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Investigation of hospital discharge cases and SARS-CoV-2 introduction into Lothian care homes

S. Cotton [a,b,*], M.P. McHugh [a,c], R. Dewar [a], J.G. Haas [a,b], K. Templeton [a,b], The COVID-19 Genomics UK (COG-UK) Consortium [d]

[a] Specialist Virology Centre, Royal Infirmary of Edinburgh, Edinburgh, UK
[b] Infection Medicine, Edinburgh Medical School, University of Edinburgh, Edinburgh, UK
[c] School of Medicine, University of St Andrews, St Andrews, UK
[d] Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

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SUMMARY

Background: The first epidemic wave of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in Scotland resulted in high case numbers and mortality in care homes. In Lothian, over one-third of care homes reported an outbreak, while there was limited testing of hospital patients discharged to care homes.

Aim: To investigate patients discharged from hospitals as a source of SARS-CoV-2 introduction into care homes during the first epidemic wave.

Methods: A clinical review was performed for all patients discharges from hospitals to care homes from 1st March 2020 to 31st May 2020. Episodes were ruled out based on coronavirus disease 2019 (COVID-19) test history, clinical assessment at discharge, whole-genome sequencing (WGS) data and an infectious period of 14 days. Clinical samples were processed for WGS, and consensus genomes generated were used for analysis using Cluster Investigation and Virus Epidemiological Tool software. Patient timelines were obtained using electronic hospital records.

Findings: In total, 787 patients discharged from hospitals to care homes were identified. Of these, 776 (99%) were ruled out for subsequent introduction of SARS-CoV-2 into care homes. However, for 10 episodes, the results were inconclusive as there was low genomic diversity in consensus genomes or no sequencing data were available. Only one discharge episode had a genomic, time and location link to positive cases during hospital admission, leading to 10 positive cases in their care home.

Conclusion: The majority of patients discharged from hospitals were ruled out for introduction of SARS-CoV-2 into care homes, highlighting the importance of screening all new admissions when faced with a novel emerging virus and no available vaccine.

Introduction

Care homes experienced high case numbers of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) during the pandemic, and this led to high mortality from coronavirus disease

* Corresponding author. Address: Specialist Virology Centre, Royal Infirmary of Edinburgh, Edinburgh, UK. Tel.: +44 (0)131 242 7129.
E-mail address: Seb.cotton@nhslothian.scot.nhs.uk (S. Cotton).

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2019 (COVID-19) [1]. Care homes have a unique population consisting of multi-disciplinary staff and many elderly residents who are particularly susceptible to severe COVID-19 [2]. SARS-CoV-2 infections can spread more quickly within care homes than in the surrounding community due to the number of residents, their proximity and the level of nursing care required [3]. Around half of the deaths reported in Scotland from COVID-19 have occurred in care home populations, resulting in life expectancy in these settings falling by 6 months [4]. One healthcare region, Lothian, reported that over one-third of care homes had an outbreak during the first epidemic wave [5]. These residents were identified as particularly susceptible to further epidemic waves without the protection of a vaccine or effective treatment [5].

Whole-genome sequencing (WGS) is a powerful tool that can add another layer to epidemiological information, providing insights into outbreak transmission dynamics and relatedness between cases. Clusters of resident and staff cases which have identical or very similar genomes have shown onward transmission within care homes [2,6—8]. The number of introductions into a care home can be established, and both single dominant clusters and multiple clusters were observed during the first epidemic wave [7,9—11].

The source of SARS-CoV-2 introductions into care homes has not been well studied to date. Potential sources include residents returning from hospitals, new residents from the community or other care homes, visitors and staff. It has been suggested that staff working across different sites could potentially be sources of introduction [12,13]. Discharged patients have also been suggested, but these studies require further investigation to answer the question [7,10]. A few specific care home outbreaks have investigated sources of introduction; however, larger studies to investigate sources for care home outbreaks are lacking [8,14].

During the first epidemic wave, many hospital patients were discharged back into care homes with limited testing available, particularly in the initial stage of the pandemic [15]. Initially, symptomatic cases alone were tested, before testing capacity increased to screen all residents and staff in care homes. A significant number of COVID-19 deaths in care homes were recorded, and this has raised interest regarding patients discharged from hospitals to care homes during that time. It is possible that SARS-CoV-2 could have been introduced into care homes following hospital discharge. This study of one healthcare region in Scotland aimed to assess whether, in the first epidemic wave, SARS-CoV-2 may have been introduced into care homes following the discharge of hospital patients using WGS data and detailed epidemiological information.

