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Early signals of Omicron severity in sentinel UK hospitals

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Abstract

On 26th November 2021, a novel SARS-CoV-2 variant B.1.1.529 (Omicron variant) was designated as a variant of concern by the World Health Organisation. Using data from the Virology laboratory at the Manchester Medical Microbiology Partnership (MMMP, a partnership between UKHSA and the Manchester Foundation Trust), we have extracted a real-time feed of Omicron samples from hospitals across Greater Manchester, an area of the United Kingdom with a population size of approximately three million individuals. Omicron hospital samples are growing exponentially across Greater Manchester (doubling time 2.7 days (95% CI: 2.1, 3.7)). The proportion of Omicron in hospital samples follows a similar trajectory to the SGTF proportion in cases, but with a two-day offset. This is consistent with the delay from testing positive to hospital admission, implying a similar proportion of Omicron cases are converting to hospital admissions as for Delta cases. Comparing the Greater Manchester data to national hospitalisation data, similar trends are observed. Therefore, there is no signal of a substantial reduction in hospital admission risk with Omicron, and Omicron epidemics are likely to place a substantial burden on public health infrastructure.

Introduction

On 26th November 2021, a novel SARS-CoV-2 variant B.1.1.529 (Omicron variant) was designated as a variant of concern by the World Health Organisation (WHO, 2021). This variant was first detected in Botswana on 11th November 2021 (GISAID, 2021). Within the next couple of weeks, cases have been detected in 77 countries worldwide (WHO, 2021). In the UK, the first case was detected on the 27th November 2021 (Department of Health and Social Care, 2021) and up to the 18th December there have been 23,168 confirmed infections of Omicron in England (UKHSA, 2021).

The Omicron variant has 30 non-synonymous substitutions with fifteen on the receptor binding domain, which will affect antibody neutralisation (Karim & Karim, 2021). Many of these mutations are believed may lead to increases in transmissibility and are shared with other variants including Beta and Mu (Karim & Karim, 2021) that thus far showed the greatest reduction in antibody neutralisation. Preliminary in vitro research has illustrated a substantial reduction in antibody-mediated neutralisation for the Omicron variant relative to the Delta variant (Wilhelm, et al., 2021). Research in the UK has found a 4.5-fold (95% CrI: 3.1, 7.1) reduction in neutralisation titres (Hogan, et al., 2021) for the Omicron variant relative to the Delta variant, which would correspond to an expected 80.1% (95% CrI: 76.3%, 83.2%) reduction in vaccine effectiveness against severe disease at 60 days post booster. Further research will be needed to understand the impact of the cell-mediated immune response to infection from the Omicron variant at reducing severity. This evidence of immune escape motivates the urgent need to understand the potential severity of Omicron infections, particularly with respect to vaccine breakthrough or reinfection.

To understand severity, early estimates have been published using data from South Africa (Wolter, et al., 2021) and the United Kingdom (Imperial College, 2021). These studies suggest that Omicron may have a reduction in severity relative to Delta, with estimates between a 20% severity reduction to 80%. Whilst a significant reduction in severity, this will not be substantial enough to remove the

burden on already stressed public health systems. With the increased severity from wild-type to Alpha (Challen, et al., 2021) and Alpha to Delta (Twohig, et al., 2021), this suggests similar levels of severity from Omicron to wild-type.

Omicron has grown rapidly since its introduction, with cases reaching record levels (Evanson, et al., 2021). Concomitant raises in hospitalisations are yet to be observed with apparently low numbers of Omicron admissions. However, an average 8-10 day delay between infection and hospital admission (Ward & Johnsen, 2021), combined with an approximate 2 day doubling time of cases (UKHSA, 2021), may mean the discrepancy in Omicron admissions and cases is only temporary. Additionally, in the UK the number of daily Delta cases, and therefore hospital admissions, have been sufficiently high to obscure potential early signals in the routinely collected hospital admissions data (Cabinet Office, 2021). Therefore, alternative data sources that distinguish admission by variant are required to identify early warning signs of expected pressure on hospitals due to Omicron.

