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Vaccination and treatment options for SARS-CoV2 infection affecting lactation and breastfeeding

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ABSTRACT

The COVID-19 pandemic has posed considerable challenges to the health of lactating individuals. Vaccination remains one of the most important strategies for prevention of moderate to severe COVID-19 infection and is associated with protective benefits for lactating individuals and their breastfed infants with overall mild side effects. The current recommendations for COVID-19 treatment in lactating individuals includes remdesivir and dexamethasone for hospitalized patients and Paxlovid® (nirmatrelavir + ritonavir) as outpatient treatment in those with mild disease. As the pandemic continues to evolve with new COVID-19 variants, alternative therapeutic options are potentially needed, and it is critical to include lactating individuals in research to evaluate the safety and efficacy of COVID-19 treatment options in this population.

1. Introduction

COVID-19 infection during pregnancy increases the risk of adverse obstetric and neonatal outcomes, such as birthing parental death, admission to intensive care, preterm birth, stillbirth, neonatal mortality, or neonatal admission to intensive care [2]. Since the start of the COVID-19 pandemic, there have been several advances in the development of vaccination and treatment strategies for COVID-19; however, the vast majority of clinical trials evaluating these strategies have excluded pregnant and lactating individuals [3]. Despite the initial lack of clinical trial data, the accumulation of safety data in pregnant individuals since the authorization of COVID-19 vaccines support recommendations for their use during pregnancy [4–6]. As of January 14, 2023, almost 72% of pregnant people aged 18–49 years had completed the primary series of COVID-19 vaccines before or during pregnancy [7]. Individuals who defer primary or booster vaccination during pregnancy may also have concerns about the risks and benefits of vaccination or treatment while breastfeeding in the postpartum period.

Breastfeeding is critically important for optimal birthing parent and infant health. Birthing parents who do not breastfeed have higher rates of breast and ovarian cancers, cardiovascular disease, and diabetes than those who breastfeed. Infants who are not breastfed had higher risk of infectious diseases in early childhood as well as longer-term adverse health outcomes, including leukemias, inflammatory bowel disease, and diabetes [8,9].

Early in the COVID-19 pandemic, the American Academy of Pediatrics (AAP) recommended separation of mothers with SARS-COV2 infection from their newborns [10,11]. While exclusive human milk feedings with expressed breast milk were recommended, this arrangement proved not to be attainable for most dyads, and reports of breastfeeding outcomes with this approach were suboptimal [12–14]. Advancements in the availability of vaccination and treatment options provide opportunities to promote health. An understanding of the risks and benefits of various options is needed to adequately counsel families. Below we summarize recommendations on vaccination and treatment of COVID-19 during lactation.

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Abbreviations

CDC	Centers for Disease Control and Prevention.
COVID-19	Coronavirus disease of 2019.
FDA	United States Food and Drug Administration.
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2.
Box	Dr. Hale's lactation risk categories for medication use while breastfeeding [1].
L1	Compatible.
L2	Probably Compatible.
L3	Probably Compatible.
L4	Potentially Hazardous.
L5	Hazardous.

2. Vaccination in lactating individuals

2.1. Overview of current recommendations

Vaccination against COVID-19 is broadly recommended for all people who are at least six months of age or older based on existing evidence supporting the safety and efficacy of the vaccines. Though pregnant and lactating adults have been largely excluded from all COVID-19 vaccine trials, the available evidence involving lactating individuals indicates important benefit and minimal risk to both the vaccinated person and their offspring. Vaccination against COVID-19 during lactation is overwhelmingly supported by recommendations from the Centers for Disease Control and Prevention (CDC) [15] and at least 20 medical organizations that distribute clinical practice guidelines, such as the American Academy of Family Physicians (AAFP), AAP, American College of Obstetricians and Gynecologists (ACOG), and Society for Maternal-Fetal Medicine (SMFM) [16–19].

Available vaccines currently in the United States include two mRNA vaccines, manufactured by Pfizer-BioNTech and Moderna, as well as the Novavax, which uses a synthetic S-protein (Table 1). The Janssen (Johnson & Johnson) vaccine, engineered using an adenovirus vector, had also received authorization for use in the US, though it is currently not recommended as first-line due to concerns for serious side effects. The AstraZeneca vaccine, which is not authorized in the US but approved in multiple countries worldwide, also uses adenovirus vector technology. This vaccine is intended for use in adults 18 years and older and has also been associated with a rare but significant side effect of thrombosis with thrombocytopenia.

