



Alterations of the male and female reproductive systems induced by COVID-19

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Summary A variety of pneumonia cases of unknown cause emerged in China in December 2019. A new virus belonging to the *Coronaviridae* family, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19). Within a few days, COVID-19 became a pandemic disease. This review aimed to investigate the possible implications of COVID-19 for human reproductive systems, as in previous studies ACE2 was highly expressed in some organs of these systems, such as the testicles. A total of 41 publications were found in the specialized databases and, after selection, 7 articles were used to build this study. Our results showed that the fever caused by COVID-19 has a negative effect on spermatogenesis, there is high expression of ACE2 in the testicles and in the uterine tubes and there is a higher level of transmembrane protease serine 2 (TMPRSS2), which is also responsible for the entry of the virus into the cell. Moreover, it was noted that there was viral genetic material in the semen and an increase in the serum concentration of luteinizing hormone (LH) in men and women, which

could cause hypogonadism. Thus, we conclude that there is the possibility of infection and malfunction in the reproductive organs as well as the plausibility of sexual transmission of this disease. Further analysis must be carried out to prove the effects of COVID-19 on the human reproductive systems.

Keywords Infertility · Pandemic · Reproduction · Virus

Introduction

The coronaviruses are a large family of viruses belonging to the family *Coronaviridae*, subfamily *Coronavirinae* and order *Nidovirales*, known since 1960 for causing respiratory infections in humans and animals [1, 2]. The newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the seventh of the family to be described associated with diseases in humans [3]. These pathogens are seen under electron microscopy as circles with spikes that end in small droplets that appear on its surface, in a shape similar to a crown [4]. The SARS-CoV-2, the agent responsible for the coronavirus disease 2019 (COVID-19), is composed of a single strand of positive sense RNA (ribonucleic acid) surrounded by a lipoprotein viral envelope, in which the spike (S) protein, activated by a cell protease, is arranged. The protein S mediates viral entry into target cells by binding to a cell receptor, the angiotensin-converting enzyme 2 (ACE2). The SARS-CoV-2 makes use of Serino Protease Cell TMPRSS2 to initiate protein S [5–8].

The COVID-19 is an acute disease, which has an incubation time in the human body of around 4.1–7.0 days, with an average of 5.2 days, with a 95% confidence interval (CI: 4.1 to 7.0) [9]. The mode of transmission is caused by coughing, sneezing, sputum, contaminated fluids and possibly patient feces

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[10, 11]. Transmission can occur through contamination of the hands, usually when after contamination the susceptible individual puts them in contact with the oral, nasal and/or ocular mucosa [12, 13].

A series of pneumonia cases with no known cause in Wuhan City, Hubei Province China, was reported to the World Health Organization (WHO) in December 2019. The declaration of being an international public health emergency came on 30 January 2020 and a pandemic on 11 March. The total number of cases rose rapidly and on 16 March 2020 the 167,511 confirmed cases in more than 140 countries exceeded the numbers of cases existing in the Chinese territory, considering Europe as the new epicenter of the pandemic [14, 15]. On 21 May 2020, the Worldometer data and monitoring website recorded 5,137,481 confirmed cases worldwide, with 2,049,806 recovered and 331,499 deaths [16].

The SARS-CoV-2 may be associated with changes in several organs and systems [17]. Some studies have shown that the respiratory, cardiovascular, digestive and urinary systems are targets of infection with the new coronavirus. In addition, human reproductive systems and functions have been reported as potential targets of infection [18]. The patients of senile age and/or with comorbidities are susceptible to infection and prone to the most severe forms, which may be associated with acute respiratory distress syndrome (ARDS) and with a so-called cytokine storm. They may, therefore, present a worse prognosis for the disease [19].

In a review [20] a variety of studies were found that indicated the presence of abnormal kidney function or even kidney damage. After analysis the results showed that ACE₂ is expressed in different amounts in each human organ and has high expression in renal tubular cells, Leydig cells and seminiferous tubules in the testes. It was argued that SARS-CoV and SARS-CoV-2 share the same ACE₂ receptor, that previous research showed that orchitis is a complication of SARS infection and that spermatogenesis can be affected. As a result, SARS-CoV-2 can cause infertility, a problem that requires a lot of attention especially among young men. In addition to the potential damage generated by the virus, the toxicity levels of antiviral drugs to the kidneys must be considered.

