

1 **Viral dynamics of Omicron and Delta SARS-CoV-2 variants with implications for timing of release from**
2 **isolation: a longitudinal cohort study**

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7

8 **Running Title:** Omicron and Delta SARS-CoV-2 dynamics

9

ACCEPTED MANUSCRIPT

1 **Abstract:**

2 *Background*

3 In January 2022, United States guidelines shifted to recommend isolation for 5 days from symptom
4 onset, followed by 5 days of mask wearing. However, viral dynamics and variant and vaccination impact
5 on culture conversion are largely unknown.

6 *Methods*

7 We conducted a longitudinal study on a university campus, collecting daily anterior nasal swabs for at
8 least 10 days for RT-PCR and culture, with antigen rapid diagnostic testing (RDT) on a subset. We
9 compared culture positivity beyond day 5, time to culture conversion, and cycle threshold trend when
10 calculated from diagnostic test, from symptom onset, by SARS-CoV-2 variant, and by vaccination status.
11 We evaluated sensitivity and specificity of RDT on days 4-6 compared to culture.

12 *Results*

13 Among 92 SARS-CoV-2 RT-PCR positive participants, all completed the initial vaccine series, 17 (18.5%)
14 were infected with Delta and 75 (81.5%) with Omicron. Seventeen percent of participants had positive
15 cultures beyond day 5 from symptom onset with the latest on day 12. There was no difference in time to
16 culture conversion by variant or vaccination status. For 14 sub-study participants, sensitivity and
17 specificity of day 4-6 RDT were 100% and 86% respectively.

18 *Conclusions*

19 The majority of our Delta- and Omicron-infected cohort culture-converted by day 6, with no further
20 impact of booster vaccination on sterilization or cycle threshold decay. We found that rapid antigen
21 testing may provide reassurance of lack of infectiousness, though guidance to mask for days 6-10 is
22 supported by our finding that 17% of participants remained culture positive after isolation.

23 **Key Words:** SARS-CoV-2, COVID-19, Viral Infection, Infection Dynamics, Omicron

24

1 **Background:**

2 Individuals with SARS-CoV-2 infection have been told to self-isolate to avoid transmission to others.

3 Early pandemic United States Centers for Disease Control and Prevention (CDC) guidelines for isolation

4 were based on estimates of the duration of infectivity, with early studies showing rare culture positivity

5 and transmission beyond 10 days in immunocompetent hosts.¹ In January 2022, US CDC guidelines

6 shifted to recommend 5 days of isolation from symptom onset or positive test if asymptomatic, followed

7 by an additional 5 days of strict mask wearing anytime there is contact with other people.² This newer

8 guidance was based on SARS-CoV-2 transmission studies showing that most transmission occurs early in

9 the course of infection,^{3,4} the increased awareness of the mental health, economic, and social impacts of

10 prolonged isolation,⁵ and that only 25-30% of cases truly isolate for a full 10 days.⁶

11

12 A proposed strategy to limit time in isolation of SARS-CoV-2 infected individuals has been to use antigen

13 rapid diagnostic testing (RDT) as a proxy for infectiousness.² A test to return program in a Massachusetts

14 school district found positivity rate of 35% when performed day 6 from symptom onset or positive test,

15 concluding that such a program helps identify those safest to return to the classroom prior to 10 days.⁷

16 Modeling efforts have further suggested that antigen RDT could be used to both reduce the self-isolation

17 period while preventing ongoing disease transmission.⁸

18

19 New SARS-CoV-2 variants have shown increased transmissibility, potentially impacting best practices for

20 isolation guidelines. Notably, the Omicron variant may be up to three times more transmissible than the

21 Delta variant,⁹ with a shorter incubation period,¹⁰ but lower viral loads at diagnosis¹¹ than previously

22 circulating SARS-CoV-2 lineages. Early SARS-CoV-2 viral challenge data with wild-type virus in

23 seronegative, healthy volunteers showed on average nasal culture clearance by day 7 with culture

1 positivity up to 12 days from SARS-CoV-2 exposure.¹² How long vaccinated individuals, both primary
2 series and boosted, can transmit virus and kinetic difference by variant remain unclear.