The recommended vaccine schedule includes a primary series of two doses of monovalent vaccine, spaced 3–8 weeks (Pfizer or Novavax), 4–8 weeks (Moderna), or 4–12 weeks apart (AstraZeneca). A booster series is recommended at least 2 months after completing the primary series with a single dose of either the Pfizer or Moderna bivalent vaccine. For individuals who received the single-dose Janssen primary series, a booster dose with either the Pfizer or Moderna bivalent booster vaccine is recommended at least two months after the single-dose primary vaccine. A booster dose of AstraZeneca vaccine is recommended 4–6 months after completing the primary vaccination series. To increase flexibility, the World Health Organization (WHO) supports interchangeability of different COVID-19 vaccines to complete the primary vaccination as well as the option for a heterologous booster dose 4–6 months after primary AstraZeneca vaccination [20].

2.2. Benefits and safety considerations for vaccination in lactating individuals

Receipt of COVID-19 vaccine during lactation has benefit for both the lactating individual and their infant, conferring active and passive immunity to both and protecting from morbidity and mortality associated with COVID-19 infection. As discussed in the prior section, vaccine types against COVID-19 include mRNA, adenovirus vector, inactivated whole-virus, and S-protein types; however, most of the information about vaccine safety in lactating individuals and their children is limited to mRNA and adenovirus vector vaccines. As the safety and efficacy of this vaccine has been well described in non-lactating individuals, this section will primarily focus on lactation-specific considerations and infant-conferred immunity in the receipt of COVID-19 vaccines.

2.3. Benefits for breastfeeding infants and children

Apart from the benefit of reduced morbidity and mortality in recipients of the COVID-19 vaccine, in lactating individuals there is additional benefit of conferred immunity to infants. Following vaccination, t-cells and antibodies against COVID-19 are present, including IgG, IgA, and secretory IgA (sIGA) antibodies in human milk (Fig. 1) [21]. The antibody response in human milk is variable and related to timing of receipt of the vaccine for the lactating individual. COVID-19 vaccination can be safely given anytime during pregnancy and lactation; however, there is evidence of greater human milk antibody presence and infant serum antibody presence if the lactating individual received the first dose of vaccine during pregnancy, versus after the delivery, with higher IgG, IgA, and sIgA response in their milk [22]. Placental transfer of IgG to the fetus is thought to be the reason for higher levels of COVID-19 IgG in infant serum.

In addition to placental transfer of immunity, there is also transfer of

Table 1
COVID-19 vaccines (as of January 2023).

Vaccine mechanism[a]	Manufacturer	Interval between 1st and 2nd dose (primary series)	Interval between primary series and booster dose	Recommended bivalent booster	Possible side effects during lactation	Considerations
mRNA	Pfizer-BioNTech Moderna	3–8 weeks 4–8 weeks	≥2 months ≥2 months	Pfizer or Moderna	Milk production decrease (short-term), discoloration of milk; child irritability/poor sleep	1st line recommendation from CDC
Adenovirus vector[b]	Janssen-Johnson & Johnson	n/a	≥2 months	Pfizer or Moderna	–	Only recommended in limited situations[c]
Synthetic S protein (plus adjuvant)	Novavax	3–8 weeks	≥2 months	Pfizer or Moderna	–	

[a] Though current FDA-approved vaccine options in the US employ one of these mechanisms, there are several vaccines available outside the US that use an inactivated whole virus vaccine (such as those manufactured by Bharat Biotech, Sinopharm, and Sinovac).

[b] Additional adenovirus vector vaccines available outside the US include those manufactured by AstraZeneca, Sputnik-V, and CanSino; lactation-specific data are limited for these options.

[c] CDC only recommends Janssen (Johnson & Johnson) in certain limited circumstances due to risk of thrombosis with thrombocytopenia (TTS); limited circumstances include having a contraindication to mRNA vaccines and Novavax, situations in which individual would otherwise not be vaccinated, and strong patient preference despite explanation of TTS risks.

