A study of imputed measurements – fraudulent Merck Molnupiravir paper in NEJM

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Merck's newest Molnupiravir study (Bernal et al., NEJM)[1], published in NEJM, contains fabricated data about coronavirus clearance in *Appendix, Table S6*. A large part of this data is not measurements but "imputed" (i.e., made up) values.

The paper acknowledges in fine print that only nasopharyngeal viral load range of 500 to 500 million copies/mL (corresponding to the log10 range 2.70 – 8.70) were measured and recorded correctly. For samples with viral load outside of this range, imputed values were recorded:

> *"The quantitative assay to generate these data was the Q2 SARS-CoV-2 Viral Load Quantitation Assay, with lower limit of quantification of 500 copies/ml and upper limit of quantification of 500,000,000 copies/ml. Post-baseline results below or above these limits were included in the mean and the mean change from baseline, with imputed value 499 and 500,000,001, respectively."* (NEJM Annex, p.23)

This means that if the viral load grew to 5 billion after the start of treatment (which is within the normal range[2]), it is recorded and used in calculations as 500,000,001.

The excuse Merck used for this was that these were the limits of the quantitation assay from Q[2] Solutions. This explanation does not work for the upper bound. The researchers could have diluted the sample as much as they needed. For the lower bound, they could have used a more sensitive assay[3].

Table 1. Table S6 from *Bernal et al. Appendix*, reformatted with added calculations.

Visit	Molnupiravir				Placebo					Mean change since Day 3		
	no.	Mean[a]	Mean change	Mean change SD	no.	Mean[a]	Mean change	Mean change SD		MOLN	Placebo	Difference
SARS-CoV-2 RNA Titer (log_{10} copies/ml)												
Baseline	549	6.81	0	0.000	544	6.81	0.00	0	**0.00**			
Day 3	499	5.74	-1.08	1.287	507	6.00	-0.84	1.258				
EOT (Day 5)	482	4.73	-2.09	1.490	482	5.04	-1.79	1.513		-1.01	-0.95	**0.06**
Day 10	447	3.64	-3.18	1.628	438	3.80	-2.99	1.678		-2.10	-2.15	**-0.05**
Day 15	424	3.18	-3.61	1.740	413	3.28	-3.48	1.836		-2.53	-2.64	**-0.11**
Day 29	373	2.88	-3.91	1.656	362	2.88	-3.99	1.712		-2.83	-3.15	**-0.32**
SARS-CoV-2 RNA titer (log_{10} copies/ml) in participants with baseline RNA titer $\leq 10^6$ copies/ml												
Baseline	160	4.66	0	0.000	162	4.61	0.00	0	**-0.05**			
Day 3	144	3.92	-0.71	1.249	146	4.32	-0.28	1.284				
EOT (Day 5)	140	3.56	-1.05	1.182	140	3.67	-0.91	1.398		-0.34	-0.63	**-0.29**
Day 10	128	3.01	-1.62	1.005	132	3.18	-1.37	1.276		-0.91	-1.09	**-0.18**
Day 15	125	2.98	-1.61	1.115	130	3.14	-1.42	1.268		-0.90	-1.14	**-0.24**
Day 29	108	2.81	-1.77	0.957	103	2.79	-1.76	0.978		-1.06	-1.48	**-0.42**
SARS-CoV-2 RNA titer (log_{10} copies/ml) in participants with baseline RNA titer $>10^6$ copies/ml												
Baseline	389	7.69	0	0.000	382	7.74	0.00	0	**0.05**			
Day 3	355	6.48	-1.23	1.273	361	6.68	-1.07	1.175				
EOT (Day 5)	342	5.21	-2.52	1.393	342	5.60	-2.15	1.409		-1.29	-1.08	**0.21**
Day 10	319	3.90	-3.81	1.394	306	4.07	-3.70	1.304		-2.58	-2.63	**-0.05**
Day 15	299	3.26	-4.44	1.184	283	3.35	-4.42	1.163		-3.21	-3.35	**-0.14**
Day 29	265	2.91	-4.78	0.924	259	2.92	-4.88	0.963		-3.55	-3.81	**-0.26**

The following table contains calculation of the fraction of imputed values in the Table S6. It generously assumes normal distribution of the actual values with sigma equal to the reported standard deviation, causing some underestimates.

