Masks Do More than Protect Others during COVID-19: Reducing the Inoculum of SARS-CoV-2

Monica Gandhi, MD, MPH[1], Chris Beyrer MD, MPH[2], Eric Goosby, MD[1]

Running title: Masks Reduce Viral Inoculum of SARS-CoV2

Corresponding Author:

[1]Monica Gandhi, MD, MPH

Professor of Medicine, University of California, San Francisco (UCSF)

Department of Medicine, Division of HIV, Infectious Diseases and Global Medicine,

995 Potrero Avenue, 4th Floor

San Francisco, CA, 94110

Email address: monica.gandhi@ucsf.edu

[2]Chris Beyrer MD, MPH

Desmond M. Tutu Professor of Public Health and Human Rights

Johns Hopkins Bloomberg School of Public Health

615 N. Wolfe Street
Suite E7152
Baltimore, Maryland 21205

cbeyrer@jhu.edu

[3]Eric Goosby MD

Professor of Medicine, University of California, San Francisco (UCSF)

Department of Medicine, Division of HIV, Infectious Diseases and Global Medicine,

995 Potrero Avenue, 4th Floor

San Francisco, CA, 94110

Email address: monica.gandhi@ucsf.edu

Abstract word count: 200

Manuscript Word Count: 1296

Number of references: 49

Number of figures: 1

ABSTRACT

Although the benefit of population-level public facial masking to protect others during the COVID-19 pandemic has received a great deal of attention, we discuss for one of the first times the hypothesis that universal masking reduces the "inoculum" or dose of the virus for the mask-wearer, leading to more mild and asymptomatic infection manifestations. Masks, depending on type, filter out the majority of viral particles, but not all. We first discuss the near-century old literature around the viral inoculum and severity of disease (conceptualized as the LD50 or lethal dose of the virus). We include examples of rising rates of asymptomatic infection with population-level masking, including in closed settings (e.g. cruise ships) with and without universal masking. Asymptomatic infections may be harmful for spread but could actually be beneficial if they lead to higher rates of exposure. Exposing society to SARS-CoV-2 without the unacceptable consequences of severe illness with public masking could lead to greater community-level immunity and slower spread as we await a vaccine. This theory of viral inoculum and mild or

asymptomatic disease with SARS-CoV-2 in light of population-level masking has received little attention so this is one of the first perspectives to discuss the evidence supporting this theory.

This perspective outlines a unique angle on why universal public masking during the COVID-19 pandemic should be one of the most important pillars of disease control. Our theory is based on the likelihood of masking reducing the viral inoculum to which the mask-wearer is exposed, leading to higher rates of mild or asymptomatic infection with COVID-19. No prior perspective has specifically focused on this link between population-level facial masking, the viral inoculum, and increasing rates of asymptomatic infection with SARS-CoV-2.

On April 3, 2020, the Centers for Disease Control and Prevention issued recommendations on wearing cloth face coverings by the public to reduce community spread.[1] The World Health Organization did not recommend population-level face masking in April,[2] but changed their guidance on June 5, 2020,[3] when the extent of transmission from pre-symptomatic or even asymptomatic individuals was clear.[4,5] One recent model showed that population-level masking is one of the most efficacious interventions to reduce further spread of SARS-CoV-2, allowing for less-stringent lock-down requirements in countries adopting this strategy.[6] Countries worldwide have had a range of responses to the recommendation on universal masking, with many countries (and U.S. states)[7] issuing mandates and enforcement strategies.[8] Countries accustomed to universal population-level masking since the SARS epidemic in 2003 adopted the intervention more readily.[9]

