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Perspective

Facial Masking for Covid-19 — Potential for "Variolation" as We Await a Vaccine

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As SARS-CoV-2 continues its global spread, it's possible that one of the pillars of Covid-19 pandemic control — universal facial masking — might help reduce the severity of disease and ensure that a greater proportion of new infections are asymptomatic. If this hypothesis is borne out, universal masking could become a form of "variolation" that would generate immunity and thereby slow the spread of the virus in the United States and elsewhere, as we await a vaccine.

One important reason for population-wide facial masking became apparent in March, when reports started to circulate describing the high rates of SARS-CoV-2 viral shedding from the noses and mouths of patients who were presymptomatic or asymptomatic — shedding rates equivalent to those among symptomatic patients.[1] Universal facial masking seemed to be a possible way to prevent transmission from asymptomatic infected people. The Centers for Disease Control and Prevention (CDC) therefore recommended on April 3 that the public wear cloth face coverings in areas with high rates of community transmission — a recommendation that has been unevenly followed across the United States.

Past evidence related to other respiratory viruses indicates that facial masking can also protect the wearer from becoming infected, by blocking viral particles from entering the nose and mouth.[2] Epidemiologic investigations conducted around the world — especially in Asian countries that became accustomed to population-wide masking during the 2003 SARS pandemic — have suggested that there is a strong relationship between public masking and pandemic control. Recent data from Boston demonstrate that SARS-CoV-2 infections decreased among health care workers after universal masking was implemented in municipal hospitals in late March.

SARS-CoV-2 has the protean ability to cause myriad clinical manifestations, ranging from a complete lack of symptoms to pneumonia, acute respiratory distress syndrome, and death. Recent virologic, epidemiologic, and ecologic data have led to the hypothesis that facial masking may also reduce the severity of disease among people who do become infected.[3] This possibility is consistent with a long-standing theory of viral pathogenesis, which holds that the severity of disease is proportionate to the viral inoculum received. Since 1938, researchers have explored, primarily in animal models, the concept of the lethal dose of a virus — or the dose at which 50% of exposed hosts die

(LD50). With viral infections in which host immune responses play a predominant role in viral pathogenesis, such as SARS-CoV-2, high doses of viral inoculum can overwhelm and dysregulate innate immune defenses, increasing the severity of disease. Indeed, downregulating immunopathology is one mechanism by which dexamethasone improves outcomes in severe Covid-19 infection. As proof of concept of viral inocula influencing disease manifestations, higher doses of administered virus led to more severe manifestations of Covid-19 in a Syrian hamster model of SARS-CoV-2 infection.[4]

If the viral inoculum matters in determining the severity of SARS-CoV-2 infection, an additional hypothesized reason for wearing facial masks would be to reduce the viral inoculum to which the wearer is exposed and the subsequent clinical impact of the disease. Since masks can filter out some virus-containing droplets (with filtering capacity determined by mask type),[2] masking might reduce the inoculum that an exposed person inhales. If this theory bears out, population-wide masking, with any type of mask that increases acceptability and adherence,[2] might contribute to increasing the proportion of SARS-CoV-2 infections that are asymptomatic. The typical rate of asymptomatic infection with SARS-CoV-2 was estimated to be 40% by the CDC in mid-July, but asymptomatic infection rates are reported to be higher than 80% in settings with universal facial masking, which provides observational evidence for this hypothesis. Countries that have adopted population-wide masking have fared better in terms of rates of severe Covid-related illnesses and death, which, in environments with limited testing, suggests a shift from symptomatic to asymptomatic infections. Another experiment in the Syrian hamster model simulated surgical masking of the animals and showed that with simulated masking, hamsters were less likely to get infected, and if they did get infected, they either were asymptomatic or had milder symptoms than unmasked hamsters.

The most obvious way to spare society the devastating effects of Covid-19 is to promote measures to reduce both transmission and severity of illness. But SARS-CoV-2 is highly transmissible, cannot be contained by syndromic-based surveillance alone,[1] and is proving difficult to eradicate, even in regions that implemented strict initial control measures. Efforts to increase testing and containment in the United States have been ongoing and variably successful, owing in part to the recent increase in demand for testing.

The hopes for vaccines are pinned not just on infection prevention: most vaccine trials include a secondary outcome of decreasing the severity of illness, since increasing the proportion of cases in which disease is mild or asymptomatic would be a public health victory. Universal masking seems to reduce the rate of new infections; we hypothesize that by reducing the viral inoculum, it would also increase the proportion of infected people who remain asymptomatic.[3]

In an outbreak on a closed Argentinian cruise ship, for example, where passengers were provided with surgical masks and staff with N95 masks, the rate of asymptomatic infection was 81% (as compared with 20% in earlier cruise ship outbreaks without universal masking). In two recent outbreaks in U.S. food-processing plants, where all workers were issued masks each day and were required to wear them, the proportion of asymptomatic infections among the more than 500 people who became infected was 95%, with only 5% in each outbreak experiencing mild-to-moderate symptoms.[3] Case-fatality rates in countries with mandatory or enforced population-wide masking have remained low, even with resurgences of cases after lockdowns were lifted.

Variolation was a process whereby people who were susceptible to smallpox were inoculated with material taken from a vesicle of a person with smallpox, with the intent of causing a mild infection and subsequent immunity. Variolation was practiced only until the introduction of the variola vaccine, which ultimately eradicated smallpox. Despite concerns regarding safety, worldwide distribution, and eventual uptake, the world has high hopes for a highly effective SARS-CoV-2 vaccine, and as of early September, 34 vaccine candidates were in clinical evaluation, with hundreds more in development.

While we await the results of vaccine trials, however, any public health measure that could increase the proportion of asymptomatic SARS-CoV-2 infections may both make the infection less deadly and increase population-wide immunity without severe illnesses and deaths. Reinfection with SARS-CoV-2 seems to be rare, despite more than 8 months of circulation worldwide and as suggested by a macaque model. The scientific community has been clarifying for some time the humoral and cell-mediated components of the adaptive immune response to SARS-CoV-2 and the

inadequacy of antibody-based seroprevalence studies to estimate the level of more durable T-cell and memory B-cell immunity to SARS-CoV-2. Promising data have been emerging in recent weeks suggesting that strong cell-mediated immunity results from even mild or asymptomatic SARS-CoV-2 infection,[5] so any public health strategy that could reduce the severity of disease should increase population-wide immunity as well.

To test our hypothesis that population-wide masking is one of those strategies, we need further studies comparing the rate of asymptomatic infection in areas with and areas without universal masking. To test the variolation hypothesis, we will need more studies comparing the strength and durability of SARS-CoV-2–specific T-cell immunity between people with asymptomatic infection and those with symptomatic infection, as well as a demonstration of the natural slowing of SARS-CoV-2 spread in areas with a high proportion of asymptomatic infections.

Ultimately, combating the pandemic will involve driving down both transmission rates and severity of disease. Increasing evidence suggests that population-wide facial masking might benefit both components of the response.

Disclosure forms provided by the authors are available at NEJM.org.

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1. Gandhi M, Yokoe DS, Havlir DV. Asymptomatic transmission, the Achilles' heel of current strategies to control Covid-19. N Engl J Med 2020;382:2158-60.
2. 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):e2618.
3. 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 July 31 (Epub ahead of print).
4. Imai M, Iwatsuki-Horimoto K, Hatta M, et al. Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. Proc Natl Acad Sci U S A 2020;117:16587-95.
5. Sekine T, Perez-Potti A, Rivera-Ballesteros O, et al. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. Cell 2020 August 11 (Epub ahead of print).

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