Twin peaks: the Omicron SARS-CoV-2 BA.1 and BA.2 epidemics in England

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Abstract

BACKGROUND

Rapid transmission of the SARS-CoV-2 Omicron variant has led to record-breaking incidence rates around the world. Sub-lineages have been detected in many countries with BA.1 replacing Delta and BA.2 replacing BA.1.

METHODS

The REal-time Assessment of Community Transmission-1 (REACT-1) study has tracked SARS-CoV-2 infection in England using RT-PCR results from self-administered throat and nose swabs from randomly-selected participants aged 5+ years. Rounds of data collection were approximately monthly from May 2020 to March 2022.

RESULTS

In March 2022, weighted prevalence was 6.37% (N=109,181), more than twice that in February 2022 following an initial Omicron peak in January 2022. Of the lineages determined by viral genome sequencing, 3,382 (99.97%) were Omicron, including 346 (10.2%) BA.1, 3035 (89.7%) BA.2 and one (0.03%) BA.3 sub-lineage; the remainder (1, 0.03%) was Delta AY.4. The BA.2 Omicron sub-lineage had a growth rate advantage (compared to BA.1 and sub-lineages) of 0.11 (95% credible interval [CrI], 0.10, 0.11). Prevalence was increasing overall (reproduction number *R*=1.07, 95% CrI, 1.06, 1.09), with the greatest increase in those aged 55+ years (*R*=1.12, 95% CrI, 1.09, 1.14) among whom estimated prevalence on March 31, 2022 was 8.31%, nearly 20-fold the median prevalence since May 1, 2020.

CONCLUSIONS

We observed unprecedented levels of SARS-CoV-2 infection in England in March 2022 and an almost complete replacement of Omicron BA.1 by BA.2. The high and increasing prevalence in older adults may increase hospitalizations and deaths despite high levels of vaccination.

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Since the emergence of Omicron as the dominant SARS-CoV-2 variant in England in mid- to late December 2021,[1,2] the peak in January 2022 associated with the BA.1 variant was the highest prevalence recorded in England to that time.[3] This was followed by replacement of BA.1 by the more transmissible BA.2.[3–5] By late March 2022, BA.2 infections had surged in many European countries[6] and had become the predominant variant in the USA.[7] Although Omicron infections lead to fewer severe outcomes than Delta infections, the risk reduction depends on age[8] and background immunity, with some deaths observed in children under 12 years of age.[9] In less vaccinated populations such as Hong Kong, with limited protection from vaccination among their oldest citizens,[10] BA.2 has spread very quickly;[11] this fifth wave has caused over 95% of the total COVID-19 death toll in Hong Kong to date.[12]

In England, during the first phase of the Omicron (BA.1) epidemic, the country saw peaks in hospital admissions in late December 2021 to early January 2022 and in deaths (within 28 days of a positive test) in mid-January 2022.[13] Since then, following falls in February 2022, in late March 2022, hospital admissions returned to levels similar to those seen in January 2022 (~2000 admissions per day on average) with deaths also increasing in England since early March 2022.

The REal-time Assessment of Community Transmission-1 (REACT-1) study has tracked the spread of the SARS-CoV-2 virus among randomly-selected community samples in England since May 2020.[14] Unlike reliance on testing of symptomatic individuals to estimate prevalence as is the case in most other countries, the use of random samples of the population means that estimates are unbiased with respect to test-seeking behaviors, availability of tests and includes asymptomatic as well as symptomatic infections.[15] With completion of the nineteenth and final round of REACT-1 data collection, we document here the transmission dynamics of SARS-CoV-2 in England since May 2020, in particular the emergence of the Omicron epidemic and the replacement of BA.1 and sub-lineages by BA.2.

Methods

STUDY DESIGN

The REACT-1 study involves a series of cross-sectional surveys of random samples of the population of England at ages 5+ years,[14] carried out approximately monthly since May

2020. Those registering for the study were sent a self-administered throat and nose swab kit with instructions and asked to complete a questionnaire. Over 2 million individuals with a valid test result for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) took part during the 19 rounds of REACT-1 to March 31, 2022 (Table 1). We focus here on the Omicron period spanning round 16 (November 23 to December 14, 2021, N=97,089), round 17 (January 5 to 20, 2022, N=102,174), round 18 (February 8 to March 1, 2022, N=94,950) and round 19 (March 8-31, 2022, N=109,459).

The sampling frame was the National Health Service (NHS) general practitioner list of patients in England (covering almost the entire population) which includes name, address, age and sex. Participants provided information on ethnicity, household size, occupation, symptoms and other variables.[16] We used residential postcode to link to an area-level Index of Multiple Deprivation (an overall relative measure of deprivation)[17] and to urban/rural status.[18] We added small incentives in rounds 18 and 19 to increase response rates among under-represented groups. We used a multiplex including influenza A and B for rounds 16 to 19; only the SARS-CoV-2 results are reported here.

A test result was positive if both N gene and E gene targets were detected or N gene was detected with cycle threshold (Ct) value below 37. We carried out viral genome sequencing (Quadram Institute, Norwich, UK) of positive samples with Ct $\leq$34 for either E or N gene. We used the ARTIC protocol[19] (version 4 for rounds 16 and 17 and version 4.1 for rounds 18 and 19) for viral RNA amplification, CoronaHiT for preparation of sequencing libraries,[20] the ARTIC bioinformatics pipeline[19] and assigned lineages using Pangolin (v4.0 with pangolin-data v1.2.133).[21]

DATA ANALYSES

We used rim weighting[22] to estimate round-specific weighted prevalence and 95% credible intervals (Supplementary Appendix). We fit a Bayesian penalised-spline (P-spline) model[23,24] to the daily data to visualise temporal trends in swab-positivity over the whole study period. Additionally, we fitted four age-group-specific P-splines (5 to 17, 18 to 34, 35 to 54, 55+ years) with the smoothing parameter obtained from the model fit to all the data.

We also fitted an exponential growth/decay model to the daily data.[24] We assumed a binomial distribution for the proportion of positives by day using a bivariate No-U-Turn Sampler and a uniform prior distribution for the probability of swab-positivity.[25] The estimated growth/decay rate, *r*, was combined with the Omicron-specific generation time[26] to estimate the reproduction number, *R*,[27] in the Omicron period.

We estimated the growth rate advantage for the transition from wild-type to Alpha, Alpha to Delta, Delta to Omicron and Omicron BA.1 (and sub-lineages) to BA.2 by fitting a Bayesian logistic regression model to the daily proportions of the competing variants.

To examine geographic trends at Lower-Tier Local Authority (LTLA) level (N=315) in England we estimated smoothed weighted prevalence using a nearest neighbour method (Supplementary Appendix). Daily data on mobility (transit, driving and walking) were downloaded for England from Apple Mobility Trends Report.[28] Seven-day moving averages, relative to the maximum seven-day average between May 1, 2020 and March 31, 2022, were plotted on the fourth of the seven days.

Statistical analyses were performed with R software, version 4.0.5.

Results

OVERALL PREVALENCE, TEMPORAL AND GEOGRAPHIC TRENDS

Of 697,055 individuals invited into the final (nineteenth) round of REACT-1, 109,181 (15.7%) registered and returned a throat and nasal swab (from March 8 to 31, 2022) with a valid SARS-CoV-2 RT-PCR test result. Of these, 6,902 were positive, yielding a weighted prevalence of 6.37% (95% credible interval [CrI], 6.21%, 6.53%), the highest weighted prevalence observed throughout the REACT-1 study (Table 1). Prevalence levels by participant characteristics are shown in Table S1.

