Female sex and SARS-CoV-2 Serostatus Predict Nasopharyngeal RNA Clearance during Early COVID-19

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BACKGROUND

- SARS-CoV-2 is primarily transmitted through viral shedding in the upper respiratory tract
- Higher nasal SARS-CoV-2 RNA levels have been linked to increased COVID-19 severity, culturable virus, and transmission
- Identifying characteristics associated with upper respiratory tract shedding are important in understanding disease pathogenesis and viral transmission

METHODS

- ACTIV-2 is a phase II/III randomized controlled platform trial to evaluate investigational agents for treatment of COVID-19 in non-hospitalized adults (NCT04518410).
- Participants:
  - Enrolled within 10 days of symptom onset;
  - Had documented SARS-CoV-2 infection;
  - Had symptoms present within 48 hours of study entry;
  - Had Nasopharyngeal (NP) samples collected at days 0, 3, 7, 14 and 28 for SARS-CoV-2 RNA testing.
- RNA was quantified with qPCR assay using Abbot m2000sp/rt platform[1]
- Seropositivity defined as detectable IgG to any of nucelocapsid, receptor binding domain, and S1 and S2 by Bio-Plex multiplex assay
- This exploratory analysis was restricted to those enrolled in phase II to the first two investigational agents in ACTIV-2:
  - Bamlanivimab or Placebo [Aug-Nov 2020][2]
  - Amubarvimab+Romlusevimab or Placebo [Jan-Feb 2021][3]
- Longitudinal analyses further restricted to those who received placebo who had quantifiable NP RNA at Day 0.
- Statistical approaches:
  - RNA values transformed to log-10 scale
  - Linear regression models evaluated baseline factors associated with $\log_{10}$ RNA at Day 0 and change in $\log_{10}$ RNA from Day 0 to Day 3 (with and without adjustment for symptom duration prior to entry and serostatus); RNA values below assay limit of quantification were handled as censored measurements.

RESULTS

Table 1. Baseline Characteristics (N=537)

Age (years), median (quartiles)	48 (37, 57)
Female Sex, n (%)	264 (49)
Gender Identity, n (%)	
Cis-gender	535 (100)
Transgender	1 (0)
Race, n (%)	
American Indian or Alaska Native	1 (0)
Asian	18 (3)
Black or African American	49 (9)
Multiple	9 (2)
Native Hawaiian or Other Pacific Islander	1 (0)
Other	17 (3)
White	444 (83)
Body Mass Index (kg/m^2), median (quartiles)	28.7 (25.4, 33.5)
> 35, n (%)	107 (21)
≤ 35, n (%)	401 (79)
Diabetes, n (%)	61 (12)
High risk of severe COVID-19*, n (%)	359 (67)
Symptom Duration prior to entry (days) median (quartiles)	6 (4, 8)
History of SARS-CoV-2 Vaccination, n (%)	2 (0)
SARS-CoV-2 IgG Serostatus, n (%)	
Positive	259 (50)
Negative	259 (50)

*High risk defined based on age and comorbid conditions

Figure 1. Day 0 NP RNA by Serostatus

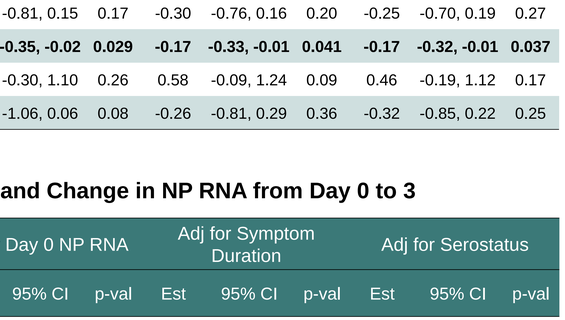

Table 2. Symptom duration at Study Entry and NP RNA ($\log_{10}$ copies/mL) at Day 0

Model	Estimate*	95% CI	p-value
Unadjusted	-0.40	-0.50, -0.30	<0.001
Adjusted for Serostatus	-0.24	-0.34, -0.14	<0.001

*Estimate is the difference in mean NP RNA (log10 copies/mL) at Day 0 for each additional day of prior symptoms

Table 3. Association between baseline factors and NP RNA ($\log_{10}$ copies/mL) at Day 0