Methods

Testing policy of care homes in the first epidemic wave in Lothian

9th March 2020 — Polymerase chain reaction (PCR) testing of the first few residents with symptoms of COVID-19 (cough, fever).

13th April 2020 — PCR testing of all residents with symptoms of COVID-19.

26th April 2020 — Two negative PCR tests 1 day apart before hospital discharge.

1st June 2020 — Screen all residents in care home weekly with PCR test.

Clinical audit and epidemiology information

An internal review was performed for all patients discharged from hospitals to care homes in Lothian from 1st March 2020 to 31st May 2020. This involved an administrative and clinical audit to identify discharged patients and the care homes to which they were transferred. These were assessed to see if there was possible acquisition of COVID-19. Cases were excluded from the review if discharged patients were readmitted to hospital on the same day or did not stay in hospital overnight. A review of COVID-19 test history was performed for all discharged patients during their hospital stay and after discharge in the care home. A timeline review was performed to establish the chronology of positive cases in each care home. A window of 14 days either side of a patient's discharge date was set, drawn from isolation guidance, to determine the possibility of the virus being acquired in hospital [16]. Therefore, a positive test within 14 days of hospital discharge could have been acquired in hospital, and led to introduction of the virus to their care home. A clinical assessment of each discharged patient, where there were subsequent positive cases in their care home, was performed to assess the likelihood of COVID-19 at discharge. Patient movements, and admission and discharge data were obtained from clinical information in electronic patient records to create care home outbreak timelines.

Ethics

Nasal and throat swab samples were obtained from NHS Lothian following ethical approval from the biorepository bank in NHS Lothian covering the sequencing of samples from March 2020 to December 2022 (20/ES/0061).

Whole-genome sequencing

In total, 300 combined nasal and throat swabs were processed for WGS. Nucleic acid extraction was performed using NUCLISENS EMAG (bioMérieux, Marcy l'Etoile, France). cDNA was synthesized from extracted RNA using LunaScript RT SuperMix (New England Biolabs, Ipswich, MA, USA). SARS-CoV-2 cDNA was amplified using a tiled amplicon approach with ARTIC Network nCoV-2019 primers (Integrated DNA Technologies, Coralville, IO, USA) to generate material for WGS (https://artic.network/resources/ncov/ncov-amplicon-v3.pdf). WGS runs included negative extraction controls, non-template controls, and a positive control derived from a viral culture lysate extract diluted to a cycle threshold (Ct) value of approximately 30.

A modified library preparation method was used from a protocol developed by the ARTIC network [17]. The protocol uses 48-plex barcoding, a reduced volume of short fragment buffer for bead washes, and the NEBNext UltraII Ligation Module (New England Biolabs) for barcode attachment in a reduced reaction size. The concentration of cDNA and the volume pooled for clean-up was increased in order to maintain barcoding efficiency in the reduced reaction size. Library pools were quantified, and 20 ng was loaded on to R9.4.1 flow cells (Oxford Nanopore Technologies, Oxford, UK) and sequenced for 12 h on a GridION device (Oxford Nanopore Technologies). Live high-accuracy base calling and demultiplexing was performed with MinKnow Version 20.10.6, requiring barcodes at both ends of the reads.

Genomics and cluster analysis

The ARTIC nCoV-2019 environment utilizing RAMPART Version 1.1.0 was used to visualize read mapping in real time (https://github.com/artic-network/rampart). The number of reads and percentage coverage at 20x depth were used to assess quality control before consensus building. Consensus genomes were mapped to the Wuhan-Hu-1 reference (Accession No. MN908947.3) and generated using the Artic field bioinformatics pipeline (https://github.com/artic-network/fieldbioinformatics). Pangolin Version 3.1.20 was used to assign lineages (https://github.com/cov-lineages/pangolin) [18]. Positive control material is designated PANGO lineage B.1 and contains seven mutations (https://clades.nextstrain.org) [19]. The consensus sequences for this study and the accession numbers are provided in the online supplementary material. Cluster analysis and sequence comparisons were performed using Cluster Investigation and Virus Epidemiological Tool (CIVET) Version 3 (https://github.com/artic-network/civet) [20]. Background data were obtained from the Medical Research Council (MRC) Cloud Infrastructure for Microbial Bioinformatics (CLIMB) COVID database. CIVET allows cluster analysis of closely related sequences by putting them into the context of known background diversity from global SARS-CoV-2 sequences within their phylogenetic subtree. Genomes were considered related if they differed by at least one single-nucleotide polymorphism (SNP) and were collected within 14 days; otherwise, they were unlikely due to direct transmission.

