

1 **Quantifying the impact of immune history and variant on SARS-CoV-2 viral kinetics and**
2 **infection rebound: a retrospective cohort study**

3
4 James A. Hay^{1*}, Stephen M. Kissler^{1*}, Joseph R. Fauver^{2,3*}, Christina Mack^{4*}, Caroline G.
5 Tai⁴, Radhika M. Samant⁴, Sarah Connolly⁴, Deverick J. Anderson⁵, Gaurav Khullar⁶, Matthew
6 MacKay⁶, Miral Patel⁶, Shannan Kelly⁶, April Manhertz⁶, Isaac Eiter⁶, Daisy Salgado⁶, Tim
7 Baker⁶, Ben Howard⁶, Joel T. Dudley⁶, Christopher E. Mason⁶, Manoj Nair⁷, Yaoxing Huang⁷,
8 John DiFiori^{8,9}, David D. Ho⁷, Nathan D. Grubaugh^{2**}, Yonatan H. Grad^{1**}

9
10 * These authors contributed equally.

11 ** Co-senior authors.

12
13 1 Harvard T.H. Chan School of Public Health, Boston, MA, USA

14 2 Yale School of Public Health, New Haven, CT, USA

15 3 University of Nebraska Medical Center, Omaha, NE, USA

16 4 IQVIA, Real World Solutions, Durham, NC, USA

17 5 Duke Center for Antimicrobial Stewardship and Infection Prevention, Durham, NC, USA

18 6 TEMPUS Labs, Chicago, IL, USA

19 7 Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA

20 8 Hospital for Special Surgery, New York, NY, USA

21 9 National Basketball Association, New York, NY, USA

22
23 Correspondence and requests for materials should be addressed to:

24 Email: ygrad@hsph.harvard.edu

25 Telephone: 617.432.2275

26
27 Funding Statement: Supported in part by CDC contract 200-2016-91779, Emergent Ventures
28 at the Mercatus Center, the Huffman Family Donor Advised Fund, the MorrisSinger Fund, the
29 National Basketball Association, and the National Basketball Players Association.

30
31 Data availability: All code and data required to reproduce the analyses are available at
32 <https://github.com/gradlab/SC2-kinetics-immune-history>.

33 **Abstract**

34 **Background**

35 The combined impact of immunity and SARS-CoV-2 variants on viral kinetics during infections
36 has been unclear.

37 **Methods**

38 We characterized 2,875 infections from the National Basketball Association occupational
39 health cohort identified between June 2020 and January 2022 using serial RT-qPCR testing.
40 Logistic regression and semi-mechanistic viral RNA kinetics models were used to quantify the
41 effect of variant, symptom status, age, infection history, vaccination and antibody titer to
42 founder SARS-CoV-2 strain on the duration of potential infectiousness and overall viral
43 kinetics. The frequency of viral rebounds was quantified under multiple cycle threshold (Ct)
44 value-based definitions.

45 **Results**

46 Among individuals detected partway through their infection, 51.0% (95% credible interval [CrI]:
47 48.2-53.6%) remained potentially infectious (Ct<30) five days post detection, with small
48 differences across variants and vaccination history. Only seven viral rebounds (0.7%; N=999)
49 were observed, with rebound defined as 3+ days with Ct<30 following an initial clearance of
50 3+ days with Ct≥30. High antibody titers against the founder SARS-CoV-2 strain predicted
51 lower peak viral loads and shorter durations of infection. Among Omicron BA.1 infections,
52 boosted individuals had lower pre-booster antibody titers and longer clearance times than non-
53 boosted individuals.

54 **Conclusions**

55 SARS-CoV-2 viral kinetics are partly determined by immunity and variant but dominated by
56 individual-level variation. Since booster vaccination protects against infection, longer
57 clearance times for BA.1-infected, boosted individuals may reflect a less effective immune
58 response, more common in older individuals, that increases infection risk and reduces viral
59 RNA clearance rate. The shifting landscape of viral kinetics underscores the need for
60 continued monitoring to optimize isolation policies and to contextualize the health impacts of
61 therapeutics and vaccines.

62 **Funding**

63 Supported in part by CDC contract 200-2016-91779, Emergent Ventures at the Mercatus
64 Center, the Huffman Family Donor Advised Fund, the MorrisSinger Fund, the National
65 Basketball Association, and the National Basketball Players Association.

66 Introduction

67 The viral kinetics of SARS-CoV-2 underlie the epidemiology of COVID-19 and the policies
68 surrounding infection control. The amount and duration of viral shedding influences
69 infectiousness (Ke et al., 2021, 2022; Marc et al., 2021; Marks et al., 2021; Puhach et al.,
70 2022; Sun et al., 2021) and the duration of test positivity affect isolation policies, test
71 recommendations, and clinical care guidelines.(Hellewell et al., 2021; Kissler, Fauver, Mack,
72 Olesen, et al., 2021; Larremore et al., 2021; Mack et al., 2022; Néant et al., 2021; Quilty et al.,
73 2021; Singanayagam et al., 2022) Descriptions of viral kinetics are also important for
74 establishing baselines to measure the effectiveness of antiviral drugs. For example, rebounds
75 of viral RNA concentrations and symptoms have been observed after antiviral treatment, but
76 it has been unclear to what extent such rebounds also occur in the absence of drug.(Boucau,
77 Uddin, et al., 2022; Charness et al., 2022) Most longitudinal viral kinetics studies pre-date the
78 emergence of the BA.1 lineage, which features dramatic antigenic divergence from prior
79 lineages, as well as the rollout of third and fourth vaccine doses.(Lusvarghi et al., 2022; Straten
80 et al., 2022) Early findings on viral kinetics therefore need to be updated to account for
81 extensive and heterogeneous immune experience across the population.(Cevik et al., 2021;
82 Kissler, Fauver, Mack, Tai, et al., 2021)

83

84 To characterize the viral kinetics of SARS-CoV-2 infection, including rebounds, for the Delta
85 and Omicron (BA.1 lineages BA.1.1529 and BA.1.1) variants in symptomatic and
86 asymptomatic individuals with varied vaccination and infection histories, we measured viral
87 RNA levels using densely-sampled RT-qPCR tests from 2,875 SARS-CoV-2 infections, each
88 taken by combined anterior nares and oral swabs, that occurred between 7th July, 2020, and
89 26th January, 2022, prior to the detection of BA.2.12.1, BA.4 and BA.5, or the regular detection
90 of BA.2, in this cohort. As a proxy for immune response to SARS-CoV-2, we used antibody
91 titers against the ancestral SARS-CoV-2 (WA1) strain spike protein measured prior to the
92 administration of booster doses, but predominantly after primary vaccination.

93

94 We interpreted the data in two ways. First, we estimated the probability of an individual having
95 a PCR cycle threshold (Ct) value less than 30, as a proxy for infectiousness, on each day post
96 detection using a logistic regression model. Second, we estimated the peak viral RNA
97 concentrations, viral RNA proliferation rate, and viral RNA clearance rate across variants,
98 immune statuses and age using a semi-mechanistic model. Our findings provide key
99 estimates for the duration and magnitude of viral RNA shedding in the upper respiratory tract
100 and its variation across symptom status, variants, immune states, and individuals.

101 **Data**

102 We identified 2,875 distinct infections from 2,678 individuals in this cohort (**Supplementary**
103 **Figure 1**). By the time of their final test, 2,460 (91.9%) individuals had one detected infection,
104 214 (7.99%) had two detected infections, three (0.11%) had three detected infections, and
105 one (0.04%) had four detected infections. A total of 587 infections were detected within one
106 day of a prior negative PCR test result, and thus the timing of the onset of test positivity can
107 be assumed with reasonable accuracy. We defined these infections as the “frequent testing”
108 group. The remaining 2,288 infections were detected two days or more from a previous
109 negative test result or were detected with no prior negative test in the dataset. These were
110 predominantly tests following suspected exposure, recent symptom onset, or periodic
111 clearance for occupational health requirements, and thus we consider this latter group of
112 detections as a reasonable proxy for infection detection in the absence of frequent testing,
113 which is the case for most populations. We define these infections as the “delayed detection”
114 group.

115

116 Of 1,086 infections with known symptom status, 766 reported symptoms at some point during
117 the infection (70.5%). Individuals in the delayed detection group were more likely to be
118 symptomatic than in the frequent testing group (73.1% vs. 64.9%; Chi-squared test statistic =
119 5.03; p-value <0.05). Most symptomatic individuals were detected around the time of symptom
120 onset (**Supplementary Figure 2**; median delay from detection to symptom onset of zero days
121 (N=553) in the delayed detection group and one day (N=171) in the frequent testing group).
122 Symptom onset preceded the peak measured Ct value by a median of two days (N=550) in
123 the delayed detection group and three days (N=171) in the frequent testing group
124 (**Supplementary Figure 3**).

125

126 Based on genome sequencing, 1561 infections were confirmed to be Omicron (1 BA.2.10
127 isolate, the rest were lineages within BA.1), 266 confirmed to be Delta, and 247 confirmed as
128 other lineages. An additional 801 infections were not sequenced; however, due to the rapid
129 replacement of the circulating lineage in this cohort, we classified many of these as suspected
130 Delta or other lineages based on the dominant lineage at time of detection (**Supplementary**
131 **Figure 4**). We excluded non-sequenced samples following the detection of Omicron BA.1 due
132 to the continued, albeit low-level, detection of Delta.

133

134 **Interpersonal variation in viral RNA trajectories**

135 Viral trajectories varied substantially across individuals regardless of lineage (**Figure 1A**).
136 Most individuals (65.5%, 95% CrI: 62.1-68.7%) in the frequent testing group remained
137 potentially infectious, defined as having a Ct<30, on day 5 post detection. This fraction
138 decreased to 20.0% (95% CrI: 17.3-22.9%) at day 10. In the delayed detection group, fewer
139 individuals remained potentially infectious at days 5 and 10, likely because they were detected
140 later in their infection. In this group, the probability of having a Ct<30 was 51.0% (95% credible
141 interval (CrI): 48.2-53.6%) on day 5 post detection and 9.42% (95% CrI: 8.04-11.0%) on day
142 10.