There are two likely reasons for the effectiveness of facial masks: The first - to prevent the spread of viral particles from asymptomatic individuals to others - has received a great deal of attention.[10,11] However, the second theory- that reducing the inoculum of virus to which a mask-wearer is exposed will result in milder disease[12-27] -has received less attention and is the focus of our perspective. Masks, depending on the material and design, filter out a majority of viral particles, but not all.[28] The theory that exposure to a lower inoculum or dose of any virus (whether respiratory, gastrointestinal or sexually-transmitted) can make subsequent illness far less likely to be severe[12-27] has been propounded for some time. Indeed, the concept of the 50% lethal dose (LD50), the virus dose at which fifty percent of exposed hosts die, determined via controlled experiments in which a range of exposure doses are administered to animals to calculate a dose-mortality curve, was first described in 1938.[18] Other studies have examined the LD50 – or the dose that leads to severe disease or death- for a variety of viruses in hosts or animal models.[17,21,29-34]

These studies have limitations, since experiments to examine the dose of virus to achieve its LD50 have necessarily not been conducted in humans. Studies to experimentally examine the dose of virus associated with different levels of diseases severity in humans has been limited to non-lethal viruses. In one experiment in preparation for vaccine development, healthy human volunteers exposed to different doses of wild-type influenza A virus developed more severe symptoms at higher inocula of administered virus.[34] Giving SARS-CoV-2 in a range of doses to humans experimentally would be unethical, but an animal model has tested this theory of masking attenuating disease severity. In a frequently-cited study showing that hamsters are less likely to contract SARS-CoV-2 infection with a surgical mask partition, those hamsters that did contract COVID-19 with simulated masking had milder manifestations of infection.[27]

Increasing rates of asymptomatic and mild infection with COVID-19 have been seen over time during the pandemic in settings adopting population-level masking. A systematic review of earlier studies, before facial masking was widely practiced, placed the proportion of asymptomatic infection with SARS-CoV-2 at 15%.[35] A more recent narrative review of 16 different studies estimated the rate of asymptomatic infection at 40-45%.[36] Closed settings, such as cruise ships, can be particularly illustrative when examining phenotypes associated with SARS-CoV-2. For example, one of the earliest estimates of the rate of asymptomatic infection due to SARS-CoV-2 was in the 20% range from a report of a COVID-19 outbreak on the Diamond Princess cruise ship.[37] In a more recent report from a different cruise ship outbreak, all passengers were issued surgical masks and all staff provided N95 masks after the initial case of COVID-19 on the ship was detected.[38] In this closed setting with masking, where 128 of 217 passengers and staff eventually tested positive for SARS-CoV-2 via RT-PCR, the majority of infected patients on the ship

(81%) remained asymptomatic,[38] compared to 18% in the cruise ship outbreak without masking.[37]

A report from a pediatric hemodialysis unit in Indiana, where all patients and staff were masked, demonstrated that staff rapidly developed antibodies to SARS-CoV-2 after exposure to a single symptomatic patient with COVID-19. In the setting of masking, however, none of the new infections were symptomatic.[39] And in a recent outbreak in a seafood processing plant in Oregon where all workers were issued masks each day at work, the rate of asymptomatic infection among the 124 infected was 95%.[40,41] Finally, in a mass testing campaign to assess the prevalence of COVID-19 in the Mission District of San Francisco, the majority of those who tested positive via RT-PCR (>50%) were asymptomatic.[42] This testing campaign was performed in a city that had mandated population-level public masking a week earlier.[43]

One model showed a correlation between population-level masking and number of COVID-19 cases in various countries, but an even stronger correlation with suppression of COVID-related death rates.[9] However, it should be acknowledged that this model could not account for all confounders that led to such low death rates in the regions examined. This group showed that, if 80% of the population wears a moderately effective mask, nearly half of the projected deaths over the next two months could be prevented.[9] Countries accustomed to masking since the 2003 SARS-CoV pandemic, including Japan, Hong Kong (**Figure 1a**)[44], Taiwan, Thailand, South Korea, and Singapore,[9] and those who newly-embraced masking early on in the COVID-19 pandemic, such as the Czech Republic,[45] have fared well in terms of rates of severe illness and death. Indeed, even when cases have resurged in these areas with population-based masking upon re-opening (e.g. South Korea, Singapore, Hong Kong, Taiwan), the case-fatality rate has remained low,[46] which is suggestive of this viral inoculum theory.