Results

A combined approach was taken to investigate hospital discharge episodes as possible sources of introduction of SARS-CoV-2 into care homes. Firstly, a clinical review of all hospital discharges to care homes was performed to identify all patients who could be a possible source of SARS-CoV-2 introduction (Table I). Sequencing information for positive cases within the identified care homes was then combined with clinical review findings. Detailed timelines were created from clinical information and, in combination with the CIVET output, the care home outbreaks were described. Overall, 776 of 787 (99%) hospital discharge episodes could be ruled out for subsequent introduction of SARS-CoV-2 into care homes. This left 10 episodes where the findings were inconclusive, and one case with an identified genomic, time and location link to hospital inpatients at the time of admission.

Clinical review

In total, 787 discharge episodes to 130 care homes were identified from 732 patients, of which five patients had three episodes and 10 patients had two episodes. Of these, 282 (36%) episodes were negative before hospital discharge (Table I). One hundred and ninety-four discharge episodes were ruled out because they were discharged to 61 care homes with no reported positive cases, and therefore no evidence of SARS-CoV-2 introduction. There were 200 discharge episodes to care homes >14 days before the first positive case was reported in the care home. These episodes were ruled out based on the timeline of the infectious period lasting no longer than 14 days.

There were 393 discharge episodes to care homes that occurred <14 days before the first positive case or to a care home with known positive cases, which therefore could not be ruled out based on timelines. Of these, 194 (57%) had a negative test before discharge and another 32 episodes were positive >14 days after the discharge date and so were ruled out. In addition, 126 episodes were ruled out based on clinical assessment of unlikely COVID-19 at discharge. The remaining 41 of 787 episodes were discharged to 21 care homes and were positive ≤14 days of discharge, so were selected for further analysis as possible SARS-CoV-2 introduction cases. These episodes were from 38 patients, including three patients who had two discharge episodes.

Whole-genome sequencing

The 41 episodes that were potential introduction cases and the 21 care homes to which they were discharged were investigated by combining the WGS data from care home cases with information from the clinical review. In total, 300 of 545 (55%) positive cases were sequenced (Table A1, see online supplementary material). It was not possible to sequence the remaining cases due to high Ct values on diagnostic real-time PCR (>30), as the viral input RNA was too low for WGS. Most cases clustered with related care home sequences and background community cases from the MRC CLIMB database. There was evidence of multiple introductions in at least 13 of 21 care homes, as these had clusters of different phylogenetic lineages (Table A1, see online supplementary material).

Table I
Coronavirus disease 2019 test history for 787 discharge episodes to 130 care homes

Clinical review group	Number of episodes	Negative before discharge	No negative test before discharge	Positive within 14 days of discharge date	Positive >14 days after discharge date
No reported cases in the care home	194	67	127	-	-
Care home cases >14 days after discharge	200	21	179	-	37
Care home cases <14 days after discharge	138	38	100	8	19
Cases in care home at discharge	255	156	99	33	21
Total	787	282	505	41[a]	77[b]

This table shows all hospital discharge episodes to care homes during the first epidemic wave: 194 discharge episodes were to 61 care homes which had no reported cases, and 593 discharge episodes were to 69 care homes with positive cases. Forty-one episodes were positive within 14 days of the hospital discharge date and were discharged to 21 care homes.

[a] Nine of these episodes had a negative test before discharge.

[b] Eight of these episodes had a negative test before discharge.

