Vaccine effectiveness against COVID-19 breakthrough infections in patients with cancer (UKCCEP): a population-based test-negative case-control study


Summary

Background People with cancer are at increased risk of hospitalisation and death following infection with SARS-CoV-2. Therefore, we aimed to conduct one of the first evaluations of vaccine effectiveness against breakthrough SARS-CoV-2 infections in patients with cancer at a population level.

Methods In this population-based test-negative case-control study of the UK Coronavirus Cancer Evaluation Project (UKCCEP), we extracted data from the UKCCEP registry on all SARS-CoV-2 PCR test results (from the Second Generation Surveillance System), vaccination records (from the National Immunisation Management Service), patient demographics, and cancer records from England, UK, from Dec 8, 2020, to Oct 15, 2021. Adults (aged ≥18 years) with a cancer diagnosis or cancer treatment had a cancer diagnosis or cancer treatment were identified via Public Health England’s Rapid Cancer Registration Dataset between Jan 1, 2018, and April 30, 2021, and comprised the cancer cohort. We constructed a control population cohort from adults with PCR tests in the UKCCEP registry who were not contained within the Rapid Cancer Registration Dataset. The coprimary endpoints were overall vaccine effectiveness against breakthrough infections after the second dose (positive PCR COVID-19 test) and vaccine effectiveness against breakthrough infections at 3–6 months after the second dose in the cancer cohort and control population.

Findings The cancer cohort comprised 377,194 individuals, of whom 42,882 had breakthrough SARS-CoV-2 infections. The control population consisted of 28,010,955 individuals, of whom 574,708 had SARS-CoV-2 breakthrough infections. Overall vaccine effectiveness was 69·8% (95% CI 69·8–69·9) in the control population and 65·5% (65·1–65·9) in the cancer cohort. Vaccine effectiveness at 3–6 months was lower in the cancer cohort (47·0%, 46·3–47·6) than in the control population (61·4%, 61·4–61·5).

Interpretation COVID-19 vaccination is effective for individuals with cancer, conferring varying levels of protection against breakthrough infections. However, vaccine effectiveness is lower in patients with cancer than in the general population. COVID-19 vaccination for patients with cancer should be used in conjunction with non-pharmacological strategies and community-based antiviral treatment programmes to reduce the risk that COVID-19 poses to patients with cancer.

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from a real-world health system in England, UK. Our use of the largest cohort of patients with cancer worldwide enabled, to our knowledge, the most comprehensive analysis of the risk that COVID-19 presents to patients with cancer. We describe how cancer subtype, treatment, and patient demographics interact to affect COVID-19 vaccine effectiveness.

Methods

Study design and data sources

The UK Coronavirus Cancer Evaluation Project (UKCCEP) is a subproject of the UK Coronavirus Cancer Monitoring Project and is the next iteration of the UK’s COVID-19 pandemic response to monitor, safeguard, and protect patients with cancer. In this population-based test-negative case-control study, we extracted PCR test results, vaccination records, patient demographics, and cancer records (eg, treatment, stage, and subtype) in England from the UKCCEP registry between Dec 8, 2020 (the start of COVID-19 vaccination in England) and Oct 15, 2021 (the study period). This period of analysis coincided with the second COVID-19 wave in the UK, which was principally driven by the delta variant (B.1.617.2).  

Patient-level COVID-19 PCR test results, including from community and hospital testing, were obtained for UKCCEP from the Second Generation Surveillance System. National Health Service (NHS) England and NHS Test and Trace use PCR testing for those with symptoms of COVID-19 and lateral flow testing (also known as antigen-detecting rapid diagnostic testing) for the identification of asymptomatic cases. During the study period, confirmatory PCR testing was mandated for individuals testing positive on lateral flow tests. In the NHS, infection and prevention control measures in secondary care required COVID-19 PCR testing of asymptomatic patients before many procedures or treatments. Vaccination records for the UKCCEP registry were obtained from the National Immunisation Management Service. All COVID-19 vaccines licensed in England were considered.