143

144 **Incidence of rebounds**

145 We next characterized the frequency of rebound viral RNA trajectories in this cohort. Viral
146 rebounds may be characterized by the duration of the “quiescent” period of low viral
147 concentration between distinct peaks, the duration of the subsequent rebound, and the timing
148 of rebound onset relative to infection, but no consensus definition of viral rebound based on
149 these quantities exists. We defined rebound as any viral trajectory with a decline in Ct value

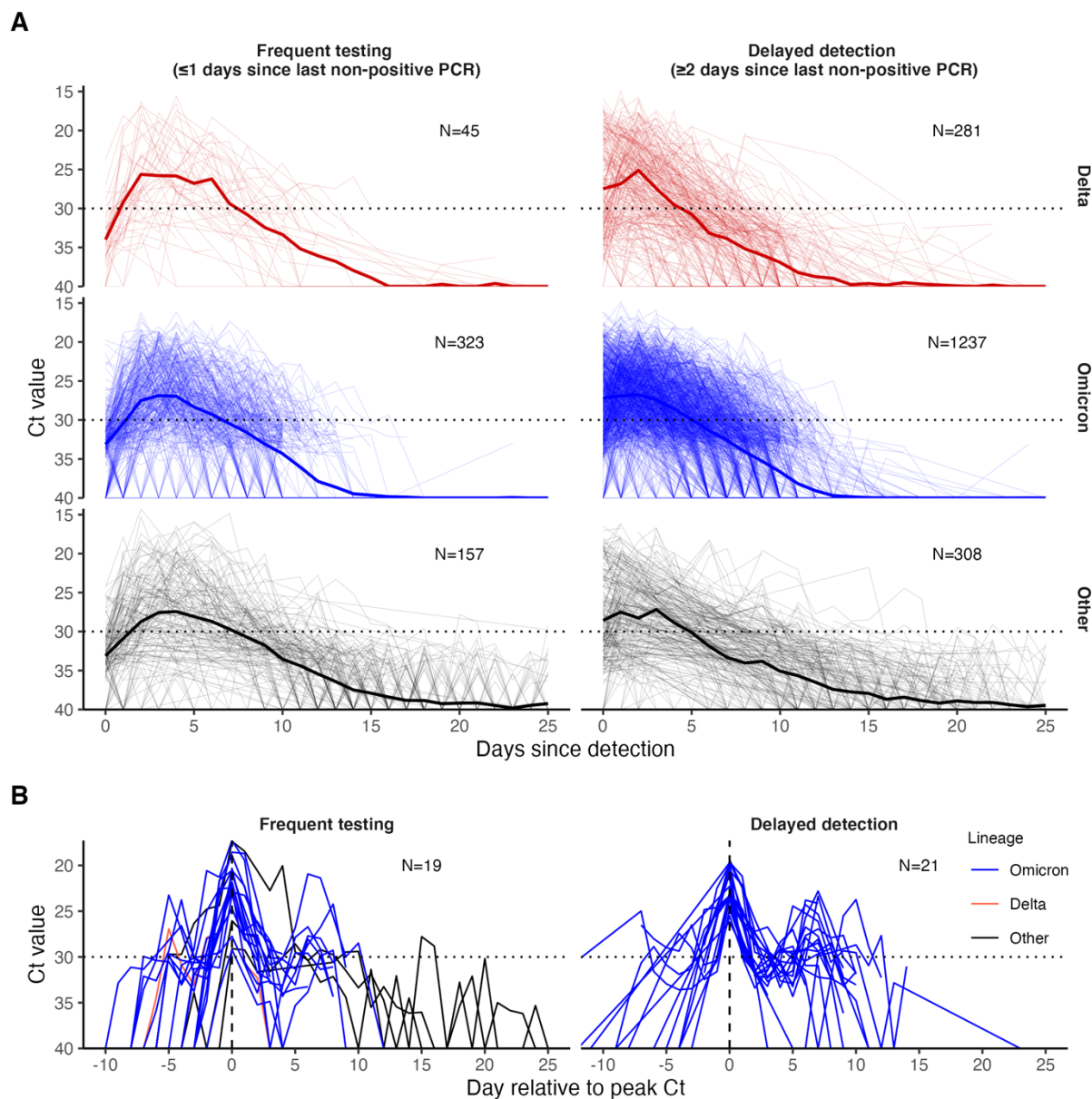
150 to <30 for 3+ days of tests (the rebound) after 3+ days of tests with Ct \geq 30 or a negative result
151 (the quiescent period) following an initial Ct value <30 (the first detection of infection). Testing
152 often ceased following initial clearance, and thus to minimize the impact of right censoring we
153 only considered those trajectories with at least three days of tests with negative or Ct \geq 30
154 following a Ct value <30 as the denominator (N=999). We detected seven viral rebounds under
155 this definition. Less stringent definitions led to more rebound classifications. For example, 40
156 (3.00%) of 1,334 infections were identified as rebounds when only 2+ consecutive days of
157 Ct \geq 30 followed by 2+ days of Ct<30 was required to be classified as such (**Table 1; Figure**
158 **1B**). All individual-level viral trajectories classified as rebounds under this less stringent
159 definition are shown in **Supplementary Figure S5**. Under this definition, we found that
160 rebound infections were more likely in Omicron BA.1 infections, with 36 (4.10%; N=877)
161 Omicron BA.1 infections resulting in rebound compared to one (0.562%; N=178) and three
162 (1.08%; N=279) Delta and other infections, respectively (**Supplementary Table 1**; Chi-
163 squared test for Omicron BA.1 (N=877) vs. non-Omicron BA.1 infection (N=457), test statistic
164 = 9.69, p-value < 0.05). Similarly, we found that rebounds were more common in boosted
165 individuals, with 32 (6.48%; N=494) rebounds in boosted individuals vs. three (0.929%;
166 N=323) and two (1.26%; N=159) rebounds in vaccinated and unvaccinated individuals,
167 respectively (**Supplementary Table 2**; Chi-squared test for boosted (N=494) vs. not-boosted
168 (N=478) infection, test statistic = 18.1, p-value < 1e-4).

169 **Table 1. Number of rebound infections classified under different definitions for initial**
 170 **clearance and subsequent rebound.**

171

Initial clearance duration (consecutive days with Ct \geq 30)	Rebound duration (days above Ct value threshold)	Ct value threshold of rebound	Rebounds	Total	Percentage
≥ 4	≥ 4	Ct<30	0	749	0.00%
≥ 4	≥ 3	Ct<30	1	749	0.13%
≥ 4	≥ 2	Ct<30	4	749	0.53%
≥ 3	≥ 4	Ct<30	2	999	0.20%
≥ 3	≥ 3	Ct<30	7	999	0.70%
≥ 3	≥ 2	Ct<30	16	999	1.60%
≥ 2	≥ 4	Ct<30	7	1334	0.53%
≥ 2	≥ 3	Ct<30	18	1334	1.35%
≥ 2	≥ 2	Ct<30	40	1334	3.00%
≥ 4	≥ 4	Ct<25	0	749	0.00%
≥ 4	≥ 3	Ct<25	0	749	0.00%
≥ 4	≥ 2	Ct<25	0	749	0.00%
≥ 3	≥ 4	Ct<25	1	999	0.10%
≥ 3	≥ 3	Ct<25	1	999	0.10%
≥ 3	≥ 2	Ct<25	2	999	0.20%
≥ 2	≥ 4	Ct<25	1	1334	0.08%
≥ 2	≥ 3	Ct<25	2	1334	0.15%
≥ 2	≥ 2	Ct<25	5	1334	0.38%

172



173

174 **Figure 1. PCR Ct value trajectories for confirmed and suspected infections. (A)** PCR Ct
 175 value trajectories for each acute Delta (red), Omicron BA.1 (blue), and other (black) infection.
 176 Individuals are grouped by the gap between detection and their most recent negative or
 177 inconclusive PCR test (Frequent testing vs. Delayed detection). Thick lines depict the mean
 178 Ct value over time, counting negative tests as Ct=40. Thin lines depict individual level Ct
 179 values over time. The horizontal dotted lines mark Ct=30, which we consider here as a proxy
 180 for possible infectiousness and antigen test positivity. **(B)** Subsets of PCR Ct value trajectories
 181 that were classified as rebounds, stratified by testing frequency group. Rebounds are defined
 182 here as any trajectory with an initial Ct value <30, followed by a sequence of two or more
 183 consecutive negative tests or tests with Ct value ≥ 30 , and subsequently followed by two or
 184 more consecutive tests with Ct value <30.

185 **Minimal differences across variants and vaccination histories in the probability of**
186 **having low Ct values over time**

187 To assess differences in the duration of test positivity and infectiousness by variant and
188 immune status, we modeled the probability of an individual having $Ct < 30$ on each day post
189 detection. As a baseline model, we fitted a logistic regression model with a smoothing spline
190 on days since detection as a predictor. We compared various models with or without variant
191 and vaccination history based on k -fold cross-validation and Bayesian model averaging.