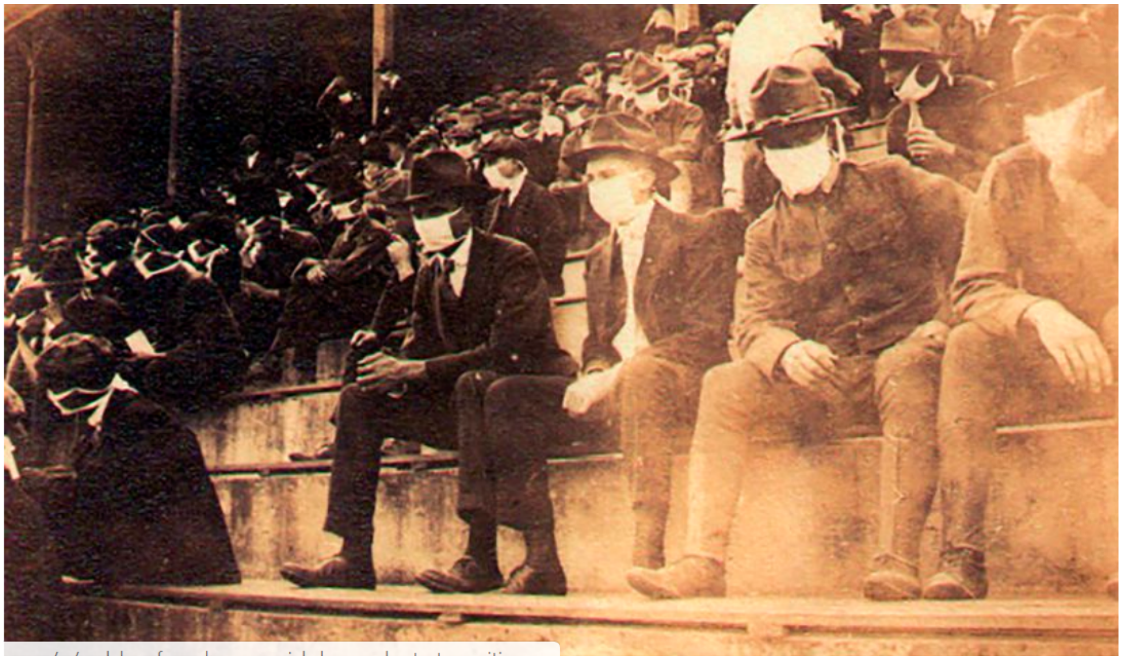
Although asymptomatic infection can be problematic in terms of increasing spread,[4] it can also be beneficial.[14] Higher rates of asymptomatic infection with SARS-CoV-2 lead to higher rates of exposure, as was seen with antibody testing campaigns in Japan[47] or the surveillance study in the pediatric hemodialysis unit in Indiana.[39] Exposing society to SARS-CoV-2 without the unacceptable consequences of severe illness could lead to greater community-level immunity[48] and slow down spread as we await a vaccine. The level of effective antibody and T-cell immune responses to different manifestations of COVID-19 is still under study, although data for T-cell immunity, even with mild disease, is increasingly hopeful.[49,50] Monitoring for upticks in illness, not asymptomatic cases, could herald a need to re-enforce more stringent social distancing measures in a society which has adopted universal public masking going forward.

For this particular pillar of pandemic control to work in the U.S., leading politicians will need to endorse and model mask-wearing. The U.S. has embraced universal public masking before, during the 1918 Spanish influenza pandemic (**Figure 1b**),[51] but the CDC recommendation made on April 3, 2020 for public masking due to COVID-19 has been unevenly followed.[7] The efforts to preserve life must be balanced against the catastrophic consequences of shutting down economies, which ultimately will lead to more suffering, poverty and death than the virus itself, especially for the working poor. Although universal public masking can certainly protect others, the "inoculum" theory argues for a major protective effect for the individual and will allow for the preservation of life, along with other COVID-19 control measures, as society re-opens. This perspective puts forth another advantage of population-level facial masking for pandemic control with SARS-CoV-2 based on an old but enduring theory[18] regarding viral inoculum, clinical manifestations in the host, and protection.