Similarly, it can occur in the female reproductive system [21] addressed the availability of ACE2 in host cells of the female reproductive system, such as in the ovaries, uterus, vagina and placenta. Furthermore, based on previous studies Jing et al. [21] listed some functions of the enzymes for which ACE2 modulates levels of angiotensin 2 and angiotensin (1-7). Due to these functional characteristics, SARS-CoV-2 can cause disturbance in female reproductive functions through the regulation of ACE2. Thus, this study focused on analyzing the possible effects of SARS-CoV-2 and the disease caused by it (COVID-19) on human male and female reproductive organs.

Methodology

This is a systematic review of the effects of the SARS-CoV-2 virus and the disease for which it is responsible, COVID-19, for the human male and female reproductive systems.

Search strategy: to conduct this review study, PubMed, Bireme and Scopus databases were searched using the specific descriptors: “genitalia”, “coronavirus infection” and “2019-nCoV”, combined with each other and with Boolean operators. There was a language restriction in the search for studies for the English language and time, considering articles published between December 2019 and May 2020 and that addressed the proposed topic. Reading the abstracts and references was recommended to search for potentially relevant studies.

Inclusion criteria: studies that were relevant to the construction of this work and related to the effects of COVID-19 on the organs of the human male and female reproductive systems were included. Interviews, studies that addressed the correlation between COVID-19 and STDs (Sexually Transmitted Diseases) and studies that do not provide sufficient data for the preparation of the work and were not related to the topic, were excluded.

Data extraction: the use of a standard form consisting of the following topics was established: first author and year of publication, title of work, methodology used, results found and conclusion of studies [22].

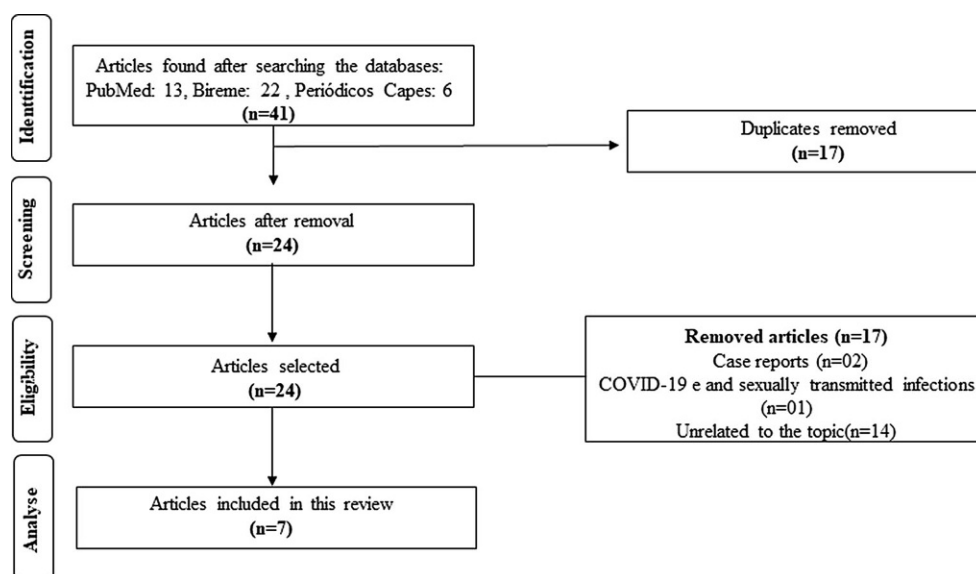
Results

The bibliographic search resulted in 41 published articles. Of these 17 were excluded due to duplication in the bibliographic databases, 17 studies were not considered for this review as they did not fit the topic in question. The remaining 7 articles published in 2020 were used for this production, which presented the possible implications of SARS-CoV-2 in the male and female reproductive systems (Fig. 1). These articles are best described in Table 1, which contains the titles of the article, name of the first author, date of publication, methodology applied in the study and the main conclusions.

