Hybrid immunity against SARS-CoV-2: Mechanisms, duration and global implications (Review)

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Abstract. Since the commencement of the coronavirus disease 2019 (COVID-19) pandemic, understanding the nature and durability of immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been central to public health strategies. Emerging evidence indicates that the combination of prior infection and vaccination, termed hybrid immunity, provides superior protection compared to infection- or vaccine-induced immunity alone. The present review synthesizes currently available evidence on the mechanisms, durability and global implications of hybrid immunity, emphasizing its relevance for vaccination strategies, pandemic preparedness and health equity. The present review conducted a narrative synthesis of peer-reviewed studies, systematic reviews and meta-analyses published between 2020 and 2023, focusing on immunological mechanisms, epidemiological outcomes and policy implications of hybrid immunity. Mechanistically, it has been demonstrated that hybrid immunity elicits broader and more potent neutralizing antibodies, enhances memory B-cell diversity and supports cross-reactive T-cell responses across variants of concern. Epidemiological evidence indicates that hybrid immunity confers the highest protection against infection, severe disease, hospitalization and mortality. Protection against reinfection wanes over time, particularly against immune-evasive Omicron subvariants, although protection against severe outcomes remains durable for at least 6-12 months. Booster vaccination further strengthens hybrid immunity. However, due to global disparities in vaccine access, individuals in high-income regions disproportionately benefit from hybrid immunity, while populations in low- and middle-income countries often rely on infection-derived immunity alone. Hybrid immunity represents the most resilient form of protection against COVID-19, combining the advantages of both natural and vaccine-induced immunity. Its superior breadth and durability have critical implications for vaccination policies, particularly regarding booster prioritization and the development of variant-proof vaccines. Ensuring equitable access to vaccines remains essential to maximize the protective benefits of hybrid immunity worldwide and to strengthen preparedness against future pandemics.

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1. Introduction

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019, the global scientific and public health response has centered on strategies to reduce morbidity and mortality from coronavirus disease 2019 (COVID-19). Vaccination campaigns have markedly reduced severe disease burden, while natural infection has also conferred varying degrees of immunity. However, accumulating evidence suggests that the combination of vaccination and prior infection, termed hybrid immunity, confers superior protection compared to either vaccination or infection alone (1-3).

Hybrid immunity is characterized by broader neutralizing antibody responses, stronger B-cell memory and enhanced T-cell cross-reactivity across variants of concern (VOCs), including Omicron sub-lineages (4,5). This layered immune protection is particularly relevant in the context of ongoing viral evolution and immune escape. Notably, hybrid immunity

not only provides greater protection against symptomatic reinfection, but also demonstrates longer-lasting defense against hospitalization and mortality (6,7).

Understanding hybrid immunity has profound global health implications. It informs optimal vaccine scheduling, booster policies and pandemic preparedness strategies. Moreover, previous SARS-CoV-2 infection and vaccination have both been associated with the reduced transmission of the Omicron variant, highlighting the importance of different forms of acquired immunity in limiting viral spread (8).

The present review aimed to synthesize currently available evidence on the mechanisms, duration and global implications of hybrid immunity against SARS-CoV-2, with emphasis on lessons for long-term COVID-19 control and preparedness for future pandemics.

Unlike reviews focusing primarily on immunological mechanisms or vaccine effectiveness, the present review integrates mechanistic and epidemiological evidence with global health inequalities. It discusses how differences in exposure history, immune durability and vaccine accessibility influence hybrid immunity across populations, providing a broader perspective on its implications for vaccination strategies and pandemic preparedness.

2. Literature search strategy

The present review employed a narrative approach to synthesize published evidence on SARS-CoV-2 hybrid immunity, focusing on immunological mechanisms, durability of protection and global public health implications. The literature considered included original research articles, systematic reviews and meta-analyses published primarily between 2020 and 2024. Studies were evaluated for relevance to the review objectives, with particular attention to differences in study design, population characteristics, exposure histories, and clinical outcomes.