Figure 1a: Busy Hong Kong Street on May 14, 2020 demonstrating universal public masking[44]; only five deaths reported in Hong Kong from COVID-19

Pedestrians in Hong Kong wear face masks as a precautionary measure against the coronavirus on May 14, 2020. | Antony Wallace/AFP via Getty Images

Figure 1b: Georgia Tech football game with fans wearing masks packed in a campus stadium in the midst of the 1918 influenza pandemic[51]



References:

1. Centers for Disease Control and Prevention. Regarding the Use of Cloth Face Coverings, Especially in Areas of Significant Community-Based Transmission. April 3, 2020. https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cloth-face-cover.html.
2. World Health Organization. Advice on the use of masks in the context of COVID-19. Interim guidance. 6 April 2020. Accessible at: https://apps.who.int/iris/handle/10665/331693.
3. World Health Organization. Advice on the use of masks in the context of COVID-19, Interim guidance, 5 June 2020. Accessible at: https://www.who.int/publications/i/item/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-healthcare-settings-in-the-context-of-the-novel-coronavirus-(2019-ncov)-outbreak.
4. Gandhi M, Yokoe DS, Havlir DV. Asymptomatic Transmission, the Achilles' Heel of Current Strategies to Control Covid-19. *N Engl J Med* 2020.
5. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med* 2020; **26**(5): 672-5.
6. Stutt R, Retkute R, Bradley M, Gilligan CA, Colvin J. A modelling framework to assess the likely effectiveness of facemasks in combination with ‘lock-down’ in managing the COVID-19 pandemic. Proceedings of the Royal Society. 10 June 2020, https://doi.org/10.1098/rspa.2020.0376.
7. Lyu W, Wehby GL. Community Use Of Face Masks And COVID-19: Evidence From A Natural Experiment Of State Mandates In The US. *Health Aff (Millwood)* 2020: 101377hlthaff202000818.
8. 3 Massachusetts cities to begin issuing fines for people not wearing face masks in public. 7 News Boston. April 29, 2020. Acccessible at: https://whdh.com/news/3-massachusetts-cities-to-begin-issuing-fines-for-people-not-wearing-face-masks-in-public/.