In this paper, we use data provided by the Virology laboratory at the Manchester Medical Microbiology Partnership (MMMP, a partnership between UKHSA and the Manchester Foundation Trust) to extract real-time data on the genotype of hospital specimens with COVID-19 taken from across Greater Manchester. This laboratory performs genotyping on all PCR positive test taken in hospitals in Greater Manchester. Based on the genotyping assay results, tests are assigned to be Delta or Omicron (or unknown). These Pillar 1 tests correspond to infections detected by hospital labs in the region, so this information provides a sentinel data stream to assess the severity of the novel Omicron variant. This cannot be obtained from the routinely collected Secondary User System (SUS) hospital admissions data, because these are only updated after patient spells are complete, and therefore too lagged to provide insights at this early stage. Moreover, testing performed in hospitals in England does not use the TaqPath technology that provides information on gene targets. Using genotyping assay results, we estimate the real-time exponential growth rate for both the Omicron admissions in Greater Manchester and the proportion of admissions with COVID-19 in Greater Manchester that are infected with the Omicron variant. Time varying instantaneous growth rate are estimated using a generalised additive model (GAM). This analysis is further conducted on national Pillar 1 data.

Data

Clinical Data – Pillar 1

The samples were tested in the Virology laboratory at the Manchester Medical Microbiology Partnership (MMMP, a partnership between UKHSA and the Manchester Foundation Trust). All the NHS clinical laboratories in Greater Manchester send their SARS-CoV-2 positive samples to MMMP for genotyping and sequencing. The genotyping is performed using the Thermo Fisher SARS-CoV-2 SNP mutation panel. This tests for the presence of wild type or mutation for E484K, K417N, K417T, and P681R. Samples with a cycle threshold (CT) value of 30 or less were tested for the panel of mutations. Samples that had a 417N mutation and 681R failure were classified as Omicron. Samples with the P681R mutation were classified as Delta. Most samples are collected from patients, but a small subset will be COVID-19 positive staff. Unfortunately, these cannot be identified in the data. We only consider samples from the acute NHS trusts in Greater Manchester and remove Bolton Foundation Trust due to reports of Omicron nosocomial cases that may affect the analysis.

The above methodology is used by all UKHSA associated Pillar 1 testing labs in the UK. Looking at all samples genotyped in this way through Pillar 1, we have data on the national picture of Omicron hospital admissions. However, in the national data we do not have information on where the specimen was collected, so cannot filter to acute NHS trusts. Therefore, the national data may be a less reliable indicator of acute hospital admissions. A small subset of the recent national Pillar 1 tests

can be linked to ECDS data on emergency care attendances, from which admissions data can be obtained.

These genotyping assays are only performed on specimens collected by NHS trusts. Therefore, most samples correspond to either staff testing regimens or patients. Throughout this paper, we use these Pillar 1 samples as a proxy for hospital admissions, grouped by specimen date. Although a subset of tests are staff, this proportion has been relatively small throughout the pandemic, so the majority reflect admissions. These are admissions with a positive SARS-CoV-2 PCR test, so will include patients with acute COVID-19 and those with incidental SARS-CoV-2 infection.

Community Testing Data – Pillar 2

Data on positive COVID-19 cases were obtained from UKHSA Pillar 2 testing using the Second Generation Surveillance System (SGSS) dataset. There are three typical targets looked for using PCR tests: N gene, Orf1ab, and the S gene. The data provided record the minimum CT at which each target amplifies. Delta variant samples will typically amplify all three targets. Omicron on the other hand typically will only amplify the N gene and ORF1ab targets, since mutations to the spike protein mean that the S gene target does not amplify. This allows Omicron and Delta to be differentiated by looking at which targets amplify: samples that exhibit S-gene target failure (SGTF, or S-) are likely to be Omicron, and samples that exhibit all three targets positive (S+) are likely to be Delta. However, sometimes certain targets may fail, particularly if the sample has a high CT (corresponding to low viral load). To account for this, we only consider individuals where the CT value for the N target is less than 30, which removes low viral load individuals. This is consistent with the requirements for genotyping of hospital tests. Only symptomatic cases were analysed to keep test seeking behaviour as consistent as possible.