3. Immunological mechanisms of hybrid immunity

Hybrid immunity results from the synergistic interaction between vaccine-induced and infection-induced immune responses. Vaccines, particularly those based on the SARS-CoV-2 spike protein, generate potent neutralizing antibody responses and durable T-cell immunity (9). Natural infection, by contrast, exposes the host immune system to a broader array of viral antigens, including nucleocapsid, membrane and accessory proteins, thereby inducing a more diverse immunological repertoire (10). In combination, these exposures lead to quantitatively and qualitatively superior immune responses compared to either mode of immunity alone (Table I).

Influence of exposure sequence, interval, vaccine platform and viral variants. The magnitude, breadth and durability of hybrid immunity depend on the sequence and timing of antigenic exposures. Infection followed by vaccination and vaccination followed by breakthrough infection can generate distinct immune responses, as pre-existing immune memory influences subsequent antigen recognition. Longer intervals between infection and vaccination may permit the further affinity maturation of memory B-cells, potentially enhancing antibody breadth and neutralization capacity. However, these effects vary according to the immune history of an individual and the interval studied (11).

Vaccine platforms also influence hybrid immune responses through differences in antigen presentation and the magnitude of humoral and cellular immunity. Furthermore, the SARS-CoV-2 variant responsible for infection affects the specificity of subsequent immune responses. Omicron subvariants, particularly those with substantial antigenic divergence from ancestral strains, can escape previously generated neutralizing antibodies (12).

Immune imprinting represents an additional consideration, as earlier exposure to particular viral antigens may shape responses to subsequent variants. Although imprinting can promote the recognition of conserved epitopes, it may also constrain the development of novel variant-specific responses. Consequently, hybrid immunity should not be considered a uniform immunological state; its protective characteristics depend on exposure history, vaccination platform, antigenic interval and viral evolution (13).

Antibody responses. Hybrid immunity enhances antibody magnitude and quality. Individuals with prior infection who subsequently receive vaccination develop higher titers of neutralizing antibodies, often several-fold greater than vaccine-naïve individuals (14). These antibodies exhibit superior affinity maturation, broader recognition across VOCs, and increased neutralization potency, even against highly immune-evasive Omicron sub-lineages (5,15). Longitudinal research has demonstrated that hybrid immunity induces memory B-cells that continue to evolve over months, producing antibodies with greater cross-reactivity (4).

Memory B-cells. Memory B-cells generated through hybrid immunity not only target spike epitopes with increased breadth, but also recognize conserved regions less affected by viral mutations (16). Re-exposure, whether by booster vaccination or reinfection, leads to rapid recall and robust production of high-affinity antibodies (17). This sustained evolution of the B-cell repertoire is a distinguishing feature of hybrid immunity.

T-cell responses. T-cell immunity, particularly $CD4^+$ and $CD8^+$ responses, is less affected by viral mutations due to the conservation of epitopes outside the spike protein (18). Hybrid immunity amplifies these responses, resulting in greater polyfunctionality and cross-variant recognition (19). Notably, T-cell immunity correlates strongly with protection from severe COVID-19, explaining why hybrid immunity provides durable defense against hospitalization and death despite waning antibody titers (20).

Innate and mucosal immunity. Emerging data suggest that hybrid immunity also augments innate and mucosal immune responses. Infection stimulates tissue-resident memory T-cells and mucosal IgA in the respiratory tract, while vaccination enhances systemic adaptive immunity (21). The combination may yield a more comprehensive 'two-tier' defense, although further studies are required to clarify these mechanisms.

Taken together, hybrid immunity provides broader and more durable immunological protection through complementary

Table I. Key features and outcomes of hybrid immunity against SARS-CoV-2.

Feature	Mechanistic evidence	Epidemiological evidence	Implications
Antibody responses	Higher neutralizing titers, broader cross-variant recognition, better affinity maturation	Greater protection against symptomatic infection and reinfection	Supports booster strategies, enhanced variant coverage
Memory B-cells	Broad and evolving repertoire, rapid recall upon re-exposure	Long-term protection against severe disease	Durable immunity; potential for long-lasting protection after boosters
T-cell responses	Polyfunctional, cross-variant recognition, conserved epitopes	Strong association with reduced hospitalization and death	Explains protection durability despite waning antibodies
Innate and mucosal immunity	Tissue-resident memory T cells, mucosal IgA	Limited epidemiological data	May reduce initial infection/ severity; research gap exists
Duration of protection	Waning neutralizing antibodies over 6-8 months	Protection against severe outcomes remains ≥6-12 months	Supports periodic booster vaccination
Booster effect	Rapid increase in antibody and memory cell activity	Enhanced protection temporarily restored	Booster prioritization for high-risk populations
Population variability	Age, comorbidities, immune status	Lower protection in older adults, immunocompromised, low-income regions	Tailored vaccination strategies; equity considerations
Global implications	Not applicable	Disparities in vaccine access	Urgent need for equitable vaccine distribution; informs pandemic preparedness and next-gen vaccines