Trends in prevalence, growth rate, predominant variants, lockdown periods in England and mobility data over the 23 months from May 1, 2020 to March 31, 2022 are shown in Figure 1A-E. The P-spline model fit to all REACT-1 data shows an initial decline during the first lockdown in England, the second wave from autumn 2020 through January 2021 and the

initial Omicron wave from December 2021 to January 2022. A fall in weighted prevalence during February 2022 was then followed by a steep increase in March 2022 (Figure 1A and 1B). We estimated doubling time in weighted prevalence of 30.5 (95% CrI 25.8, 37.0) days in round 19 (March 8 to 31, 2022), corresponding to a within-round *R* of 1.07 (95% CrI 1.06, 1.09) with >0.99 posterior probability that *R*>1 (Table S2).

Estimated daily growth rates (Figure 1C) clearly show periods of rapid growth associated with i) the second wave in England as Alpha variant replaced wild-type in late summer and autumn 2020, ii) as Delta replaced Alpha in late spring and summer 2021, iii) as Omicron replaced Delta in November to December 2021, and iv) as BA.2 replaced BA.1 during February and March 2022 (Figure 1E and 1F). The growth rate plateaued at 0.06 (95% CrI 0.03, 0.07) on ~March 10, 2022 (Figure 1C). March 2022 also corresponded to a period of high and increasing mobility (Figure 1D), with indices for driving, walking and transit reaching by March 31 respectively 92.9%, 85.0%, and 84.2% of the maximum observed throughout the study period.

During the Omicron period, peak weighted prevalence was observed during rounds 17 and 19, with highest prevalence at ages 5 to 11 years (Figure 2A, Table S1A). P-splines fit to daily weighted prevalence in four broad age groups (Figure 2B) indicated a steep increase in weighted prevalence between round 18 and round 19 at all ages, and i) a possibly decreasing prevalence late in round 19 in those aged 5 to 17 years, ii) a possibly plateauing prevalence in those aged 18 to 35 and 35 to 54 years, and iii) a within-round increasing trend in those aged 55+ years. From an exponential model fit to data from round 19 we estimated a within-round *R* of 1.10 (95% CrI, 1.07, 1.12) at ages 18 to 34 years, 1.04 (95% CrI, 1.02, 1.07) at 35 to 54 years, 1.12 (95% CrI 1.09, 1.14) at ages 55+ years (all >0.99 posterior probability that *R*>1, Table S2); while it was 1.00 (95% CrI 0.97, 1.03) at ages 5 to 17 years with 0.58 posterior probability that *R*>1.

On March 31, 2022, estimated prevalence was 5.50% at ages 5 to 17 years and 8.31% at ages 55+ years (Figure 2B), respectively 4-fold and nearly 20-fold the median weighted prevalence at these ages across the whole study period from May 1, 2020.

In round 13 only 2.86% (weighted estimate) of children aged 12 to 17 years had been vaccinated. At that time, weighted prevalence of SARS-CoV-2 swab-positivity was 1.53 (95%

CrI 1.00, 2.06) times higher among 12 to 17 year-olds than in those aged 5 to 11 years. Since then, as the vaccine programme in older children in England took off, the ratio of weighted prevalence in children aged 12 to 17 years relative to that of 5 to 11 year-olds (almost all unvaccinated) dropped to 0.53 (95% CrI 0.28, 0.78) in round 19.

Region-specific weighted prevalence in round 19 ranged from 5.28% (95% CrI 4.85%, 5.75%) in West Midlands to 8.13% (95% CrI 7.59%, 8.71%) in South West (Figure 3A, Table S1A) with within-round 19 R>1 in all regions except London (Table S2B). Nearest neighbour smoothed estimates indicated 'twin peaks' in weighted prevalence in rounds 17 and 19. There was a strong North-to-South decreasing prevalence gradient in round 17 (Figure 3C) but a strong North-to-South increasing gradient in round 19 (Figure 3E) with 19 LTLAs (all in South West and East of England) having smoothed prevalence estimates >8.0%.

VIRAL GENOME SEQUENCING

Viral genome sequencing of 4,038 positive samples obtained to March 22, 2022 resulted in 3,383 (83.8%) determined lineages with more than 50% genome coverage; one (0.03%, 95% CI 0.00%, 0.17%) was AY.4 Delta sub-lineage while all others were Omicron sub-lineages (Table S3). Among these 10.2% (95% CI 9.23%, 11.3%; N=346) corresponded to BA.1 or its sub-lineages, 89.7% (95% CI 88.6%, 90.7%; N=3,035) to BA.2 or its sub-lineages, and 0.03% (0.00%, 0.16%, N=1) to BA.3. Eight samples with >90% genome coverage were identified as BA.1/BA.2 recombinants (N=5 XE, N=3 XL).

Using exponential models we estimated a daily growth rate advantage of 0.11 (0.10, 0.11) in the odds of BA.2 (vs all other Omicron sub-lineages), a 94.7% (95% CI 93.9%, 95.4%) proportion of BA.2 as of March 22, 2022 (Figure 1F), and an estimated 54.7 (95% CrI 52.3, 57.2) days for the proportion of BA.2 to grow from 5% to 95%. This is approximately two-fold slower than our estimate for the Delta-to-Omicron transition (28.5, 95% CI 26.3, 30.7 days), over 20% faster than the Alpha-to-Delta transition and almost four-fold faster than the wild-type-to-Alpha transition (Table 2).

Discussion

Within a purpose-designed series of large cross-sectional population-based surveys with random selection of participants, we document here the transmission dynamics of

SARS-CoV-2 in England from May 1, 2020 to March 31, 2022, at the height of the Omicron BA.2 wave. The Omicron epidemic in England is characterised by two distinct phases: i) very rapid replacement of Delta by Omicron during December 2021 and early January 2022, leading to the highest rates of infection since the start of REACT-1; ii) rapid replacement of Omicron BA.1 and sub-lineages by BA.2 during February to March 2022. Mobility indices also reached their highest levels (since October 2021) in March 2022, reflecting increased social mixing as restrictions were eased. Weighted prevalence in March 2022 increased most rapidly among older adults who – despite high levels of vaccination – remain the most vulnerable to serious illness, hospitalizations and death from COVID-19. Of concern, hospitalizations and deaths from COVID-19 in England also increased in March 2022 as infections were rising.[29]

We show a transmission advantage for Alpha compared to wild-type in the second wave of infections in England, peaking in January 2021, for Delta as it replaced Alpha during April-June 2021, for Omicron (BA.1) as it rapidly replaced Delta and most recently for BA.2 versus BA.1 and its sub-lineages. Data showing a transmission advantage for BA.2 compared to BA.1 have also been reported from the national routine testing data in the UK[30] and in Denmark.[31]

The Omicron epidemic in England – involving 'twin peaks' as the epidemic transitioned from Delta to Omicron (BA.1) and then from BA.1 to BA.2 – has unfolded over a three-month period, ahead of similar epidemics in most other countries. While the immune landscape due both to natural infection and vaccination differs by country and over time,[15] the transmission dynamics in England are highly relevant to other high-income countries that, like England, experienced Alpha, Delta and subsequently Omicron waves of infection alongside an extensive vaccination programme.