	Unadjusted			Adj for Symptom Duration			Adj for Serostatus			Adj for Serostatus + Symptom Duration		
	Est	95% CI	p-val	Est	95% CI	p-val	Est	95% CI	p-val	Est	95% CI	p-val
Age (per 10 years)	**0.29**	**0.13, 0.46**	**<0.001**	**0.28**	**0.13, 0.43**	**<0.001**	**0.23**	**0.08, 0.38**	**0.002**	**0.23**	**0.09, 0.37**	**0.001**
Sex (Female vs Male [ref])	-0.06	-0.53, 0.41	0.79	-0.08	-0.51, 0.36	0.73	-0.13	-0.55, 0.30	0.56	-0.13	-0.54, 0.28	0.54
Race/Ethnicity*												
(Black not Hispanic/Latino)	**-2.10**	**-3.09, -1.12**	**<0.001**	**-1.52**	**-2.45, -0.59**	**0.001**	**-1.52**	**-2.42, -0.61**	**0.001**	**-1.27**	**-2.16, -0.38**	**0.005**
(Hispanic/Latino, any race)	-0.31	-0.84, 0.21	0.24	-0.60	-1.07, -0.10	0.019	-0.40	-0.66, 0.29	0.44	-0.40	-0.87, 0.07	0.10
(Multiracial/Others)	-0.71	-0.75, 0.32	0.18	-0.65	-1.62, 0.32	0.19	-0.62	-1.54, 0.30	0.19	-0.62	-1.52, 0.28	0.18
High Risk (Yes vs No [ref])	-0.46	-0.97, 0.05	0.08	-0.33	-0.81, 0.15	0.17	-0.30	-0.76, 0.16	0.20	-0.25	-0.70, 0.19	0.27
BMI (per 5 kg/m^2)	**-0.20**	**-0.38, -0.02**	**0.032**	**-0.19**	**-0.35, -0.02**	**0.029**	**-0.17**	**-0.33, -0.01**	**0.041**	**-0.17**	**-0.32, -0.01**	**0.037**
Diabetes (Yes vs No [ref])	0.61	-0.13, 1.36	0.11	0.40	-0.30, 1.10	0.26	0.58	-0.09, 1.24	0.09	0.46	-0.19, 1.12	0.17
Obesity (Yes vs No [ref])	-0.48	-1.08, 0.13	0.12	-0.50	-1.06, 0.06	0.08	-0.26	-0.81, 0.29	0.36	-0.32	-0.85, 0.22	0.25

*White not Hispanic/Latino is reference group for race/ethnicity comparisons

Table 4. Association between baseline factors and Change in NP RNA from Day 0 to 3

	Unadjusted			Adj for Day 0 NP RNA			Adj for Symptom Duration			Adj for Serostatus		
	Est	95% CI	p-val	Est	95% CI	p-val	Est	95% CI	p-val	Est	95% CI	p-val
Sex (Female vs Male [ref])	**-0.731**	**-1.15, -0.31**	**<0.001**	**-0.709**	**-1.12, -0.30**	**<0.001**	**-0.781**	**-1.20, -0.36**	**<0.001**	**-0.826**	**-1.25, -0.40**	**<0.001**

Associations with age, race/ethnicity, high risk, BMI, diabetes, obesity and serostatus not significant (p>0.13)

- 537 participants from US sites, largely unvaccinated, enrolled during pre-omicron phase of pandemic (Table 1)
- Day 0 NP RNA:
  - Median (Q1, Q3): 5.21 (3.24, 6.69) log10 copies/mL
  - 17% below lower limit of quantification (LLoQ), including 9% undetectable (< LOD [Limit of Detection])
- Seronegativity and fewer days of symptoms associated with higher Day 0 NP RNA (Figure 1 and Table 2)
- Older age, lower BMI, White non-Hispanic race/ethnicity (vs Black non-Hispanic) associated with higher Day 0 NP RNA (Table 3)
  - White non-Hispanic more likely to be seronegative and have shorter symptom durations suggesting they enter study earlier in infection, with attenuate association in adjusted models, implying associations may be confounded
- Female participants had faster decline in NP RNA (Table 4)
  - Other baseline factors not associated with changes in NP RNA

CONCLUSIONS

- **Older age was associated with higher Day 0 NP RNA, which may reflect unmeasured immune deficiencies with aging[4]**
- **Shorter symptom duration and seronegativity were also associated with higher NP RNA at Day 0 likely representing individuals earlier in their infections**
- **Female participants had faster declines in NP RNA compared with males, which was robust to adjustments for serostatus and symptom duration**
  - **Consistent with other studies, the faster decline in NP RNA level may explain sex-based differences observed with other COVID-19 outcomes such as disease severity[5]**

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[1]Berg MG, Zhen W, Lucic D, et al. Development of the RealTime SARS-CoV-2 quantitative Laboratory Developed Test and correlation with viral culture as a measure of infectivity. J Clin Virol Off Publ Pan Am Soc Clin Virol. 2021; 143:104945.

[2]Chew KW, Moser C, Daar ES, et al. Antiviral and clinical activity of bamlanivimab in a randomized trial of non-hospitalized adults with COVID-19. Nature Communications. 2022 Aug 22; 13(1):1-2.

[3]Evering TH, Giganti M, Chew KW, et al. LB2. Safety and Efficacy of Combination SARS-CoV-2 Monoclonal Neutralizing Antibodies (mAb) BRII-196 and BRII-198 in Non-Hospitalized COVID-19 Patients. Open Forum Infect Dis. 2021; 8(Suppl 1):S807–S808.

[4]Shodell M, Siegal FP. Circulating, interferon-producing plasmacytoid dendritic cells decline during human ageing. Scand J Immunol. 2002; 56(5):518–521.

[5]Takahashi T, Ellingson MK, Wong P, et al. Sex differences in immune responses that underlie COVID-19 disease outcomes. Nature. Nature Publishing Group; 2020; 588(7837):315–320.