Figure 1: Temporal trends in the number of S positive (S+) and SGTF (S-) cases across Greater Manchester. (A) and (B) look at the proportion of cases with SGTF, (C) and (D) look at the absolute number of cases with each variant.

Results

Cases

Estimating the instantaneous growth rate in the number of S- SARS-CoV-2 positive samples (see Methods), we find exponential growth across Greater Manchester, with a doubling time of 1.9 days (95% CI: 1.7, 2.1) as of 20 December 2021 (Figure 1). Delta attributed S+ cases have plateaued across the region, with large uncertainty that includes a decline in cases. Combined S+ and S- cases are growing (doubling time 3.0 days (95% CI: 1.8, 4.3)), but this hides the exponential growth of Omicron.

The relative proportion of cases that have SGTF has also grown rapidly. This proportional growth follows a logistic curve, consistent with Omicron replacing Delta. Prior to reaching 50%, this logistic growth followed an approximately exponential rate, with an initial 1.7 day (95% CI: 1.1, 3.2) doubling time. After approaching 50%, the instantaneous growth rate slowed down, as expected in a logistic growth curve, with a current doubling time of 4.0 days (95% CI: 2.0, 4.3). Despite the exponential growth of Omicron, there is not currently evidence that Delta cases are rapidly declining. Therefore, it is likely we will observe a period of coexistence between the two variants, which poses substantial risk to the healthcare system through the additive pressure from both variants.

Figure 2: Temporal trends in the number of Pillar 1 tests (probably hospital admissions) across Greater Manchester assigned to the Omicron and Delta variants. (A) and (B) look at the proportion of Pillar 1 tests with Omicron, (C) and (D) look at the absolute number of Pillar 1 tests with each variant.

Hospital admissions and Pillar 1 data

When approximating the new COVID-19 patients in hospital using the Pillar 1 hospital testing data, the number of daily hospital admissions with the Omicron variant across Greater Manchester has grown exponentially from 01/12/2021 to 15/12/2021, with a 2.7 day (95% CI: 2.1, 3.7) doubling time (Figure 2). When looking at total admissions, the Omicron rate of growth is currently masked by the hospital demand from Delta, with overall admissions seeing a 39 day (95% CI: 17.8, -185) doubling time. This illustrates that without breaking admissions down by variant, the incoming risk posed by Omicron could presently be substantially underestimated. Looking at the proportion of admissions with the Omicron variant, the percentage is currently increasing exponentially, with a doubling time of 2.9 days (95% CI: 2.3, 4.2). With the proportion under 50%, relative Omicron admissions are still in the exponential phase of logistic growth.

In the England level data (Figure 3), the trends are similar, with a 2.8 day (95% CI: 2.1, 4.3) doubling time in absolute Omicron and 3.0 day (95% CI: 2.5, 4.3) doubling time in relative Omicron. Since the national proportion of Omicron has crossed 50%, the real-time relative doubling time has increased, from a peak of 2.2 days (95% CI: 1.7, 3.2) days. Figure 4 looks at a subset of Pillar 1 data that we can link to hospital admissions. In this data, we observe exponential growth with a 3.8 day (95% CI: 2.9, 5.6) doubling time in the proportion of admissions that are Omicron. Absolute growth cannot be calculated as there is a lag in obtaining hospital admission records, so data are only partially complete.

Figure 3: Temporal trends in the number of Pillar 1 tests across England assigned to the Omicron and Delta variants. (A) and (B) look at the proportion of Pillar 1 tests with Omicron, (C) and (D) look at the absolute number of Pillar 1 tests with each variant.

Figure 4: Temporal trends in the number of admissions across England assigned to the Omicron and Delta variants. (A) and (B) look at the proportion of admissions with Omicron, (C) and (D) look at the absolute number of admissions with each variant.