192

193 The best-performing model used days since detection, stratified by both the cumulative
194 number of previous exposures (infection or vaccination) and virus lineage, to predict the time
195 course of low Ct values. The models including only vaccination status and lineage or days
196 since previous exposure and lineage also performed well (**Supplementary Table 3 and 4**).
197 This indicates that the interpersonal variation in low Ct values over time is better captured by
198 models that account for exposure history than by models that account for time since detection
199 alone. However, the difference in classification accuracy between the models was small. The
200 baseline model, which included only the number of days since detection as a predictor, gave
201 an overall classification accuracy for an individual having $Ct < 30$ or ≥ 30 /negative of 81.9% with
202 an AUC of 88.7% (group-level classification accuracies: $Ct < 30 = 59.7\%$; $Ct \geq 30$ /negative =
203 89.5%) for the frequent testing group, and an overall classification accuracy of 84.0% with an
204 AUC of 90.4% ($Ct < 30 = 72.4\%$; $Ct \geq 30$ /negative = 87.7%) in the delayed detection group. In
205 contrast, the best model, which included the cumulative number of exposures and virus
206 lineage in addition to days since detection, gave an overall classification accuracy of 82.8%
207 with an AUC of 90.0% ($Ct < 30 = 63.7\%$; $Ct \geq 30$ /negative = 89.4%) for the frequent testing group
208 and an overall classification accuracy of 84.8% with an AUC of 91.2% ($Ct < 30 = 69.6\%$;
209 $Ct \geq 30$ /negative = 89.5%) in the delayed detection group. These results indicate that while
210 exposure histories help to explain mean viral RNA kinetics, they provide little assistance in
211 predicting an individual's course of infectiousness over time, due to a high degree of individual-
212 level variation, which may be dominated by stochastic effects or other unmeasured
213 characteristics.

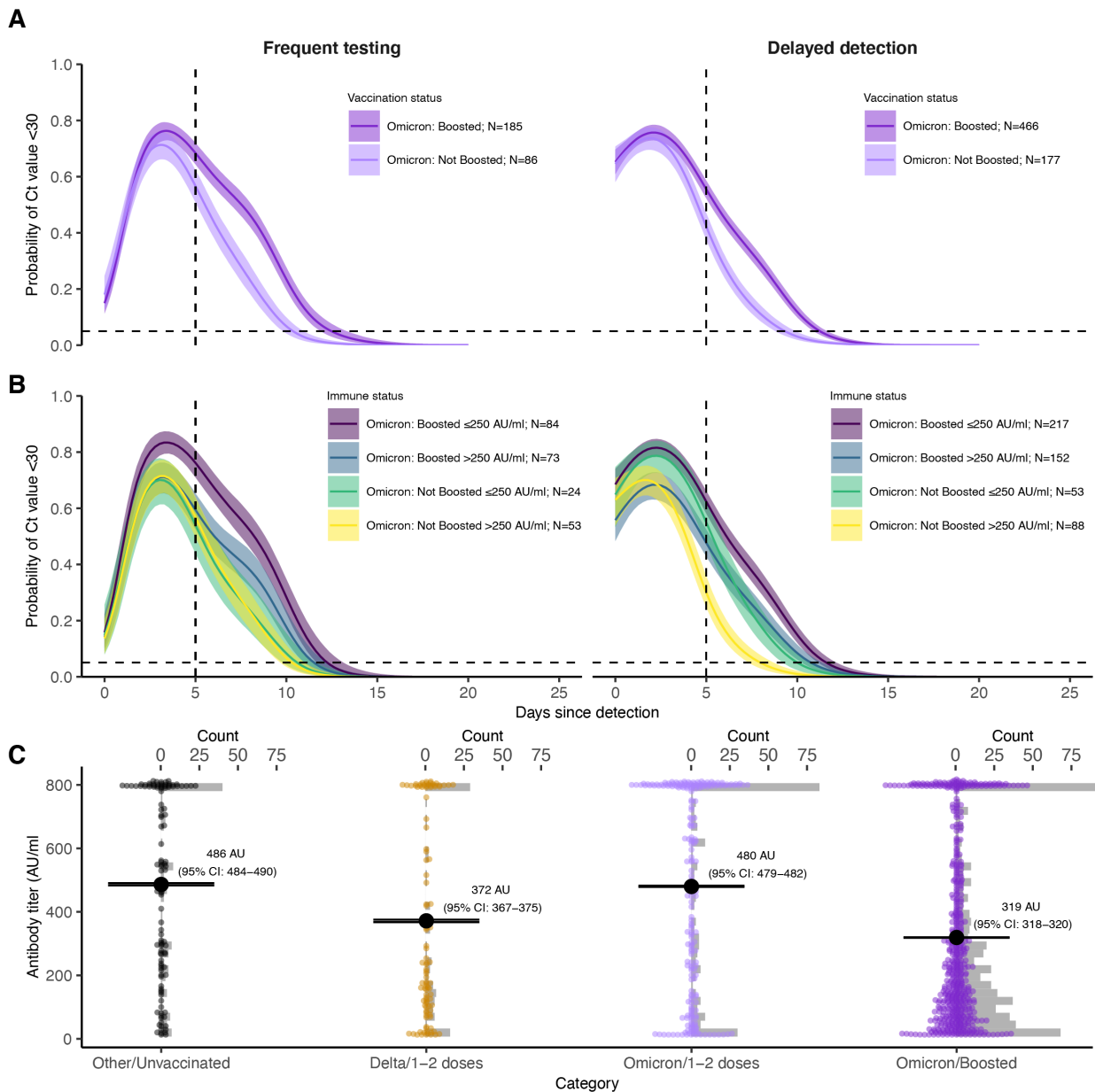
214

215 Vaccination provides multiple layers of protection against SARS-CoV-2, leading to reduced
216 rates of infection (Tai et al., 2022) and faster clearance of the virus.(Kissler, Fauver, Mack,
217 Tai, et al., 2021) Consistent with these findings, individuals who received two vaccine doses
218 prior to infection with pre-Delta and pre-Omicron variants (N=17) cleared to negative results
219 or high Ct values faster than unvaccinated individuals (N=216) (**Supplementary Figure 6**).
220 While boosting reduced rates of infection in our cohort,(Tai et al., 2022) boosted individuals
221 with Omicron BA.1 infections (N=651) tended to sustain low Ct values for longer durations
222 than individuals who had only undergone an initial vaccine course (N=251), defined as either
223 two doses of an mRNA vaccine or a single dose of the Ad.26.COVS adenovirus vector-
224 based vaccine (**Figure 2A; Supplementary Figure 6**). This pattern was robust to refitting the
225 model after excluding player infections, resulting in a subpopulation more representative of
226 the general population in age and health status (**Supplementary Figure 7**). We also found
227 similar patterns after subsetting infections by their symptom status (**Supplementary Figure**
228 **8**).

229

230 We also considered a possible effect of age, as boosted individuals in this cohort were typically
231 older than non-boosted individuals at the time of BA.1 infection (mean age of 37.6 years in
232 the BA-1 infected, boosted group vs. 31.3 years in the BA.1-infected, non-boosted group), and
233 thus the differences between vaccination groups could be driven by an age-specific effect.
234 Refitting the regression model including an additional spline term for the interaction of days
235 since detection and age group (categorized as < 30 , 30-50 or > 50 years old) suggested that

236 older individuals did maintain Ct<30 for longer on average than younger individuals after
237 conditioning on vaccination status (**Supplementary Figure 9A**). However, the effect of a
238 higher proportion with Ct<30 in boosted individuals relative to non-boosted individuals also
239 remained after conditioning on age, suggesting that both older age and booster status explain
240 some variation in duration of Ct<30 (**Supplementary Figure S9B**). Furthermore, models
241 including age were universally better supported in the model comparison analysis and
242 provided an improvement in classification accuracy, but in both cases the gains were small.



243

244 **Figure 2. (A)** Proportion of confirmed and suspected Omicron BA.1 infections with Ct<30 on
 245 each day post detection by vaccination status and detection group. Solid colored lines and
 246 shaded ribbons depict posterior estimates from a generalized linear model predicting
 247 probability of Ct<30 as a function of days since detection, vaccination status and variant,
 248 showing the posterior mean (solid line) and 95% credible intervals (shaded ribbon) of each
 249 conditional effect. Dotted horizontal and vertical lines mark 5% probability and day 5 post
 250 detection, respectively. **(B)** As in (A), but additionally stratified by single point-in-time anti-
 251 spike antibody titer against the ancestral SARS-CoV-2 (WA1) strain as measured by the
 252 Diasorin Trimeric Assay. **(C)** Distribution of antibody titers (colored points) stratified by variant
 253 and vaccination status of each detected infection, with mean titers (large black points) and
 254 bootstrapped 95% confidence intervals for the mean (horizontal lines). Grey bars are
 255 histograms of antibody titer counts in bins of 10 arbitrary units (AU)/ml. Note that stratification
 256 is by infection and not individual, and that antibody titers were measured at a single point in
 257 time rather than near the time of infection. The Diasorin Trimeric Assay values are truncated
 258 between 13 and 800 AU/ml.

259 Pre-Omicron antibody titer explains variation in viral RNA clearance

260 To assess the mechanisms behind the unexpected slower clearance in boosted Omicron BA.1
261 infections, we assessed viral kinetics stratified by antibody titer. In addition to exposure history
262 information, 979 individuals were tested at least once (1,017 measurements total) with the
263 Diasorin Trimeric Assay for antibody titers against the spike protein from the ancestral SARS-
264 CoV-2 (WA1) strain (**Supplementary Figure 10**). Most titers were obtained from mid-
265 September to mid-October 2021, and thus we consider these titers to represent an individual's
266 post primary vaccination course response rather than post-boost/post-Omicron infection
267 immunity (**Supplementary Figure 11**). The median time between the most recent vaccine
268 dose and the titer draw was 162 days (interquartile range: 129–180 days) (**Supplementary**
269 **Figure 12**).

270
271 We hypothesized that these single point-in-time SARS-CoV-2 antibody titer measurements
272 represented a proxy of the strength of the immune response to SARS-CoV-2 and thus would
273 be reflected in the features of viral kinetics over the course of infection. A total of 494
274 measurements were classified as low antibody titers (≤ 250 arbitrary units [AU]/ml) and 523 as
275 high titers (> 250 AU/ml). This cutoff was chosen as a conservative upper bound for defining
276 risk of Delta infection (see **Materials & Methods**). Most individuals either had very low titers
277 (< 13 AU/ml) or titers at the upper limit of detection (800 AU/ml) of the assay (**Figure 2C**).