9. Kai D. et al. Universal Masking is Urgent in the COVID-19 Pandemic: SEIR and Agent Based Models, Empirical Validation, Policy Recommendations. April 22, 2020. Accessible at: https://arxiv.org/pdf/2004.13553.pdf.
10. Gandhi M, Havlir D. The Time for Universal Masking of the Public for Coronavirus Disease 2019 Is Now. *Open Forum Infect Dis* 2020; **7**(4): ofaa131.
11. Eikenberry SE, Mancuso M, Iboi E, et al. To mask or not to mask: Modeling the potential for face mask use by the general public to curtail the COVID-19 pandemic. *Infect Dis Model* 2020; **5**: 293-308.
12. Handel A, Li Y, McKay B, Pawelek KA, Zarnitsyna V, Antia R. Exploring the impact of inoculum dose on host immunity and morbidity to inform model-based vaccine design. *PLoS Comput Biol* 2018; **14**(10): e1006505.
13. Miller DS, Kok T, Li P. The virus inoculum volume influences outcome of influenza A infection in mice. *Lab Anim* 2013; **47**(1): 74-7.
14. Raoult D, Zumla A, Locatelli F, Ippolito G, Kroemer G. Coronavirus infections: Epidemiological, clinical and immunological features and hypotheses. *Cell Stress* 2020; **4**(4): 66-75.
15. Yang R, Gui X, Xiong Y. Comparison of Clinical Characteristics of Patients with Asymptomatic vs Symptomatic Coronavirus Disease 2019 in Wuhan, China. *JAMA Netw Open* 2020; **3**(5): e2010182.
16. Chan JF, Zhang AJ, Yuan S, et al. Simulation of the clinical and pathological manifestations of Coronavirus Disease 2019 (COVID-19) in golden Syrian hamster model: implications for disease pathogenesis and transmissibility. *Clin Infect Dis* 2020.
17. McKenney DG, Kurath G, Wargo AR. Characterization of infectious dose and lethal dose of two strains of infectious hematopoietic necrosis virus (IHNV). *Virus Res* 2016; **214**: 80-9.
18. Reed LJ, Muench H. A simple method of estimating fifty per cent endpoints. The American Journal of Hygiene. 1938;27(3):493-7.
19. Casadevall A. The Pathogenic Potential of a Microbe. *mSphere* 2017; **2**(1).
20. Bouvier NM, Lowen AC. Animal Models for Influenza Virus Pathogenesis and Transmission. *Viruses* 2010; **2**(8): 1530-63.
21. Tao X, Garron T, Agrawal AS, et al. Characterization and Demonstration of the Value of a Lethal Mouse Model of Middle East Respiratory Syndrome Coronavirus Infection and Disease. *J Virol* 2016; **90**(1): 57-67.
22. Gralinski LE, Ferris MT, Aylor DL, Whitmore AC, Green R, Frieman MB, et al. Genome Wide Identification of SARS-CoV Susceptibility Loci Using the Collaborative Cross. PLoS genetics. 2015;11(10):e1005504. .
23. Roberts A, Deming D, Paddock CD, et al. A mouse-adapted SARS-coronavirus causes disease and mortality in BALB/c mice. *PLoS Pathog* 2007; **3**(1): e5.
24. Subbarao K, McAuliffe J, Vogel L, et al. Prior infection and passive transfer of neutralizing antibody prevent replication of severe acute respiratory syndrome coronavirus in the respiratory tract of mice. *J Virol* 2004; **78**(7): 3572-7.
25. Virlogeux V, Fang VJ, Wu JT, et al. Brief Report: Incubation Period Duration and Severity of Clinical Disease Following Severe Acute Respiratory Syndrome Coronavirus Infection. *Epidemiology* 2015; **26**(5): 666-9.
26. Davis N. Who is most at risk of contracting coronavirus? The Guardian2020 [Last accessed 2020-06-06]; Available from: https://www.theguardian.com/world/2020/feb/21/who-is-most-at-risk-of-contracting-coronavirus.

27. 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.
28. Smereka J, Ruetzler K, Szarpak L, Filipiak KJ, Jaguszewski M. Role of mask/respirator protection against SARS-CoV-2. *Anesth Analg* 2020.
29. Engelking HM, Leong JC. The glycoprotein of infectious hematopoietic necrosis virus elicits neutralizing antibody and protective responses. *Virus Res* 1989; **13**(3): 213-30.
30. S.E. LaPatra, J.L. Fryer, J.S. Rohovec. Virulence comparison of different electropherotypes of infectious hematopoietic necrosis virus. Dis. Aquat. Org., 16 (1993), pp. 115-1.
31. Kim R, Faisal M. Comparative susceptibility of representative Great Lakes fish species to the North American viral hemorrhagic septicemia virus Sublineage IVb. *Dis Aquat Organ* 2010; **91**(1): 23-34.
32. Brown JD, Stallknecht DE, Berghaus RD, Swayne DE. Infectious and lethal doses of H5N1 highly pathogenic avian influenza virus for house sparrows (Passer domesticus) and rock pigeons (Columbia livia). *J Vet Diagn Invest* 2009; **21**(4): 437-45.
33. S.E. LaPatra, J.L. Fryer, J.S. Rohovec. Virulence comparison of different electropherotypes of infectious hematopoietic necrosis virus. Dis. Aquat. Org., 16 (1993), pp. 115-120.
34. 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.
35. Buitrago-Garcia D et al. The role of asymptomatic SARS-CoV-2 infections: rapid living systematic review and meta-analysis. May 24, 2020. Accessible at: doi: https://doi.org/10.1101/2020.04.25.20079103.this.
36. Oran DP, Topol EJ. Prevalence of Asymptomatic SARS-CoV-2 Infection: A Narrative Review. *Ann Intern Med* 2020.
37. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. *Euro Surveill* 2020; **25**(10).
38. Ing AJ, Cocks C, Green JP. COVID-19: in the footsteps of Ernest Shackleton. BMJ Thorax. http://dx.doi.org/10.1136/thoraxjnl-2020-215091.
39. Hains DS, Schwaderer AL, Carroll AE, et al. Asymptomatic Seroconversion of Immunoglobulins to SARS-CoV-2 in a Pediatric Dialysis Unit. *JAMA* 2020.
40. Cline S. Cases at seafood plant cause spike in Oregon COVID numbers. The Associated Press. June 9, 2020. Accessible at: https://www.newsbreak.com/oregon/salem/news/0PI8ZP7b/cases-at-seafood-plant-cause-spike-in-oregon-covid-numbers.
41. 124 COVID-19 cases reported at Pacific Seafood in Newport. KGW. June 8, 2020. Newport, Oregon. Accessible at: https://www.kgw.com/article/news/health/coronavirus/pacific-seafood-outbreak-increases-to-124-covid-19-cases/283-ffeb0712-76c0-45ea-b6c8-b7644def0ad1.
42. Chamie G, Marquez C, Crawford E, Peng J, Petersen M, Schwab D, Schwab J, Martinez J, Jones D, Black D, Gandhi M, Kerkhoff AD, Jain V, Sergi F, Jacobo J, Rojas S, Tulier-Laiwa V, Gallardo-Brown T, Appa A, Chiu CY, Rodgers M, Hackett J, Kistler A, Hao S, Kamm J, Dynerman D, Batson J, Greenhouse B, DeRisi J, Havlir DV. SARS-CoV-2 Community Transmission During Shelter-in-Place in San Francisco. medRxiv 2020.06.15.20132233; doi: https://doi.org/10.1101/2020.06.15.20132233.