Temporal shift between cases and admissions

The proportion of Omicron admissions in Greater Manchester closely matches the temporally offset trend in Omicron case proportions (Figure 5). If this temporal shift is substantially longer than the expected testing to admission delay, then this may suggest Omicron is substantially less severe. Linking national Pillar 2 testing to hospital admissions in the NHS Secondary Uses Service, the mean delay from testing to admission for individuals tested before admission is 5.6 days. Since 01/12/21, approximately 48% of admissions nationally were tested prior to admission, with 52% tested on or after admission (taken from the NHS sitrep newly admitted COVID-19 and newly diagnosed COVID-19). Therefore, we expect an average delay of 2.6 days between cases and admissions. Applying the time delay model (see Methods) to the Omicron proportions, the optimal temporal shift is 2 days. This suggests there is no substantial reduction in the Omicron infection hospitalisation rate.

Figure 5: *Proportion of cases with SGTF compared to the proportion of Pillar 1 tests with Omicron. The specimen date for Pillar 1 tests has been shifted back 2 days, as estimated by the time delay model. Confidence intervals are generated assuming observed Omicron Pillar 1 counts are binomially distributed from total Pillar 1 tests.*

Discussion

The growth rates for SGTF attributed Omicron cases are following a parallel pattern to the growth observed in Omicron genotyped hospital testing data. We find a similar proportion of Omicron cases are resulting in hospital admission as currently observed for Delta cases. The Pillar 1 genotyping testing data in the United Kingdom provides an essential sentinel data source for investigating the severity of the Omicron variant in real time. Using Pillar 1 to approximate admissions, hospitalisations with Omicron are growing exponentially across Greater Manchester, with a 2.7 day (95% CI: 2.1, 3.7) doubling time. Combined with a plateau in Delta pressure, approximately 100 general and acute beds occupied each day, and the concurrent forces of a large elective waiting list and typical winter pressures, this Omicron wave has the potential to exert unsustainable strain on the healthcare system. Without the sentinel data provided by Pillar 1, we are unable to stratify admissions by variant in real-time due to hospital reporting lags, which obscures any growth in admissions and suggests a 39 day (95% CI: 17.8, -185) doubling time over the same period.

Cross protective immunological factors and transmission advantages could allow for multiple variants to co-exist (Gupta, 1998). The immunological escape that has been observed for the Omicron variant may allow for a transmission advantage amongst the vaccinated and the Delta variant able to spread more easily amongst the immunologically naïve. However, due to the diminished size of this group in the UK it is unlikely that the Delta variant would be able to sustain cycles of transmission. Moreover, there is currently no evidence that would suggest the Delta variant has a transmission advantage in the immunologically naïve. Therefore, it is a realistic possibility that Omicron may be replacing rather than additive.

Analysis of earlier variants shows that booster doses of SARS-CoV-2 vaccines produce more robust neutralising antibody titres (Cevik, et al., 2021). However, the impact of vaccination is substantially diminished for Omicron (Dejnirattisai, et al., 2021) and inter-country epidemiological comparisons of severity should be interpreted with care. In our analysis, we only detect a subset of total admissions across Greater Manchester, so cannot infer severity by looking at a case hospitalisation rate. Instead, we looked at the proportion of Pillar 1 tests that are genotyped as Omicron relative to those with Delta. If the hospitalisation rate is similar between variants, the temporal trend in the Omicron Pillar 1 proportion should reflect the SGTF cases proportion, with a temporal offset equal to the average testing-to-admission delay. Otherwise, if the hospitalisation rate of Omicron was significantly smaller than that of Delta, we would expect a longer temporal offset than the average testing-to-admission delay. We found significant agreement in the trends, using a temporal shift of 2 days, suggesting there is no substantial change in severity, provided testing-to-admission delays are similar for both variants. Without substantial changes in severity, the potential hospitalisation burden of the Omicron wave cannot be dismissed.