The transmission advantage for one variant over another will depend on the immune background (which varies over time due to natural infection and vaccination) as well as transmissibility[32] and mean generation time so it is not possible to assess directly how much more intrinsically transmissible Omicron is compared to wild-type or Alpha; nonetheless, our data show that each new variant of concern has demonstrated a transmission advantage over the previous variants. In addition, we detected recombinant infections, notably XE (BA.1/BA.2). Little is known about the clinical manifestations of XE and whether it may lead

to more severe disease than BA.1 or BA.2, but early indications suggest a growth advantage compared with BA.2.[33] Continued surveillance of such recombinant infections is warranted.

To deal with the initial phase of the Omicron epidemic, some countries re-initiated social distancing policies,[34] while in the USA healthcare systems struggled to cope with the increase in healthcare demands[35] and in England the vaccination programme was accelerated. Subsequently, the UK government (on February 24, 2022) removed all domestic legal restrictions concerning COVID-19 in England[36] as part of the government's plan for 'Living with COVID-19';[37] from February 24, 2022 legal requirement to self-isolate for COVID-19 was lifted and since April 1, 2022, all remaining restrictions in England were removed[36]. Also, from April 1, 2022, with a few exceptions, free lateral flow and PCR tests were no longer available, and other surveillance measures were curtailed, with greater reliance on the vaccine programme to manage the ongoing epidemic. In this regard, our most recent data on infections in children show much higher infection rates in 5-to-11 year olds (for whom vaccination rollout only commenced April 2022) than 12-to-17 year olds, around 70% of whom had been vaccinated (one or two doses) by end of March 2022.[38]

Our study has limitations. We rely on unsupervised, self-swabbing at home by named individuals selected at random from the NHS registers. While response rates of over 30% were achieved during the first lockdown in England in May 2020, they fell to 12.2% by round 17 (January 2022). We included a small monetary incentive in rounds 18 and 19 (February to March 2022) among participants aged 13 to 44 years, which increased overall response rates in those rounds to ~15.0%. Additionally, we used within-round rim weighting[22] to correct the sample to be representative of the base population. During the 23 months of the study, we have adapted the way samples were handled (courier to post, no cold chain) and also included a multiplex PCR assay in the latter rounds. Although these changes may have introduced small effects into between-round comparisons, they should not have affected within-round trends.

In conclusion, we report unprecedented and increasing prevalence of SARS-CoV-2 infections in England during March 2022. We observed Omicron 'twin peaks' as BA.1 replaced Delta and BA.2 replaced BA.1, while at the same time, society opened up with all legal restrictions related to COVID-19 in England lifted as part of its 'Living with COVID-19' strategy.

Nonetheless there are worrying signs of increasing hospitalizations and deaths due to COVID-19 in England during March 2022, which may reflect the very high and increasing rates of infection particularly in older people. These trends in England may presage what might be expected in the USA and other countries as BA.2 takes hold as the predominant variant worldwide.

Data availability:

Access to REACT-1 individual-level data is restricted to protect participants' anonymity. Summary statistics, descriptive tables, and code from the current REACT-1 study are available at https://github.com/mrc-ide/reactidd (doi 10.5281/zenodo.5574472). REACT-1 study materials are available for each round at https://www.imperial.ac.uk/medicine/research-and-impact/groups/react-study/react-1-study-materials/
Sequence read data are available without restriction from the European Nucleotide Archive at https://www.ebi.ac.uk/ena/browser/view/PRJEB37886, and consensus genome sequences are available from the Global initiative on sharing all influenza data (GISAID).

Ethics: We obtained research ethics approval from the South Central-Berkshire B Research Ethics Committee (IRAS ID: 283787).

Public involvement: A Public Advisory Panel provides input into the design, conduct, and dissemination of the REACT research program.

Contributors: PE, CAD and MC-H are corresponding authors. PE, MC-H and CAD conceived the study and the analytical plan. MC-H, OE, NS, DT, BB and HWang performed the statistical analyses. HWang, OE, BB, and MW curated the data. JE, CA, PJD, DA, WB, GT, HWard, AD and GC provided study oversight and results interpretation. AJP and AJT generated the sequencing data. AD and PE obtained funding. All authors revised the manuscript for

important intellectual content and approved the submission of the manuscript. PE, CAD, MC-H had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis and for the decision to submit for publication.

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Tables and Figures

Table 1. Unweighted and weighted prevalence of SARS-CoV-2 swab-positivity from REACT-1 across rounds 1 to 19.

Round	Tested swabs	Positive swabs	Unweighted prevalence (95% CI)	Weighted prevalence (95% CrI)	First sample	Last sample
1	120,620	159	0.13% (0.11%, 0.15%)	0.16% (0.13%, 0.19%)	01/05/20	01/06/20
2	159,199	123	0.08% (0.07%, 0.09%)	0.09% (0.07%, 0.11%)	19/06/20	07/07/20
3	162,821	54	0.03% (0.03%, 0.04%)	0.04% (0.03%, 0.05%)	24/07/20	11/08/20
4	154,325	137	0.09% (0.08%, 0.11%)	0.13% (0.01%, 0.15%)	20/08/20	08/09/20
5	174,949	824	0.47% (0.44%, 0.50%)	0.60% (0.55%, 0.71%)	18/09/20	05/10/20
6	160,175	1,732	1.08% (1.03%, 1.13%)	1.30% (1.21%, 1.39%)	16/10/20	02/11/20
7	168,181	1,299	0.77% (0.73%, 0.82%)	0.94% (0.87%, 1.01%)	13/11/20	03/12/20
8	167,642	2,282	1.36% (1.31%, 1.42%)	1.57% (1.49%, 1.66%)	06/01/21	22/01/21
9	165,456	689	0.42% (0.39%, 0.45%)	0.49% (0.44%, 0.55%)	04/02/21	23/02/21
10	140,844	227	0.16% (0.14%, 0.18%)	0.20% (0.17%, 0.23%)	11/03/21	30/03/21
11	127,408	115	0.09% (0.07%, 0.11%)	0.10% (0.08%, 0.13%)	15/04/21	03/05/21
12*	108,911	135	0.12% (0.10%, 0.15%)	0.15% (0.12%, 0.18%)	20/05/21	07/06/21
13	98,233	527	0.54% (0.49%, 0.58%)	0.63% (0.57%, 0.69%)	24/06/21	12/07/21
14**	100,527	764	0.76% (0.71%, 0.82%)	0.83% (0.76%, 0.89%)	09/09/21	27/09/21
15***	100,112	1,399	1.40% (1.33%, 1.47%)	1.57% (1.48%, 1.66%)	19/10/21	05/11/21
16****	97,089	1,192	1.23% (1.16%, 1.30%)	1.41% (1.33%, 1.51%)	23/11/21	14/12/21
17†	102,174	4,073	3.99% (3.87%, 4.11%)	4.41% (4.25%, 4.56%)	05/01/22	20/01/22
18‡§	94,950	2,731	2.88% (2.77%, 2.98%)	2.88% (2.76%, 3.00%)	08/02/22	01/03/22
19§	109,181	6,902	6.32% (6.18%, 6.47%)	6.37% (6.21%, 6.53%)	08/03/22	31/03/22

* Sampling strategy changed for round 12 and subsequent rounds. Therefore unweighted prevalence is not directly comparable with previous rounds

** Including N=509 samples from 28-30 September 2021. Sample handling changed in round 14. Therefore prevalence is not directly comparable with previous rounds

*** Including N=93 samples (all negatives) from 6-8 November 2021, and N=86 samples with no collection/arrival dates

**** Including N=661 samples (including 12 positives) from 15-17 December 2021. Swab positivity was assessed using a multiplex assay from round 16 onwards. Test diagnostic characteristics may slightly differ with previous rounds

† Including N=862 (including 36 positives) from 21-24 January 2022

‡ Including N=685 (including 18 positives) from 2-4 March 2022

§ Incentives were used in rounds 18 and 19 to increase the response rates in previously under-represented groups

Table 2. Growth rate advantage estimates from exponential growth models of the odds of the main SARS-CoV-2 (sub-) lineages. Point estimates and 95% CrI intervals are reported along with the estimated time (in days) for the proportion of the lineage of interest to grow from 5 to 50% and from 5 to 95%. Results are presented for the Wild-type-to-Alpha, the Alpha-to-Delta, the Delta-to-Omicron, and the other Omicron-to-BA.2 sub-lineages transitions separately.