Discussion

The importance of this review is based on demonstrating, through data from the literature, the possible changes in the human reproductive system caused by COVID-19 and in this way motivating research on the topic addressed. The infectious disease caused by the new coronavirus has spread rapidly all over the world causing thousands of deaths, affecting the health system and the global economy, which could cause a drop in the world gross domestic product (GDP) from 2.9% to 2.4% [11, 27]. According to the

Fig. 1 Flow diagram: identification, screening, eligibility and analysis of studies included in the literature review



results found, the literature presents evidence that the pathogen that causes this disease affects several systems of the human organism, including the reproductive system.

According to Segars et al. [25] it was noted that the fever caused by COVID-19 negatively affects spermatogenesis, decreasing the concentration of sperm and impairing the mobility of these cells. An experimental study carried out in mice reported that hyperthermia causes serious damage to the sperm formation process, such as damage to the head and tail. The animals were divided into groups and subsequently exposed to different temperatures (20 and 36°C). In view of the results, it was possible to observe that the mice exposed to a high temperature had higher testicular weight, lower concentration of gametes, increased diameter and loss of seminiferous tubule epithelium in addition to lower sperm motility. Furthermore, it has been noted that high temperatures damage sperm chromatin and cause sperm damage in its various stages of development [28].

The SARS-CoV-2 virus is known to use ACE2 receptors to enter human cells; however, TMPRSS2 expression is also a target of the virus to infect human cells [25, 26]. Studies reported that it is possible to identify ACE2 in the male and female reproductive systems, having a greater expression of this enzyme in testicular cells, mainly in Leydig cells, spermatogonia and Sertoli cells [20, 23, 26]. In this context, an experiment that proposed to investigate the level of expression of ACE2 and TMPRSS2 in cells of different organs of the human systems, using the scRNA-seq data, demonstrated a significant proportion of these enzymes in human testicles. Based on the results, it was possible to group the organs with the highest risk of being affected by the virus. Among them are the lungs and testicles with the highest expression of ACE2. The lungs, large intestine, fallopian tubes and

nasal airways, on the other hand, showed greater expression of TMPRSS2. Thus, it is possible to verify that the organ that has the highest risk of suffering injury by SARS-CoV-2 is the lungs. Then, with a high level of injury comes the testicles, followed by the organs of the digestive system, brain and heart. It has also been reported that there is a low expression of ACE2 in cells of the ovary and uterus [17, 21] demonstrated, through GeneCards that there is a significant presence of ACE2 receptors in ovarian cells, indicating that the organ may be a potential target for COVID-19.

The presence of ACE2 was verified in sperm cells through immunohistochemistry, concluding again that the testes may be the target of infection by the new coronavirus. This same study conducted a search of 112 patients diagnosed with COVID-19, whose objective was to analyze whether they had any symptoms in their reproductive organs. Based on this 3 of these patients with severe COVID-19, presented with orchidoptosis for 3 days. Then, a screening was carried out for the presence of SARS-CoV-2 nRNA in the semen of 17 patients in need of fertility and 9 showed positive results, demonstrating the presence of the genetic material of the virus in the semen [24].

Liu et al. [26] reported in their studies that patients with SARS-CoV-2 had a higher concentration in serum levels of luteinizing hormone (LH). The LH is active in the fertility of men and women acting on the gonads, assisting in the production of sex hormones and gametes [29]. In high quantities, LH can lead to testicular dysfunction and changes in testosterone concentration [30]. Thus, it was concluded that the virus can cause the malfunction of the reproductive glands (hypogonadism). A search for expression of ACE2 in primordial germ cells through tissues of the testicles of male donors was also carried out. During the experiment, ACE2 expression was compared in two healthy patients with different ages (30 and 60 years old) and

