***BMJ Editorial***

**Lightening the load: reduce viral transmission dose to lessen Covid-19 severity***Adherence to separation measures is key*

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While the number of positive tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) across many European countries has risen sharply, increases in the number of hospitalizations and deaths due to coronavirus disease 2019 (Covid-19) have not been as steep. The case fatality rate (the proportion of deaths per positive test) in the UK was lower in May and June than in March and April1, and appears to be have been declining steadily throughout July and August2. Reductions were also observed in the early stages of the outbreak across many countries3. Case fatality rates have varied in different countries, with relatively lower estimates observed in several African countries4. Why have case fatality rates decreased, and how does this relate to measures used to control the epidemic?

*Possible reasons*

The first reason for reductions in the Covid-19 case fatality rate is the changing demographic of cases5. Age is a strong predictor of Covid-19 mortality6. In many Western countries, while the absolute number of cases in over-60s is increasing, the proportion of cases in over-60s is decreasing5. This suggests that public health measures to curb the spread of SARS-CoV-2 have been successful in reducing the relative burden of disease in elderly individuals, who are the most vulnerable demographic group.

The second reason is improved treatment. This includes pharmacological agents such as systemic corticosteroids, which have recently been shown to improve outcomes in Covid-19 patients7. Further, clinical management of cases is likely also improving, through accumulated experience of the disease.

A third reason may relate to the number of infectious viral particles to which a case is exposed at the point of their infection (the “inoculum”). While SARS-CoV-2 human challenge trials to investigate this are in early stages of development, studies of influenza A virus in humans have demonstrated that initial exposure to a lower inoculum results in fewer and shorter symptoms as well as lower likelihood of viral shedding8 9. This parallels animal experiments for influenza and for other viral diseases10, and more recently for SARS-CoV-2 in Syrian hamsters11 and ferrets12, in which inoculum size correlated with severity of ensuing disease. Viral load in patients with Covid-19 has been shown to be greater in those with more severe illness13.

In humans, randomized trials of patients with viral upper respiratory tract infections have shown reductions in viral droplet emissions from mask wearing14. Furthermore, masks have been demonstrated to reduce inhalation of particles15. Several epidemiological studies have indicated benefits of mask wearing and other social distancing measures in reducing the severity of Covid-1916 17. Additionally, the use of masks has been shown in a laboratory setting to reduce both disease transmission and severity of SARS-CoV-2 infection in hamsters18. A case series in humans comparing three transmission clusters with different degrees of social distancing showed differences in outcome severity between the clusters19. Differences in social practices and living conditions that lead to variation in the inoculum may partly explain discrepancies in case fatality rates between countries.

*Successful measures*

The relation of inoculum size to infection severity has clear public health implications. As the northern hemisphere winter draws in and more time is spent in confined spaces, it is important to emphasize that separation measures such as mask wearing, ventilation, and social distancing may not only reduce the spread of the virus, but also disease severity. Even imperfect adherence to such measures is likely to be beneficial. A question that remains open is the relative contribution of droplet versus aerosol transmission20. Although measures such as screens and face-shields intercept droplets, they are less likely to reduce aerosol transmission in poorly ventilated spaces. While no approach is without risk, prioritizing those measures that are most effective in reducing substantial viral transmission events enables a balance between managing the Covid-19 pandemic and allowing society to continue to function.

Although the increased number of cases is alarming, the relatively lower fatality rate is a sign that current public health measures have had some success in protecting the most vulnerable, as well as potentially reducing disease severity in those that are infected. Ensuring adherence to control measures that reduce viral exposure is critical to minimizing the severity of the pandemic, particularly in the knowledge of the severe harm that is caused by a hard lockdown.

**References**

1. Dennis JM, McGovern AP, Vollmer SJ, et al. Improving Survival of Critical Care Patients With Coronavirus Disease 2019 in England: A National Cohort Study, March to June 2020. *Critical Care Medicine* 2020 doi: 10.1097/CCM.0000000000004747

2. Centre for Evidence-Based Medicine. The Declining Case Fatality Ratio in England [Available from: <https://www.cebm.net/covid-19/the-declining-case-fatality-ratio-in-england/> accessed 9 October 2020.