The number of COVID-19 contacts was obtained from individuals who had supplied information as part of the Contact Tracing and Advice Service, which records information about the number of interpersonal contacts before infection or following exposure to COVID-19. Data on COVID-19-related hospitalisation and death were extracted from the Secondary Use Statistics datasets between Dec 8, 2020, and Oct 15, 2021.

From those who had SARS-CoV-2 PCR testing in the Second Generation Surveillance System, we identified adults (aged ≥18 years) with cancer to comprise our cancer cohort via Public Health England’s Rapid Cancer Registration Dataset between Jan 1, 2018, and April 30, 2021. This date range was selected to better represent individuals with active cancer, excluding those with a more historical diagnosis. The national Rapid Cancer Registration Dataset includes information about receipt of radiotherapy and systemic anticancer treatments, which is an umbrella term of cancer treatments, including chemotherapy and targeted therapy. It includes incident cases with cancer diagnoses and hospital admissions and deaths. The dataset is updated weekly and contains detailed information about cancer stage, subtype, and treatment. Cancer Registration Dataset between Jan 1, 2018, and Oct 15, 2021. This period of analysis coincided with the second COVID-19 wave in the UK, which was principally driven by the delta variant (B.1.617.2).  

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The coprimary outcomes of the study were overall vaccine effectiveness (defined relative to breakthrough infections [positive PCR test] following the second dose of COVID-19 vaccine during the period of assessment) and vaccine effectiveness against breakthrough infections at 3–6 months after the second dose. A test-negative case-control method was used to estimate vaccine effectiveness in the cancer cohort and the control population. Test-negative case-control studies have high concordance with findings from randomised clinical trials and are a standardised measure of vaccine effectiveness for phase 4 surveillance studies.20,21 Within the test-negative case-control study design, exposure was defined as any positive PCR test result within the study period. Vaccine effectiveness was calculated with the test-negative case-control method formula: 1 minus the ratio of PCR-positive vaccinated to PCR-positive unvaccinated individuals divided by the ratio of PCR-negative vaccinated to PCR-negative unvaccinated individuals. Each datapoint corresponds to a single PCR test and higher vaccine effectiveness would be shown if there were lower numbers of vaccinated individuals among those who had positive tests than among those who had negative tests. The negative tests act as an internal control, comprising individuals who might have symptoms from non-COVID-19 causes. This design addresses challenges that are often present in observational studies, such as differences in health-seeking behaviours or access to testing. Vaccine manufacturers were combined in our evaluation because the focus of our study was a description of vaccine effectiveness and waning in the cancer cohort relative to the control population. Additionally, vaccine effectiveness according to different manufacturers is relatively well described in the literature.22

Predefined subgroup analyses of overall vaccine effectiveness were done in the cancer cohort by vaccine type (BNT162b2 [Pfizer–BioNTech], ChAdOx1 nCoV-19 [AZD1222; AstraZeneca], or mixed and other), cancer type (solid organ vs haematological) and subtype (as determined by codes from the tenth revision of the International Classification of Diseases), cancer stage, date of cancer diagnosis (≤12 months vs >12 months relative to data cutoff), and receipt of systemic anticancer treatment or radiotherapy (none vs any and received ≤12 months ago vs received >12 months ago relative to data cutoff). Within the cancer cohort, exploratory multivariable logistic regression with the Wald test was used to describe vaccine effectiveness (overall and at 3–6 months) in the aforementioned predefined subgroups, excluding vaccine type, and was adjusted for the clinically important covariates of age, sex, ethnicity, and Index of Multiple Deprivation (determined by geographical location),23 which might have acted as confounders, effect modifiers, or both for analysing vaccine effectiveness. Further prespecified exploratory analyses of cancer subtypes, receipt of radiotherapy or systemic anticancer treatment, and time of diagnosis (≤12 months vs >12 months relative to data cutoff) were done to identify whether any subgroups were more likely to develop waning vaccine effectiveness at 3–6 months following multivariable correction. Waning vaccine effectiveness was defined as the change in percentage points between vaccine effectiveness over the study period subtracted from vaccine effectiveness at 3–6 months. Wald test z values were used to assess statistical significance. Variables were either binary (sex, cancer treatments, cancer type, time from diagnosis, PCR status, and vaccination status) or grouped (age, ethnicity, Index of Multiple Deprivation, cancer subtypes, and stage), with age categorised in 10-year age bands (18–19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, 80–89 years, and ≥90 years) in accordance with a previous vaccine effectiveness study.20 We used information from the Contact Tracing and Advice Service for post-hoc analyses of patient behaviour by patient age band and cancer stage. Contacts included both household and non-household contacts. The mean numbers of contacts and SDs were calculated for each subgroup.