278
279 We fitted a logistic regression model for the probability of having a $Ct < 30$ on each day since
280 detection, stratified by the interaction of an individual's booster status and their pre-booster
281 antibody titer status (**Figure 2B**; **Supplementary Figure 13**). Boosted individuals with a low
282 antibody titer had the highest and longest duration of $Ct < 30$ over time since detection in both
283 the frequent testing and delayed detection group. In the delayed detection group, individuals
284 with low antibody titers were more likely to have $Ct < 30$ than individuals with high antibody
285 titers regardless of booster status, though boosted individuals with high antibody titers
286 maintained $Ct < 30$ for longer than non-boosted individuals with low titers. To account for
287 potential confounding from waning immunity, in which low titers simply represent a longer time
288 since previous exposure, we restricted the dataset to include only individuals who had their
289 titer measured within 100-200 days after a previous exposure. We also repeated the analysis
290 after restricting to only infections detected 60-90 days following an antibody titer
291 measurement. These trends were maintained in both sensitivity analyses (**Supplementary**
292 **Figure 14**).

293 Based on these findings, we hypothesized that boosted individuals who nevertheless were
294 infected with Omicron BA.1 may have had relatively poor BA.1-specific immune responses to
295 prior SARS-CoV-2 exposures, leading to uncharacteristically long infections. To test this
296 hypothesis, we stratified each infection by vaccination status and variant and compared
297 antibody titers between these groups (**Figure 2C**). Antibody titers were lower among fully
298 vaccinated individuals who were subsequently infected with Delta than individuals who had
299 been infected with a pre-Delta variant. This suggests that individuals with a high antibody titer
300 at around the time of Delta circulation were less likely to be infected with Delta. In contrast,
301 we found that mean antibody titers among Omicron BA.1-infected, fully vaccinated individuals
302 were similar to individuals in the pre-Delta, unvaccinated group, suggesting that higher titer
303 individuals were not substantially less likely to be infected than lower titer individuals. Finally,
304 we found that antibody titers were lowest among Omicron BA.1 infected boosted individuals,
305 suggesting that individuals with a high titer measurement prior to being boosted were less
306 likely to have Omicron BA.1 infections.

307
308 These results are consistent with an additional age group-level effect also contributing towards
309 differences in the proportion of individuals with $Ct < 30$ over time. We found that younger BA.1-

310 infected individuals had higher antibody titers on average than older BA.1-infected individuals,
311 but that still BA.1-infected boosted individuals had consistently lower mean antibody titers than
312 BA.1-infected non-boosted individuals within each age group (**Supplementary Figure S15A**).
313 Furthermore, refitting the logistic regression model including terms for both age group and the
314 interaction of vaccination status and antibody titer group showed a consistent trend of boosted,
315 low titer individuals maintaining Ct<30 for longer than other high titer individuals within each
316 age group (**Supplementary Figure S15B**). However, we note that at this level of stratification,
317 the sample sizes for each subgroup are small and thus there is considerable uncertainty for
318 some combinations of age group, titer group and vaccination status.

319

320 **The effect of immune status and variant on viral proliferation, peak viral RNA titers, and** 321 **clearance**

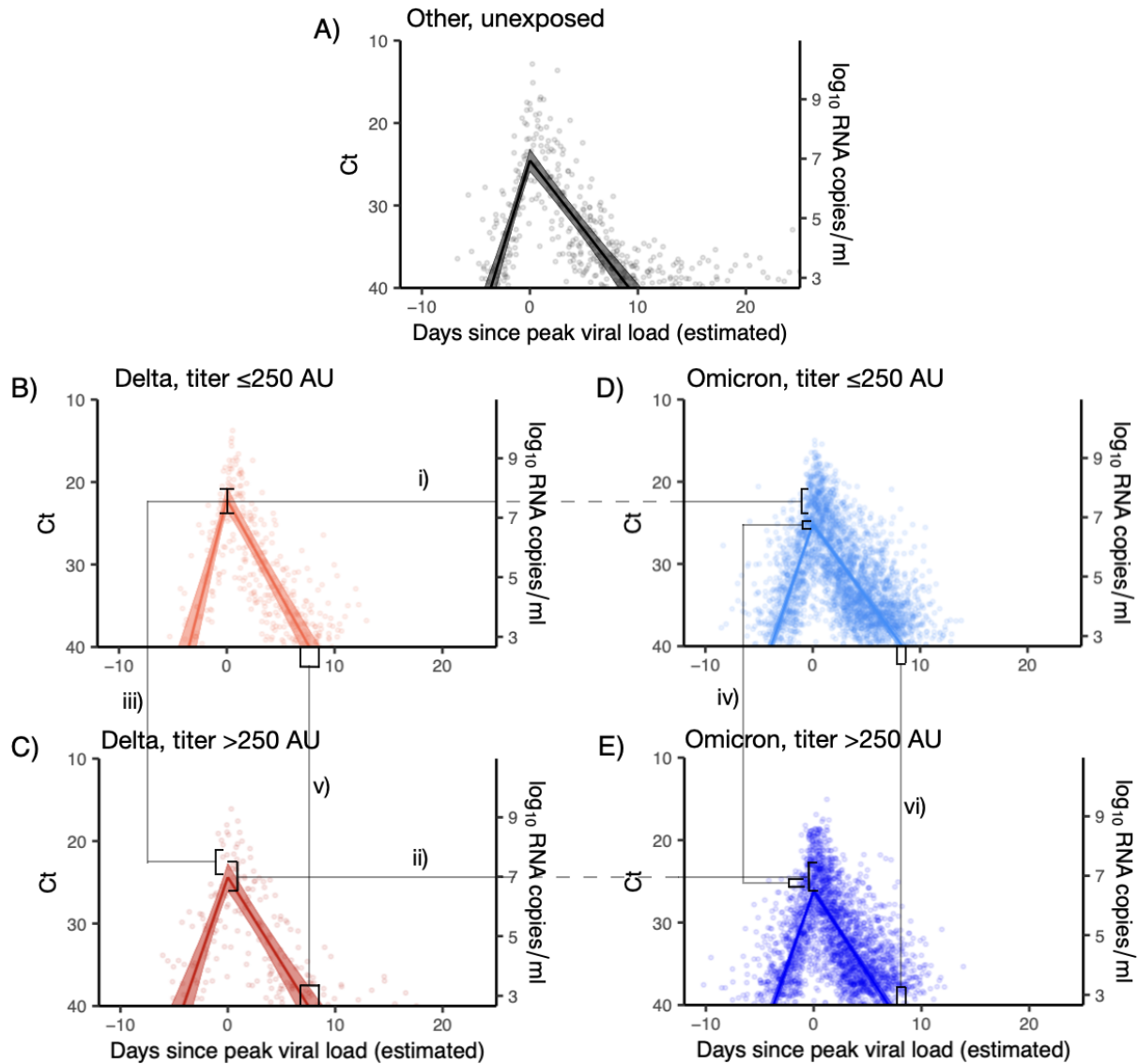
322 We next adapted a framework to estimate the impact of antibody titer, vaccination status, and
323 variant on peak viral RNA concentrations, proliferation phase duration, and clearance duration
324 (**Figure 3**). (Kissler, Fauver, Mack, Olesen, et al., 2021; Kissler, Fauver, Mack, Tai, et al., 2021)
325 According to the viral kinetic model, and among Omicron BA.1 infections, boosted individuals
326 had a longer estimated viral clearance time than non-boosted individuals (8.4 days (95% CrI:
327 8.0-8.7) vs. 6.2 days (95% CrI: 5.8-6.6), respectively), in line with the results from the logistic
328 regression model. Viral proliferation times and peak viral RNA were similar among boosted
329 and non-boosted individuals with Omicron BA.1 infections (**Supplementary Table 5**). When
330 stratifying by post-initial vaccination antibody titer, Delta infections featured a consistently
331 higher peak viral RNA than Omicron BA.1 infections. Among Omicron BA.1 infections, high
332 antibody titers were associated with faster viral clearance times and lower peak viral RNA.
333 Proliferation times were similar across variants and titers (**Supplementary Table 6**).

334

335 We fitted the viral RNA kinetic model to Omicron BA.1 infections after stratifying individuals
336 based on their symptom status as well as vaccination status or antibody titer group. We found
337 the same pattern of longer clearance times for boosted individuals relative to fully vaccinated
338 individuals, with symptomatic boosted individuals demonstrating longer clearance times than
339 asymptomatic boosted individuals (**Supplementary Table 7**). Among those with low antibody
340 titer, presence of symptoms was associated with higher peak viral RNA and longer clearance
341 times, while for those with high antibody titer, peak viral RNA and clearance times were similar
342 between symptom statuses (**Supplementary Table 8**).

343

344 Finally, we fitted the models allowing for BA.1 viral RNA kinetics to vary by age in addition to
345 vaccination status or antibody titer. Consistent with the logistic regression results, older
346 individuals demonstrated longer average clearance times than younger individuals across
347 vaccination and antibody titer groups. When stratifying by immune status, individuals aged
348 50+ years took between roughly 1–2 days longer to clear than individuals aged 30–50, and
349 2–3 days longer to clear than individuals under 30 (**Supplementary Tables 9 & 10**). However,
350 we still found a consistent effect of antibody titer and booster status on clearance time despite
351 this additional age effect. Individuals with low antibody titer and boosted individuals took 1-2
352 days longer to clear than individuals with high antibody titer and non-boosted individuals in
353 both the <30- and 30–50-year age groups (**Supplementary Tables 9 & 10**).