mechanisms involving antibodies, B-cells, T-cells and innate immunity (4,9,21). These immunological differences between infection-induced, vaccine-induced and hybrid immunity are summarized schematically in Fig. 1. This mechanistic basis underpins the superior clinical outcomes associated with hybrid immunity observed in epidemiological studies.

4. Duration of hybrid immunity

The durability of hybrid immunity has been the subject of intensive investigation as the COVID-19 pandemic has progressed. Evidence consistently indicates that hybrid immunity provides stronger and more sustained protection than vaccine-induced or infection-induced immunity alone, although the degree of protection varies depending on the outcome of interest (infection vs. severe disease), the circulating variant and time since the last exposure (1,2).

Protection against re-infection. Hybrid immunity provides superior protection against symptomatic SARS-CoV-2 infection compared with vaccine-only or infection-only immunity. However, protection against re-infection is not permanent and wanes over time. Previous studies have suggested that effectiveness against symptomatic infection with Omicron begins at ~60-80% shortly following hybrid exposure and declines to ~30-50% within 6-8 months (3,7). This pattern reflects both waning neutralizing antibody titers and the immune-evasive capacity of Omicron sub-lineages (12). Nonetheless, individuals with hybrid immunity consistently maintain higher baseline protection than those with vaccination or prior infection alone (22).

Protection against severe outcomes. More durable protection is observed for severe COVID-19 outcomes. Hybrid immunity maintains effectiveness against hospitalization, critical illness and mortality at levels >80-90% in the first 6 months, with only modest waning thereafter (6,23). Previous research has demonstrated that hybrid immunity provides substantial protection against severe COVID-19 outcomes, including during Omicron predominance (7,24). This durability is largely attributed to sustained memory B-cell evolution and cross-reactive T-cell responses (4).

Influence of booster doses. Booster vaccination further strengthens hybrid immunity, producing rapid increases in neutralizing antibodies and memory cell activation (25). Protection against infection is temporarily restored to high levels after boosting but again declines within months. Booster vaccination can improve protection against symptomatic SARS-CoV-2 infection, although the magnitude and durability of protection vary according to vaccination history, previous infection, and circulating variants (26). These findings support the use of periodic boosters, particularly for high-risk populations.

Variability across populations. The duration of hybrid immunity may vary according to age, comorbidities and immune