Steps were taken to reduce bias at several study stages, including robust adherence to the data analysis plan, minimising selection bias, and ensuring that the full dataset was reviewed and interpretations were approved by multiple consortium authors. Participants with missing or not specified data were excluded from our analyses.

In further post-hoc analyses, we examined COVID-19 hospitalisation (defined as admission to hospital from 1 day before to 14 days after a positive PCR test) and COVID-19 death (death occurring up to 28 days after a
### Table 1: Baseline characteristics of the cancer cohort and control population

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Cancer cohort</th>
<th>Control population</th>
</tr>
</thead>
<tbody>
<tr>
<td>White or White British</td>
<td>1533 (89.5%)</td>
<td>4785 (85.30%)</td>
</tr>
<tr>
<td>Asian or Asian British</td>
<td>7085 (4.14%)</td>
<td>3245 (5.78%)</td>
</tr>
<tr>
<td>Black or Black British</td>
<td>5063 (2.92%)</td>
<td>2051 (3.66%)</td>
</tr>
<tr>
<td>Mixed or other ethnic group</td>
<td>1588 (9.93%)</td>
<td>617 (1.10%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4288 (2.50%)</td>
<td>2333 (4.16%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Index of Multiple Deprivation</th>
<th>Cancer cohort</th>
<th>Control population</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>129 (7.55%)</td>
<td>428 (7.63%)</td>
</tr>
<tr>
<td>2</td>
<td>134 (7.85%)</td>
<td>430 (7.83%)</td>
</tr>
<tr>
<td>3</td>
<td>143 (8.40%)</td>
<td>471 (8.40%)</td>
</tr>
<tr>
<td>4</td>
<td>151 (8.87%)</td>
<td>439 (7.73%)</td>
</tr>
<tr>
<td>5</td>
<td>157 (9.19%)</td>
<td>410 (7.22%)</td>
</tr>
<tr>
<td>6</td>
<td>161 (9.57%)</td>
<td>431 (7.79%)</td>
</tr>
<tr>
<td>7</td>
<td>168 (9.81%)</td>
<td>445 (8.92%)</td>
</tr>
<tr>
<td>8</td>
<td>166 (9.74%)</td>
<td>418 (7.45%)</td>
</tr>
<tr>
<td>9</td>
<td>168 (9.86%)</td>
<td>417 (7.45%)</td>
</tr>
<tr>
<td>10</td>
<td>160 (9.39%)</td>
<td>391 (7.97%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>167 (9.78%)</td>
<td>1219 (22.50%)</td>
</tr>
</tbody>
</table>

Data are median (IQR) or n (%).

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

**Results**

During the study period from Dec 8, 2020, to Oct 15, 2021, 77 399 018 COVID-19 PCR tests for 28 010 955 individuals were done. 491 007 PCR tests were excluded because they were void and 4084 667 were excluded because they contained no or invalid NHS identifiers. 171 728 PCR tests were done for 377 194 individuals identified in the Rapid Cancer Registration Dataset. The cancer cohort comprised 377 194 individuals who had 56 102 positive PCR tests, corresponding to 4 288 821 individuals infected with breakthrough SARS-CoV-2. The control population consisted of 28 010 955 individuals, of whom 5 748 708 had SARS-CoV-2 breakthrough infections. Baseline characteristics of test-positive cases and test-negative controls in both the cancer and control cohorts are shown in Table 1. Overall vaccine effectiveness following the second vaccine dose against COVID-19 during the study period was 69.8% (95% CI 69.8–69.9) in the control population and 65.5% (65.1–65.9) in the cancer cohort. Vaccine effectiveness at 3–6 months after the second dose was...
lower in the cancer cohort (47.0%, 95% CI 46.3–47.6) than in the control population (61.4%, 61.4–61.5). Waning vaccine effectiveness in the cancer cohort reached its lowest point at 24–32 weeks following administration of the second vaccine dose (figure 1; appendix p 6).

