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SARS-CoV-2: eye protection might be the missing key

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Remarkably, a year after the COVID-19 outbreak, we remain ineffectual against widespread community infection. Perhaps, something major is missing in our approach?

The importance of aerosols versus droplets[1] is debated—most viral transmission appears to be via virus-laden droplets, with the greatest risk in crowded, inadequately ventilated environments. Proximity to those infected poses the greatest risk. Currently, the presumed major viral invasion modalities involve inhalation or hand contamination of mucosal surfaces, despite studies to the contrary from a century ago[2] showing the importance of eyes as an influenza infection route. Ocular surface droplet deposition is greatly underappreciated as a probable, frequent route for SARS-CoV-2 transmission.[3]

An observational study, referred to in a commentary,[4] reported an apparent protective effect against SARS-CoV-2 transmission from routinely wearing spectacles for more than 8 h per day. Spectacles acting as a barrier to eye touching was hypothesised to help prevent SARS-CoV-2 transmission. We believe that a physical barrier to the deposition of virus-containing droplets is another explanation for the study findings. The commentary[4] provides an epidemiologist's caution of avoiding the inference of a causal relationship from a single observational study, yet the criteria of temporality (ie, spectacles worn before viral exposure) plus biological plausibility (ie, ocular viral transmission with spectacles as a direct barrier or indirectly against digital contamination) were met.

Eye-protective face shields have been proposed to prevent community transmission.[5] A large study[6] showed that 19% of health-care workers became infected, despite wearing three-layered surgical masks, gloves, and shoe covers and using alcohol rub. After the introduction of face shields, no worker was infected.

In his landmark 1919 study,[2] Maxcy used an atomised solution of *Serratia marcescens* as a marker to show that in adequately masked patients who had their eyes exposed, bacteria could be readily cultured from the nasopharynx. The ocular surface and its connection via the nasolacrimal duct, permits access of respiratory viruses, to the respiratory system, gut, and circulation. These viruses are more appropriately termed oculotropic.[7]

The eyes are located at a vantage point, simultaneously sensing high bandwidth information but are also exposed to the airborne risk.[3] Ocular surface area, including periocular structures, is large compared with the surface of the mouth and nares and is readily available for droplet deposition.[2] This area has been calculated to be around 10 000 mm², two orders of magnitude greater than for the nares and mouth.[3] The tear film protects the ocular surface but also provides an unrecognised vehicle for viral carriage into the nose. The most superficial lipid tear film layer is likely to attract SARS-CoV-2 by both electrostatic and lipophilic properties.[3] A seemingly paradoxical low rate of conjunctivitis and keratitis of around 12% in people with COVID-19, despite the presence of viral invasion-enabling receptors (although receptor expression is substantially lower than in the respiratory tract) as well as low tear viral detection rates,[8] could be explained by the physical tear barrier, high tear turnover rates (5–21% per min) and tear film antiviral activity.

The predominant physical barrier approach, by masking mouths and noses, provides variable protection and ease of use and comfort but could be inadequate when worn for extended periods of time. Masks serve a dual purpose of preventing droplet transmission and wearer protection. However, a 2020 meta-analysis concluded that the wearing of surgical masks in non-health-care settings was not associated with a significant reduction in acute respiratory illness incidence;[9] furthermore, there are several supportive studies.[10] In 1919 and during the great world plague epidemics, "masking of the whole face, eyes included, [had] been wonderfully effective"[2], yet the relative importance of protecting eyes remains unexplored.

Eye protection is underappreciated but still has problems. Various eye protectors might not exclude circumventing air currents, such as the human convective boundary layer. Protectors can obstruct vision, fog up, get in the way (particularly with optical instruments), are uncomfortable (hence diminished or improper use), and when worn as part of a helmet device, reduce communication. Hermetically sealed eye protectors, are generally designed for short-term or medium-term use rather than for 4–8 h intensive care unit shifts. Fogging remains a major problem,[11] due

to tear and sweat evaporation, limiting usability and compliance.

COVID-19 has brought into focus many important factors that limit personal protective equipment efficacy, including frequent failure to use eye protection. Inadequate eye protection might explain why front-line workers who, despite wearing apparently adequate gloves, gowns, and masks, still can remain at increased risk of infection.

The ocular surface can also serve as a site for prophylactic and early treatment. In the eye, angiotensin-converting enzyme 2 and associated receptors are located on the apical (rather than basolateral) cell surfaces, so are best accessed via topical (rather than systemic) treatment.[3] Any drugs applied to the ocular surface will rapidly reach the nose via the nasolacrimal ducts. Many drugs can be safely used topically in the eye, repurposed from use for other ocular conditions,[3] and, when used in this way, will reduce the risk of systemic side-effects and cost.

Thus, there is strong circumstantial evidence that person-to-person transmission can be mediated via viral-laden particles that access the eyes and tear film and are relatively quickly transmitted via lacrimal drainage to a nasopharyngeal reservoir. This pathway had been "disregarded in planning measures for the prevention of the spread of contagious diseases"[2] in 1919,and little has changed. We need to better protect the eyes, at least from droplets, by increasing the use of eye protection devices, such as face shields. The importance of a strong evidence base to any intervention is understood, yet an apparent rigorous approach, within narrow silos of knowledge, evident in this pandemic, might not have served us well. The failure to acknowledge historical precedent might also have delayed an effective response to this crisis. There is an urgent need to develop better eye protective strategies, based on the understanding of ocular interactions with the environment, and also to reconsider the potential of early topical interventions as prophylaxis.

MTC has filed patent applications in relation to treatment methods, as well as personal and slit-lamp protective devices, relevant to viral infection. Over the past 3 years, MTC has received royalties from Alcon, Dutch Ophthalmic Research Center International, and Katena Products in relation to intellectual property. MTC has received consulting fees from Allgenesis and Novartis Pharma. PJC declares no competing interests.

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