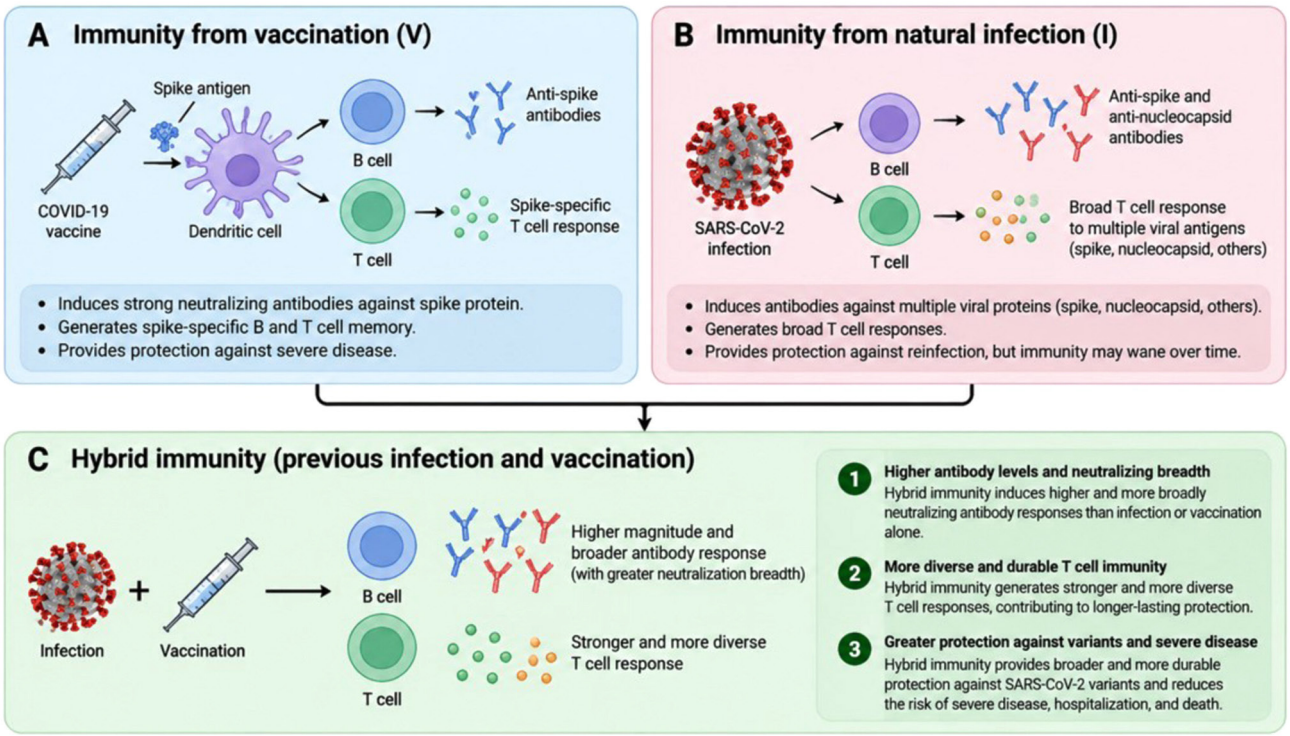


Figure 1. Immune responses induced by vaccination, natural infection, and hybrid immunity against SARS-CoV-2. (A) Vaccination induces neutralizing antibodies against the SARS-CoV-2 spike protein and generates spike-specific B-cell and T-cell memory, contributing to protection against severe disease. (B) Natural infection induces immune responses against multiple viral antigens, including spike and nucleocapsid proteins, and generates broader antigen-specific T-cell responses. However, protection against reinfection may decline over time. (C) Hybrid immunity, resulting from the combination of natural infection and vaccination, is generally associated with enhanced antibody magnitude, broader neutralizing activity, and strengthened immunological memory. These complementary responses contribute to improved protection against SARS-CoV-2 infection and severe clinical outcomes, including hospitalization and death. The illustration is conceptual and does not represent quantitative experimental measurements. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

status. Older adults and immunocompromised individuals exhibit more rapid waning and lower peak effectiveness (27). Furthermore, vaccination and previous SARS-CoV-2 infection can both contribute to reducing Omicron transmission, although the degree of protection varies according to immune history and the circulating variant (8). Continued monitoring is necessary to understand long-term protection across diverse global contexts.

5. Hybrid immunity and long COVID outcomes

The potential influence of hybrid immunity on post-acute sequelae of SARS-CoV-2 infection, commonly referred to as long COVID, represents a key area of investigation. Emerging epidemiological evidence suggests that vaccination prior to SARS-CoV-2 infection is associated with a reduced risk of developing long COVID compared with infection in unvaccinated individuals (28). However, the extent to which hybrid immunity provides additional protection against persistent symptoms remains uncertain (29).

Previous infection and vaccination may reduce the severity of subsequent infections through enhanced immune responses, potentially lowering the risk of post-acute complications. Nevertheless, long COVID can occur following breakthrough infections, including among individuals with hybrid immunity. Differences in study populations, vaccination histories, circulating variants, follow-up periods and definitions of long COVID complicate comparisons across studies. Further longitudinal investigations are warranted to determine whether exposure sequence, booster vaccination, and the durability of hybrid immunity influence the incidence, severity and persistence of long COVID (29).

6. Global and public health implications

The recognition that hybrid immunity provides superior protection against SARS-CoV-2 has profound consequences for global vaccination strategies, pandemic preparedness and health equity. Its implications span optimal vaccine deployment, booster timing, global access and the design of next-generation vaccines.

