ACS Infectious Diseases

Viewpoint

COVID-19 and Other Pandemics: How Might They Be Prevented?

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Cite This: https://dx.doi.org/10.1021/acsinfecdis.0c00291 Read Online

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ABSTRACT: Pandemics such as influenza, smallpox, and plague have caused the loss of hundreds of millions of lives and have occurred for many centuries. Fortunately, they have been largely eliminated by the use of vaccinations and drugs. More recently, Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and now Coronavirus Disease 2019 (COVID-19) have arisen, and given the current absence of highly effective approved vaccines or drugs, brute-force approaches involving physical barriers are being used to counter virus spread. A major basis for physical protection from respiratory infections is eye, nose, and mouth protection. However, eye protection with goggles is problematic due to "fogging", while nose/mouth protection is complicated by the breathing difficulties associated with non-valved respirators. Here, we give a brief review of the origins and development of face masks and eye protection to counter respiratory infections on the basis of experiments conducted 100 years ago, work that was presaged by the first use of personal protective equipment, "PPE", by the plague doctors of the 17th Century. The results of the review lead to two conclusions: first, that eye protection using filtered eye masks be used to prevent ocular transmission; second, that new, pre-filtered, valved respirators be used to even more effectively block viral transmission.

The current Coronavirus Disease 2019 (COVID-19) pandemic is the most serious global pandemic in 100 years. However, in the past, there have been many other, far more deadly pandemics or epidemics, primarily, the Black Death,[1] smallpox,[1] and influenza[2], each of which killed hundreds of millions of individuals. So, what have we learned about how to control (or prevent) pandemics? While vaccinations and/or effective drugs would by definition solve the current COVID-19 problem and it is often said that these are 12−18 months away, the questions arise: what do we do "next time" when a new pandemic threatens? What can be done in the shorter term to protect healthcare workers? What smallpox, influenza, pneumonic plague, and COVID-19 have in common is that they are transmitted by a respiratory route as well as in many cases via the eye. We thus give a brief history of how viral and bacterial transmission routes were discovered, since this leads to new ways to more effectively prevent transmission.

■ COUGHS AND SNEEZES SPREAD DISEASES: 100 YEARS OF "MASKS"

On October 12, 1918, just over one hundred years ago, Doust and Lyon reported in the *Journal of the American Medical Association* the results of an investigation into the effects of face masks on infections of the respiratory tract.[3] They chose the bacterium *Bacillus prodigiosus* (now called *Serratia marcescens*, an opportunistic pathogen), and a volunteer was instructed to gargle with a suspension of the organism. Agar plates were then placed at 1, 2, 3, . . ., 10 ft, and the volunteer was instructed to talk in an ordinary conversational tone for 5 or 30 min or a loud tone for 5 min or to cough as much as possible for 5 min. The volunteer then left the room; plates were exposed for 10 min (for large droplets to settle), followed by 72 h of incubation and colony counting (which was facilitated due to the production of the red pigment, prodigiosin, by the bacterium). The results were fascinating in that they showed there was a "**4 ft danger zone** about the patient" during normal or loud speech and this extended to "**a minimum radius of 10 ft**" during coughing. These results led to the first concept of social distancing, now at ∼6 ft (2 m). About 100 years later, high-speed cameras[4,5] and laser light scattering[6] have been used to study particulate emissions, the conclusions being in accord with the century old work; that is, coughs and sneezes spread diseases and so does talking.[3−6]

In the second part of the Doust and Lyon experiment,[3] it was concluded that face masks made of coarse or medium gauze from two to ten layers did not prevent the projection of inhaled material during coughing and that "such masks are worthless, therefore, in preventing the dissemination of respiratory infections". However, "three-layer butter cloth masks were effective and should be worn in connection with respiratory diseases". This is the genesis of the use of face masks to prevent the transmission of infective droplets, carried out at the time of the Spanish flu pandemic.

In another paper, in October 1919, Hurley[7] reviewed the Doust and Lyon paper and made the following proposal: "It is a reasonable corollary to deduce from their experiments that if the infected subject **or carrier** and the noninfected person both wore three-ply butter-cloth face masks when in contact, the protection afforded the noninfected would be doubly efficient and secure. In other words, **during an influenza epidemic if everyone would, or was required to wear a face mask of that character the transmission of the infection from those in the incubation period, sick, convalescent, or from well carriers to the healthy noninfected population would be greatly minimized**". This is the first proposal for the universal use of face masks as well as an interesting comment about "well [asymptomatic] carriers".

