Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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SARS-CoV-2 in semen: Potential for sexual transmission in COVID-19

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Direct contact with respiratory droplets serves as a major mechanism for efficient human-to-human transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections on a pandemic scale. Although the transmission of SARS-CoV-2 occurs predominantly through respiratory droplets, the virus has also been isolated from blood and fecal samples of patients with coronavirus disease of 2019 (COVID-19) indicating that the infection may at times be systemic [1]. This has raised concerns over the shedding of SARS-CoV-2 through other body fluids, including semen, thereby acting as an alternative mode of transmission. Li et al. (2020) have reported that the semen collected from patients with COVID-19 had oligozoospermia and increased levels of leucocytes [2]. Moreover, there was also an increase in the seminal levels of tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1). Further, the impairment of spermatogenesis can be attributed to the elevated immune responses in patients with COVID-19. The occurrence of autoimmune orchitis in some patients with COVID-19, confirms the same [2].

SARS-CoV-2 enters the target host cell via angiotensin-converting enzyme 2 (ACE2). Single-cell transcriptome analysis has pointed out that both ACE2 and transmembrane serine protease 2 (TMPRSS2) are expressed at lower levels in human testes than that in the tissues of respiratory system [3]. However, among the different cell-types present within the testis, ACE2 receptors are enriched in spermatogonia, Sertoli, and Leydig cells indicating potential vulnerability to SARS-CoV-2 infection [4]. Nevertheless, the expression of ACE2 receptors in these cells alone is not sufficient to conclude that the testis is a site for SARS-CoV-2 infection. At this point of time, it is still unclear whether SARS-CoV-2 is capable of crossing the blood-testis barrier [5]. In addition to the testis (sperm cells and Sertoli or Leydig cells), the available data on *ACE2* and *TMPRSS2* expression suggest that SARS-CoV-2 might infect accessory sex glands such as prostate or seminal vesicles and the urinary tract of the male urogenital system [5].

The presence of SARS-CoV-2 in semen has been investigated mainly in recovering patients. It has been shown that SARS-CoV-2 is undetectable in the semen of recovering patients with COVID-19 after one month of diagnosis, indicating that sexual transmission is not possible from convalescent patients [3]. Similar results were obtained when the presence of SARS-CoV-2 RNA was investigated in the semen of patients with COVID-19 in acute stage with a positive nasopharyngeal swab test [6]. Guo et al. (2020) have investigated the presence of SARS-CoV-2 RNA in the semen samples of patients with COVID-19 in acute and recovery phases [4]. However, the SARS-CoV-2 RNA was found to be undetectable in both the cohorts of patients with COVID-19. Holtmann et al. (2020) have performed qualitative analysis of semen samples collected from active as well as recovered patients with COVID-19 and compared the same with that of healthy individuals (control) [7]. The results revealed that SARS-CoV-2 RNA was undetectable in any of the samples collected from recovered and acute patients with COVID-19. However, the sperm quality was found to be impaired in patients with moderate infection. As a result, it can be implied that the mild form of COVID-19 does not affect the functions of testis and epididymis [7].

In contrast, Li et al. (2020) have reported the presence of SARS-CoV-2 in the semen samples collected from six patients (out of 38 patients) with COVID-19, including two recovering individuals [8]. The findings of this study have re-opened the discussion on possible viral shedding in semen and sexual transmission of COVID-19. Li et al. (2020) have also hypothesized that SARS-CoV-2 transmission to the male reproductive tract may occur due to the imperfect blood-testes/deferens/epididymis barrier associated with the systemic and local inflammation [8]. They further stated that the virus may persist in the male reproductive system because of the privileged immunity status of the testes. However, the study had several limitations that might have compromised the findings and the conclusions made. These limitations include a very small sample size (38 patients) and lack of subsequent follow-up that could have helped in confirming the results. Furthermore, the diagnosis was performed using qualitative RT-PCR but lacked details regarding the limits of detection and threshold values [5]. The authors also failed to provide information on the method of semen collection. This data would have helped to eliminate the possibility of contamination of semen samples with SARS-CoV-2 RNA fragments during sample collection either manually or from respiratory droplets.