354

355 **Figure 3. Estimated viral trajectories by variant and titer.** Points depict measured Ct
 356 values, lines depict the estimated population mean viral trajectories, and shaded regions
 357 depict the 95% credible intervals for the estimated population viral trajectories. A) Non-Delta
 358 and non-Omicron infections in individuals who were previously unexposed (no prior record of
 359 vaccination or infection), B) Delta infections with titer ≤ 250 , C) Delta infections with titer > 250 ,
 360 D) Omicron infections with titer ≤ 250 , E) Omicron infections with titer > 250 . Peak viral loads
 361 were higher for Delta infections than for Omicron infections when stratifying by titer (i and ii),
 362 and titers ≤ 250 were associated with higher viral loads when stratifying by variant (iii and iv).
 363 Low titers were also associated with longer clearance times (v and vi).

364 Discussion

365 We found that individuals infected with SARS-CoV-2 often had Ct values <30 beyond the five-
366 day isolation period following SARS-CoV-2 infection currently recommended by the
367 CDC.(Centers for Disease Control and Prevention, n.d.) This finding is in line with other
368 studies measuring Ct values from upper respiratory tract samples, the duration of antigen test
369 positivity, and the duration of infectious viral load or culturable virus.(Boucau, Marino, et al.,
370 2022; Earnest et al., 2022; Ke et al., 2022; Landon et al., 2022; Lefferts et al., 2022) While we
371 do not have data on infectiousness by day to clarify the exact link between Ct and
372 infectiousness, nearly half of the individuals in this cohort had potentially infectious viral loads
373 (Ct<30) five days after their initial detection, even in those detected later in their infection
374 course (Singanayagam et al., 2020a). By day 10, the number of individuals with Ct<30 was
375 substantially reduced but still high. The duration of positivity was highly variable across
376 individuals, and low Ct values consistent with potential infectiousness were sometimes
377 maintained for up to two weeks. These observations suggest the use of test-based, rather
378 than time-based, protocols for defining the duration of isolation to limit the spread of SARS-
379 CoV-2.

380

381 Rebounds with recurrence of symptoms and positive rapid antigen tests after a period of
382 negative test results have been increasingly reported in individuals treated with SARS-CoV-2
383 antiviral drugs.(Boucau, Uddin, et al., 2022; Charness et al., 2022) but estimates for the
384 frequency of viral rebounds in the absence of antiviral treatment have been lacking. Among
385 infected boosted individuals in this cohort, who were predominantly infected with Omicron
386 BA.1, we detected seven rebounds in viral trajectory, stringently defined as any Ct value
387 trajectory with at least 3 consecutive days of negative tests or tests with Ct≥30 after the initial
388 peak followed by 3 or more consecutive days with Ct<30. However, more rebounds were
389 detected when using less stringent Ct value-based definitions and were more frequent in
390 Omicron-infected or boosted individuals, occurring in ~6% of infections in contrast to ~1% of
391 infections in the pre-booster pre-Omicron phase of the pandemic. It was not routine for testing
392 to continue following suspected clearance in this cohort, and thus these results may represent
393 a lower bound on the incidence of rebound infections. The frequency of viral trajectory
394 rebounds depends on the definition of 'rebound', highlighting the need for standardized
395 definitions to enable comparisons across studies. We did not measure the recurrence of
396 culturable virus during these resurgent low Ct periods, and thus further work is needed to
397 understand if viral RNA rebounds are a reliable proxy for infectivity. Moreover, we did not have
398 sufficient information to define rebounds with respect to clearance and recurrence of
399 symptoms, though the experience of the occupational health team is that rebounds of a clinical
400 nature have been extremely rare, with only one documented case.(Mack et al., 2021) Overall,
401 these findings suggest that symptom monitoring after clearing isolation may be warranted,
402 and a return to isolation may be necessary for individuals with rebound infections.(Charness
403 et al., 2022)

404

405 Boosted individuals in this cohort were less likely to be infected with Omicron BA.1,(Tai et al.,
406 2022) and those who had a breakthrough infection tended to have a low antibody titer
407 measurement to the WA1 spike protein after their initial vaccine course. In this context, test
408 positivity following Omicron BA.1 infection lasted longer for boosted individuals than for non-
409 boosted individuals, regardless of symptom status. This observation was further supported by
410 a viral kinetic model that found longer clearance times for Omicron BA.1 infections in boosted
411 relative to non-boosted individuals. Moreover, high antibody titers to the WA1 spike protein
412 were associated with lower peak viral RNA concentrations and faster clearance times for both
413 Delta and Omicron BA.1 infections. Together, these results suggest that the low antibody titers
414 in infected boosted individuals conferred increased risk for infection as well as slower control
415 and clearance of infection.

416 The effect of age on viral kinetics complicates the interpretation of these findings. Prior to the
417 detection of Omicron BA.1, older individuals have been found to take longer to clear infection
418 on average than younger individuals.(Caputo et al., 2021; Cevik et al., 2021; Jones et al.,
419 2021; Long et al., 2021; Néant et al., 2021; Singanayagam et al., 2022) However, these
420 findings are not unequivocal, as a previous systematic review found the effect of age on viral
421 kinetics was diminished after accounting for disease severity.(Chen et al., 2021) Our data
422 support an effect of age on viral clearance times, with longer times from peak to clearance in
423 individuals >50 years compared to those <30 years regardless of lineage and immune state.
424 In this cohort, older individuals were more likely to be boosted prior to becoming infected with
425 BA.1 than younger individuals, and thus the finding of delayed clearance in BA.1-infected,
426 boosted individuals can be partially attributed to delayed clearance in older individuals.
427 However, we found consistent delayed clearance in boosted relative to non-boosted
428 individuals within each age group, notably in the <30 years group. Furthermore, the pattern of
429 lower antibody titers to WA1 spike in BA.1-infected, boosted individuals relative to BA.1-
430 infected, non-boosted individuals was also consistent within each age group, suggesting that
431 low WA1 spike titers correlate with increased infection risk and slower clearance in addition to
432 any age-specific effects.

433

434 An important limitation of this study is that the cohort is not representative of the general
435 population, as it is predominately male, young, and includes professional athletes. However,
436 our key findings were preserved in analyses after excluding the players. We did not test for
437 the presence of infectious virus, and our findings are based on Ct values obtained from
438 combined nasal and oropharyngeal swabs.(Ke et al., 2022) While low Ct values have been
439 associated with potential infectiousness and antigen test positivity,(Bullard et al., 2020; Jaafar
440 et al., 2021; Jefferson et al., 2020; Singanayagam et al., 2020b) this is an imperfect proxy. It
441 is possible that some infections were undetected, and thus the reported number of prior
442 infections should be interpreted as a lower bound for each member of the cohort. SARS-CoV-
443 2 antibody titers were only measured from mid-September to mid-October 2021 and were
444 taken at varying time points after initial vaccination course (between 0 and 290 days), so we
445 could not assess the relationship between antibody waning and viral kinetics. Antibody titers
446 were measured against the spike protein of the WA1 lineage, which correlate poorly with
447 protection against the antigenically distinct Omicron lineages; thus, it is unclear how these
448 data are associated specifically to Omicron-immunity, beyond representing a proxy for overall
449 immune response.

450

451 Variants and immune statuses interact, sometimes in unexpected ways, to produce viral
452 kinetics that differ in duration and intensity. Collecting longitudinal viral load data in more
453 diverse cohorts will help to ensure that isolation and quarantine policies are based on the best
454 available evidence and will help to properly contextualize results from ongoing drug and
455 vaccine trials. Similarly, our findings suggest that SARS-CoV-2 control measures may be
456 better informed by measurements of immune status than proxies such as number or timing of
457 receipt of vaccine doses or of infections. Testing this hypothesis will require widespread
458 collection and analysis of serological, infection, and vaccination data in diverse cohorts and
459 broader availability of quantitative antibody tests designed for the spike protein of Omicron
460 lineages.

461 **Methods**

462 **Study design**

463 The data reported here represent a convenience sample including team staff, players, arena
464 staff, vendors, and others affiliated with the NBA as described previously.(Kissler, Fauver,
465 Mack, Olesen, et al., 2021; Kissler, Fauver, Mack, Tai, et al., 2021) The retrospective study
466 includes samples collected between 7th July 2020 and 26th January 2022 (**Supplementary**
467 **Figure 1**). Clinical samples were obtained by combined swabs of the anterior nares and
468 oropharynx, collected separately from each anatomical site, for each patient administered by
469 a trained provider. Daily testing was required for most individuals prior to vaccination
470 availability, with less frequent testing but close monitoring required after vaccination. Cycle
471 threshold (Ct) values were generated using the Roche cobas target 1 assay. For the viral
472 kinetics model analyses, Ct values were converted to viral genome equivalents using a
473 standard curve.(Kissler, Fauver, Mack, Olesen, et al., 2021)

474

475 We classified all individuals as having Ct value <30 or not on each day post-detection. This
476 threshold was chosen based on a combination of antigen sensitivity and studies of virus
477 culture by Ct, where the presence of culturable virus is often assumed to correlate with
478 infectivity.(Brihn et al., 2021; Bullard et al., 2020; Pilarowski et al., 2021; Singanayagam et al.,
479 2020b; Thommes et al., 2021) We stratified infections by those who had a negative or
480 inconclusive test ≤ 1 day prior to detection and those whose last negative or inconclusive test
481 was ≥ 2 days ago. We assumed that individuals testing negative at the end of an acute infection
482 remained negative for the remainder of the study period, whereas those ending in a positive
483 test are right-censored. Rebound trajectories were defined as any trajectory with a sequence
484 of two or more consecutive Ct values ≥ 30 or negative tests after the initial peak followed by
485 two or more consecutive Ct values <30 . We considered more stringent definitions both for
486 initial clearance (3+ or 4+ days of Ct ≥ 30 or negative test following initial peak) and subsequent
487 rebound (3+ or 4+ days of Ct < 30). In some instances, individuals were tested multiple times
488 per day and thus for ease of model fitting we excluded 3,751 positive or inconclusive and
489 14,713 negative samples from repeat tests on the same day in our analyses, prioritizing the
490 earliest test and then lowest Ct value test on each day.