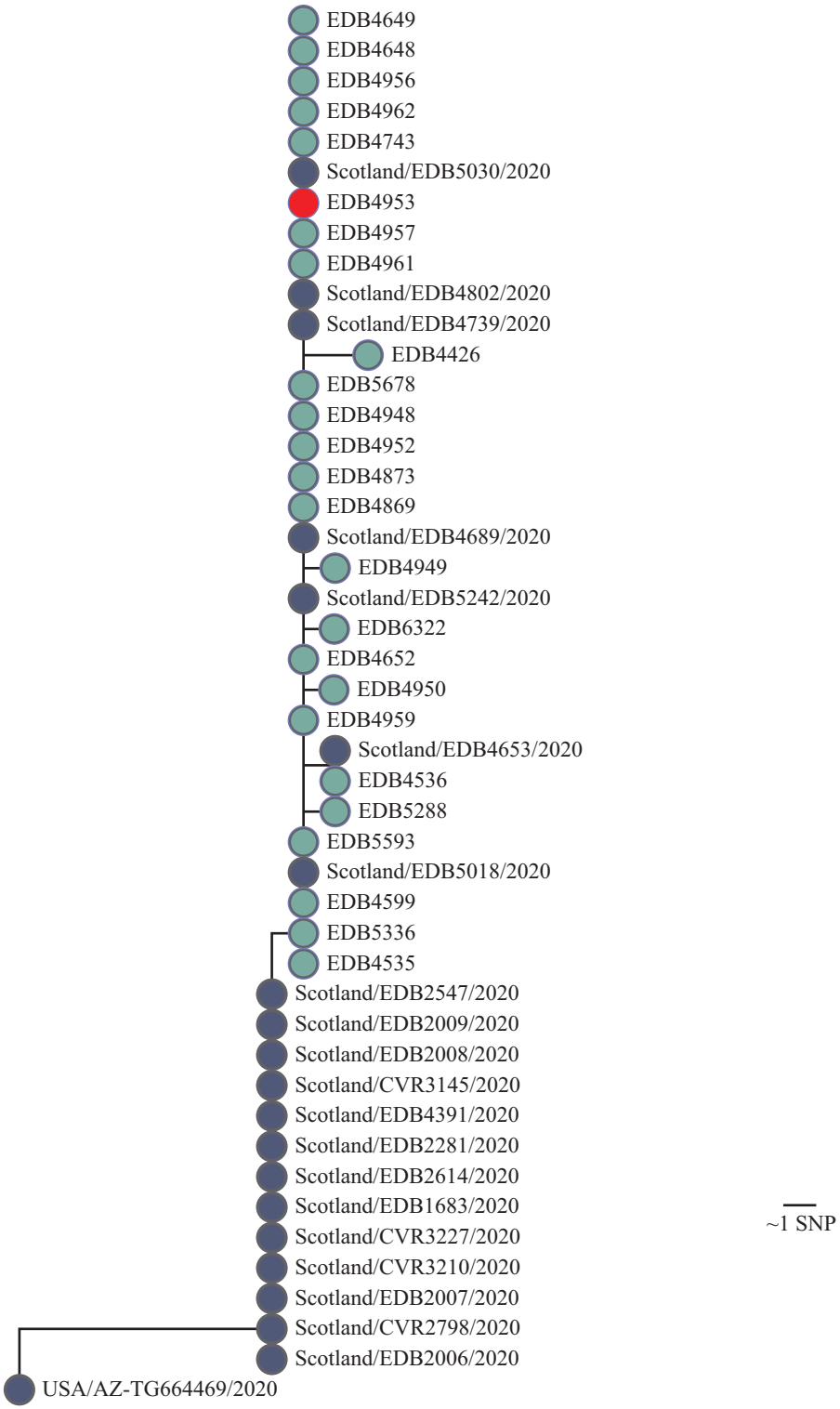

Figure 1. Severe acute respiratory syndrome coronavirus-2 phylogenetic tree output from CIVET displaying sequences from Care Home 20 (CH20) and background data. Green, care home sequences; blue, background community sequences from the COG-UK dataset (location/Sample_ID/date_collected). Care home sequences are from samples collected between 4th May 2020 and 2nd June 2020. The sequence circled in red is the patient discharged from hospital, and was collected on 14th May 2020. The x-axis scale shows genetic divergence [single-nucleotide polymorphisms (SNPs) per genome length]. All CH20 consensus sequences were very closely related and clustered together with pangolin lineage B.1.1.14. There were 19 consensus genomes which were identical, and six consensus genomes displaying two or fewer SNP differences.