3
4 When to start the clock on the isolation period has proven to be an additional complication when
5 implementing the CDC guidelines. Schools and other large organizations may use day of positive test,
6 while the CDC recommends that Day 0 is the day of symptom onset and only the day of positive test for
7 cases that remain asymptomatic. For large scale screening programs, using repeat SARS-CoV-2 testing at
8 regular intervals for early case identification, the complications with operationalizing the use of the start
9 of symptoms can be prohibitive. However, for those who develop symptoms after testing, this practice
10 may shorten the isolation period and release them back into conjugate living situations where strict
11 mask wearing is difficult.

12
13 We aimed to document within-host viral dynamics of two recent SARS-CoV-2 variants, Delta and
14 Omicron, during the period when most individuals would leave isolation based on CDC guidelines. We
15 recruited participants from a university campus which had a multi-faceted surveillance testing and
16 COVID-19 control program¹³. We compared infection with Omicron versus Delta, the vaccination and
17 booster status of the infected individual, and the difference from test date and symptom onset date on
18 detectable virus and culture positivity.

19

20

21 **Methods:**

22 The SARS-CoV-2 Viral Dynamics Post-vaccination Study (CoViD Post-vax) is an observational cohort study
23 that, beginning in November 2021, has been enrolling Boston University (BU) students, faculty, and
24 staff. Participants are enrolled after a verbal assent or electronic self-consent process following

1 diagnosis with SARS-CoV-2 by PCR as a part of the BU SARS-CoV-2 screening program which includes
2 regular testing 1-2 times per week. Participants undergo an initial clinical questionnaire and thereafter
3 self-performed daily symptom screens and anterior nasal swabs with electronic medical record and
4 diagnostic specimen laboratory data abstraction performed by study staff.

5

6 Following study enrollment, participants can also opt into an antigen RDT sub-study. For those who
7 provide verbal assent, they are provided with three Abbott BinaxNOW kits to self-perform according to
8 manufacturer directions on days 4-6 from diagnosis. Participants are asked to upload a photograph of
9 the test strip at the time it is read into our REDCap database (version 12.1.1, Vanderbilt University),
10 where study staff then interpret the results.

11

12 Diagnostic isolates are tested with RT-qPCR using a two-target SARS-CoV-2 assay with RNase P control¹
13 as a part of the BU SARS-CoV-2 surveillance program at the BU Clinical Testing Laboratory.³ Positive
14 samples are then transferred to the National Emerging Infectious Diseases Laboratories (NEIDL), where
15 viral genomes are sequenced using a modified ARTIC primer-based protocol for amplification and the
16 Illumina platform for sequencing.¹⁴ For participants whom diagnostic isolate sequencing was not yet
17 available (N=32), variant determination was made based on the timing of the diagnostic isolate: all
18 infections after December 28, 2021 were considered Omicron because BU sequencing surveillance
19 activities detected <1% Delta circulating.¹¹ Study isolates are collected in viral transport media and
20 frozen following collection. Samples are then analyzed in two different ways. First, the presence of
21 SARS-CoV-2 viral nucleic acid in the sample is determined by SARS-CoV-2 CDC N1 RT-PCR and second,
22 200 microliters of sample are incubated with Caco2 cells for 4 days. At the end of culturing, cells are
23 fixed, and the presence or absence of SARS-CoV-2 viral replication is determined through indirect
24 immunofluorescence microscopy using an antibody recognizing SARS-CoV-2 N protein. Cultures are

1 determined to be positive for viral growth if they show cytoplasm-restricted fluorescence signal above
2 background.