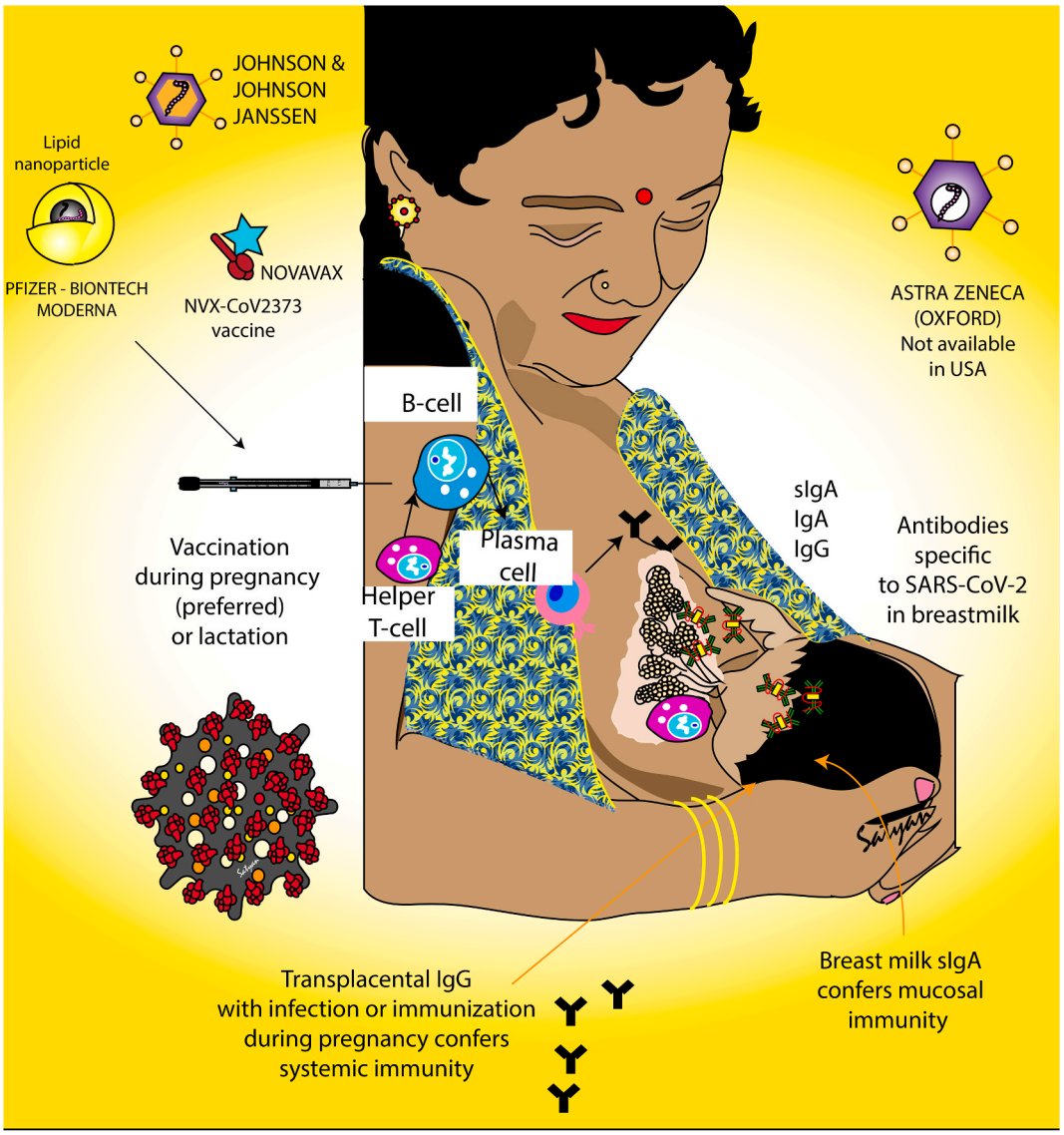

Fig. 1. Transfer of antibody immunity to COVID-19 to breastfeeding infant with birthing parent vaccination or infection. Transplacental transmission of IgG antibodies and provision of secretory IgA (sIgA) through breast milk are shown. Modified from Cheema et al. Am J Perinatol 2023. Copyright Satyan Lakshminrusimha