Table 1 Characteristics of studies included in this literature review

Author and year	Title	Methodology	Reported results	Conclusion
Fan et al., 2020 [20]	ACE2 expression in kidney and testis may cause kidney and testis damage after 2019-nCoV infection	Review of literature	"We reviewed the latest 3 studies focused on the clinical features of patients with abnormal renal function or kidney damage. In these 3 cohorts (with 6, 99 and 41 patients each study), two of them suggest that about 3–10% of patients infected with 2019-nCoV had abnormal renal function, including elevated creatinine or urea nitrogen. Moreover, 7% of patients experienced acute renal impairment. About the mechanism of abnormal renal function, we found in the CCLE and GTEx portal that the ACE2 mRNA expression level is relatively higher in kidney cells, especially the expression of ACE2 in renal tubular cells, according to the Human Protein Atlas portal. We also found that the protein and mRNA expression of ACE2 in the testes is almost the highest in the body. Both cells in seminiferous ducts and Leydig cells showed high ACE2 expression level." [20]	"Our study demonstrated the high expression of ACE2 in kidney and testicular tissue and facilitated the understanding of the mechanisms of abnormal renal function and kidney damage in 2019-nCoV-infected patients. Our findings also suggest the patient cares regarding the possible occurrence of orchitis. Follow-up and evaluation of the reproductive functions may be necessary in recovering male SARS patients, especially the young male patients." [20]
Wang et al., 2020 [23]	scRNA-seq profiling of human testes reveals the presence of the ACE2 receptor, a target for SARS-CoV-2 infection in spermatogonia, leydig and sertoli cells	Meta-analysis	"The total of 16,632 testicular cells was identified in nine major cell clusters (spermatogonia, early spermatocytes, late spermatocytes, round spermatids, elongated spermatids, endothelial cells, Sertoli and Leydig cells and monocytes) based on the uniform manifold approximation and projection (UMAP). The RNA expression profile of ACE2 was analyzed at single-cell resolution to determine the specific cell types expressing ACE2. The spermatogonia and Leydig and Sertoli cells' clusters demonstrated high expression of ACE2. Early and late spermatocytes, spermatids and other somatic cells had very low expression levels of ACE2. The expression of transmembrane serine protease 2 (TMPRSS2), which is used for viral spike (S) protein priming, was concentrated and spermatogonia and spermatids. Thus, TMPRSS2 expression in spermatogonia and ACE2 expression in spermatogonia and Leydig and Sertoli cells suggest a high potential of SARS-CoV-2 infection in human testes. The GSEA results suggest that male germ cell specific genes and genes that are collectively involved in spermatogenesis are compromised in ACE2 positive cells. Therefore, SARS-CoV-2 may directly target ACE2-positive spermatogonia and disrupt spermatogenesis. Moreover, SARS-CoV-2 may replicate and transfer through cell-cell junctions and, in ACE2 positive Leydig and Sertoli cells, there is a lower potential to support spermatogenesis." [23]	"By analyzing the expression pattern of ACE2 in adult human testes at single-cell transcriptome resolution, we found that ACE2 is primarily expressed in spermatogonia and Leydig and Sertoli cells in the human testis. ACE2-positive spermatogonia expresses a higher number of genes associated with viral reproduction and transmission, and a lower number of genes related to spermatogenesis compared to ACE2-negative spermatogonia. ACE2-positive Leydig and Sertoli cells express higher genes involved in cell-cell junction and immunity, and lower genes associated with mitochondria and reproduction. These findings suggest that the testis is a high-risk organ vulnerable to SARS-CoV-2 infection that may result in spermatogenic failure. Our study provides bioinformatics evidence that the testis may be potentially vulnerable to SARS-CoV-2 infection. These investigations suggest that the reproductive functions should be followed and evaluated in recovered COVID-2019 male patients." [23]
Ning et al., 2020 [24]	Effects of 2019 novel coronavirus on male reproductive system: a retrospective study	Retro-spective study	"The dataset from GTEx suggested that the mRNA expression level of ACE2 is relatively higher in the small intestine and testis than in other organs. Furthermore, a dataset from the HPA revealed the presence and relatively high level of ACE2 protein in the testis. Meanwhile, immunohistochemistry (IHC) data from the HPA showed the presence of ACE2 protein in the testis, mainly in spermatogenic cells. These results suggested that 2019-nCoV infection may cause testis injury. The study population included 112 male hospitalized patients infected with 2019-nCoV whose median age was 55.5 years (range, 23–83 years), 40 (35.7%) patients were classified as mild COVID-19 and 72 (64.3%) were classified as severe COVID-19. Signs and symptoms, including testicular pain, orchidopositis, scrotal swelling, testicular enlargement and testicular tenderness were related on the day of hospital admission for all male patients. The semen analysis of 17 male COVID-19 patients (the median age was 35 years) shows that 52.9% (9 patients) remained positive for 2019-nCoV in the semen according to the throat swab analysis and 47.1% became negative. The median time from onset of COVID-19 to semen detection was 27 days (range, 12–64 days)." [24]	"The online datasets indicated the potential impairment of the male reproductive system by 2019-nCoV. However, this group of cases suggested that male patients have few reproductive symptoms and signs, and 2019-nCoV was not present in the male reproductive system of patients with confirmed COVID-19. In view of the potential impairment, the long-term follow-up for male COVID-19 patients with fertility needs is of great significance." [24]