491

492 Vaccination information was reported and verified by NBA staff and a clinical operational team.
493 828 individuals had been boosted by the time of their last PCR test, 529 had completed their
494 primary vaccination course (two doses of an mRNA vaccine or one dose of Janssen /
495 Ad.26.COVS adenovirus vector-based vaccine), 8 had received one vaccine dose, and 13
496 confirmed to be unvaccinated. The vaccination statuses of the remaining individuals were
497 unknown. The time course of individual vaccination and exposure times is shown in
498 **Supplementary Figure 11**.

499

500 **Study oversight**

501 In accordance with the guidelines of the Yale Human Investigations Committee, this work with
502 de-identified samples was approved for research not involving human subjects by the Yale
503 Institutional Review Board (HIC protocol # 2000028599). This project was designated exempt
504 by the Harvard Institutional Review Board (IRB20-1407).

505

506

507 **Classification of infections**

508 We tagged each series of positive tests buffered by at least 14 days of negative or missing
509 tests on each side as a distinct infection. After an infection was flagged, subsequent positives
510 were not classified as a new infection for 90 days. Isolated positive tests with no other positive
511 within 14 days either side were not considered as detections. We track the cumulative number
512 of exposures (defined as either receiving a vaccination or infection) over time. Individuals who
513 received the Janssen/Ad.26.COVS adenovirus vector-based vaccine were counted as
514 having received two vaccine doses. 351 additional infections were reported to the program
515 outside of the main testing regime, either through an external PCR or rapid antigen test, or
516 from a positive antibody test result (not including the Diasorin Trimeric Assay results described
517 below). We consider these detections as contributing towards an individual's infection history
518 but are unable to include them in the Ct value trajectory analyses.

519

520 **Genome sequencing and lineage assignment**

521 RNA was extracted and confirmed as SARS-CoV-2 positive by RT-qPCR.(Vogels et al., 2021)
522 Next Generation Sequencing was performed with the Illumina COVIDSeq ARTIC viral
523 amplification primer set (V4, 384 samples, cat# 20065135). Library preparation was performed
524 using the amplicon-based Illumina COVIDseq Test v033 and sequenced 2x74 on Illumina
525 NextSeq 550 following the protocol as described in Illumina's documentation. The resulting
526 FASTQs were processed and analyzed on Illumina BaseSpace Labs using the Illumina
527 DRAGEN COVID Lineage Application;(BaseSpace Labs. *DRAGEN COVID Lineage*, 2021)
528 versions included are 3.5.0, 3.5.1, 3.5.2, 3.5.3 and 3.5.4. The DRAGEN COVID Lineage
529 pipeline was run with default parameters recommended by Illumina. Lineage assignment and
530 phylogenetics analysis using the most updated version of Pangolin(Rambaut et al., 2020) and
531 NextClade(Aksamentov & Neher, 2021), respectively. All sequenced Omicron infections were
532 lineage BA.1 apart from 1 BA.2.10 infection. Sequenced Delta infections were a combination
533 of lineages B.1.617.2 and AY.x.

534

535 There were 3 and 482 non-sequenced infections in the window of time when Alpha was
536 replaced by Delta (29th May 2021 to 18th July 2021) and after the first detection of Omicron
537 BA.1 (3rd December 2021 onwards), respectively (**Supplementary Figure 4**). We removed
538 these 485 infections from variant-specific analyses and assigned all non-sequenced infections
539 prior to the detection of Omicron BA.1 to the dominant lineage at the time of detection (i.e., all
540 infections prior to 29th May 2021 were assumed "Other" and all infections between 18th July
541 2021 and 3rd December 2021 were assumed "Delta"). We removed all non-sequenced
542 infections detected after 3rd December 2021 from variant-specific analyses rather than
543 classifying them as Omicron BA.1 due to the continued presence of Delta. Omicron BA.2 was
544 not regularly detected until after this period, with only 1 confirmed BA.2 infection (BA.2.10),
545 which was removed from these analyses.

546

547 **Antibody titers**

548 Individuals were tested with the Diasorin Trimeric Assay for IgG antibody titers against the
549 ancestral SARS-CoV-2 (WA1) strain spike protein during the 2021 pre-season period
550 (September-October 2021). The majority (>90%) of blood draws were from mid-September to
551 early October 2021. We classified individuals with a titer of >250 AU/ml as being in the high
552 titer group and in the low titer group otherwise, chosen based on its correlation with authentic
553 virus neutralization results for wildtype and Delta.(Liu et al., 2021; Wang et al., 2021)
554 Specifically, an authentic virus neutralization titer of 100 was found to be well correlated with
555 a 50% protective neutralization level for wildtype(Khoury et al., 2021) and found to correspond
556 to a DiaSorin AU of 189.09 (95%CI: 147.61-235.75) (**Supplementary Figure 16**). The cutoff

557 of 250 was therefore chosen as a conservative upper bound classifying an individual as at
558 lower risk of infection with Delta or wildtype SARS-CoV-2. Note that this cutoff does not predict
559 infection risk with Omicron and was simply chosen as a proxy for an individual's immune
560 competence.

561

562 **Logistic regression models**

563 We used the RStan package *brms* to fit Bayesian logistic regression models estimating the
564 probability of having Ct value <30 on each day post detection, stratified by detection
565 speed.(Bürkner, n.d.) As a baseline, we considered a model without variant-specific effects,
566 using smoothing splines to estimate the probability of having a Ct value less than 30 on each
567 day post detection. We then fitted additional logistic regression models, adding additional
568 spline terms capturing the effect of vaccination status, cumulative number of previous
569 exposures or days since previous exposure, and/or lineage with days since detection. We
570 then ranked models based on the expected log predictive density calculated using *k*-folds
571 cross-validation (25 folds) and evaluated their classification accuracy and area under the
572 receiver operator curve. For the antibody titer analyses, we fitted Bayesian logistic regression
573 models for the probability of Ct value <30 as a function of days since detection, stratified by
574 the interaction of titer group (above or below 250 AU/ml), lineage and vaccination status. To
575 account for possible confounding from age effects, we ran sensitivity analyses refitting all of
576 the logistic regression models including an additional spline term for the effect of age group
577 on probability of Ct value <30 on each day since detection. We grouped individuals into three
578 age groups: <30 years, 30-50 years, >50 years. Further details on the fitting process can be
579 found in the **Supplementary Methods**.

580

581 **Viral kinetic model**

582 We extended a previously reported model for capturing SARS-CoV-2 viral kinetics to estimate
583 the viral proliferation time, viral clearance time, and peak viral load by variant and immune
584 status.(Kissler, Fauver, Mack, Olesen, et al., 2021; Kissler, Fauver, Mack, Tai, et al., 2021)
585 The model approximates viral kinetics on a logarithmic scale as a piecewise linear function,
586 corresponding to an exponential increase of virus followed by an exponential clearance at
587 possibly different rates. To estimate the relationship between booster status and viral kinetics,
588 we first stratified the model by (1) Omicron boosted and (2) Omicron non-boosted individuals.
589 There were too few boosted individuals who were infected with other variants to reliably fit the
590 model to non-Omicron infections. Next, to estimate the relationship between antibody titer and
591 viral kinetics, we stratified the model by (1) Delta infections with titer ≤ 250 , (2) Delta infections
592 with titer > 250 , (3) Omicron infections with titer ≤ 250 (4) Omicron infections with titer > 250 ,
593 and finally (5) non-Delta and non-Omicron infections in individuals who had not had any prior
594 exposure either through infection or vaccination, to serve as a baseline. Full details on the
595 fitting procedure may be found in (Kissler, Fauver, Mack, Olesen, et al., 2021; Kissler, Fauver,
596 Mack, Tai, et al., 2021) and the **Supplementary Methods**.