To ascertain whether predefined subgroups within the cancer cohort showed greater differences in vaccine effectiveness against breakthrough infections, exploratory analyses were done (table 2; figure 2; appendix p 2). In the cancer cohort, vaccine effectiveness was higher in individuals (n=123,060) who had been vaccinated with two doses of BNT162b2 (72.1%, 95% CI 71.6–72.7) than in individuals (n=157,138) who had received two doses of ChAdOx1 nCov-19 (59.0%, 58.5–59.6; table 2).

Cancer subtype analysis identified that vaccine effectiveness (overall and at 3–6 months) was lower...
among patients with haematological malignancies than among those with solid organ malignancies, driven principally by those with a diagnosis of lymphoma or leukaemia (table 2; figure 2; appendix p 2). By contrast, we observed that overall and 3–6-month vaccine effectiveness in the myeloma subgroup was high (table 2). Among the solid cancers, vaccine effectiveness was lowest in those with head and neck malignancies (lip, oral cavity, and pharynx; table 2, appendix p 3). Patients who received systemic anticancer therapy or radiotherapy had a lower vaccine effectiveness overall and at 3–6 months compared with those who had not received these types of treatment (table 2). Patients who received systemic anticancer treatments or radiotherapy

<table>
<thead>
<tr>
<th>Cancer subtype</th>
<th>Exposed (PCR positive)</th>
<th>Not exposed (PCR negative)</th>
<th>Vaccine effectiveness (95% CI)</th>
<th>Exposed (PCR positive)</th>
<th>Not exposed (PCR negative)</th>
<th>Vaccine effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip, oral cavity, and pharynx (C00–C14)</td>
<td>441</td>
<td>684</td>
<td>16718</td>
<td>13798</td>
<td>46.8%</td>
<td>(43.5–50.2)</td>
</tr>
<tr>
<td>Non-colorectal gastrointestinal (C15–C17 and C22–C26)</td>
<td>921</td>
<td>2698</td>
<td>61577</td>
<td>45 563</td>
<td>74.7%</td>
<td>(73.3–76.2)</td>
</tr>
</tbody>
</table>

(Continued from previous page)

<table>
<thead>
<tr>
<th>Type of malignancy</th>
<th>Overall vaccine effectiveness</th>
<th>Vaccine effectiveness at 3–6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed (PCR positive)</td>
<td>Not exposed (PCR negative)</td>
<td>Vaccine effectiveness (95% CI)</td>
</tr>
<tr>
<td>Vaccinated (two doses)</td>
<td>Unvaccinated</td>
<td>Vaccinated (two doses)</td>
</tr>
<tr>
<td>Solid organ malignancy</td>
<td>15 070</td>
<td>26 203</td>
</tr>
<tr>
<td>Haematological malignancy</td>
<td>3222</td>
<td>5446</td>
</tr>
</tbody>
</table>

Table 2: Number of PCR positive and negative test results and vaccine effectiveness in cancer cohort subgroups

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within 12 months of data cutoff versus more than 12 months had lower vaccine effectiveness at 3–6 months (table 2). Patients with a more recent diagnosis (≤12 months relative to data cutoff) had a lower vaccine effectiveness at 3–6 months than those with an older diagnosis (>12 months relative to data cutoff; table 2). For every cancer stage, vaccine effectiveness at 3–6 months was lower than overall vaccine effectiveness (table 2).

To examine clinically relevant covariates that might drive these differences in the cancer cohort, a multivariable logistic regression model was fitted to adjust for the effects of the age, sex, Index of Multiple Deprivation, and ethnicity (figure 3; appendix p 7). At 3–6 months, vaccine effectiveness was significantly lower for those who had received systemic anticancer treatments at any time or within the last 12 months, radiotherapy at any time or within the last 12 months, or a cancer diagnosis within the last 12 months compared with those who had not, but was not different between those with versus without haematological malignancies (appendix p 7).