antibodies via consumption of human milk from a vaccinated, or previously infected, individual. Lactating individuals who have had COVID-19 infection and/or vaccination have presence of immunoglobulins (sIgA, IgA, and IgG) against COVID-19 in their milk. Even though studies simulating the gastric and intestinal environment of infants drinking human milk have demonstrated that immunoglobulins against COVID-19 are not completely destroyed by the digestion process [23], there is no evidence that breastfeeding infants have detectable anti-COVID IgG in their serum unless the birthing parent was vaccinated during pregnancy [24]. The evidence is somewhat conflicting, however, as there is presence of IgG in infant stool and saliva following immunization or infection during pregnancy [24].

2.4. Immune response in human milk

Following COVID-19 immunization or infection in the lactating individual there is presence of COVID-19 antibodies in human milk [25]. After vaccination, IgG, IgA, and sIgA are present as soon as 2 weeks after vaccine. Serum levels of IgG are higher compared to IgA, which is thought to be secondary to the vaccine's parenteral administration [26]. When deciding between mRNA or other vaccine options, mRNA vaccines given to lactating individuals have consistently demonstrated higher immunogenicity (IgA, IgG levels) in human milk than vector-based vaccines [27,28]. Additional doses, or boosters, of the COVID-19 mRNA vaccines cause a robust immune response with an increase in both IgG and IgA levels, however, with IgG milk levels against COVID-19 reaching higher levels than IgA. For mRNA vaccines, there is evidence that small amounts of mRNA are present in human milk up to 48 h after receipt of vaccine. Levels of mRNA detected in milk have mostly been described around 70 ng/L, with the highest concentration reported in the literature at 2 mcg/L [29,30]. Given the effect of the infant digestion on human milk, it is not surprising that there is no evidence of any detectable mRNA in infant serum following maternal vaccination.

2.5. Side effects of COVID-19 vaccine in lactating individuals

Immunization against COVID-19 does have well-described side effects, including fever, chills, and pain at the injection site. These side effects are described in lactating individuals as well, along with several temporary effects specific to lactation, including descriptions of an increase and decrease in perceived supply by lactating individuals [31].

Additionally, there have been reports of temporary unilateral lymphatic effects (neck and axilla lymphadenopathy) in lactating individuals. Lactating parents have reported a slight change in color to their milk (e.g., greenish/blue), and small numbers have experienced breast engorgement and mastitis following vaccination [32]. Lactation-related side effects occurred more frequently after the second dose of the vaccine and with the Moderna, versus Pfizer, vaccine and was thought to be secondary to decreased breastfeeding intensity and infant fussiness following vaccine administration [33].

2.6. Side effects of COVID-19 immunization of lactating parents in infants/toddlers

There are some mild side effects in infants described following vaccination of lactating parents. These side effects include fussiness, sleepiness, fever, rash, and a self-limiting diarrhea [31]. mRNA vaccines contain Polyethlene Glycol (PEG), which can cause anaphylaxis following COVID-19 vaccine; however, there is no evidence of PEGylated proteins present in human milk before or after birthing parent vaccination [24]. There are limited data on the side effects in breastfed children after lactating parent immunization with the adenovirus vector vaccines; however, as these vaccines do not contain live virus, they are unlikely to pose a significant risk to breastfed infants.

2.7. Bivalent COVID-19 mRNA vaccine safety

With the emergence of COVID-19 variants, the US Food and Drug Administration (FDA) has authorized the bivalent formulations of the Pfizer and Moderna mRNA COVID-19 vaccines, which target the original strain of SARS-CoV-2 and the Omicron variants BA.4 and BA.5 [34]. While data specific to the bivalent vaccines in lactating people are not available, a review of the adverse events reported during August 31, 2022 to October 23, 2022, which was the time period after initial authorization of the bivalent vaccines, indicated that most events were nonserious. Among the 211,959 persons who voluntarily reported to the v-safe system, the most common event was injection site reaction (e.g., itching, pain, redness, swelling or hardness) (60.8%), followed by fatigue (40.4%), headache (30.6%), and myalgia (29.6%) within the week after vaccination [34]. Of the 5542 reports received through the Vaccine Adverse Event Reporting System (VAERS) during the same time period, most were also considered nonserious, such as headache (11.9%), fatigue (10.9%), and fever (10.6%). The minority (4.5%) of reports were considered serious based on need for hospitalization, prolonged hospitalization, life-threatening illness, permanent disability, congenital anomaly or birth defect, or death. Examples included thrombotic event (n = 31) and COVID-19 infection (n = 20) [34].