3

4 In this analysis, we compared demographic and clinical characteristics of participants infected with the
5 Delta and Omicron SARS-CoV-2 variants. Fully vaccinated individuals had completed an initial vaccine
6 series with either a single vector or two mRNA vaccines listed for emergency use by the World Health
7 Organization (WHO), with the exception of one participant who received a non-WHO listed vaccine and
8 was subsequently boosted with an mRNA vaccine. We compared culture positivity beyond day 5, time to
9 culture conversion, and duration of positive cultures when calculated from date of diagnostic test to
10 symptom onset. Culture conversion was defined as day of first negative culture result with no
11 subsequent positive cultures. For the purposes of all cycle threshold (Ct) comparisons, we used the N1
12 genes from both assays. We plotted scatter plots and fit mixed-effect models to assess the relationship
13 between Ct values and time since diagnosis and symptom onset, and by variant and vaccination status.
14 Curve fits were performed using generalized additive mixed models with random intercept and a cubic
15 B-spline with four knots, to incorporate individual participants' Ct trajectories. To look at time to culture
16 conversion for the whole cohort and by variant and vaccination status, we generated Kaplan Meier plots
17 where the event was defined as the first negative SARS-CoV-2 culture with no subsequent positives.
18 Heat-treated baseline diagnostic isolates were not culturable and were presumed positive for the
19 purposes of this analysis. When the first recorded negative culture was preceded by missed tests, we
20 used interval censoring with the earliest point of the interval being the time of the last positive test or
21 diagnosis if there were no positive cultures recorded. Additionally, we compared median Ct values at
22 diagnosis by variant and vaccine status, using Wilcox non-parametric tests. Finally, for the antigen RDT
23 sub-study, we calculated the sensitivity and specificity of the Abbott BinaxNow compared to culture

1 positivity at days 4 through 6 from diagnosis and plotted Ct values by day from diagnosis and RDT result.
2 Analyses were conducted with R (version 4.0).

3
4 The study was approved by both the BU Charles River Campus Institutional Review Board and the BU
5 Medical Campus Institutional Review Board.

7 **Results:**

8 Of 92 SARS-CoV-2 RT-PCR positive participants enrolled in the study cohort, 17 (18.5%) were infected
9 with the SARS-CoV-2 Delta variant and 75 (81.5%) with Omicron (Table 1). Most participants (N=65,
10 69.1%) had symptoms at the time of diagnosis. While a greater proportion individuals infected with
11 Omicron had received a booster vaccine compared to those infected with Delta [42.7% (N=32) vs 5.9%
12 (N=1), $p=0.004$, Table 1), all participants had completed the initial SARS-CoV-2 vaccine series (Table 1).
13 The median days from most recent vaccination to infection was 245 days (IQR: 202-282) for fully
14 vaccinated, not boosted participants and 42 days (IQR: 30-55) for fully vaccinated, boosted participants
15 (Supplementary Figure 1).

16
17 Overall, 84% of participants from diagnostic test and 71% of participants from symptom onset had
18 culture converted (no growth) by day 6 (Table 2). Overall, 48% (N=44) of participants never had a culture
19 positive research isolate. We next considered the impact of calculating the isolation period as days from
20 diagnosis (common in large institutional settings, like universities) in comparison to days from symptom
21 onset (US CDC guidance)² on viral dynamics at release from isolation. In this cohort, almost half of the
22 participants were diagnosed after symptom onset (N=38, 41.3%), while ten (10.9%) tested positive while
23 pre-symptomatic. Using time from symptom onset rather than time from diagnosis shifted the axis right
24 for those diagnosed after symptom onset and left for pre-symptomatic participants. In comparison to

1 within-host viral load decay over time from diagnosis (Figure 1a), the mixed-effect model of within-host
2 viral load decay from symptom onset (Figure 1b) shows a plateau in the pre-symptomatic period (days -
3 3 to 0) followed by a more gradual viral decline. Similarly, adjusting the viral culture results from days
4 since diagnosis (Figure 1c) to days from symptom onset (Figure 1d) reveals a considerable drop in
5 culture positivity following day 4 with associated reduction in the maximum duration of culture
6 positivity by 3 days (from 15 days to 12 days, Table 2).