Face masks have indeed been widely used in many parts of Asia since the earlier SARS (SARS-Cov-1) epidemic in 2002–2003 as well as in influenza outbreaks and are now being mandated in many countries outside Asia. However, as noted by Kellogg and Macmillan in 1920,[8] simple masks such as those used by Doust and Lyon are susceptible to leakages around the edges of the masks, which would reduce their efficiency in blocking virus transmission from an infected donor to an uninfected acceptor. They also estimated only an ~50% efficacy in blocking droplet transmission.[8]

More recently, N95 "respirators" have been developed that are quite effective in blocking particle inhalation. They have a very complex microstructure, and the "95" refers to the specification that such masks block 95% of the entry of 0.3 μm particles, which unfortunately means that 5% of particles are not trapped; these could be infective given that masks may need to be worn for extended time periods. The question then arises: why not make "N100" respirators that block 100% particle (virus, bacterial droplet, aerosol) inhalation? In fact, N100 respirators are made, by the 3M Company, and are designed to block 99.97% particulate inhalation[9]. So, why are N100 respirators not generally discussed? Presumably, this is due to the fact that, while N95 (or KN95) masks are in short supply, N100 masks are in even shorter supply. However, technologically, it is possible to reduce particle transmission from ~5% (N95) to ~0.03% (N100), which corresponds to a ~170× improvement in blocking particle transmission, at least via the nose and mouth. The percentage of particles that penetrate a surgical mask is very variable[10] and probably averages around 30%.

On the other hand, while N95 or N100 respirator masks are highly efficacious in blocking the intake of particles, they are far more difficult to breathe through than are face masks, leading to the desirability of a medical evaluation prior to use. The high impedance of N95/N100 respirators is considerably reduced by the incorporation of a simple "flapper" valve (Figure 1a) that reduces the work required in exhalation, albeit at a loss of much of the efficacy in trapping exhaled particles. While this is of course not a problem when the respirator's sole purpose is to trap "dust" particles, it reduces a respirator's efficiency in trapping exhaled viral/bacterial infectious droplets since they can pass straight through the valve. This has resulted in a directive prohibiting the use of valved respirators as acceptable "face coverings" for the general public in San Francisco, CA[11].

One logical solution we propose to this drawback is to simply incorporate a section of a surgical mask on the inside of the respirator mask valve as a pre-filter, Figure 1b. Unlike the use of full surgical masks for protection, in which there are inevitable leakages around the edges of the mask on inhalation and exhalation, a pre-filtered, valved respirator will provide excellent protection against both inhaled particles, droplets and aerosols, at or slightly better than the efficiency of the unfiltered respirator (since even a "closed valve" may leak slightly) as well as a major reduction in the level of exhaled particles, comparable to or better than that afforded by leaky surgical masks.

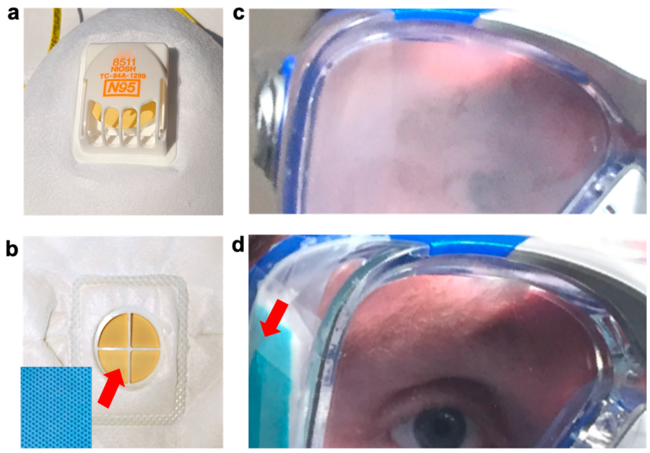

Figure 1. Filtered nose/mouth respirators and filtered eye masks. (a) Standard N95 respirator, outside view showing the valve. (b) Inside view of an N95 respirator showing the valve (yellow) and surgical mask insert (blue) to be sealed over the valve. (c) Hermetically sealed goggles showing fogging after 5 min of use. (d) A filtered eye mask (FEM) showing no fogging after 1 h of use. The FEM was made from the same goggles as in (c) but with the incorporation of a circular vent covered by a sheet cut from an N95 respirator, indicated by the red arrow, to prevent aerosolized particle entry but allow water vapor exit. (c, d) provided by David Douglas, Harvard T.H. Chan School of Public Health, and reprinted from *International Journal of Infectious Diseases* Vol. 95, David Douglas and Robert Douglas, Addressing the corona virus outbreak: will a novel filtered eye mask help? Pages 340–344 (ref 18), Copyright 2020, with permission from Elsevier.