3. SARS CoV-2 treatment options during lactation

This next section discusses the appropriateness of various treatment options in COVID-19 infected lactating people and includes recommendations for practices according to clinical guidelines to avoid exposing the infant to SARS-CoV-2. The beneficial effects of breastfeeding on infant health and development should be weighed against lactating parent's necessity for COVID-19 treatments, along with consequences of the underlying maternal condition to the infant and side effects of treatments on the infant.

3.1. Hospitalized patients

As in the general population, remdesivir along with dexamethasone are the preferred initial therapy for patients with severe illness, needing oxygen support, with the hope that treatment will decrease the duration of symptoms and hasten recovery from illness.

- **Remdesivir:** This antiviral medication inhibits viral replication by blocking RNA-dependent RNA polymerase. It is administered intravenously usually for 5–10 days depending on severity of illness. Limited available information indicates very low levels of remdesivir and its active metabolite in human milk. However, it has poor oral absorption, and the metabolite is only partially orally absorbed so infants are less likely to absorb it in clinically significant amounts from milk [35]. Reassuringly, this medication has been used in infants intravenously without serious adverse drug reactions for COVID-19 and Ebola infection [36,37]. Hence, lactating people receiving remdesivir do not need to avoid breastfeeding or expressing/pumping and providing milk for the infant. (L3 – Limited data, probably compatible)
- **Dexamethasone:** This corticosteroid is administered at low doses orally for 5–10 days to decrease inflammation secondary to infection. It is safe to use a short course of steroids while breastfeeding as the amount of corticosteroid secretion in milk is low, although data on dexamethasone during breastfeeding are limited [38,39]. It is worth mentioning that high-dose corticosteroids may temporarily decrease milk production. (L3 – Limited data, probably compatible)
- **Baricitnib:** This orally administered, Janus-associated kinase (JAK)-inhibitor is reported to quicken the pace of recovery in COVID-19 hospitalized patients when given in addition to remdesivir and may potentially decrease mortality when added to corticosteroids. This treatment works by interrupting the signaling of multiple cytokines implicated in COVID-19 pathogenesis and may also have antiviral activity by blocking viral cell entry and suppressing type I interferon-driven angiotensin-converting-enzyme-2 upregulation. It is a small molecule, which is rapidly absorbed and likely to be present in human milk as inferred from studies in lactating rats in which baricitinib was detected in the milk at exposures ~45-fold higher than corresponding plasma exposures. Lack of human studies on pharmacokinetics or safety of baricitinib in lactation preclude its use in lactating patients [40]. However, if this medication is absolutely required, breastfeeding should be withheld during treatment and for 4 days after the last dose. The option to express and discard milk to maintain milk production during this time period should be discussed with lactating individuals. (L4 – No data, potentially hazardous).
- **Tocilizumab:** This treatment is usually administered intravenously in patients with worsening respiratory status despite 24–48 h of remdesivir and dexamethasone if no contraindications are present. Tocilizumab is a recombinant humanized monoclonal immunoglobulin G1 antibody that blocks interleukin-6 binding to its receptor, thus reducing downstream inflammatory signaling. Given the large molecular weight of Tocilizumab (148 kDa), this drug has decreased ability to pass into human milk, and any minimal excreted drug in milk is further degraded in the digestive tract, resulting in decreased oral absorption in the infant [41]. No adverse effects have been observed in reports of breastfed infants whose lactating parents were treated with tocilizumab. (L3 – Limited data, probably compatible)

3.2. Non-hospitalized patients

In the general population, Paxlovid® (nirmatrelavir + ritonavir) and molnupiravir are the oral options for treatment of mild-to-moderate COVID-2019 infections, especially in those who are at high risk for progression to severe COVID-19, which includes hospitalization or death. An additional treatment for non-hospitalized patients is a 3-day course of intravenous (IV) remdesivir but this option can only be administered if patients are hospitalized or have arrangements for IV infusion at infusion centers. Monoclonal antibodies like bebtelovimab are no longer considered active against the prevalent new Omicron variants worldwide and hence, are not discussed as a viable treatment option at this point. Generally, the use of anti-SARS-CoV-2 monoclonal

antibodies are not a contraindication to breastfeeding as they may not be found in clinically relevant amounts due to their large size and likely lack of an active transport mechanism into human milk [42].