7
8 There were no significant differences in time to viral culture conversion between Delta and Omicron
9 variants, even when stratified based on whether participants had received a COVID-19 booster
10 vaccination or had completed the initial vaccine series alone (Figure 2B). The trends for within-host viral
11 load decay over time were similar in those who completed the initial vaccine series and were infected
12 with the Delta variant (Figure 3B) and the Omicron variant (Figure 3C). However, for participants who
13 had received a COVID-19 booster vaccination, there was a trend towards slower with-in host viral load
14 decay (Figure 3D), though daily culture conversion rates were similar (Figure 2B) and RT-PCR Ct was
15 higher in those boosted with Omicron at diagnosis (median 27.5) than in those fully vaccinated with
16 either Delta (median 18.8, $p=0.004$) or Omicron infections (median 26.4, $p=0.36$, Supplementary Figure
17 2).

18
19 For the sub-set of 14 participants in the RDT sub-study, the sensitivity and specificity of the Abbott
20 BinaxNOW test were 100% and 86% respectively at day 4 through 6 from diagnosis when compared to
21 SARS-CoV-2 culture (N=32 isolates, Table 3), yielding a negative predictive value of 100% and positive
22 predictive value of 50%. RT-PCR Ct values were higher in those who tested negative on the RDT
23 (Supplementary Figure 3).

24
25

1 **Discussion:**

2 Our findings suggest that in young, healthy, vaccinated adults, the majority have a limited infectious
3 period for SARS-CoV-2 based on culturable virus and rapid viral decay. We found that beyond 5 days
4 from symptom onset only 17% remained culture positive. Our median time to Omicron culture
5 conversion was 2 days (IQR: 1-5) for boosted participants with Omicron, 3 days (IQR: 1-5) for vaccinated,
6 unboosted participants with Omicron, and 3 days (IQR: 1-6.5) for participants with Delta. This is notably
7 earlier than the median 6 days to culture conversion reported in an older cohort with more medical
8 comorbidities.¹⁴ Our results are similar to data from the National Basketball Association cohort which
9 found 40% with cycle thresholds of less than 30 at day 5, though this study did not examine culture
10 positivity.¹⁵

11
12 Whether we calculated days to culture clearance from date of diagnosis or from symptom onset led to
13 differences on likelihood that individuals released from isolation were still infectious and how quickly
14 some were released. Reliance on time from diagnosis for determining duration of isolation kept 41% of
15 people in isolation longer than necessary (using culture conversion as a measure of non-infectiousness).
16 Additionally, for the 10 (11%) who were pre-symptomatic at the time of diagnosis, these individuals
17 were released from isolation before they had reached the CDC-recommended 5-day point, although
18 only two (20%) remained culture positive at that point which was similar to the overall cohort fraction. It
19 is much easier programmatically for large institutions with serial testing programs to rely on time from
20 diagnosis, a number they capture through these programs, rather than symptom development, which
21 requires additional follow up for those without symptoms and honest reporting of those diagnosed. It is
22 reassuring to see that only 17% of our cohort failed to culture convert by day 6, however it will be key to
23 continue to reinforce strict masking for days 6-10 from symptom onset, especially in scenarios with
24 asymptomatic screening strategies where symptoms may develop after testing.

25

1 We found no major differences in culture conversion or viral load decay between delta and omicron
2 variants. This is consistent with previous data showing no major differences in Omicron infection
3 duration when compared to Delta¹⁶ or time to culture or PCR conversion between the two variants.¹⁵
4 Similar to the findings of Boucau et al.¹⁵, we found no significant difference in culture or PCR conversion
5 in boosted participants when compared to those who were fully vaccinated. This suggests that the
6 population level protection provided by COVID-19 booster vaccination doses against Omicron^{17,18} result
7 from protection against infection rather than altered viral kinetics in vaccinated individuals causing
8 reduced transmission or more rapid clearance.