Lineages competing	Growth rate advantage	Time (5% to 50%)	Time (5% to 95%)
Alpha vs Other (Nov 2020-Apr 2021)	0.029 (0.019 , 0.042)	100.1 (157.8 , 70.5)	200.2 (315.5 , 141.0)
Delta vs Alpha (Apr - Jul 2021)	0.085 (0.070 , 0.104)	34.8 (42.2 , 28.4)	69.6 (84.4 , 56.8)
Omicron vs Delta (Dec 2021 -Jan 2022)	0.207 (0.192 , 0.224)	14.2 (15.4 , 13.1)	28.5 (30.7 , 26.3)
BA.2 vs non-BA.2 Omicron (Feb - Apr 2022)	0.108 (0.103 , 0.113)	27.4 (28.6 , 26.1)	54.7 (57.2 , 52.3)

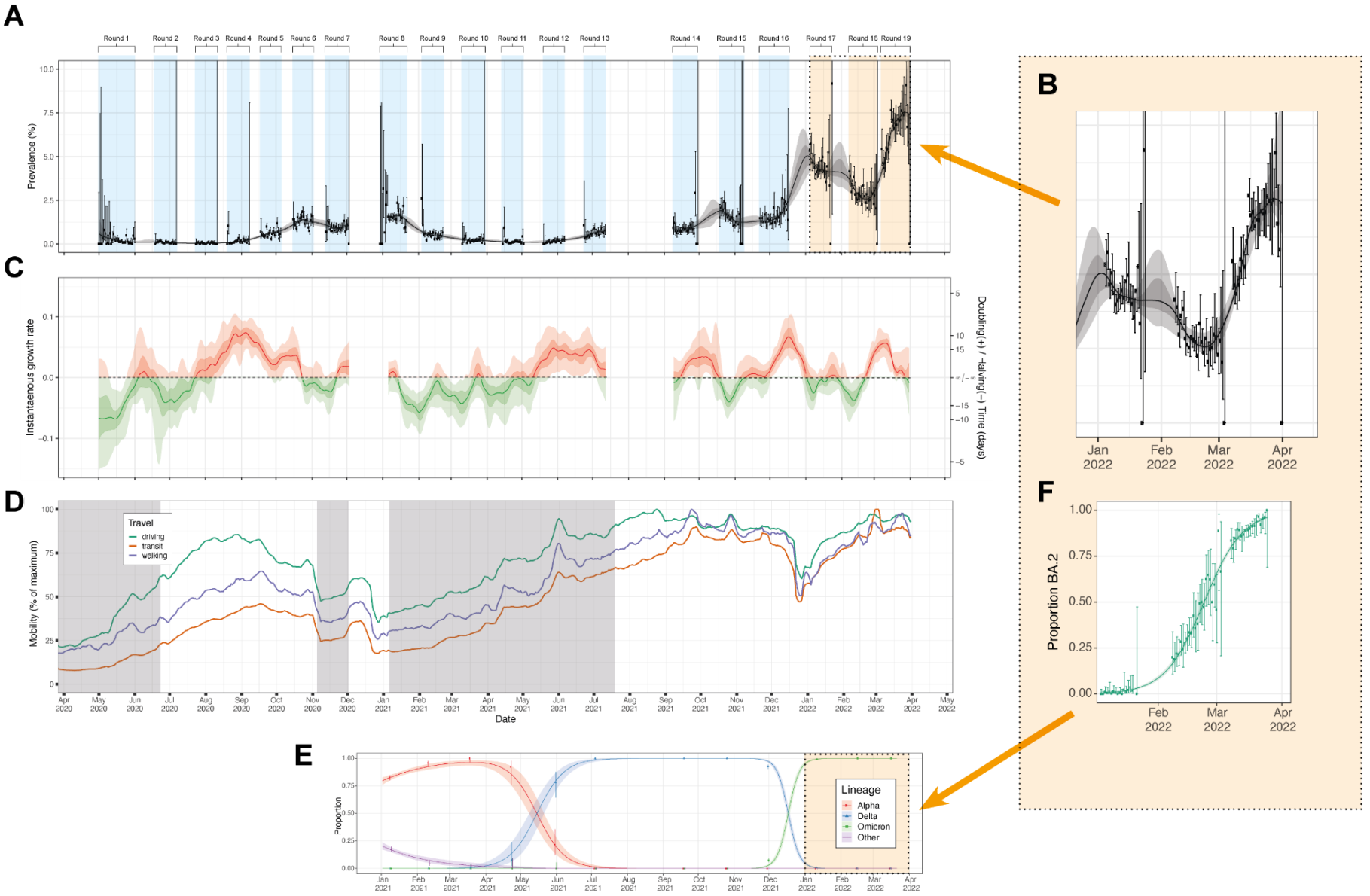
A
Round 1
Round 2
Round 3
Round 4
Round 5
Round 6
Round 7
Round 8
Round 9
Round 10
Round 11
Round 12
Round 13
Round 14
Round 15
Round 16
Round 17
Round 18
Round 19
Prevalence (%)
B
Jan 2022
Feb 2022
Mar 2022
Apr 2022
C
Instantaneous growth rate
Doubling(+) / Halving(−) Time (days)
D
Travel
driving
transit
walking
Mobility (% of maximum)
Date
F
Proportion BA.2
E
Proportion
Lineage
Alpha
Delta
Omicron
Other

Figure 1. Overview of SARS-CoV-2 swab-positivity across the 19 rounds of REACT-1 study. **(A)** P-spline model fit to all rounds of REACT-1. Shaded grey region shows 50% (dark grey) and 95% (light grey) posterior credible interval for the P-spline model. Weighted prevalence of swab-positivity (Y axis) is represented for each day of sampling (X axis). Weighted observations (black dots) and 95% credible intervals (vertical lines) are also shown on an ordinal scale. **(B)** Blow up of the P-spline model for rounds 16 to 19. **(C)** Instantaneous growth rate for each of the swab days of the REACT study from the log-transformed P-spline. Posterior median estimates are represented as a smoothed solid line and 50% (dark shaded regions) and 95% (light shaded regions) are plotted in red for positive and in green for negative growth rates. **(D)** Daily Apple mobility indices for walking, driving and transit from phone location data for the duration of the REACT-1 study (1 May 2020 to 31 March 2022). We report seven-day moving averages of the indices and have scaled them to the maximum observed during the study period. Grey shaded regions represent periods when lockdown was implemented in England - details given in the Supplementary Appendix **(E)** Daily proportion of Alpha (red), Delta (blue), Omicron (green) and other (purple) SARS-CoV-2 lineages across rounds 8 to 19 of the REACT-1 study. Mean daily proportions (solid lines) and their 95% credible intervals (shaded regions) **(F)** Daily proportion of BA.2 and its sub-lineages (vs all other Omicron sub-lineages) infections among positive swabs with determined lineage and at least 50% genome coverage in round 17, round 18 and round 19 for samples obtained to 22 March 2022. Point estimates are represented (dots) along with 95% confidence intervals (vertical lines). Smoothed estimates of the proportion are also shown (solid line) together with their 95% credible intervals (shaded regions).