- **Paxlovid (nirmatrelvir + ritonavir tablets)**: Nirmatrelvir prevents viral replication by inhibiting SARS-CoV-2 main protease (M^{pro}) and rendering it incapable of processing polyprotein but has poor oral bioavailability. Hence, it is given in combination with an HIV-1 protease inhibitor, ritonavir, which by itself is not active against SARS-CoV-2 M^{pro} but inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir. Given nirmatrelvir's modest protein binding and molecular weight, only moderate transfer into the milk is anticipated although no data are available on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A transient decrease in body weight was observed in the nursing offspring of rats administered nirmatrelvir at higher doses but may not be clinically significant at the recommended treatment doses. Ritonavir has been detected in human milk based on reports in lactating individuals being treated for HIV, but no adverse effects have been reported. The poor oral bioavailability of nirmatrelvir along with only small amounts of ritonavir in human milk makes this combination unlikely to adversely affect the breastfeeding infant with a short 5-day course therapy [43,44]. (L3 – Limited data, probably compatible)
- **Molnupiravir:** This antiviral inhibits RNA-dependent RNA polymerase (RdRp) by acting as a ribonucleoside analog for viral RNA polymerase, thus producing mutated copies of virus. Given mutagenic potential in animal studies, its use is not recommended in pregnant individuals. For lactating individuals, the low oral bioavailability of the N4-hydrocytidine intermediary drug after absorption may potentially limit the risk to the infant. Nevertheless, this drug is secreted in human milk and human studies are needed to evaluate the risks associated with molnupravir use. Hence, the current recommendation is that this treatment should not be used during lactation. However, if other approved or FDA-authorized COVID-19 treatment options are not accessible or clinically appropriate and the benefit of using a short 5-day course of molnupiravir while using breastfeeding outweighs potential risks, lactating individuals may consider expressing and discarding milk during treatment and for 4 days after the last dose [45]. (L4 – No data, potentially hazardous)

4. Conclusions

The 21st Century Cures Act had established a Task Force on Research Specific to Pregnant Women and Lactating Women to advise the Secretary of Health and Human Services on identifying gaps in research and to provide recommendations to increase research on therapeutics in pregnant and lactating individuals [46]. Since establishment of this task force, the COVID-19 pandemic has highlighted the importance of including pregnant and lactating people into clinical trials, especially when these historically excluded populations have more severe health outcomes when affected by the disease or condition. The lack of initial trial data promotes hesitancy in both clinicians from recommending and patients from receiving vaccinations or treatment that could have significant benefit to both the patient and their infant.

In terms of prevention, COVID-19 vaccination remains one of the most important preventive strategies for moderate to severe COVID-19 infection. Vaccination is associated with protective benefits for lactating individuals and their breastfed infants with overall mild side effects for both parties. While long-term data on any future risks of vaccination are lacking, current evidence indicates that the benefits of vaccination outweigh the risks. As the pandemic continues to change with the emergence of new COVID-19 variants, treatment recommendations will also continue to evolve. The current recommendations for COVID-19 treatment in hospitalized lactating individuals includes remdesivir and dexamethasone and Paxlovid® for outpatient treatment in those with mild disease. As with most new drugs with limited data on safety in lactating individuals, concern for theoretical or unknown harm often precludes treatment use or involves a recommendation to express and discard milk during treatment. Given the multitude of known health risks to both birthing people and infants from not breastfeeding, it is important that clinicians and policymakers consider this risk and to preserve lactation and human milk feeding unless harm from the milk outweighs harms of not breastfeeding.

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Declaration of competing interest

The authors do not have any personal or financial conflicts of interest with the content of this article.

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