9
10 Among participants who used an antigen RDT in days 5-7 following SARS-CoV-2 diagnosis, RDT had
11 perfect negative predictive value and sensitivity when compared to culture. While we used a single type
12 of antigen RDT in our sub-study, the Abbott BinaxNOW has been shown to successfully detect the
13 Omicron variant.¹⁹ Our findings are similar to early reports in other settings suggesting 30-55% positive
14 antigen RDT between days 5-10 of illness.^{20,21,7} One study, using a different antigen test, showed higher
15 antigen RDT positivity (75%), but similar culture positivity (35%) at day 6.²⁰ Given the similar negative
16 predictive value, the work by Cosimi et al.²² highlights possible differing performance characteristics at
17 the end of infection across tests. Our preliminary findings suggest that a young, healthy, fully vaccinated
18 individual can be reassured with negative antigen RDT that they are unlikely to be shedding viable virus
19 towards the end of their infection. However, reliance on antigen RDT for release from isolation would
20 also result in prolongation of isolation for those who do not have culturable virus, for potentially up to
21 50% of those with positive antigen tests.

22
23 Our study is limited in its generalizability, as most participants were young, healthy, and all had
24 completed at least the initial COVID-19 vaccination series. Additionally, many participants had recently
25 received booster vaccination when omicron began to circulate possibly resulting in higher neutralizing

1 antibody titers than those further out from their last vaccine. We were also limited by the delay from
2 diagnosis to enrollment in the study as many participants moved into isolation housing resulting in 48%
3 of participants not having a culture positive research isolate. The diagnostic isolates were heat treated
4 and therefore not available for culturing. Additionally, our work was likely not well powered to
5 determine differences between Delta and Omicron variants stratified on COVID-19 vaccination status.
6 While our study is strengthened by our daily sampling and culture data, it is not clear how well culture
7 positivity in the laboratory correlates to transmissibility of SARS-CoV-2 at the end of an infection, nor did
8 we rule out reinfection in individuals with persistently positive isolates. More work needs to be done to
9 understand why certain immunocompetent individuals have prolonged culture positivity and how to
10 predict which cases will remain at risk of transmitting beyond the isolation period. Regardless, it is clear
11 that even in a young and healthy cohort, with presumably optimal response to initial and booster
12 vaccination, an overwhelming majority of both Delta and Omicron variant SARS-CoV-2 infections culture
13 convert by day 6. Our work provides further support to the guidelines for strict masking beyond the
14 initial 5-day isolation period for SARS-CoV-2 infections to help prevent transmission from the minority of
15 cases who remain culture positive.

16
17 **NOTES**

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21

22

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5
6 **Conflicts of Interest:**

7 DHH reports funding from the CDC for GeoSentinel (1 U01CK000632-01-00) paid to institution and
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22

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1 **Tables:**

2 Table 1: Characteristics of participants overall and by SARS-CoV-2 variant

	Total (N=92)	Delta (N= 17)	Omicron (N= 75)	p-value
Age				0.485
Mean (SD)	22 (3)	22 (2)	22 (3)	
Range	18 - 33	19 - 25	18 - 33	
Sex, N (%)				0.396
Male	35 (38.0)	8 (47.1)	27 (36.0)	
Female	57 (62.0)	9 (52.9)	48 (64.0)	
Race, N (%)				0.730
White	51 (56.0)	9 (52.9)	42 (56.8)	
Black	6 (6.6)	2 (11.8)	4 (5.4)	
Asian	29 (31.9)	5 (29.4)	24 (32.4)	
Multiracial	5 (5.5)	1 (5.9)	4 (5.4)	
Missing	1	-	1	
Vaccination Status, N (%)				0.004
Fully Vaccinated, not boosted	59 (64.1)	16 (94.1)	43 (57.3)	
Fully vaccinated, boosted	33 (35.9)	1 (5.9)	32 (42.7)	
Vaccine Type, N (%)				0.196
Pfizer	61 (66.3)	10 (58.8)	51 (68.0)	
Moderna	22 (23.9)	4 (23.5)	18 (24.0)	

Janssen	3 (3.3)	2 (11.8)	1 (1.3)
Other ^a	6 (6.5)	1 (5.9)	5 (6.7)
Symptomatic at baseline, N (%)			0.241
No	27 (30.9)	3 (17.6)	10 (30.9)
Yes	65 (69.1)	14 (82.4)	65 (69.1)

1 ^aCovishield (Serum Institute of India), AstraZeneca (Oxford), Sinovac (CoronaVac), Sinopharm

2 BIBPVerocell

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1 Table 2: Culture positivity when calculated from day of diagnosis in comparison to day of symptom
 2 onset