In the adjusted multivariable logistic regression, patients with stage 4 cancers versus all other stages and those aged 70 years or older versus those younger than 70 years had reduced frequencies of breakthrough infections and higher vaccine effectiveness (figures 2, 3). To investigate whether this result might be due to variations in patient behaviour, we did an exploratory post-hoc analysis in which we linked the cancer cohort to the Contact Tracing and Advice Service dataset. We found that patients with stage 4 cancer had fewer mean contacts than those with stage 1 cancer (1.32 [SD 4.36] vs 2.04 [7.76]) and that the mean number of contacts was lower for patients older than 70 years compared with those younger than 70 years (appendix pp 4, 8). We identified evidence of an inverse relationship between age group and the number of contacts (appendix pp 4, 8). The greatest levels of waning vaccine effectiveness were observed in those with a diagnosis of lymphoma or leukaemia, in those who were diagnosed within 12 months of data cutoff, and in those who had received systemic anticancer treatments or radiotherapy (figure 4; appendix p 5).

In a post-hoc analysis, we observed that there were higher levels of protection afforded against COVID-19 hospitalisation (84.5%, 95% CI 83.6–85.4) and death (93.5%, 95% CI 93.0–94.0) than against breakthrough infections in our cancer cohort following the second dose (appendix p 6). Similar to vaccine effectiveness against breakthrough infections, vaccine effectiveness against more severe COVID-19 outcomes waned at 3–6 months (appendix p 6).

**Discussion**

Patients with cancer initially had high COVID-19 vaccine effectiveness, similar to the control population, but this vaccine effectiveness rapidly waned. Reduced vaccine effectiveness was observed in individuals who had been diagnosed with cancer or had received radiotherapy or systemic anticancer treatments within the preceding 12 months. A diagnosis of lymphoma or leukaemia was also associated with both lower, and more rapidly waning,
vaccine effectiveness. Our findings reflect published clinical data from a US cohort of 184 485 patients with cancer and a cohort of 2391 patients with cancer from France.24,25 Waning of vaccine effectiveness at 3–6 months was less pronounced for the outcomes of COVID-19 hospitalisation or death than for breakthrough infections, although we note that these metrics are a lagged indicator of vaccine effectiveness. Although this study cannot address the mechanisms for this drop in vaccine effectiveness, the findings match those of previous studies that have identified reduced levels of protective antibody and T-cell responses after vaccination in this cohort.8,10 These patients, especially those with lymphoma and leukaemia, might have a limited capacity to maintain immunological vaccine memory, in many cases as a consequence of cancer treatments that specifically suppress immune responses. For patients in the cancer cohort, the BNT162b2 vaccine resulted in higher levels of vaccine effectiveness than the ChAdOx1 nCoV-19 vaccine, in keeping with studies in the general population.21

We found that the absolute difference in vaccine effectiveness against breakthrough infections in people with cancer compared with the control population was 4.3 percentage points. However, at 3–6 months, this
difference in vaccine effectiveness widened to 14.4 percentage points, representing a reduction in vaccine effectiveness of nearly a third in patients with cancer. Waning vaccine effectiveness has been described in other studies of COVID-19 vaccines in people without cancer. In parallel to this work, an analysis of a UK cohort has identified waning vaccine effectiveness against symptomatic disease of 25 percentage points at week 20 after second-dose vaccination for both BNT162b2 and ChAdOx1 nCoV-19 in a clinically extremely vulnerable group, which comprised patients with a range of different medical conditions, including trisomy 21, obesity, post-splenectomy, and cancer. Our evaluation had the advantage of being done at the population level, reducing the risk of sampling error, and included larger numbers of patients than any previously published analysis on cancer and COVID-19, enabling a more granular cancer subgroup evaluation.

