

# Plague rampant: two sides of the coin

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In 2021, SARS-CoV-2 has changed our lives permanently in some way. As ancient Chinese philosopher Lao Tzu said, 'Good fortune hides in disaster; Disaster lurks within good fortune'. In this global health crisis, we may have gained a better understanding of the body's immune mechanisms while enhancing public health.

In the early stages of the outbreak, ophthalmology manifestations related to SARS-CoV-2 were noted.<sup>1-3</sup> Ocular surface symptoms are common during COVID-19 and conjunctivitis is the primary ocular disorder associated with the disease.<sup>4</sup> However, the viral load in the conjunctival epithelium is usually low and present only in the initial phase of the SARS-CoV-2 infection.

After 1 year, immunisation against SARS-CoV-2 was rapidly introduced to limit the spread of the disease and reduce its associated morbidity and mortality.<sup>5</sup> As a novel type of vaccine, the potential efficacy of mRNA vaccines in treating different types of malignant and infectious diseases was reported.<sup>6</sup> However, the immune response and the long-term protective effects of vaccination to the SARS-CoV-2 virus remain unknown. Along with mass vaccinations, some concerns have arisen.

It is known that the cornea is an immune privilege site. However, the most frequent cause of graft failure is allogeneic rejection.<sup>7</sup> During the COVID-19 pandemic, the expression of multiple viral entry factors on human cornea was reported.<sup>8</sup> There are some case reports showed that primary SARS-CoV-2 infection might temporally associated with rejection.<sup>9</sup> The relationships between SARS-CoV-2 and cornea are peculiar and they raise some issues that are not yet fully addressed. The SARS-CoV-2 receptors ACE2 and transmembrane serine protease 2 are present in the superficial corneal, limbal and conjunctival epithelium.<sup>10-12</sup> These ocular surface epithelial cells may then act as a possible inoculation site for the virus.

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Conversely, corneal transplantation is a potential route for donor transmission of SARS-CoV-2, leading to decreased donor tissue procurement in European countries.<sup>13</sup> It should be noted that the corneal epithelium appears to be refractory to SARS-CoV-2 infection.<sup>14</sup> Last, the corneal endothelium has been shown to express the ACE2 receptor<sup>8</sup>; a finding that was not confirmed by others.<sup>15</sup>

The cytokine release syndrome (cytokine storm) observed in severe patients infected with COVID-19 consists of a disproportionate response of the immune system to the viral infection leading to the release of interleukin (IL)-1 $\beta$ , IL-6, IL-8, IL-17 and tumor necrosis factor (TNF)- $\alpha$ .<sup>16</sup> Some of these cytokines are known also involved in corneal allograft rejection.<sup>17</sup> This transplant complication has been reported associated with primary SARS-CoV-2 infection, the cytokine storm coinciding with acute corneal allograft rejection.<sup>9,10</sup>

The viral ligand of the ACE receptor is the spike protein, a membranous glycoprotein, which is associated with host range, tissue tropism and virulence. Most current COVID-19 vaccines trigger the spike protein. Although corneal transplantation rejection triggered by vaccination has been reported (mainly after the influenza vaccine), it is considered a rare event. The present report of two cases of endothelial corneal allograft rejection following immunisation with SARS-CoV-2 mRNA vaccine raises<sup>18</sup> the issue of a relationship between the vaccine which elicits an immunological response to the spike protein, the expression of the ACE2 receptor by corneal endothelial cells and the rejection reaction targeting the corneal endothelium. It is worth thinking that a recent study into COVID-19 vaccine response, which includes mRNA vaccine in 187 solid organ transplant recipients, did not report any episodes of acute rejection.<sup>19</sup> Is it possible that the host antibody response in days post vaccination and antibody against SARS-CoV-2 may initiate the allogeneic response which results in graft injury? In the postpandemic era, we need a deeper understanding of corneal immune mechanisms. With advancing national vaccination programmes we can expect an increase in similar clinical case reports in the future, especially in the case of corneal

transplantation, that may change our current perceptions.

Back to the present, the world epidemic is not under satisfactory control, and we are still at a point when plague is rampant. The Oxford–AstraZeneca vaccine causes unusual thromboembolic events similar to clouds above us. Although some studies have suggested that vaccination and thromboembolic events are not related,<sup>20</sup> we need more relevant studies to prove it. As ophthalmologists, we should be alert for possible postvaccination rejection and report cases to the relevant authorities and professional journals. At the time of earliest reports of ophthalmic complications such as corneal allograft rejection reported in this issue by Phylactouet *al*,<sup>18</sup> proof of a causal relationship with vaccination can be difficult. Similar to adverse reactions to drugs, recognition of a true association depends on subsequent reporting of similar complications by colleagues.

**Contributors** LMH and VMB conceived of the presented work. LMH drafted and VB critically revised the manuscript. LMH and VB both approved the final version of the manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; internally peer reviewed.

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**To cite** Heindl LM, Borderie VM. *Br J Ophthalmol* 2021;**105**:891–892.  
Published Online First 27 May 2021



► <http://dx.doi.org/10.1136/bjophthalmol-2021-319338>

*Br J Ophthalmol* 2021;**105**:891–892.  
doi:10.1136/bjophthalmol-2021-319687

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