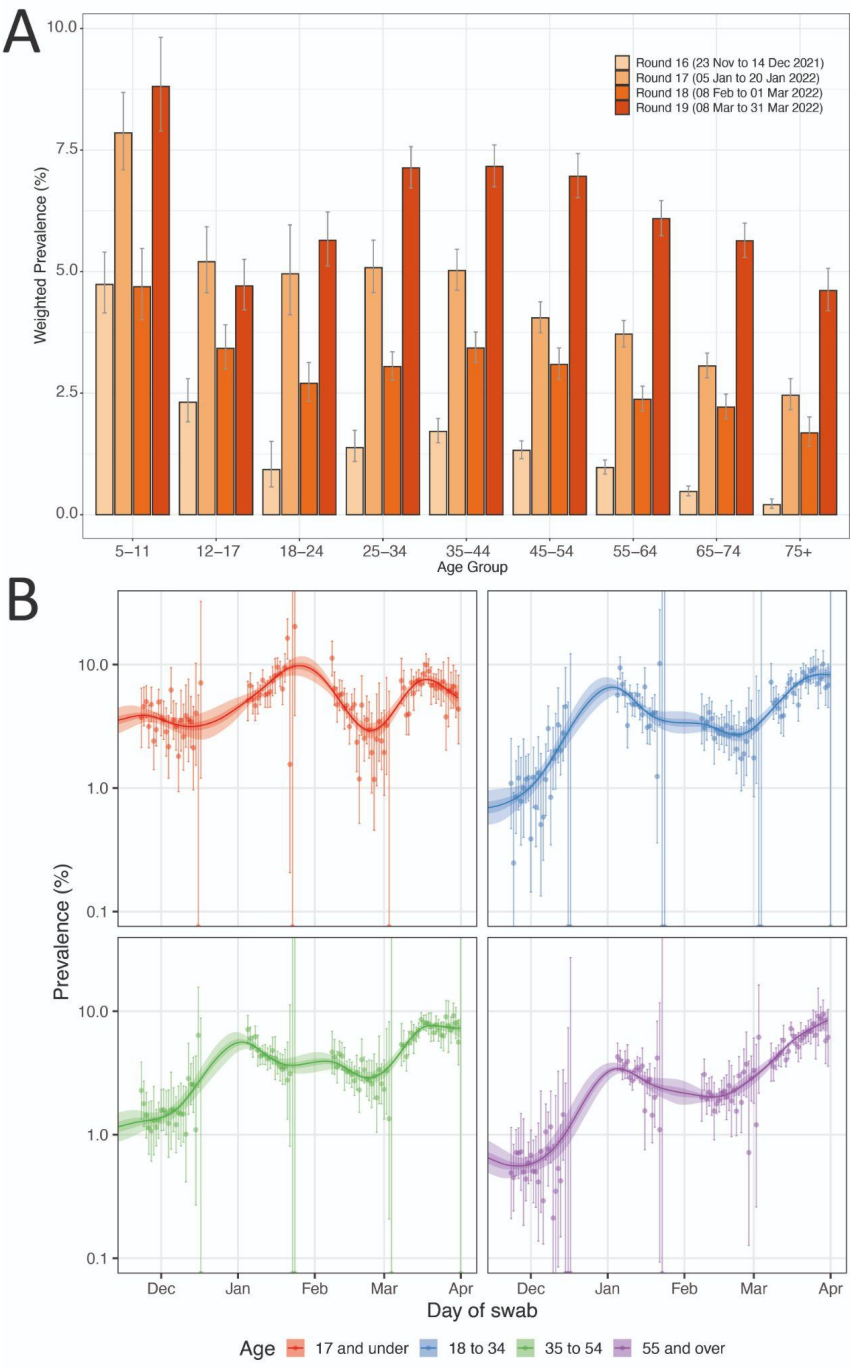

Figure 2. Weighted prevalence by age. (A) Weighted prevalence of SARS-CoV-2 swab-positivity by age group from round 16 (light orange) to round 19 (dark orange). Bars show the weighted prevalence point estimates and the vertical lines represent the 95% credible intervals. **(B)** Comparison of P-spline models fit to SARS-CoV-2 swab-positivity data from all rounds of REACT-1 for those aged 17 years and under (red), those aged 18 to 34 years (blue), those aged 35 to 54 years (green), and those aged 55 years and over (purple). Shaded regions show 50% (dark shade) and 95% (light shade) posterior credible interval for the P-spline models. Results are presented for each day (X axis) of sampling for rounds 16, 17, 18, and 19, and the prevalence of swab-positivity is shown (Y axis) on a log scale. Weighted observations (dots) and 95% credible intervals (vertical lines) are also shown.