Vaccine policy and booster strategies. Hybrid immunity has redefined the benchmarks for protective immunity. Individuals with prior infection followed by vaccination, or vice versa, achieve stronger protection than those with vaccination alone (1). These findings highlight the importance of considering previous SARS-CoV-2 infection and vaccination history when evaluating the durability of hybrid immunity and potential booster strategies (30). For high-risk groups, including older adults and those with comorbidities, timely booster doses remain essential to sustain protection against severe outcomes, particularly in the face of immune-evasive Omicron subvariants (23,25). For healthy younger populations,

hybrid immunity may allow for extended booster intervals, optimizing resource allocation (7).

Equity in vaccine access. Hybrid immunity underscores inequities between high-income and low-income countries. In high-income settings, individuals often benefit from multiple vaccine doses alongside prior infection, whereas limited vaccine access in resource-constrained regions can result in different patterns of vaccination and infection exposure (33). This reliance on infection-derived immunity carries greater risks of morbidity and mortality, particularly where healthcare infrastructure is weak (31). Although global initiatives, such as COVAX have attempted to close these gaps, disparities remain (32,33). Ensuring equitable vaccine distribution is therefore critical, not only for direct protection, but also for reducing the unequal health burden of COVID-19.

Global disparities in vaccination and hybrid immunity. Global differences in COVID-19 vaccination coverage have contributed to heterogeneous patterns of population immunity. By July, 2023, ~75% of individuals in high-income countries had completed primary vaccination, compared with only 27% in low-income countries (33). Booster administration exhibited similarly substantial disparities, reflecting unequal access to vaccines and differences in national vaccination strategies.

These inequalities were influenced by vaccine procurement, healthcare infrastructure and regional manufacturing capacity (31,33). Limited local vaccine production in Africa increased dependence on international supplies, particularly during the early vaccination campaigns. Consequently, populations across regions experienced different sequences and intervals of infection and vaccination, potentially influencing the development and the durability of hybrid immunity.

These findings highlight the importance of considering regional vaccination coverage, exposure histories and healthcare capacity when interpreting epidemiological evidence on hybrid immunity. Strengthening regional vaccine manufacturing, improving booster accessibility and expanding surveillance of population immunity may reduce disparities in protection against severe COVID-19 (31,33).

7. Implications for pandemic preparedness

The lessons of hybrid immunity extend beyond COVID-19. They highlight the importance of layered immune exposures in generating durable protection, which may inform the design of vaccines against other rapidly mutating pathogens, such as influenza or emerging coronaviruses (34). In addition, monitoring hybrid immunity levels across populations can help predict future waves of infection, guiding the timing of booster campaigns and non-pharmaceutical interventions (35).

Toward universal coronavirus vaccines. Hybrid immunity provides insight into the development of pan-coronavirus or variant-proof vaccines. By revealing conserved epitopes targeted by hybrid responses, researchers may design vaccines capable of inducing similarly broad and durable immunity without requiring prior infection (36). Investment in such vaccine technologies will be central to long-term global health security.

8. Critical appraisal of the evidence

Although substantial evidence supports the protective benefits of hybrid immunity against SARS-CoV-2, several methodological limitations require consideration. Differences in study design, including observational cohorts, case-control studies, and immunological investigations, introduce variability in the strength and interpretation of findings. Population characteristics, such as age, comorbidities, vaccination history and previous infection status, further complicate comparisons. Additionally, variations in antibody assays, neutralization methods, and definitions of hybrid immunity limit direct comparisons across studies. Differences in circulating viral variants, follow-up periods, and clinical outcome definitions may also influence estimates of protection. Observational studies are particularly susceptible to confounding, selection bias, and incomplete documentation of previous infections. Consequently, although the overall evidence supports enhanced protection associated with hybrid immunity, estimates of its magnitude and durability should be interpreted cautiously, considering methodological heterogeneity and study-specific limitations (7).

9. Challenges and knowledge gaps

Despite the compelling evidence supporting hybrid immunity, several challenges and uncertainties remain. These limitations affect how hybrid immunity should be interpreted and applied to vaccination policies worldwide.