3. Pachetti M, Marini B, Giudici F, et al. Impact of lockdown on Covid-19 case fatality rate and viral mutations spread in 7 countries in Europe and North America. *J Transl Med* 2020;18(1):338. doi: 10.1186/s12967-020-02501-x

4. Chibwana MG, Jere KC, Kamng'ona R, et al. High SARS-CoV-2 seroprevalence in Health Care Workers but relatively low numbers of deaths in urban Malawi. *medRxiv* 2020 doi: 10.1101/2020.07.30.20164970

5. Venkatesan P. The changing demographics of COVID-19. *Lancet Respir Med* 2020 doi: 10.1016/S2213-2600(20)30461-6

6. Pastor-Barriuso R, Pérez-Gómez B, Hernán MA, et al. Infection fatality risk for SARS-CoV-2 in community dwelling population of Spain: nationwide seroepidemiological study. *BMJ* 2020;371:m4509. doi: 10.1136/bmj.m4509

7. The WHO Rapid Evidence Appraisal for Covid-Therapies Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA* 2020;324(13):1330-41. doi: 10.1001/jama.2020.17023

8. Han A, Czajkowski LM, Donaldson A, et al. A Dose-finding Study of a Wild-type Influenza A(H3N2) Virus in a Healthy Volunteer Human Challenge Model. *Clin Infect Dis* 2019;69(12):2082-90. doi: 10.1093/cid/ciz141

9. Memoli MJ, Czajkowski L, Reed S, et al. Validation of the wild-type influenza A human challenge model H1N1pdMIST: an A(H1N1)pdm09 dose-finding investigational new drug study. *Clin Infect Dis* 2015;60(5):693-702. doi: 10.1093/cid/ciu924

10. Marois I, Cloutier A, Garneau E, et al. Initial infectious dose dictates the innate, adaptive, and memory responses to influenza in the respiratory tract. *J Leukoc Biol* 2012;92(1):107-21. doi: 10.1189/jlb.1011490

11. Imai M, Iwatsuki-Horimoto K, Hatta M, et al. Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. *P Natl Acad Sci USA* 2020;117(28):16587-95. doi: 10.1073/pnas.2009799117/-/DCSupplemental.

12. Ryan KA, Bewley KR, Fotheringham SA, et al. Dose-dependent response to infection with SARS-CoV-2 in the ferret model: evidence of protection to re-challenge. *bioRxiv* 2020:2020.05.29.123810. doi: 10.1101/2020.05.29.123810

13. Liu Y, Yan L-M, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. *The Lancet Inference Diseases* 2020;20(6):656-57. doi: 10.1016/S1473-3099(20)30232-2

14. Leung NHL, Chu DKW, Shiu EYC, et al. Respiratory virus shedding in exhaled breath and efficacy of face masks. *Nat Med* 2020;26(5):676-80. doi: 10.1038/s41591-020-0843-2

15. van der Sande M, Teunis P, Sabel R. Professional and Home-Made Face Masks Reduce Exposure to Respiratory Infections among the General Population. *PLoS One* 2008;3(7)

16. Greenhalgh T, Schmid MB, Czypionka T, et al. Face masks for the public during the covid-19 crisis. *BMJ* 2020;369:m1435. doi: 10.1136/bmj.m1435

17. Gandhi M, Beyrer C, Goosby E. Masks Do More Than Protect Others During COVID-19: Reducing the Inoculum of SARS-CoV-2 to Protect the Wearer. *J Gen Intern Med* 2020 doi: 10.1007/s11606-020-06067-8

18. Chan JF, Yuan S, Zhang AJ, et al. Surgical mask partition reduces the risk of non-contact transmission in a golden Syrian hamster model for Coronavirus Disease 2019 (COVID-19). *Clin Infect Dis* 2020 doi: 10.1093/cid/ciaa644

19. Guallar MP, Meiriño R, Donat-Vargas C, et al. Inoculum at the time of SARS-CoV-2 exposure and risk of disease severity. *International Journal of Infectious Diseases* 2020;97:290-92.

20. Wilson N, Corbett S, Tovey E. Airborne transmission of covid-19. *BMJ* 2020;370:m3206. doi: 10.1136/bmj.m3206

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