There are some limitations to this analysis. First, we only included patients recorded as having cancer up to April 30, 2021, excluding those who were diagnosed more recently. This restriction is likely to have resulted in underestimation of the reduction in vaccine effectiveness in the cancer cohort, as those who were recently diagnosed were more likely to have been receiving active treatment but will not have been counted among the positive SARS-CoV-2 test results of the cancer cohort. The effect might be additionally compounded by the older median age of the cancer cohort versus the control population; we found that older patients might have had fewer social contacts and therefore fewer potential transmission events. Second, we note that the reduced vaccine effectiveness with radiotherapy might have been driven by concurrent systemic cytotoxic treatment. Third, we are not able to exclude the possibility that the control population might display differences in behaviour compared with patients with cancer. Specifically, there might have been differences in attendance rates for confirmatory PCR following a positive lateral flow test, which might have been exacerbated by patients with cancer being monitored more closely, having tests offered more frequently, and being able to access care more readily. Some of the aforementioned behavioural differences could alter the denominator in test-negative case-control analyses and make it more difficult to make highly certain population inferences. Fourth, we have not corrected our analyses for causes of death other than COVID-19, partly due to the challenges of identifying whether cause of death was due to COVID-19 or associated with COVID-19. Fifth, our analysis comprised patients who had received two doses of COVID-19 vaccine and patients with cancer in England are now routinely offered a third or fourth vaccine booster dose. Sixth, time-to-event analyses were not in the data analysis plan because breakthrough infections occur in waves and vaccination was implemented during several months by age groups. Finally, our analysis also pre-dates the most recent wave of SARS-CoV-2 infection with the omicron variant (B.1.1.529); further follow-up is required to determine whether the same differences in vaccine effectiveness are present between controls and patients with cancer—whether our study is generalisable—in this new situation, although we envisage that findings would be similar.

To conclude, we found that individuals with cancer have demonstrable, albeit impaired, overall vaccine effectiveness against breakthrough infections with SARS-CoV-2. Vaccine effectiveness for those with cancer waned more rapidly than for the control population; this effect was more pronounced in those with haematological malignancies. Put into the wider context of the ongoing emergence of highly transmissible COVID-19 strains, such as omicron, our findings support the global prioritisation and evaluation of vaccination booster types and programmes for people with cancer, including analyses on the impact of different treatments. Patients with cancer should also be encouraged to use non-pharmacological strategies, such as behaviour modifications or personal protective equipment, to prevent transmission when community rates are high; the general population should also be conscious about getting tested before being in contact with high-risk individuals. We have identified groups at high risk of breakthrough infections who can be prioritised for research or pandemic response interventions, early community treatment, or pre-exposure prophylaxis programmes. Such measures will be crucially important as global health-care and cancer care systems adapt to living with COVID-19 as an endemic disease.
Articles

Contributors
LYWL, TS, MCI, ML, MT, ART, HSM, LB, MB, SR, TWR, AP, GM, MM, MWF, TF, and PJ contributed to study design; LYWL, MCI, LB, MB, JC, SR, and MP contributed to data acquisition; LYWL, TS, MCI, LB, and MB accessed and verified the data; LYWL, TS, MCI, ML, MT, ART, HSM, YA-H, MB, LB, AB, ELIC, JC, JJC, SK, QQ, GI, CH-W, RJH, AJXL, PCLI, JKHL, MP, JSP, JRP, VAP, AR, ASR, TMR, TWR, RLR, SR, MHT, TW, SW, TI, SMJ, GM, MM, AP, MWF, TF, and PJ interpreted the data; and LYWL, TS, MCI, ML, MT, ART, HSM, YA-H, MB, LB, AB, ELIC, JC, JJC, SK, QQ, GI, CH-W, RJH, AJXL, PCLI, JKHL, MP, JSP, JRP, VAP, AR, ASR, TMR, TWR, RLR, SR, MHT, TW, SW, TI, SMJ, GM, MM, AP, MWF, TF, and PJ wrote the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests
We declare no competing interests.

Data sharing
To comply with data privacy laws, data from this study, including individual participant data, are not available for sharing. Data field definition within the data dictionary is available by reasonable request to the corresponding author. The privacy statement for individuals defined within the data dictionary is available at https://www.gov.uk/government/publications/phe-privacy-information/privacy-information.

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We declare no competing interests.

References