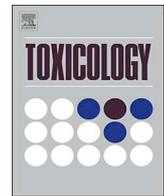




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Letter to the editor

Wuhan Covid19 data – more questions than answers



Recently published data seem to suggest that the public health measures in Wuhan were successful in containing the recent Covid-19 outbreak (Pan, Liu et al. 2020). At closer inspection these and other data (Chinazzi, Davis et al. 2020; Tian, Liu et al. 2020) pose more questions than answers.

The Wuhan data (Pan, Liu et al. 2020) do indeed seem to suggest a close temporal association between the instalment of public health measures – closure of public transport and the Wuhan airport, cordoning off the city, keeping people at home and mass testing as well as quarantining all those with positive Covid-19 tests. In order to arrive at these suggestions the time axis was partitioned into 5 periods: early period 1, from Dec 8 when first cases were visible until January 10. It was followed by period 2, when massive migrations for the spring festival began until January 23rd, when the Wuhan airport was closed and the city cordoned off by suspension of travel and public transport. It is important to note that during the beginning of the spring festival which started on Jan 10 and lasted altogether 40 days in the whole of China, i.e. period 2 (Tian, Liu et al. 2020), there were no restrictions or measures in place whatsoever and massive travel movements were noticeable all across China from and to Wuhan (Chinazzi, Davis et al. 2020). Only 2 days before the end of that festival was the airport closed and period 3 followed, which lasted until February 2nd and was characterized by cordon sanitaire around Wuhan, with all inbound and outbound travel suspended. The following two periods were characterized by more stringent public health measures, with quarantining and a gradual easing of the infectiological pressure.

The peak of the number of cases was observed on February 2 and from then on the number of cases gradually fell. The replication number of the virus was calculated to cross the barrier of $R_0 = 1$ between February 5th and 6th (eTable 3 (Pan, Liu et al. 2020)) and thus it seems that the travel ban 2 weeks earlier was efficient in reducing the spreading of the infection.

However, if we look at the data presented in eFigure 3b (Pan, Liu et al. 2020), which presents the time lag between symptom onset and diagnosis a different picture emerges. During period 1 the approximate median time from symptom onset to official diagnosis and thus case definition is about 20 days, during period 2 the peak time lag between symptom onset and diagnosis is about 14 days and because of the skewness of the distribution the median time lag is slightly larger. Now, if we take this time lag into account, then the actual time point for the $R_0 < 1$ is shifted backwards in time by 14 days from Feb 6 to the time point between the 23rd and the 24th of January, exactly on the day of the beginning of the travel ban. As the case definition was by confirmed diagnosis (Prof. Wu, personal communication) and the calculation was by a 5 day sliding average window, the crossing point might even be shifted backwards in time by another 2.5 days. Even by conservative standards this means the replication of the virus was on the verge of falling below 1 even without any measures in place. It is unsurprising that further public health measures kept the spreading of the virus

below 1, as it had already moved beyond that point by its own inherent replication dynamic.

Further, in eTable 2 (Pan, Liu et al., 2020) we see as a result of the Poisson regression that the chance of being a severe or critical case was already lower by 29 % in period 2 (adjusted relative risk = 0.71; $p < 0.001$), during the spring festival period, when no public health measures were in place.

Were the public health measures indeed causal, as is widely assumed, in halting the spread of the virus? The data do not seem to support this conclusion. Why then would the reproduction number R_0 fall under 1 already on the 24th of Jan, just one day after traffic lockdown, when the median incubation time is assumed to be roughly 5 days? Why would a person have a 29 % lower chance during the second period to become a severe or critical case, when no public health measures were in place, if the lockdown and following measures were in fact causal for not only containing the virus but also preventing severe cases? Presumably the case definition being mainly clinical was robust independent of insecurities with testing facilities. The same picture – peaking infection rates and fall of these rates before public health measures – can be seen in German data (An der Heiden and Hamouda, 2020). Moreover, a new analysis shows that the infection runs its course, peaks at about 7–8 weeks and then falls off, regardless of what public health measures are taken (Ben-Israel, 2020). Countries like Sweden and Israel that adopted completely opposite types of measures run the same course of the epidemic. What might be influenced by those measures is the number of cases and consequently the number of fatalities, if these measures are taken early. But it seems that, once the epidemic is visible it runs its course and then falls off.