SARS-CoV-2 can also be detected in semen if the virus can infect the accessory sex organs, particularly the prostate gland [5]. This hypothesis, if found true, could provide an explanation for the presence of

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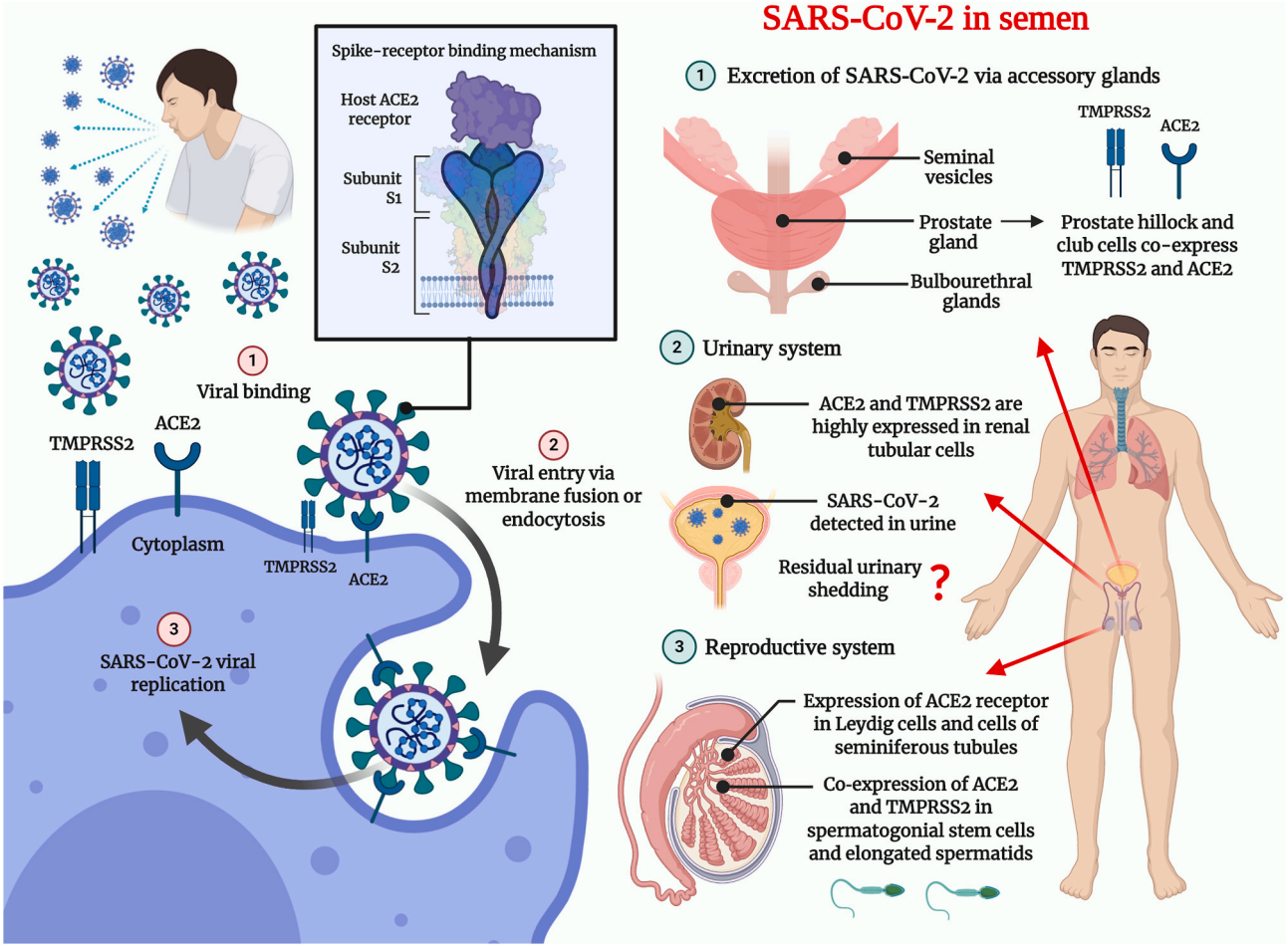

Fig. 1. Mechanism of viral entry and possible scenarios for SARS-CoV-2 in semen. SARS-CoV-2 infection is dependent on both angiotensin-converting enzyme 2 (*ACE2*) and transmembrane serine protease 2 (*TMPRSS2*) expression for the entry of the virus into the host cell.

SARS-CoV-2 in the semen as reported by Li et al. (2020) [8]. Another possible scenario is the presence of SARS-CoV-2 in semen as a consequence of the residual urinary shedding. This is a valid hypothesis, as the urinary and genital tract are overlapped in males at the distal end [5]. Therefore, further studies are required in a larger cohort to identify the mechanism of possible viral shedding via semen (Fig. 1).

Respiratory secretions contribute more risk of SARS-CoV-2 transmission between partners during sexual contact than the semen [9]. Therefore, the available data indicate that SARS-CoV-2 is not a sexually transmitted virus. Even if SARS-CoV-2 can be transmitted via semen, sexual transmission will only have a negligible impact, as the virus can predominantly transmit between partners through the respiratory route. However, further studies are necessary to evaluate the impairment caused by SARS-CoV-2 on spermatogenesis, reversibility of the impairment, and development of potential therapeutics.

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All the authors substantially contributed to the conception, design, analysis, and interpretation of data, checking, and approving the final version of the manuscript, and agree to be accountable for its contents.

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