43. San Francisco Department of Public Health. Order of the Health Officer of the City and County of San Francisco Generally Requiring Members of the Public and Workers to Wear Face Coverings. April 17, 2020. Accessible at: https://www.sfdph.org/dph/alerts/files/OrderNoC19-12-RequiringFaceCovering-04172020.pdf.
44. Ward A. How masks helped Hong Kong control the coronavirus. Vox. May 18, 2020. Accessible at: https://www.vox.com/2020/5/18/21262273/coronavirus-hong-kong-masks-deaths-new-york.
45. Czechs get to work making masks after government decree. The Guardian. March 30, 2020. Accessible at: https://www.theguardian.com/world/2020/mar/30/czechs-get-to-work-making-masks-after-government-decree-coronavirus.
46. World Health Organization (WHO) Coronavirus Disease (COVID-19) Dashboard. June 19, 2020 (updated daily). Accessible at: https://covid19.who.int/.
47. Doi A et al. Seroprevalence of novel coronavirus disease (COVID-19) in Kobe, Japan. May 1, 2020. medRxiv preprint doi: https://doi.org/10.1101/2020.04.26.20079822.
48. Leslie M. T cells found in COVID-19 patients 'bode well' for long-term immunity. Science. May. 14, 2020. https://www.sciencemag.org/news/2020/05/t-cells-found-covid-19-patients-bode-well-long-term-immunity?utm.
49. Sekine T et al. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. bioRxiv 2020.06.29.174888; doi: https://doi.org/10.1101/2020.06.29.174888.
50. Deng W, Bao L, Liu J, et al. Primary exposure to SARS-CoV-2 protects against reinfection in rhesus macaques. *Science* 2020.
51. Niemietz B. Photo of 1918 college football fans wearing face masks points to the past and future. New York Daily News. May 25, 2020. Accessible at: https://www.nydailynews.com/coronavirus/ny-photo-mask-georgia-tech-1918-pandemic-flu-coronavirus-20200525-fbkqrf6tqjgf7plck2emfjdjvi-story.html.

CONFLICT OF INTEREST STATEMENT: None of the authors have any conflicts of interest to report

ACKNOWLEDGEMENTS: We would like to acknowledge all the brave health care workers fighting COVID-19. Funding source for this perspective: NIAID/NIH 2P30 AI027763 (Gandhi, P.I.)