Omicron is rapidly replacing Delta as the main variant associated with community cases and Pillar 1 tests across Greater Manchester. However, with the proportion of Omicron below 50% in the Pillar 1 data, total admissions trends are subsuming any clear signal of Omicron growth. Therefore, there is potentially substantial growth about to enter the healthcare system that cannot be identified without stratifying hospitalisation data by variant. Applying the methods to national Pillar 1 data, we observe similar trends to those identified in Greater Manchester. This demonstrates that the impact of Omicron on hospital admissions is widespread throughout the country, and is likely to place substantial burden on the National Health Service as a whole. When linking Pillar 1 to hospital

records, Omicron is taking over from Delta slightly slower than in the Pillar 1 data, but is still growing exponentially, suggesting hospital admission rates of a similar magnitude across Omicron and Delta. The high rate at which Omicron is spreading in the hospital testing data, and the rate at which it is taking over from Delta, show that if there is a reduction in severity in relation to Delta (Wolter, et al., 2021; Imperial College, 2021), it is unlikely to be sufficient to prevent substantial hospital burden.

In the UK, the rollout of the booster vaccination programme has rapidly escalated over the last few weeks. Coupled with the rollout of mild non-pharmaceutical interventions, this may act to slow the spread of Omicron, and ease some of the upcoming hospital burden. However, with such short doubling times and the long lag between infection and detection, there are potentially multiple doublings left in both case and admissions data before the influence of these interventions are observed in the data (Pellis, et al., 2021). In this time, substantial pressure could be applied to the healthcare system.

Methods

Instantaneous Growth Rate

Time varying growth rates are estimated using a Generalised Additive Model (GAM) with a canonical link (Ward, et al., 2021; Pellis, et al., 2021) with negative binomial error structure, using the default knots (Wood, 2006) and fit to a P-spline (Eilers & Marx, 1996). The model assumes the number of hospitalisation $y(t)$ is proportional to $\exp(s(t))$ for some smoother $s(t)$. We then estimate the instantaneous growth rate at time t as the time derivative of the smoother, $r_s(t) = \dot{s}(t)$, with instantaneous doubling time calculated as $t_D(t) = \log(2) / r_s(t)$. The asymptotic confidence intervals (CIs) on $r_s(t)$ are indicative of the uncertainty on $t_D(t)$.

Time delay

The temporal offset between case SGTF percentage and Pillar 1 Omicron percentage is assumed to be given by an integer, since the data are daily censored. For each day, we assume the Pillar 1 Omicron percentage is drawn from a binomial distribution out of all Pillar 1 COVID-19 specimens, with success probability given by the case SGTF percentage x days earlier. That is, for each day t , we have the likelihood function $l(t) = f(a(t), n(t), p(t - \tau))$, where $a(t)$ is Omicron Pillar 1 specimens on day t , $n(t)$ is total Pillar 1 specimens on day t , $p(t - \tau)$ is the community case SGTF percentage on day $t - \tau$, and $f(x, y, z)$ is the binomial probability density function for x successes, y trials, and probability z . Summing this across all days and taking the logarithm gives the log-likelihood of the data given time shift τ . Performing a grid search over $\tau \in \{0, 1, 2, \dots, 27, 28\}$, we estimate the optimal temporal offset as the one with the highest likelihood.

Author contributions

CO, TW, TH and SA developed the project
SA, BB, ED, BK, NM, and RO generated the data
CO, AC, TH, and SA sourced the data
CO, TW, and LP wrote the manuscript
CO, RP, and TW developed the methods
TW performed the literature review
All authors reviewed the manuscript

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Conflict of Interest

The authors have declared that no competing interests exist. The authors were employed by the UK Health Security Agency and the NHS, but received no specific funding for this study.

Ethics

This study was conducted in line with national data regulations. It only employed and accessed fully anonymised population level data from UKHSA in a secure research environment.

Data Availability Statement

To access the data used for this study, an application can be made to UKHSA. Data requests can be made to the Office for Data Release (<https://www.gov.uk/government/publications/accessing-public-health-england-data/about-the-phe-odr-and-accessing-data>) and contacting odr@phe.gov.uk. All requests to access data are reviewed by the ODR and are subject to strict confidentiality provisions in line with the requirements of:

- the common law duty of confidentiality
- data protection legislation (including the General Data Protection Regulation)
- 8 Caldicott principles
- the Information Commissioner's statutory data sharing code of practice
- the national data opt-out programme

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