597 **References**

- 598 Aksamentov, I., & Neher, R. (2021). *NextClade*.
- 599 *BaseSpace Labs. DRAGEN COVID Lineage*. (2021).
- 600 Boucau, J., Marino, C., Regan, J., Uddin, R., Choudhary, M. C., Flynn, J. P., Chen, G.,
601 Stuckwisch, A. M., Mathews, J., Liew, M. Y., Singh, A., Lipiner, T., Kittilson, A., Melberg,
602 M., Li, Y., Gilbert, R. F., Reynolds, Z., Iyer, S. L., Chamberlin, G. C., ... Barczak, A. K.
603 (2022). Duration of Shedding of Culturable Virus in SARS-CoV-2 Omicron (BA.1)
604 Infection. *The New England Journal of Medicine*. <https://doi.org/10.1056/NEJMc2202092>
- 605 Boucau, J., Uddin, R., Marino, C., Regan, J., Flynn, J. P., Choudhary, M. C., Chen, G.,
606 Stuckwisch, A. M., Mathews, J., Liew, M. Y., Singh, A., Reynolds, Z., Iyer, S. L.,
607 Chamberlin, G. C., Vyas, T. D., Vyas, J. M., Turbett, S. E., Li, J. Z., Lemieux, J. E., ...
608 Siedner, M. J. (2022). Characterization of virologic rebound following nirmatrelvir-
609 ritonavir treatment for COVID-19. In *Clinical Infectious Diseases*.
610 <https://doi.org/10.1093/cid/ciac512>
- 611 Brihn, A., Chang, J., OYong, K., Balter, S., Terashita, D., Rubin, Z., & Yeganeh, N. (2021).
612 Diagnostic Performance of an Antigen Test with RT-PCR for the Detection of SARS-
613 CoV-2 in a Hospital Setting — Los Angeles County, California, June–August 2020.
614 *MMWR. Morbidity and Mortality Weekly Report*, 70(19), 702–706.
- 615 Bullard, J., Dust, K., Funk, D., Strong, J. E., Alexander, D., Garnett, L., Boodman, C., Bello,
616 A., Hedley, A., Schiffman, Z., Doan, K., Bastien, N., Li, Y., van Caesele, P. G., &
617 Poliquin, G. (2020). Predicting infectious SARS-CoV-2 from diagnostic samples. *Clinical*
618 *Infectious Diseases: An Official Publication of the Infectious Diseases Society of*
619 *America*, 71(10), 2663–2666.
- 620 Bürkner. (n.d.). brms: An R package for Bayesian multilevel models using Stan. *Journal of*
621 *Statistical Software*. <http://138.232.16.156/article/view/v080i01>
- 622 Caputo, V., Termine, A., Fabrizio, C., Calvino, G., Luzzi, L., Fusco, C., Ingrassi, A., Peconi,
623 C., D'Alessio, R., Mihali, S., Trastulli, G., Megalizzi, D., Cascella, R., Rossini, A., Salvia,
624 A., Strafella, C., & Giardina, E. (2021). Age and Sex Modulate SARS-CoV-2 Viral Load
625 Kinetics: A Longitudinal Analysis of 1735 Subjects. *Journal of Personalized Medicine*,
626 11(9), 882.
- 627 Centers for Disease Control and Prevention. (n.d.). *COVID-19 Quarantine and Isolation*.
628 Retrieved July 12, 2022, from [https://www.cdc.gov/coronavirus/2019-ncov/your-](https://www.cdc.gov/coronavirus/2019-ncov/your-health/quarantine-isolation.html)
629 [health/quarantine-isolation.html](https://www.cdc.gov/coronavirus/2019-ncov/your-health/quarantine-isolation.html)
- 630 Cevik, M., Tate, M., Lloyd, O., Maraolo, A. E., Schafers, J., & Ho, A. (2021). SARS-CoV-2,
631 SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and
632 infectiousness: a systematic review and meta-analysis. *The Lancet Microbe*, 2(1), e13–
633 e22.
- 634 Charness, M., Strymish, J., Boston, V. A., System, H., Adams, E., Lindy, D., & Ho, D.
635 (2022). *Rapid Relapse of Symptomatic Omicron SARS-CoV-2 Infection Following Early*
636 *Suppression with Nirmatrelvir/Ritonavir*. <https://doi.org/10.21203/rs.3.rs-1588371/v3>
- 637 Chen, P. Z., Bobrovitz, N., Premji, Z. A., Koopmans, M., Fisman, D. N., & Gu, F. X. (2021).
638 SARS-CoV-2 shedding dynamics across the respiratory tract, sex, and disease severity
639 for adult and pediatric COVID-19. *eLife*. <https://doi.org/10.7554/eLife.70458>
- 640 Earnest, R., Chen, C., Chaguza, C., Grubaugh, N. D., & Wilson, M. S. (2022). Daily Rapid
641 Antigen Testing in a University Setting to Inform COVID-19 Isolation Duration Policy.
642 *medRxiv*, 2022.03.11.22272264.
- 643 Hellewell, J., Russell, T. W., Beale, R., Kelly, G., Houlihan, C., Nastouli, E., & Kucharski, A.
644 J. (2021). Estimating the effectiveness of routine asymptomatic PCR testing at different

- 645 frequencies for the detection of SARS-CoV-2 infections. *BMC Medicine* 2021 19:1, 19(1),
646 1–10.
- 647 Jaafar, R., Aherfi, S., Wurtz, N., Grimaldier, C., Van Hoang, T., Colson, P., Raoult, D., & La
648 Scola, B. (2021). Correlation Between 3790 Quantitative Polymerase Chain Reaction–
649 Positives Samples and Positive Cell Cultures, Including 1941 Severe Acute Respiratory
650 Syndrome Coronavirus 2 Isolates. In *Clinical Infectious Diseases* (Vol. 72, Issue 11, pp.
651 e921–e921). <https://doi.org/10.1093/cid/ciaa1491>
- 652 Jefferson, T., Spencer, E. A., Brassey, J., & Heneghan, C. (2020). Viral Cultures for
653 Coronavirus Disease 2019 Infectivity Assessment: A Systematic Review. *Clinical
654 Infectious Diseases: An Official Publication of the Infectious Diseases Society of
655 America*, 73(11), e3884–e3899.
- 656 Jones, T. C., Biele, G., Mühlemann, B., Veith, T., Schneider, J., Beheim-Schwarzbach, J.,
657 Bleicker, T., Tesch, J., Schmidt, M. L., Sander, L. E., Kurth, F., Menzel, P., Schwarzer,
658 R., Zuchowski, M., Hofmann, J., Krumbholz, A., Stein, A., Edelmann, A., Corman, V. M.,
659 & Drosten, C. (2021). Estimating infectiousness throughout SARS-CoV-2 infection
660 course Downloaded from. *Science*. <https://doi.org/10.1126/science.abi5273>
- 661 Ke, R., Martinez, P. P., Smith, R. L., Gibson, L. L., Mirza, A., Conte, M., Gallagher, N., Luo,
662 C. H., Jarrett, J., Zhou, R., Conte, A., Liu, T., Farjo, M., Walden, K. K. O., Rendon, G.,
663 Fields, C. J., Wang, L., Fredrickson, R., Edmonson, D. C., ... Brooke, C. B. (2022). Daily
664 longitudinal sampling of SARS-CoV-2 infection reveals substantial heterogeneity in
665 infectiousness. *Nature Microbiology* 2022 7:5, 7(5), 640–652.
- 666 Ke, R., Zitzmann, C., Ho, D. D., Ribeiro, R. M., & Perelson, A. S. (2021). In vivo kinetics of
667 SARS-CoV-2 infection and its relationship with a person’s infectiousness. *Proceedings of
668 the National Academy of Sciences*, 118(49), e2111477118.
- 669 Khoury, D. S., Cromer, D., Reynaldi, A., Schlub, T. E., Wheatley, A. K., Juno, J. A.,
670 Subbarao, K., Kent, S. J., Triccas, J. A., & Davenport, M. P. (2021). Neutralizing
671 antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-
672 2 infection. *Nature Medicine*, 27(7), 1205–1211.
- 673 Kissler, S. M., Fauver, J. R., Mack, C., Olesen, S. W., Tai, C., Shiue, K. Y., Kalinich, C. C.,
674 Jednak, S., Ott, I. M., Vogels, C. B. F., Wohlgemuth, J., Weisberger, J., DiFiori, J.,
675 Anderson, D. J., Mancell, J., Ho, D. D., Grubaugh, N. D., & Grad, Y. H. (2021). Viral
676 dynamics of acute SARS-CoV-2 infection and applications to diagnostic and public
677 health strategies. *PLoS Biology*, 19(7), e3001333.
- 678 Kissler, S. M., Fauver, J. R., Mack, C., Tai, C. G., Breban, M. I., Watkins, A. E., Samant, R.
679 M., Anderson, D. J., Metti, J., Khullar, G., Baits, R., MacKay, M., Salgado, D., Baker, T.,
680 Dudley, J. T., Mason, C. E., Ho, D. D., Grubaugh, N. D., & Grad, Y. H. (2021). Viral
681 Dynamics of SARS-CoV-2 Variants in Vaccinated and Unvaccinated Persons. *The New
682 England Journal of Medicine*, 385(26), 2489–2491.
- 683 Landon, E., Bartlett, A. H., Marrs, R., Guenette, C., Weber, S. G., & Mina, M. J. (2022). High
684 rates of rapid antigen test positivity after 5 days of isolation for COVID-19. In *bioRxiv*.
685 <https://doi.org/10.1101/2022.02.01.22269931>
- 686 Larremore, D. B., Wilder, B., Lester, E., Shehata, S., Burke, J. M., Hay, J. A., Tambe, M.,
687 Mina, M. J., & Parker, R. (2021). Test sensitivity is secondary to frequency and
688 turnaround time for COVID-19 screening. *Science Advances*, 7(1), eabd5393.
- 689 Lefferts, B., Blake, I., Bruden, D., Hagen, M. B., Hodges, E., Kirking, H. L., Bates, E., Hoeldt,
690 A., Lamont, B., Saydah, S., MacNeil, A., Bruce, M. G., & Plumb, I. D. (2022). Antigen
691 Test Positivity After COVID-19 Isolation — Yukon-Kuskokwim Delta Region, Alaska,
692 January–February 2022. In *MMWR. Morbidity and Mortality Weekly Report* (Vol. 71,
693 Issue 8, pp. 293–298). <https://doi.org/10.15585/mmwr.mm7108a3>