Looking at the modeling data (Chinazzi, Davis et al. 2020; Tian, Liu et al. 2020) we see that the lockdown of Wuhan airport on 23rd of January would have delayed the spread of the virus to the rest of China only by 3–5 days. Since other airports in the country remained open until 1st of March the spread would not have been halted at all to Europe, the USA and the rest of the world (Chinazzi, Davis et al. 2020). Considering that, although level 1 emergency was declared everywhere in China until the 29th of January, only 40 % of all large cities implemented all measures (Tian, Liu et al. 2020). Yet the modeling predicts that only with full level 1 response the number of infected cases would plateau and decline (Figure 4b (Tian, Liu et al. 2020)).

This data signature seems to suggest that the Covid-19 infection runs its course undetected for quite some time and when it is detected it is already in a recessive mode. Might this be due to a rapid mutation (Tang, Wu et al. 2020), or due to the fact that a large number of infections are subclinical with no major symptoms, or due to a molecular switch that switches off the virulence once certain conditions are reached? (Harris, Moran et al. 2018)

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References

- An der Heiden, M., Hamouda, O., 2020. Schätzung der aktuellen Entwicklung der SARS-CoV-2-epidemie in Deutschland – Nowcasting. *Epidemiologisches Bulletin* 17, 10–15.
- Ben-Israel, I., 2020. The End of Exponential Growth: the Decline in the Spread of the Coronavirus. Retrieved 22nd April, 2020, from. <https://www.timesofisrael.com/the-end-of-exponential-growth-the-decline-in-the-spread-of-coronavirus/>.
- Chinazzi, M., Davis, J.T., Ajelli, M., Gioannini, C., Litvinova, M., Merler, S., Pastore y Piontti, A., Mu, K., Rossi, L., Sun, K., Viboud, C., Xiong, X., Yu, H., Halloran, M.E., Longini, I.M., Vespignani, A., 2020. The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak. *Science*, eaba9757.
- Harris, J.D., Moran, M.J., Aprahamian, I., 2018. New molecular switch architectures. *Proc. Natl. Acad. Sci.* 115 (38), 9414–9422.
- Pan, A., Liu, L., Wang, C., Guo, H., Hao, X., Wang, Q., Huang, J., He, N., Yu, H., Lin, X., Wei, S., Wu, T., 2020. Association of public health interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China. *JAMA*. <https://doi.org/10.1001/jama.2020.6130>. online first.
- Tang, X., Wu, C., Li, X., Song, Y., Yao, X., Wu, X., Duan, Y., Zhang, H., Wang, Y., Qian, Z., Cui, J., Lu, J., 2020. On the origin and continuing evolution of SARS-CoV-2. *Sci. Rev.* <https://doi.org/10.1093/nsr/nwaa036>.
- Tian, H., Liu, Y., Li, Y., Wu, C.-H., Chen, B., Kraemer, M.U.G., Li, B., Cai, J., Xu, B., Yang, Q., Wang, B., Yang, P., Cui, Y., Song, Y., Zheng, P., Wang, Q., Bjornstad, O.N., Yang, R., Grenfell, B.T., Pybus, O.G., Dye, C., 2020. An investigation of transmission control measures during the first 50 days of the COVID-19 epidemic in China. *Science*, eabb6105. <https://doi.org/10.1126/science.abb6105>.

Harald Walach^{a,b,c}^a Poznan University of Medical Sciences, Department Pediatric Gastroenterology, Poznan, Poland^b University Witten-Herdecke, Department Psychology, Germany^c Change Health Science Institute, Berlin, Germany

Stefan Hockertz*

tpi consult, Bollschweil, Germany

E-mail address: prof.hockertz@tpi-consult.de.

* Corresponding author.