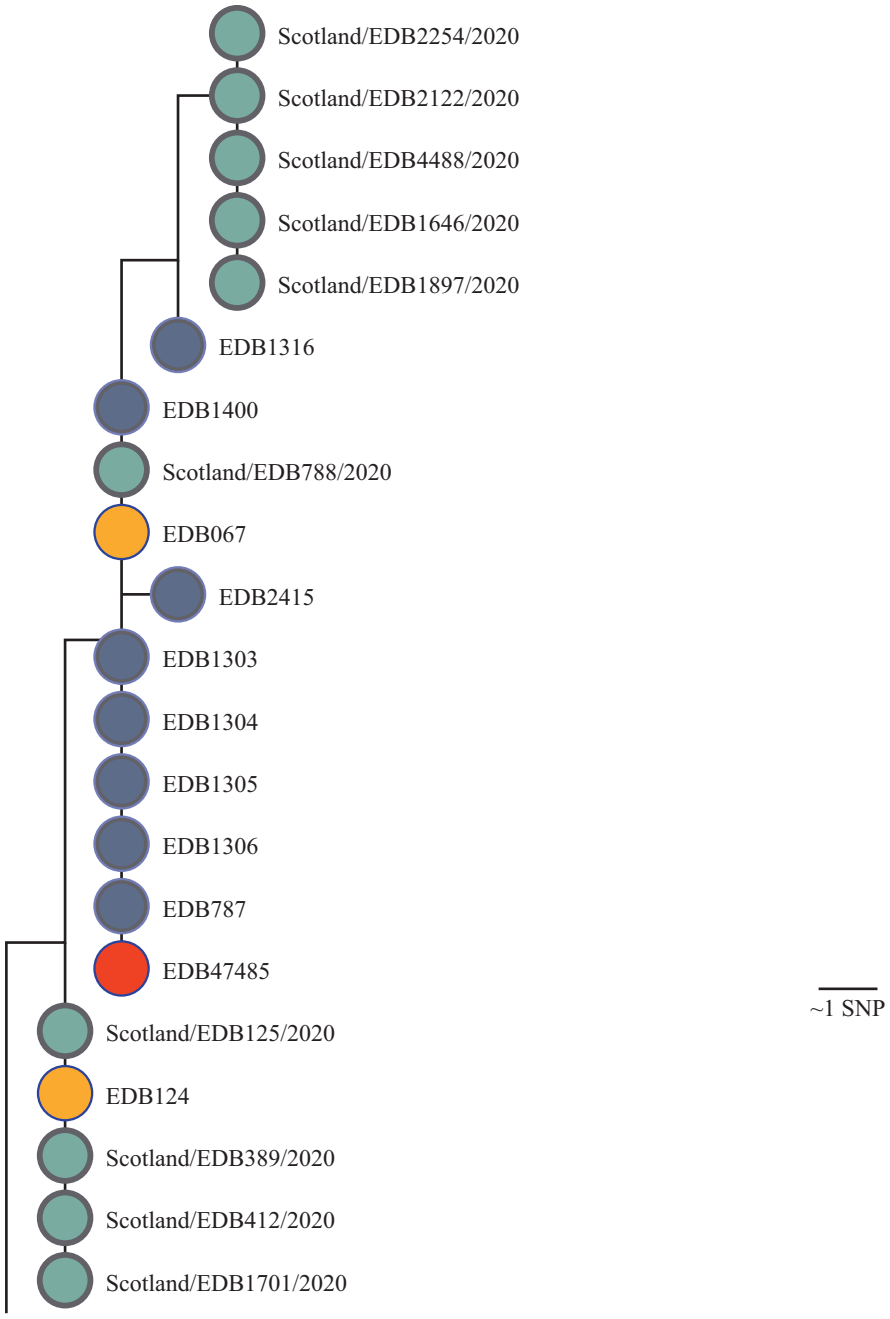

Figure 2. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) phylogenetic tree output from CIVET displaying sequences from Care Home 1 (CH1) and background data. In total, it was possible to sequence 10 of 11 SARS-CoV-2-positive cases identified in CH1, including the positive case discharged from hospital. Cluster analysis by CIVET showed nine CH1 sequences clustered with two hospital inpatient cases. The x-axis scale shows genetic divergence [single-nucleotide polymorphisms (SNPs) per genome length]. Blue, care home sequences; green, background sequences; red, patient discharged from hospital; orange, hospital inpatients. Collection dates for these samples are shown in Figure 3. Data used from COG-UK dataset (location/Sample ID/date collected). There was one sequence from CH1 which was a different phylogenetic lineage to the other cases; however, this was the last positive case in the care home, and 12 days apart from the previous positive case.

