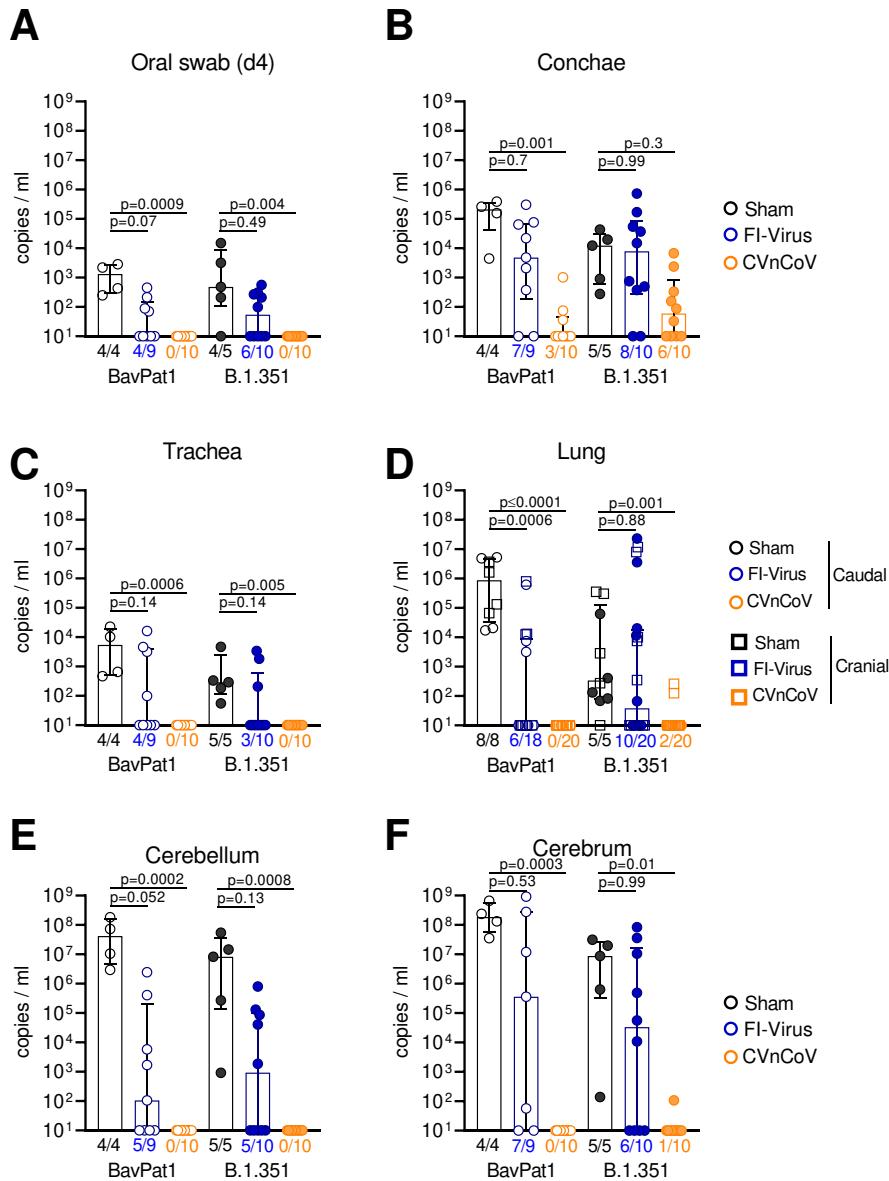
316 Fig. 1



317

318 Fig. 2

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