- 694 Liu, L., Iketani, S., Guo, Y., Chan, J. F.-W., Wang, M., Liu, L., Luo, Y., Chu, H., Huang, Y.,
695 Nair, M. S., Yu, J., Chik, K. K.-H., Yuen, T. T.-T., Yoon, C., To, K. K.-W., Chen, H., Yin,
696 M. T., Sobieszczyk, M. E., Huang, Y., ... Ho, D. D. (2021). Striking antibody evasion
697 manifested by the Omicron variant of SARS-CoV-2. *Nature*, 602(7898), 676–681.
- 698 Long, H., Zhao, J., Zeng, H.-L., Lu, Q.-B., Fang, L.-Q., Wang, Q., Wu, Q.-M., & Liu, W.
699 (2021). Prolonged viral shedding of SARS-CoV-2 and related factors in symptomatic
700 COVID-19 patients: a prospective study. *BMC Infectious Diseases*, 21(1), 1–10.
- 701 Lusvardi, S., Pollett, S. D., Neerukonda, S. N., Wang, W., Wang, R., Vassell, R., Epsi, N.
702 J., Fries, A. C., Agan, B. K., Lindholm, D. A., Colombo, C. J., Mody, R., Ewers, E. C.,
703 Lalani, T., Ganesan, A., Goguet, E., Hollis-Perry, M., Coggins, S. A., Simons, M. P., ...
704 Weiss, C. D. (2022). SARS-CoV-2 BA.1 variant is neutralized by vaccine booster-elicited
705 serum, but evades most convalescent serum and therapeutic antibodies. *Science*
706 *Translational Medicine*. <https://doi.org/10.1126/SCITRANSLMED.ABN8543>
- 707 Mack, C. D., DiFiori, J., Tai, C. G., Shiue, K. Y., Grad, Y. H., Anderson, D. J., Ho, D. D.,
708 Sims, L., LeMay, C., Mancell, J., & Maragakis, L. L. (2021). SARS-CoV-2 Transmission
709 Risk Among National Basketball Association Players, Staff, and Vendors Exposed to
710 Individuals With Positive Test Results After COVID-19 Recovery During the 2020
711 Regular and Postseason. *JAMA Internal Medicine*.
712 <https://doi.org/10.1001/jamainternmed.2021.2114>
- 713 Mack, C. D., Wasserman, E. B., Killerby, M. E., Soelaeman, R. H., Hall, A. J., MacNeil, A.,
714 Anderson, D. J., Walton, P., Pasha, S., Myers, E., O'Neal, C. S., Hostler, C. J., Singh,
715 N., Mayer, T., & Sills, A. (2022). Results from a Test-to-Release from Isolation Strategy
716 Among Fully Vaccinated National Football League Players and Staff Members with
717 COVID-19 - United States, December 14-19, 2021. *MMWR. Morbidity and Mortality*
718 *Weekly Report*, 71(8), 299–305.
- 719 Marc, A., Keroui, M., Blanquart, F., Bertrand, J., Mitjà, O., Corbacho-Monné, M., Marks, M.,
720 & Guedj, J. (2021). Quantifying the relationship between SARS-CoV-2 viral load and
721 infectiousness. *eLife*, 10. <https://doi.org/10.7554/ELIFE.69302>
- 722 Marks, M., Millat-Martinez, P., Ouchi, D., Roberts, C. h., Alemany, A., Corbacho-Monné, M.,
723 Ubals, M., Tobias, A., Tebé, C., Ballana, E., Bassat, Q., Baro, B., Vall-Mayans, M., G-
724 Beiras, C., Prat, N., Ara, J., Clotet, B., & Mitjà, O. (2021). Transmission of COVID-19 in
725 282 clusters in Catalonia, Spain: a cohort study. *The Lancet Infectious Diseases*, 21(5),
726 629–636.
- 727 Néant, N., Lingas, G., Le Hingrat, Q., Ghosn, J., Engelmann, I., Lepiller, Q., Gaymard, A.,
728 Ferré, V., Hartard, C., Plantier, J.-C., Thibault, V., Marlet, J., Montes, B., Bouiller, K.,
729 Lescure, F.-X., Timsit, J.-F., Faure, E., Poissy, J., Chidiac, C., ... French COVID Cohort
730 Investigators and French Cohort Study groups. (2021). Modeling SARS-CoV-2 viral
731 kinetics and association with mortality in hospitalized patients from the French COVID
732 cohort. *Proceedings of the National Academy of Sciences of the United States of*
733 *America*, 118(8). <https://doi.org/10.1073/pnas.2017962118>
- 734 Pilarowski, G., Consortium, T. C., Lebel, P., Consortium, T. C., Sunshine, S., Consortium, T.
735 C., Liu, J., Consortium, T. C., Crawford, E., Consortium, T. C., Marquez, C., Consortium,
736 T. C., Rubio, L., Consortium, T. C., Chamie, G., Consortium, T. C., Martinez, J.,
737 Consortium, T. C., Peng, J., ... Consortium, T. C. (2021). Performance Characteristics of
738 a Rapid Severe Acute Respiratory Syndrome Coronavirus 2 Antigen Detection Assay at
739 a Public Plaza Testing Site in San Francisco. *The Journal of Infectious Diseases*, 223(7),
740 1139–1144.
- 741 Puhach, O., Adea, K., Hulo, N., Sattonnet, P., Genecand, C., Iten, A., Bausch, F. J., Kaiser,
742 L., Vetter, P., Eckerle, I., & Meyer, B. (2022). Infectious viral load in unvaccinated and
743 vaccinated individuals infected with ancestral, Delta or Omicron SARS-CoV-2. *Nature*

- 744 *Medicine*, 1–1.
- 745 Quilty, B. J., Clifford, S., Hellewell, J., Russell, T. W., Kucharski, A. J., Flasche, S.,
746 Edmunds, W. J., Atkins, K. E., Foss, A. M., Waterlow, N. R., Abbas, K., Lowe, R.,
747 Pearson, C. A. B., Funk, S., Rosello, A., Knight, G. M., Bosse, N. I., Procter, S. R., Gore-
748 Langton, G. R., ... Davies, N. G. (2021). Quarantine and testing strategies in contact
749 tracing for SARS-CoV-2: a modelling study. *The Lancet Public Health*, 6(3), e175–e183.
- 750 Rambaut, A., Holmes, E. C., O’Toole, Á., Hill, V., McCrone, J. T., Ruis, C., du Plessis, L., &
751 Pybus, O. G. (2020). A dynamic nomenclature proposal for SARS-CoV-2 lineages to
752 assist genomic epidemiology. *Nature Microbiology* 2020 5:11, 5(11), 1403–1407.
- 753 Singanayagam, A., Hakki, S., Dunning, J., Madon, K. J., Crone, M. A., Koycheva, A., Derqui-
754 Fernandez, N., Barnett, J. L., Whitfield, M. G., Varro, R., Charlett, A., Kundu, R., Fenn,
755 J., Cutajar, J., Quinn, V., Conibear, E., Barclay, W., Freemont, P. S., Taylor, G. P., ...
756 Lackenby, A. (2022). Community transmission and viral load kinetics of the SARS-CoV-2
757 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a
758 prospective, longitudinal, cohort study. *The Lancet Infectious Diseases*, 22(2), 183–195.
- 759 Singanayagam, A., Patel, M., Charlett, A., Bernal, J. L., Saliba, V., Ellis, J., Ladhani, S.,
760 Zambon, M., & Gopal, R. (2020a). Duration of infectiousness and correlation with RT-
761 PCR cycle threshold values in cases of COVID-19, England, January to May 2020.
762 *Eurosurveillance*, 25(32), 2001483.
- 763 Singanayagam, A., Patel, M., Charlett, A., Bernal, J. L., Saliba, V., Ellis, J., Ladhani, S.,
764 Zambon, M., & Gopal, R. (2020b). Duration of infectiousness and correlation with RT-
765 PCR cycle threshold values in cases of COVID-19, England, January to May 2020.
766 *Eurosurveillance*, 25(32), 2001483.
- 767 Straten, K. van der, Guerra, D., van Gils, M. J., Bontjer, I., Caniels, T. G., van Willigen, H. D.
768 G., Wynberg, E., Poniman, M., Burger, J. A., Bouhuijs, J. H., van Rijswijk, J., Lavell, A.
769 H. A., Appelman, B., Sikkens, J. J., Bomers, M. K., Han, A. X., Nichols, B. E., Prins, M.,
770 Vennema, H., ... Sanders, R. W. (2022). Mapping the antigenic diversification of SARS-
771 CoV-2. *medRxiv*, 2022.01.03.21268582.
- 772 Sun, K., Wang, W., Gao, L., Wang, Y., Luo, K., Ren, L., Zhan, Z., Chen, X., Zhao, S.,
773 Huang, Y., Sun, Q., Liu, Z., Litvinova, M., Vespignani, A., Ajelli, M., Viboud, C., & Yu, H.
774 (2021). Transmission heterogeneities, kinetics, and controllability of SARS-CoV-2.
775 *Science*, 371(6526).
776 https://doi.org/10.1126/SCIENCE.ABE2424/SUPPL_FILE/ABE2424_SUN_SM.PDF
- 777 Tai, C. G., Maragakis, L. L., Connolly, S., DiFiori, J., Anderson, D. J., Grad, Y. H., & Mack,
778 C. D. (2022). Association Between COVID-19 Booster Vaccination and Omicron
779 Infection in a Highly Vaccinated Cohort of Players and Staff in the National Basketball
780 Association. *JAMA: The Journal of the American Medical Association*.
781 <https://doi.org/10.1001/jama.2022.9479>
- 782 Thommes, L., Burkert, F. R., Öttl, K. W., Goldin, D., Loacker, L., Lanser, L., Griesmacher,
783 A., Theurl, I., Weiss, G., & Bellmann-Weiler, R. (2021). Comparative evaluation of four
784 SARS-CoV-2 antigen tests in hospitalized patients. *International Journal of Infectious
785 Diseases: IJID: Official Publication of the International Society for Infectious Diseases*,
786 105, 144.
- 787 Vogels, C. B. F., Breban, M. I., Ott, I. M., Alpert, T., Petrone, M. E., Watkins, A. E., Kalinich,
788 C. C., Earnest, R., Rothman, J. E., de Jesus, J. G., Claro, I. M., Ferreira, G. M., Crispim,
789 M. A. E., Singh, L., Tegally, H., Anyaneji, U. J., Hodcroft, E. B., Mason, C. E., Khullar, G.,
790 ... Williamson, C. (2021). Multiplex qPCR discriminates variants of concern to enhance
791 global surveillance of SARS-CoV-2. *PLoS Biology*, 19(5), e3001236.
- 792 Wang, P., Nair, M. S., Liu, L., Iketani, S., Luo, Y., Guo, Y., Wang, M., Yu, J., Zhang, B.,

793 Kwong, P. D., Graham, B. S., Mascola, J. R., Chang, J. Y., Yin, M. T., Sobieszczyk, M.,
794 Kyratsous, C. A., Shapiro, L., Sheng, Z., Huang, Y., & Ho, D. D. (2021). Antibody
795 resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature*, 593(7857), 130–135.
796