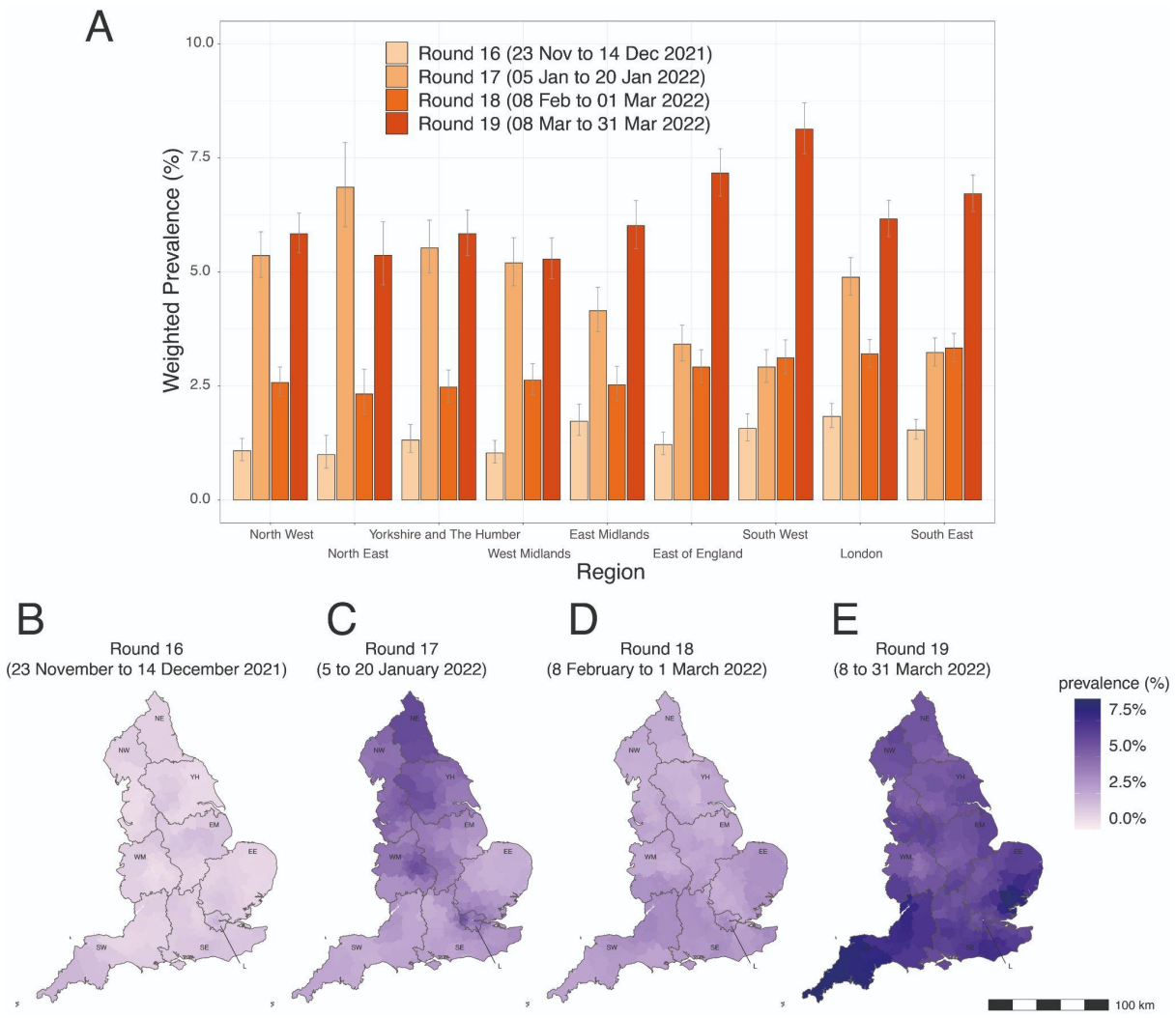

Figure 3. SARS-CoV-2 swab-positivity by region. (A) Weighted prevalence of SARS-CoV-2 swab-positivity by region from round 16 (light orange) to round 19 (dark orange). Bars show the weighted prevalence point estimates and the vertical lines represent the 95% credible intervals. **(B-E)** Neighbourhood smoothed average SARS-CoV-2 swab-positivity prevalence by lower-tier local authority area for round 16 (B), round 17 (C), round 18 (D), and round 19 (E). Neighbourhood prevalence calculated from nearest neighbours (the median number of neighbours within 30 km in the study). Average neighbourhood prevalence displayed for individual lower-tier local authorities for the whole of England. Regions: NE = North East, NW = North West, YH = Yorkshire and The Humber, EM = East Midlands, WM = West Midlands, EE = East of England, L = London, SE = South East, SW = South West

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Elliott P, Eales O, Steyn N, et al. Twin peaks: the Omicron SARS-CoV-2 BA.1 and BA.2 epidemics in England.

Supplementary Methods

STUDY DESIGN

Initially we aimed to obtain approximately equal numbers of participants in each lower-tier local authority (LTLA) in England (N=315), but from round 12 (May 20 to June 7, 2021) we switched to obtaining a random sample in proportion to population size at LTLA level. We use random iterative method (rim) weighting[22] to provide prevalence estimates for the population of England as a whole, adjusting for age, sex, deciles of the Index of Multiple Deprivation, LTLA counts, and ethnic group. Incentives were added to improve response among under-represented groups in rounds 18 and 19. For return of a completed test, a gift voucher worth £10 was offered to those aged 13 to 17 and 35 to 44 years and £20 to those aged 18 to 34 years.

Up to round 13 (June 24 to July 12, 2021), we collected dry swabs sent by courier to the laboratory on a cold chain but from round 14 (September 9 to 27, 2021 including 509 samples from 28-30 September) we switched to 'wet' (saline) swabs which (round 14) were sent to the laboratory either by courier (no cold chain) or priority post, and from round 15 onwards by priority post only. Because of delays in the post for return of swabs, we include a small proportion of samples obtained after the nominated closing date for the study.

CONFIRMATION OF Ct VALUES

RT-PCR was performed on 96 randomly chosen samples using the CDC assay[39] by the Quadram Institute as a secondary confirmation of the Ct values.

P-SPLINES

To fit the P-splines we used a No-U-Turn Sampler in logit space, partitioning the data into approximately 5-day sections by regularly spaced knots, and minimising edge effects by adding further knots beyond the study period. We used day of swabbing where reported or otherwise day of pick-up by courier or first Post Office scan where available. We guarded against over-fitting by use of fourth-order basis splines (b-splines) over the knots including a second-order random-walk prior distribution on the coefficients of the b-splines; the prior distribution penalised against changes in growth rate unless supported by the data [24].

THE EXPONENTIAL GROWTH/DECAY RATE AND THE REPRODUCTION NUMBER

We estimated r, the exponential growth/decay rate, over the entire period of the study (since May 1, 2020).[24] The reproduction number, R, for the Omicron period was estimated assuming a gamma-distributed generation time with Omicron-specific mean 3.3 days and standard deviation 3.5 days (shape n=0.89 and rate β=0.27) as:[26]

$$R = \left(1 + \frac{r}{\beta}\right)^{n}.$$

The estimate of a constant exponential growth rate, r, is not affected by being estimated from the prevalence of swab-positivity rather than incident infections. However, the use of prevalent swab-positivity data does mean that changes in the exponential growth rate, r, are not detected immediately. Instead, following a change in the true growth rate, the estimates move smoothly between the previous value and the more recent one.

CONSTANT GROWTH RATE MODELS

The daily relative growth rates in the log-odds of Alpha, Delta, Omicron and other lineages were estimated, assuming constant growth rates, using a Bayesian multinomial logistic regression model fit to the categorical outcome variable (Alpha, Delta, Omicron, other) over rounds 8 to 19 with Delta set as the reference category.

The time taken for the proportion of one lineage to increase from 0.05 to 0.5 was calculated assuming only two lineages were present and using the pairwise difference in their growth rates, r, in the equation:

$$T_{5\%\ to\ 50\%} = \frac{log(\frac{0.05}{1-0.05}) - log(\frac{0.5}{1-0.5})}{r}.$$

For example, in calculating Delta's rise against Alpha, *r* would be the difference in growth rates of Alpha and Delta. Due to the assumed symmetry, the time of one lineage to increase from 0.05 to 0.95 is just two times the above equation.

GEOGRAPHICAL VARIATION IN PREVALENCE

We used a neighbourhood spatial smoothing method to examine geographical variation in SARS-CoV-2 prevalence at the LTLA level. For each of 15 randomly selected participants within an LTLA, we calculated the prevalence of infection among the nearest M people, where M was the median number of study participants within 30 km, and then estimated the smoothed neighbourhood prevalence in that area.

PROTECTIVE BEHAVIORS

Swab-positivity data are stratified by protective behaviors (specifically shielding and indoor mask wearing) in Table S1B. These data were obtained from the study questionnaires.