	Time From Diagnosis (N=92)	Time From Symptom Onset (N=92)	p-value
Individuals with a culturable isolate >5 days			
Culture converted by day 6, N (%)	77 (84)	65 (71)	0.05
Culture positive >5 days, N (%)	10 (11)	16 (17)	0.38
Missing, N (%)	5 (5)	11 (12)	0.19
Last culturable day, days	15	12	NA

3

4

5 Table 3: Sensitivity and specificity of rapid antigen testing when compared to culture growth at
 6 days 4 through 6 from SARS-CoV-2 diagnosis.

Days since							
Diagnostic		True	True	False	False		
Test	N	Positive	Negative	Positive	Negative	Sensitivity	Specificity
Day 4	10	2	6	2	0	1	0.75
Day 5	12	2	9	1	0	1	0.9
Day 6	10	0	9	1	0	NA	0.9
Overall	32	4	24	4	0	1	0.86

7

8

1 **Figure Legends:**

2 Figure 1: Progression of polymerase chain reaction N1 cycle threshold values from (a) diagnosis and (b)
3 symptom onset, and culture growth from (c) diagnosis and (d) symptom onset.

4

5 Figure 2. Kaplan-Meier curves indicating days from diagnosis to negative viral culture for all participants
6 (a) and by SARS-CoV-2 variant and vaccination status (b).

7

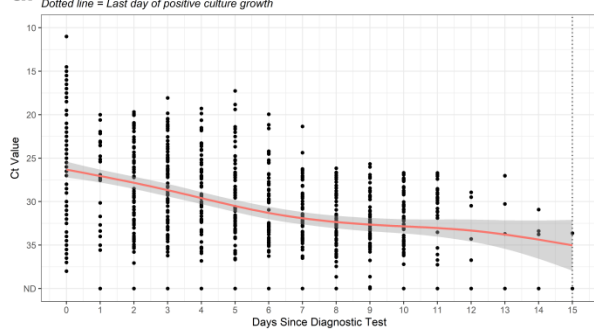
8 Figure 3: Polymerase chain reaction N1 cycle threshold at days since symptom onset for (a) all
9 participants, (b) delta-infected, fully vaccinated participants, (c) Omicron-infected, fully vaccinated
10 participants, and (d) Omicron-infected, boosted participants.

11

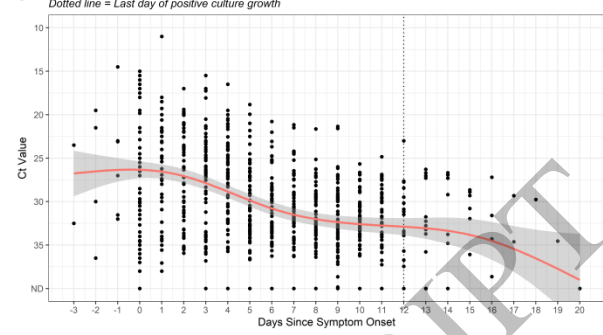
12

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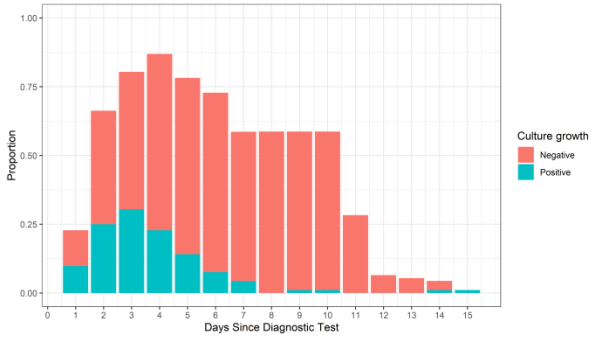
a. All Participants (N=92)