Waning immunity and variant evolution. Although hybrid immunity provides substantial protection against SARS-CoV-2, its effectiveness is influenced by ongoing viral evolution. Antigenic changes in emerging variants, particularly Omicron sub-lineages, may reduce recognition by previously generated neutralizing antibodies (12,37). These findings highlight the importance of distinguishing short-term protection against infection from longer-term protection against severe clinical outcomes (7). The mechanisms underlying these differences and their epidemiological implications are discussed in the preceding sections.

Limited data in vulnerable populations. Evidence concerning the durability of hybrid immunity remains less comprehensive for some vulnerable and underrepresented populations, particularly in low- and middle-income countries. Differences in vaccination coverage, healthcare access and pandemic preparedness may further complicate comparisons between populations (32,33). Age-related differences in immune responses to SARS-CoV-2 vaccination also highlight the importance of evaluating protection in older adults (27). Further research is required to characterize the magnitude and durability of hybrid immunity among immunocompromised individuals, older adults and children.

Heterogeneity of measurement methods. Variations in study designs, definitions of infection and immune assays complicate comparisons across studies. For example, some studies define 'hybrid immunity' as infection followed by vaccination, while others include vaccination followed by infection (7). The lack

of standardized methodologies hinders the precise estimation of the duration and breadth of protection.

Ethical considerations. Although hybrid immunity is generally associated with enhanced protection against SARS-CoV-2, deliberately encouraging infection to acquire immunity is not an appropriate public health strategy as infection carries risks of severe disease, long COVID and mortality. Reliance on infection-induced population immunity also presents important limitations (38). Vaccination should therefore remain the preferred approach to reducing COVID-19 morbidity and mortality, while recognizing that previous infections contribute to population-level immune protection.

Knowledge gaps for long-term outcomes. The long-term trajectory of hybrid immunity remains incompletely understood, particularly as SARS-CoV-2 continues to evolve. Further investigations are required to determine how repeated vaccination and infection influence the breadth and durability of immune protection over extended periods. Although T-cell responses contribute to protection against severe COVID-19 (20), the long-term effects of repeated antigenic exposure require further study. Similarly, mucosal antibody responses have been demonstrated following vaccination in previously infected individuals (21); however, their contribution to sustained protection against reinfection remains uncertain.

10. Conclusion and future perspectives

Hybrid immunity, derived from the combination of vaccination and natural infection, represents the most robust form of immune protection against SARS-CoV-2 described to date. Mechanistic studies (4,14-16) have shown that hybrid immunity enhances both the magnitude and breadth of antibody responses, supports the ongoing evolution of memory B-cells and augments T-cell cross-reactivity across variants. Together, these mechanisms translate into superior real-world protection against both infection and, more importantly, severe outcomes, such as hospitalization and mortality.

Epidemiological evidence indicates that hybrid immunity provides durable defense against severe COVID-19 for at least 6-12 months, with slower waning compared to vaccine-only or infection-only immunity. Nevertheless, protection against reinfection diminishes over time, particularly in the face of immune-evasive Omicron sub-lineages. Booster vaccination restores protection and further strengthens hybrid immunity, highlighting the importance of adaptive vaccination policies.

At the global level, hybrid immunity raises both opportunities and challenges. It reinforces the value of vaccination as the safest route to durable immunity, while exposing inequities in vaccine access that leave low- and middle-income countries more reliant on infection-derived immunity. These disparities underscore the need for equitable vaccine distribution, surveillance of immunity at the population level, and investment in next-generation vaccines capable of eliciting broad, variant-proof protection.

Looking ahead, hybrid immunity offers critical lessons for pandemic preparedness. Understanding how layered immune exposures shape long-term protection can guide strategies against other emerging pathogens. While uncertainties remain, particularly regarding long-term durability, impacts in vulnerable populations and future viral evolution, hybrid immunity remains a cornerstone of global resilience against COVID-19.

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Authors' contributions

TAHS conceptualized and designed the study, performed the literature review, and drafted the manuscript. MOK contributed to data interpretation, critical revisions and the refinement of key mechanistic and epidemiological discussions. Both authors reviewed, edited and approved the final version of the manuscript and agree to be accountable for all aspects of the work. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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