As suggested by Hurley[7] in 1919, having both infected donors and uninfected acceptors wear masks will reduce the incidence of transmission and that incidence will be given to a first approximation by the product of the probability that a particle escapes from the donor mask multiplied by the probability that it enters the acceptor mask. For example, for the 50% efficiency face mask value suggested by Kellogg and Macmillan,[8] if the donor generates N particles in a given volume, that would by definition be reduced to $N/2$ by the donor mask, a value that would then be reduced to $N/4$ by the acceptor mask, a factor of 4 reduction from the no-mask case. For two N95 masks, the result would be on the order of $(5/100)^2 = 0.0025$ or 400×, and for two N100 masks, it would be $\sim(0.03/100)^2 = 9 \times 10^{-8}$ or $\sim 10^7\times$. For filtered, valved respirators, the effects would be less but would still be very large. However, transmission of infective particles is not just via the nose/mouth.

■ YOUR DOCTOR NEEDS GOGGLES: YOU DO TOO

In 1919, Maxcy carried out a second set of remarkable experiments using *B. prodigiosus* in a paper entitled "The transmission of infection through the eye".[12] This was carried out at the time of the third wave of the Spanish flu pandemic, and in the introduction to his paper, Maxcy stated that: "Recently the eye has received little or no attention as a factor in the transmission of acute respiratory infections. It has been disregarded in planning measures for the prevention of the spread of contagious diseases. This was especially true in the recent epidemic of influenza".

https://dx.doi.org/10.1021/acsinfecdis.0c00291
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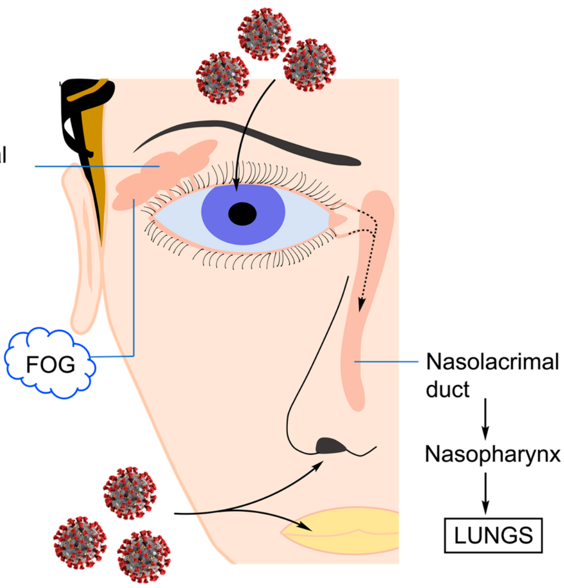

Figure 2. Illustration of the entry of viruses (or bacteria) into the respiratory system. Both viruses and bacteria can enter via the eyes as well as by the nose and mouth. In the eyes, lacrimal gland secretions and blinking sweep pathogens into the nasolacrimal duct and thence to the nasopharynx and then to the lungs. Entry into the nose leads more directly to the nasopharynx and lungs. Lacrimal gland secretions are also responsible for the fogging of hermetically sealed goggles, reducing their utility. In an infected individual, exhalation via the nose and mouth contributes to disease transmission.

Maxcy then calculated the relative importance of eye, nose, and mouth exposure to direct droplet spray (including estimates of the effect of blinking, expiration/air currents, and talking) and concluded that there was a 600 mm^2 area of eye exposure but only 100 mm^2 for the nose and very little for mouth exposure[12]. Building on the work of Doust and Lyon, Maxcy then instilled *B. prodigiosus* into one eye in each of five subjects. The results were that bacteria instilled into the conjunctival sac were recovered on a nasal swab within 5 min of the instillation. Then, after 15−30 min, bacteria were recovered (via a long wire swab) from the nasopharynx, and 24 h later, they were recovered from stool samples, just as with COVID-19. Thus, bacteria can enter the respiratory system via the eye, nasolacrimal duct, and nasopharyngeal system, as can other respiratory viruses,[13−17] as illustrated in Figure 2.

Maxcy then noted that: "The obvious means of protection is the wearing of a large lens or pair of goggles in addition to the gauze mask by those who are within range of a droplet spray from heavily infected individuals. In this connection, it is interesting to note that during the great epidemics of plague that have from time to time swept over the Old World, masking of the whole face, eyes included, has been wonderfully effective". The comment by Maxcy is remarkably prescient, and it is of interest to note the many similarities between the first personal protective equipment, "PPE", worn by the 17th Century plague doctors and the PPE used at present, Figure 3.