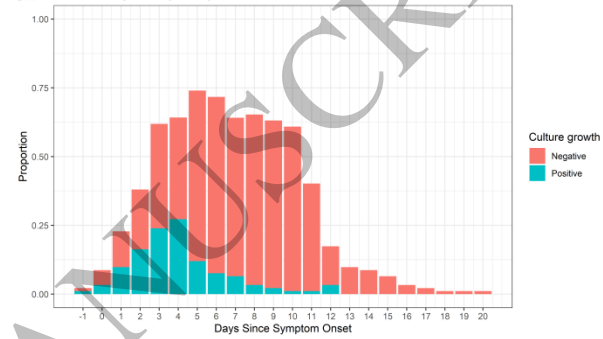
b. All Participants (N=92)



c. All Participants (N=92)



d. All Participants (N=92)



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Figure 1
165x97 mm (.55 x DPI)

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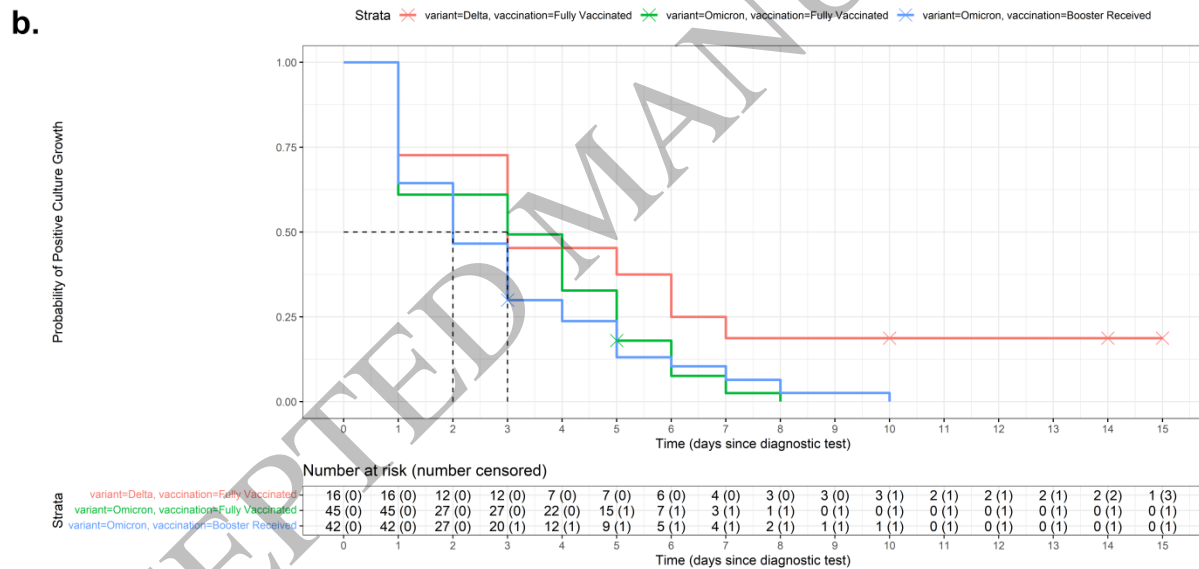