The question relating to shielding was:

> Are you taking specific precautions because you are concerned that you/ your child will become severely ill with COVID-19?
>
> 1. Yes
>
> 2. No

The question relating to indoor mask wearing was:

> How often do you/does your child wear any kind of face covering or mask indoors or in enclosed spaces? Please do not include when you/they are in your/their own home or when eating or drinking.
>
> 1. All of the time
>
> 2. Some of the time

3. Hardly ever

4. Never

5. Don’t know

The full questionnaire for Round 19 is available here:

https://www.imperial.ac.uk/media/imperial-college/institute-of-global-health-innovation/REACT1_Round-19_ANTIGEN-Individual-Questionnaire_March-2022.pdf

Those for other rounds can be found here:

https://www.imperial.ac.uk/medicine/research-and-impact/groups/react-study/for-researchers/react-1-study-materials/

APPLE MOBILITY DATA

Days were defined from midnight to midnight, US Pacific time. Random rotating identifiers, rather than Apple IDs, are used for data sent from Apple users to the Apple Maps service. Thus no profiles are collected on individual movements. As Apple Maps thus has no demographic data on users, it is not possible to assess the representativeness of the mobility data provided.

LOCKDOWN DATES

In Figure 1D grey shaded regions represent periods when lockdown was implemented in England. The following dates were used as start and end dates (from May 1, 2020 to March 31, 2022):

June 23, 2020 The first national lockdown was announced on March 23, 2020.[40] The Prime Minister announced key changes to lockdown restrictions on June 23, 2020.[41]

November 5, 2020 The second national lockdown was announced on November 5, 2020.[42]

December 2, 2020 The second national lockdown ended on December 2, 2020[43] after four weeks. England moved to a stricter three-tiered system of restrictions.

January 6, 2021 The third national lockdown was announced on January 6, 2021.[44]

July 18, 2021 On March 8, 2021 England started a phased release of lockdown regulations.[45] Lockdown laws cease to be in force on July 18, 2021.[46]

The easing of restrictions was not complete at a single time point so these dates should not be regarded as representing a simple lockdown yes or no situation.

Table S1A. Weighted prevalence of SARS-CoV-2 swab-positivity in rounds 18 and 19 by sex, age, region, urban/rural area, employment, and ethnic group.

		Round 18			Round 19		
Variable		Positive	Total	Weighted Prevalence	Positive	Total	Weighted Prevalence
Sex	Male	1,199	40,936	2.97% (2.80%, 3.15%)	2,960	47,514	6.41% (6.17%, 6.66%)
	Female	1,532	54,005	2.79% (2.64%, 2.95%)	3,942	61,663	6.32% (6.12%, 6.54%)
	Unknown	0	9	*	0	4	*
Age	05-11	161	3,392	4.69% (4.01%, 5.48%)	319	3,627	8.81% (7.89%, 9.82%)
	12-17	261	7,584	3.42% (3.00%, 3.91%)	428	9,132	4.71% (4.21%, 5.25%)
	18-24	205	7,407	2.70% (2.33%, 3.13%)	444	7,705	5.65% (5.11%, 6.23%)
	25-34	463	14,970	3.05% (2.77%, 3.35%)	1,150	15,620	7.13% (6.72%, 7.57%)
	35-44	492	14,386	3.43% (3.13%, 3.76%)	1,115	15,206	7.16% (6.75%, 7.61%)
	45-54	371	11,976	3.09% (2.79%, 3.43%)	920	13,055	6.96% (6.52%, 7.43%)
	55-64	343	14,405	2.37% (2.13%, 2.64%)	1,094	17,897	6.09% (5.74%, 6.46%)
	65-74	308	13,635	2.21% (1.98%, 2.48%)	981	17,321	5.63% (5.29%, 6.00%)
	75+	127	7,195	1.68% (1.41%, 2.01%)	451	9,618	4.61% (4.20%, 5.07%)
Region	North West	291	11,386	2.58% (2.28%, 2.92%)	787	13,281	5.84% (5.42%, 6.29%)
	North East	100	4,364	2.33% (1.88%, 2.87%)	263	4,987	5.37% (4.72%, 6.10%)
	Yorkshire and The Humber	229	9,133	2.48% (2.15%, 2.85%)	615	10,678	5.84% (5.36%, 6.36%)
	West Midlands	264	9,745	2.63% (2.31%, 2.99%)	617	11,471	5.28% (4.85%, 5.75%)
	East Midlands	211	8,295	2.53% (2.18%, 2.93%)	582	9,763	6.02% (5.51%, 6.56%)
	East of England	298	10,658	2.92% (2.58%, 3.29%)	845	12,102	7.17% (6.67%, 7.70%)
	South West	316	9,911	3.12% (2.77%, 3.51%)	908	11,479	8.13% (7.59%, 8.71%)
	London	508	15,480	3.20% (2.92%, 3.52%)	1,065	17,061	6.16% (5.77%, 6.57%)
	South East	514	15,978	3.33% (3.04%, 3.66%)	1,220	18,359	6.72% (6.32%, 7.13%)
Living in urban area	Yes	2,217	76,453	2.92% (2.80%, 3.06%)	5,418	87,429	6.22% (6.05%, 6.40%)
	No	501	18,249	2.68% (2.44%, 2.94%)	1,473	21,487	6.97% (6.60%, 7.35%)
	Unknown	13	248	3.90% (2.22%, 6.75%)	11	265	4.63% (2.41%, 8.74%)
Employment type	Health care or care home worker	269	7,812	3.27% (2.87%, 3.73%)	623	8,659	7.27% (6.66%, 7.93%)
	Other essential/key worker	418	13,396	3.14% (2.83%, 3.48%)	1,052	14,134	7.29% (6.83%, 7.77%)
	Other worker	1,093	37,420	3.01% (2.83%, 3.21%)	2,804	41,832	6.70% (6.44%, 6.97%)
	Not full-time, part-time, or self-employed	885	34,073	2.54% (2.36%, 2.72%)	2,284	42,132	5.44% (5.20%, 5.68%)
	Unknown	66	2,249	2.79% (2.16%, 3.60%)	139	2,424	6.02% (5.06%, 7.16%)
Ethnic group	White	2,346	80,897	2.90% (2.78%, 3.03%)	6,014	93,599	6.49% (6.32%, 6.67%)
	Asian	194	6,642	2.95% (2.52%, 3.43%)	399	7,463	5.26% (4.71%, 5.87%)
	Black	44	2,063	2.27% (1.66%, 3.10%)	114	2,140	5.43% (4.44%, 6.63%)
	Mixed	63	1,997	3.29% (2.50%, 4.31%)	141	2,188	6.80% (5.65%, 8.18%)
	Other	29	1,083	2.94% (1.97%, 4.36%)	70	1,163	5.86% (4.53%, 7.54%)
	Unknown	55	2,268	2.27% (1.70%, 3.02%)	164	2,628	6.16% (5.24%, 7.24%)

* Prevalence estimates are not reported if based on less than 10 observations

Table S1B. Weighted prevalence of SARS-CoV-2 swab-positivity in round 18 and round 19 by household size, number of children in the household, contact with a COVID-19 case, reported previous COVID-19, protective behaviours, symptom status.