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This is an enhanced version of https://trialsitenews.com/mercks-molnupiravir-paper-in-nejm-imputed-values-study/

Table 2. Estimated fraction of made up ("imputed") measurements in *Bernal et al., Table S6*

Limits	Total	2.70	8.70	Total	2.70	8.70
	Molnupiravir			Placebo		
SARS-CoV-2 RNA Titer (log_{10} copies/ml)						
Baseline						
Day 3	**2.0%**	0.9%	1.1%	**2.0%**	0.4%	1.6%
EOT (Day 5)	**9.0%**	8.6%	0.4%	**6.9%**	6.1%	0.8%
Day 10	**28.3%**	28.2%	0.1%	**25.8%**	25.6%	0.2%
Day 15	**39.2%**	39.1%	0.1%	**37.7%**	37.6%	0.2%
Day 29	**45.7%**	45.6%	0.0%	**45.8%**	45.8%	0.0%
SARS-CoV-2 RNA titer (log_{10} copies/ml) in participants with baseline RNA titer ≤10^6 copies/ml						
Baseline						
Day 3	**16.4%**	16.4%	0.0%	**10.4%**	10.3%	0.0%
EOT (Day 5)	**23.3%**	23.3%	0.0%	**24.4%**	24.4%	0.0%
Day 10	**37.8%**	37.8%	0.0%	**35.3%**	35.3%	0.0%
Day 15	**40.1%**	40.1%	0.0%	**36.4%**	36.4%	0.0%
Day 29	**45.4%**	45.4%	0.0%	**46.3%**	46.3%	0.0%
SARS-CoV-2 RNA titer (log_{10} copies/ml) in participants with baseline RNA titer >10^6 copies/ml						
Baseline						
Day 3	**4.2%**	0.1%	4.1%	**4.3%**	0.0%	4.3%
EOT (Day 5)	**4.2%**	3.6%	0.6%	**3.4%**	2.0%	1.4%
Day 10	**19.5%**	19.4%	0.0%	**14.7%**	14.7%	0.0%
Day 15	**31.8%**	31.8%	0.0%	**28.8%**	28.8%	0.0%
Day 29	**41.0%**	41.0%	0.0%	**40.9%**	40.9%	0.0%

Thus, at least 25% of measurements used to produce results for Days 10, 15, and 29 are made up. This is after Merck had a lot of opportunity to select results of which subjects to measure.

Given the track record of this trial, it is easy to conclude that Merck had something to hide. Perhaps less patients in the Molnupiravir treatment group cleared the virus by Day 29, compared to the placebo group. Given Molnupiravir's mechanism of action, this raises the possibility that Molnupiravir breeds SARS-COV-2 variants that can survive for a long period, causing chronic or periodic disease.

Using this made-up data, Bernal et al. incorrectly concluded that *"molnupiravir treatment was associated with greater reductions from baseline in mean viral load than placebo at days 3, 5 (end-of-treatment visit), and 10 (Fig. S6 and Table S6). Results at other time points were similar in the two groups."*

Methodological Note

Measurements which are outside of the plausible range can be considered erroneous and replaced with estimates, when the impact is not substantial. Measurements that are too low to matter can be assumed 0. But values outside the range of Merck selected methods and materials are plausible and important, and the impact of the "imputation" is impossible to determine. Also, Merck has not selected reasonable estimates, which could be top bound multiplied by 3 and low bound divided by 3. If Merck could not or did not take measurements correctly, it should not report their results.

Other Notes

Notice that the fine print under Table S6 uses copies/mL, which are hard to relate to the log10 numbers in the table.

Table S6 has the same baseline viral load value 6.81 (on log10 scale) in both Molnupiravir and Placebo arms. This is not a typing mistake. The respective values in the sub-groups also differ by only 0.05, and perfectly sum up (weighted) to 6.8069 and 6.8079, respectively. The difference is only 0.001, not very likely to happen by chance.

Slower Viral Clearance

Because of the mechanism of action, Day 3, rather than the "baseline", should be used as the starting point. Molnupiravir driven mutations cannot do not take effect until the first generation of mutated virions became the majority. If NHC concentrations in the body remain constant, at ~3 mcg/mL, this would happen in approximately 36-48 hours. Even at this point, the effect may not be strong enough and may require a few more generations. So, at the earliest, Day 3 is when Molnupiravir starts to work. Recalculated in reference to Day 3, viral load change values show that Molnupiravir is associated with slower viral clearance compared to placebo (Table 1, column *Difference*).

Conclusion

This is in accordance with other findings showing that Molnupiravir increases severity of COVID-19[4], slows down viral clearance[5], and carcinogenic.

Reference

1. Bernal et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients | NEJM. Published online December 16, 2021. https://www.nejm.org/doi/full/10.1056/NEJMoa2116044

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3. Broder K, Babiker A, Myers C, et al. Test Agreement between Roche Cobas 6800 and Cepheid GeneXpert Xpress SARS-CoV-2 Assays at High Cycle Threshold Ranges. *J Clin Microbiol*. Published online May 22, 2020. doi:10.1128/JCM.01187-20

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