Table 1 (Continued)

Author and year	Title	Methodology	Reported results	Conclusion
Qi et al., 2020 [17]	The scRNA-seq expression profiling of the receptor ACE2 and the cellular protease TMPRSS2 reveals human organs susceptible to COVID-19 infection	Meta-analysis	"In the respiratory system, at the lung, AT2 cells contain an average of 0–79% ACE2-expressed cells across 8 samples and the expression levels of ACE2 and TMPRSS2 are high in the AT2 cells. The nose contains ACE2-expressed and TMPRSS2-expressed cell clusters, which have the ratios of ACE2-expressed all over 0–79%. Thus, the nose is identified as the high-risk organ. In the digestive system, the primordium cells from the gall bladder contain 2–6% TMPRSS2-expressed cells and 2–2% ACE2-expressed cells, which means the gall bladder is vulnerable to the COVID-19 infection. Moreover, small and large intestines and esophagus are identified as high-risk organs. In the nervous system, the results show that ACE2 is expressed in the oligodendrocyte precursor cells (1–6%) and astrocytes (1–9%) of the substantia nigra and cortex with a high level, and TMPRSS2 is expressed as well. Therefore, the substantia nigra and cortex are predicted as high-risk tissues, and the brain is identified as high-risk organ. In the reproductive system, the fallopian tube is identified as a high-risk organ (the ratios of the TMPRSS2-expressed cell and the ACE2-expressed cell are 26–5% and 1–4% respectively). The testis is also identified as a high-risk organ because of the high expression level of TMPRSS2 and ACE2. In the circulatory system, the cardiomyocytes and cardiovascular progenitor cells from heart contain 6–6% and 12–5% ACE2-expressed cells respectively, and the TMPRSS2 is expressed in both cell clusters as well. Consequently, the heart is considered as a high-risk organ. In the urinary system, the kidney scRNA-seq data show high ACE2 and TMPRSS2 expression levels in the nephron epithelial cells, epithelial cells, endothelial cells and mesangial cells. Particularly, the ratios of TMPRSS2-expressed are 10–7%, 9–6%, 12–8% and 14–5% respectively, and the ratios of ACE2 expressed are 2–7%, 2–7%, 2–7% and 3–0% respectively. The organs from the endocrine, motor and immune systems do not show high ACE2 and TMPRSS2 expression levels." [17]	"Based on TMPRSS2 expression level, we grouped the susceptible organs into three risk levels. The lung, large intestine (colon and rectum), fallopian tube, and nose (nasal airway epithelium) are the most susceptible organs with TMPRSS2-expressed ratio over 20%, and the result indicates the SARS-CoV-2 mainly attacks the respiratory system, the digestive system and the reproductive system. The kidney, small intestine (duodenum and jejunum) and testis are susceptible organs with moderate risk. In addition, the esophagus, gall bladder, brain (substantia nigra and cortex) and heart are identified to be the potentially susceptible organs." [17]
Segars et al., 2020 [25]	Prior and novel coronavirus, COVID-19, and human reproduction: what is known?	Review of literature	"Seventy-nine reports formed the basis of the review. Coronavirus binding to cells involves the S1 domain of the spike protein to receptors present in reproductive tissues, including angiotensin converting enzyme-2 (ACE2), CD26, Ezrin and cyclophilins. SARS-CoV1 may cause severe orchitis leading to germ cell destruction in males. Reports indicate decreased sperm concentration and motility for 72–90 days following COVID-19 infection. Gonadotropin-dependent expression of ACE2 was found in human ovaries, but it is unclear whether SARS-CoV-2 adversely affects female gametogenesis. Evidence suggests that COVID-19 infection has a lower maternal case fatality rate than SARS or MERS, but anecdotal reports suggest that infected, asymptomatic women may develop respiratory symptoms postpartum. COVID-19 infections in pregnancy are associated with preterm delivery. Postpartum neonatal transmission from mother to child has been reported." [25]	"COVID-19 infection may adversely affect some pregnant women and their offspring. Additional studies are needed to assess effects of SARS-CoV-2 infection on male and female fertility." [25]
Liu et al., 2020 [26]	Single-cell transcriptome analysis of the novel coronavirus (SARS-CoV-2) associated gene ACE2 expression in normal and non-obstructive azoospermia (NOA) human male testes	Experimental study	"We found that ACE2-expressed cells existed in almost all testis cell types and Sertoli cells had highest expression level and positive cells ratio. Moreover, we also found that the level of ACE2 expression decreased with the increase of age and that Sertoli cells might be more vulnerable to SARS-CoV-2 infection. In addition, we discovered that the ACE2 positive cells had high expressions of stress response and immune activation-related genes. Analyzing the TMPRSS2 expression, we noted that almost all the cell types had TMPRSS2-expressed cells except for the S4 and tMq (testicular macrophages) groups. The spermatogenesis-related genes were significantly decreased in NOA Sertoli cells." [26]	"Our study made a deep analysis to explore the possible COVID-19-related gene expression in different testicular cell types. We also analyzed ACE2 expression in three NOA patients (with and without spermatogenic cells). Our findings allow better understanding of the potential risks of SARS-CoV-2 infection in different testis cell types and the results may provide more insights into the study of the effects of ACE2 on male infertility. More robust evidence still needs clinical and experimental research." [26]
Jing et al., 2020 [21]	Potential influence of COVID-19/ACE2 on the female reproductive system	Review of literature	"We analyzed ACE2 data from the GeneCards database and found that ACE2 is most abundantly expressed in the ovary. In the meantime, data obtained from Bgee showed that the expression level of ACE2 in oocytes is relatively high. Therefore, the ovary and oocyte might be potential targets of 2019-nCoV. The Human Protein Atlas and the GeneCards confirm the presence of ACE2 in the uterus and vagina. ACE2 is widely expressed in human placenta and ACE2 reaches the highest level in early gestation. According to the GeneCards, the expression of ACE2 in the placenta is greater than that detected in the lung, suggesting a possibility of viral infection of the placenta. Additionally, the Human Protein Atlas and GeneCards database showed the presence of ACE2 in female breasts. A study claimed that 1 of 3 samples of breast milk was positive for 2019-nCoV in nucleic acid testing indicating the chance of transmission through breastfeeding." [21]	"2019-nCoV may infect the ovary, uterus, vagina and placenta through the ubiquitous expression of ACE2. Moreover, 2019-nCoV/ACE2 may disturb the female reproductive functions, resulting in infertility, menstrual disorder and fetal distress." [21]
ACE2 angiotensin-converting enzyme 2				