Thus, in the context of the current COVID-19 pandemic and for past pandemics such as influenza, pneumonic plague, and smallpox as well as for other respiratory viruses, a second transmission route exists and is via the eyes, which is of course why healthcare workers wear goggles. The problem with wearing goggles is that, if they are hermetically sealed, they very rapidly fog up, Figure 1c, while if they are ventilated (have holes), they do not protect against aerosols. The problem of fogging arises because aqueous secretions are continuously produced by the lacrimal glands, Figure 2, and in a

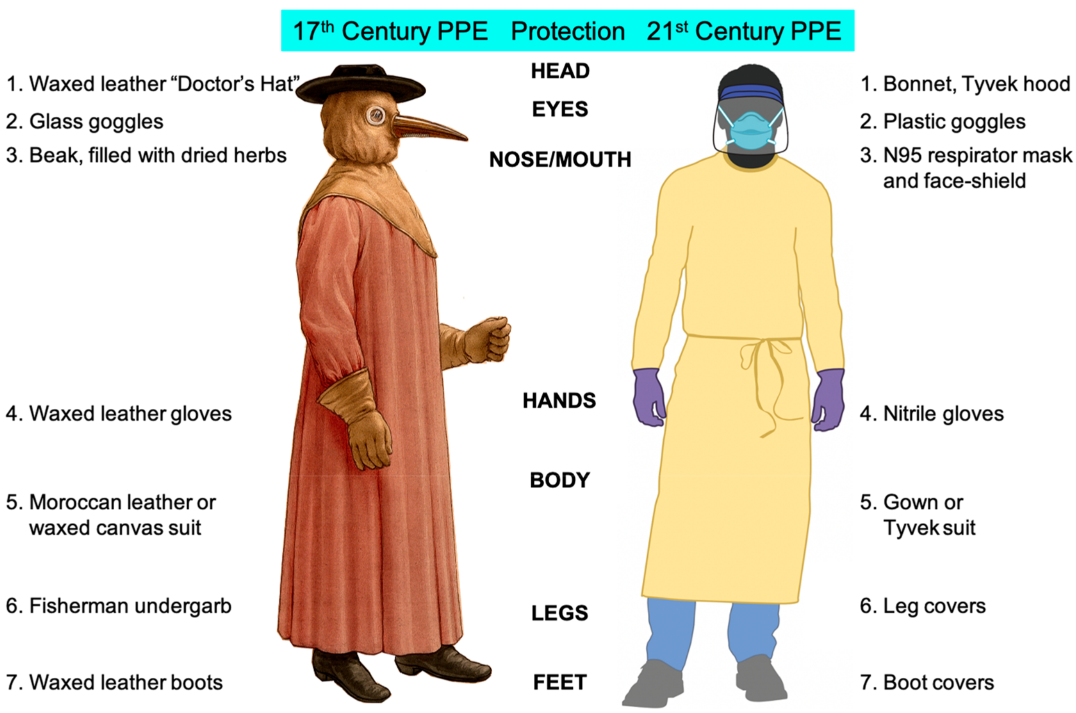

Figure 3. Comparison between the personal protective equipment, PPE, used by the 17th Century plague doctors and by 21st Century medical personnel. The plague doctor image is derived from the original image, A physician wearing a seventeenth century plague preventive costume; Wellcome Library, London, under Creative Commons license CC BY 4.0 (https://creativecommons.org/licenses/by/4.0). The 21st Century PPE image is derived from the CDC Website, https://www.cdc.gov/coronavirus/2019-ncov/downloads/COVID-19_PPE_illustrations-p.pdf.

https://dx.doi.org/10.1021/acsinfecdis.0c00291
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hermetically sealed environment, condensation occurs. One ingenious approach to solving the "foggy goggles" problem is the development of filtered eye masks, FEMs,[18] which incorporate a vent that is protected from aerosols by a filter, such as a piece of an N95 mask. Such a filtered eye mask based on (hermetically sealed, swimming) goggles was recently reported[18] in which there was a major increase in the time required for fogging, from 5 min to >1 h (Figure 1c,d), and it seems very likely that this first proof-of-principle experiment will soon be improved upon by the use of hydrophilic, anti-fog coatings, as currently used in vented goggles (which do not protect against infectious aerosolized particles).

CONCLUSIONS

During the current COVID-19 pandemic, it is clear that very large numbers of healthcare workers are being infected, and without improvements in PPE, this would likely occur in future respiratory disease outbreaks in which the ocular route is also involved. The development and use of filtered eye masks would decrease infection, and pre-filtered N100 masks would decrease infection as well as transmission. For the general public, very early use of eye as well as nose/mouth protection would again reduce the number of infected individuals, making testing, contact tracing, and isolation more feasible. However, it does appear that prompt action involving contact tracing/isolation combined with the universal use of PPE has been effective in Taiwan and Austria, at least so far, although face masks are still required in Wuhan and Taiwan, and eye protection may also be needed. What is not known is the degree to which "herd immunity" (without vaccines) will be effective in reducing overall morbidity and mortality: the Swedish Experiment, results of which are eagerly awaited.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank David Douglas, Harvard T.H. Chan School of Public Health, for providing Figure 1c,d.

ABBREVIATIONS

SARS, Severe Acute Respiratory Syndrome; MERS, Middle East Respiratory Syndrome; COVID-19, Coronavirus Disease 2019

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