		Round 18			Round 19		
Variable		Positive	Total	Weighted Prevalence	Positive	Total	Weighted Prevalence
Household size	1	288	14,239	1.87% (1.65%, 2.11%)	914	17,093	5.26% (4.92%, 5.63%)
	2	845	33,450	2.50% (2.33%, 2.68%)	2,422	39,996	6.03% (5.79%, 6.28%)
	3	543	18,194	3.06% (2.79%, 3.35%)	1,416	20,059	6.91% (6.54%, 7.30%)
	4	716	19,042	3.88% (3.58%, 4.20%)	1,475	21,416	7.13% (6.74%, 7.53%)
	5	219	6,570	3.33% (2.87%, 3.85%)	462	7,051	6.97% (6.28%, 7.73%)
	6+	120	3,455	3.36% (2.76%, 4.09%)	213	3,566	6.02% (5.17%, 6.99%)
Number of children in the household	0	1,407	58,734	2.31% (2.19%, 2.44%)	4,114	69,000	5.89% (5.71%, 6.08%)
	1+	1,072	28,474	3.88% (3.63%, 4.14%)	2,334	30,809	7.55% (7.22%, 7.89%)
	Unknown	252	7,742	3.16% (2.78%, 3.60%)	454	9,372	4.72% (4.29%, 5.19%)
COVID case contact	No	1,187	69,708	1.73% (1.62%, 1.84%)	3,130	78,334	4.00% (3.86%, 4.16%)
	Yes, contact with a confirmed/tested COVID-19 case	1,056	10,312	10.35% (9.72%, 11.02%)	2,724	15,387	17.84% (17.17%, 18.52%)
	Yes, contact with a suspected COVID-19 case	142	2,098	6.86% (5.77%, 8.15%)	398	3,243	12.50% (11.28%, 13.83%)
	Unknown	346	12,832	2.55% (2.27%, 2.85%)	650	12,217	5.29% (4.87%, 5.74%)
Shielding	Yes	426	17,277	2.39% (2.16%, 2.65%)	1,216	20,353	6.00% (5.66%, 6.37%)
	No	1,953	64,720	3.08% (2.93%, 3.23%)	5,021	76,481	6.64% (6.45%, 6.84%)
	Unknown	352	12,953	2.58% (2.31%, 2.89%)	665	12,347	5.33% (4.91%, 5.78%)
Frequency wearing mask indoors	Always	717	24,303	2.85% (2.64%, 3.08%)	1,196	17,895	6.59% (6.21%, 6.99%)
	Sometimes	1,111	37,147	3.01% (2.83%, 3.20%)	2,767	39,189	7.07% (6.80%, 7.35%)
	Hardly ever	109	3,901	2.89% (2.37%, 3.52%)	326	5,254	6.12% (5.45%, 6.87%)
	Never	36	1,378	2.40% (1.70%, 3.40%)	89	1,595	5.48% (4.40%, 6.80%)
	Unknown	758	28,221	2.77% (2.56%, 3.00%)	2,524	45,248	5.81% (5.56%, 6.06%)
Symptom status	Classic COVID symptoms*	1,175	7,845	15.06% (14.21%, 15.95%)	3,230	11,602	27.57% (26.68%, 28.47%)
	Other symptoms	530	13,651	3.85% (3.52%, 4.22%)	1,343	16,963	7.87% (7.43%, 8.33%)
	No symptoms	682	60,676	1.17% (1.08%, 1.27%)	1,687	68,450	2.60% (2.47%, 2.74%)
	Unknown	344	12,778	2.53% (2.26%, 2.84%)	642	12,166	5.21% (4.80%, 5.66%)

* Classic COVID symptoms: loss or change of sense of smell or taste, fever, new persistent cough

Table S2. Table of growth rates per day (r), reproduction numbers (R) and doubling/halving times (in days) of SARS-CoV-2 swab-positivity from exponential model fits on data from round 19 (March 8 to 31, 2022)

		Growth rate per day (r)	Reproduction number (R)**	Probability R>1, r>0	Doubling (+) / Halving (-) time (in days)
All positives		0.023 (0.019 , 0.027)	1.07 (1.06 , 1.09)	>0.99	30.5 (37.0 , 25.8)
Age	Aged 17 and under	0.001 (-0.009 , 0.011)	1.00 (0.97 , 1.03)	0.58	* (* , *)
	Aged 18 to 34	0.029 (0.021 , 0.038)	1.10 (1.07 , 1.12)	>0.99	23.5 (33.0 , 18.1)
	Aged 35 to 54	0.013 (0.005 , 0.020)	1.04 (1.02 , 1.07)	>0.99	* (* , 34.5)
	Aged 55 and over	0.036 (0.029 , 0.044)	1.12 (1.09 , 1.14)	>0.99	19.1 (24.1 , 15.8)
Region	East Midlands	0.019 (0.004 , 0.033)	1.06 (1.01 , 1.11)	0.99	37.1 (* , 21.0)
	West Midlands	0.022 (0.008 , 0.036)	1.07 (1.03 , 1.12)	>0.99	31.5 (* , 19.4)
	East of England	0.034 (0.022 , 0.045)	1.11 (1.07 , 1.15)	>0.99	20.7 (31.6 , 15.5)
	London	0.004 (-0.007 , 0.014)	1.01 (0.98 , 1.05)	0.75	* (* , 49.7)
	North West	0.029 (0.017 , 0.041)	1.09 (1.05 , 1.13)	>0.99	24.2 (41.7 , 17.1)
	North East	0.041 (0.020 , 0.062)	1.14 (1.07 , 1.20)	>0.99	16.8 (34.6 , 11.2)
	South East	0.016 (0.006 , 0.026)	1.05 (1.02 , 1.08)	>0.99	42.9 (* , 27.0)
	South West	0.025 (0.013 , 0.036)	1.08 (1.04 , 1.12)	>0.99	28.3 (* , 19.4)
	Yorkshire and The Humber	0.045 (0.031 , 0.059)	1.15 (1.10 , 1.19)	>0.99	15.5 (22.1 , 11.8)

* Doubling/Halving time had an estimated magnitude greater than 50 days and so represented approximately constant prevalence

** Within-round R was calculated assuming an Omicron-specific Gamma-distributed generation time with mean 3.3 days and standard deviation of 3.5 days.

Table S3. Proportion of each of the N=3,383 SARS-CoV-2 lineage detected in positive samples with at least 50% genome coverage from round 19. Results are based on 4,038 positive sequenced samples.

Lineage	N (3383)	Percentage
Omicron sub-lineage		
BA.1	23	0.68% (0.45% , 1.02%)
BA.1.1	223	6.59% (5.80% , 7.48%)
BA.1.1.1	13	0.38% (0.22% , 0.66%)
BA.1.1.10	1	0.03% (0.01% , 0.17%)
BA.1.1.12	6	0.18% (0.08% , 0.39%)
BA.1.1.13	4	0.12% (0.05% , 0.30%)
BA.1.1.14	10	0.30% (0.16% , 0.54%)
BA.1.1.15	10	0.30% (0.16% , 0.54%)
BA.1.1.9	1	0.03% (0.01% , 0.17%)
BA.1.10	2	0.06% (0.02% , 0.22%)
BA.1.13	3	0.09% (0.03% , 0.26%)
BA.1.15	4	0.12% (0.05% , 0.30%)
BA.1.15.1	4	0.12% (0.05% , 0.30%)
BA.1.16	6	0.18% (0.08% , 0.39%)
BA.1.17	35	1.03% (0.74% , 1.44%)
BA.1.5	1	0.03% (0.01% , 0.17%)
BA.2	2820	83.36% (82.07% , 84.58%)
BA.2.1	96	2.84% (2.33% , 3.45%)
BA.2.2	4	0.12% (0.05% , 0.30%)
BA.2.3	115	3.40% (2.84% , 4.06%)
BA.3	1	0.03% (0.01% , 0.17%)
Delta sub-lineage		
AY.4	1	0.03% (0.01% , 0.17%)

* Note lineage data are only available up to 22 March 2022