a greater presence of this enzyme was observed in the 30-year-old patient, demonstrating that the presence of ACE2 may be related to age, decreasing during adulthood [26]. A study sought to justify the ancestry of SARS in young people and aimed to relate ACE2 as a viral receptor and age. The research was carried out with young and old rats and at the end it was possible to observe that in the older rats, the expression of the enzyme was significantly decreased and that the syndrome can affect the young age group [31]. Thus, SARS-CoV-2 may cause greater reproductive harm in younger people.

Conclusion

Therefore, it was noted that SARS-CoV-2 receptors, such as ACE2 and TMPRSS2, are found in organs of the various systems of the human body. Thereby, through COVID-19 studies and symptomatology it is possible to highlight that the respiratory system, which has a large expression of the viral receptors, is the most affected. In this perspective, our review found that the human reproductive system also has a significant expression of ACE2 and TMPRSS2, demonstrating a possible infection in the primordial germ cells. This cellular invasion causes a malfunction of the reproductive glands and a possible alteration in the gametes; however, there must be more analytical studies to prove the action of COVID-19 in the reproductive system and a possible transmission of the disease through sex.

Conflict of interest P.R. Carneiro Gomes, M.D. Rodrigues da Rocha, F.A. da Rocha Coelho, J.A. Sousa Pinho de Lira, R.R. de Sousa Carmo, H.M. Silva Nascimento, S. Marques de Oliveira, W. Rodrigues da Silva, E.H. Pereira Alves, A. dos Santos Carvalho, R. Galdino Medeiros and D.F. Pereira Vasconcelos declare that they have no competing interests.

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