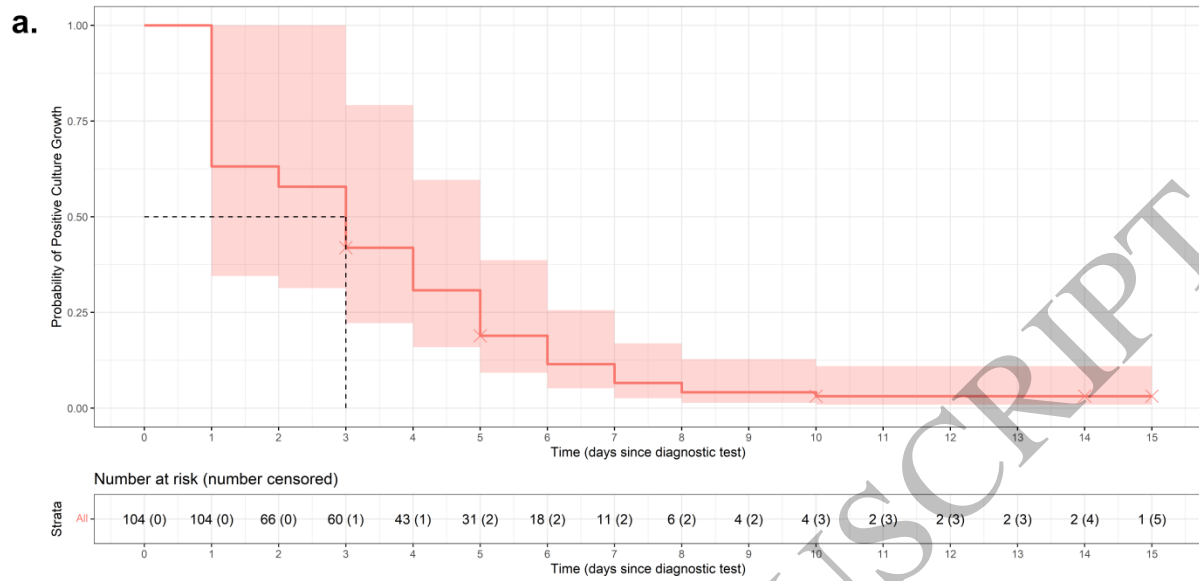
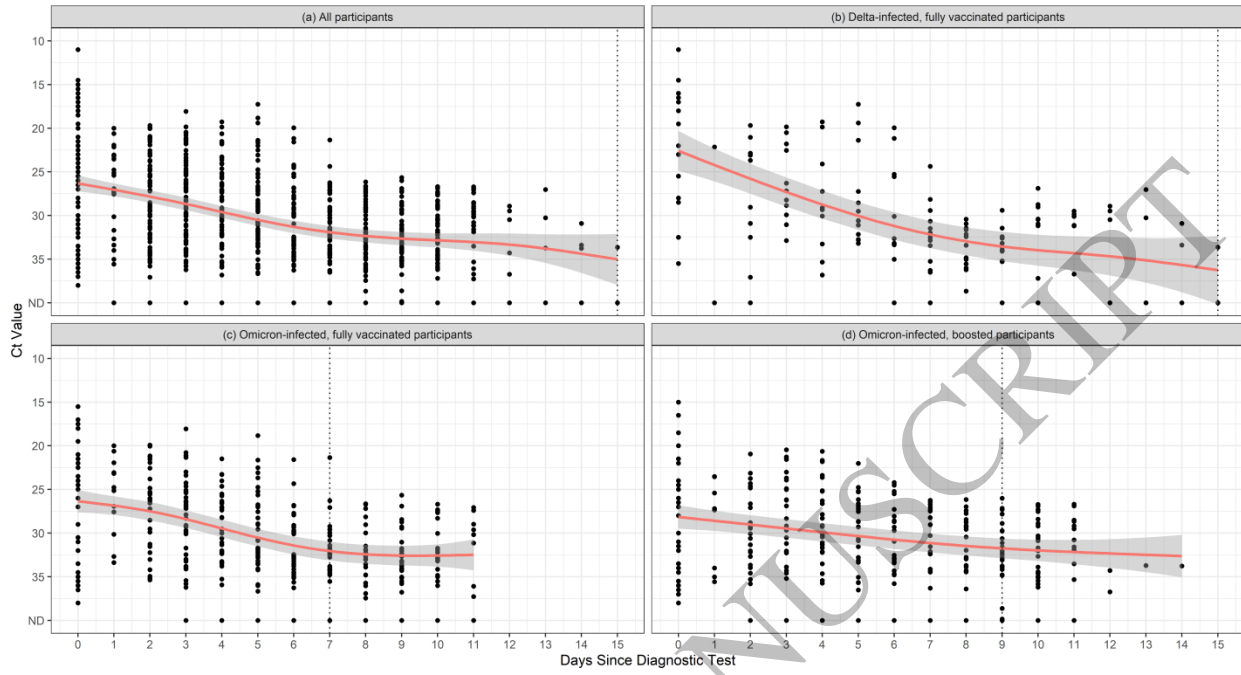


Figure 2
165x162 mm (.55 x DPI)

1
2
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All Participants (N=92)



1
2
3
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Figure 3
165x162 mm (.55 x DPI)

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