Discharge episodes ruled out for SARS-CoV-2 introduction

In total, 30 of 41 discharge episodes were ruled out for SARS-CoV-2 introduction because there was evidence that SARS-CoV-2 had already been introduced to the care home. For 27 of these episodes, SARS-CoV-2 infection was likely acquired from outbreaks that were already present in the care homes (Table I). For 16 episodes, cluster analysis showed that the consensus genomes differed by at least one SNP from other residents in the care home who had an earlier positive test. These 16 episodes related to eight care homes, and an example

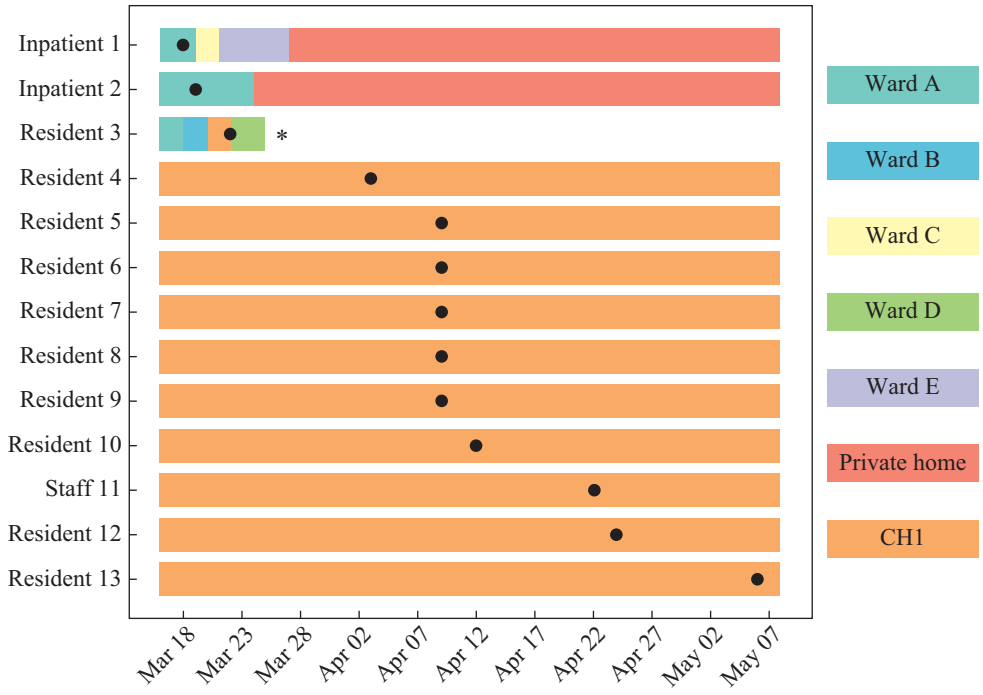

Figure 3. Timeline of first discharge of patient to Care Home 1 (CH1) and related background cases in hospital. Day 1 is the first hospital admission date for Resident 3 (discharged patient). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-positive tests are represented by black dots (•), with hospital and care home locations by colour. During the first hospital admission for Resident 3, Inpatient 1 and Inpatient 2 were on the same ward and positive for SARS-CoV-2 at the time. After Resident 3 was discharged back to CH1, a further 10 positive cases were identified at CH1. This figure was created using modified R script (https://github.com/wlhamilton/Patient-ward-movement-timelines). Both inpatients were discharged to private homes after admission. *Resident 3 died during their second admission to hospital.

for one care home is shown in Figure 1. In addition, 12 of these episodes were positive prior to or within 2 days of hospital admission. Cluster analysis was difficult for eight episodes with no sequencing data, and three episodes that showed low genomic diversity in the consensus genomes. However, eight episodes were either positive prior to or within 2 days of hospital admission, or were not the first positive case in the care home. One patient had a negative test in the care home before their positive test, and two patients were not admitted to hospital and were only seen in the emergency department.

A further three episodes were ruled out based on likely acquired infection from the community, as these were the first positive cases in their respective care homes. In all three episodes, the consensus sequences clustered with community cases from background data and no cases from hospital inpatients, which suggests that SARS-CoV-2 was not introduced from patients discharged from hospital (Figure A1, see online supplementary material). One of these episodes was positive prior to or within 2 days of hospital admission.

Discharge episode cluster with hospital cases

Cluster analysis for one of 41 discharge episodes to Care Home 1 (CH1) showed the consensus sequence clustered with other cases from this care home and two hospital inpatient cases during the time of their hospital admission (Figure 2). The discharged patient tested negative on hospital admission 3 days prior to discharge, but was then readmitted 2 days after discharge and was positive on readmission. During the first hospital admission, Inpatient 1 and Inpatient 2 were on the same ward as the discharged patient, with both inpatients positive at the time. After the resident was discharged back to the care home, a further 10 positive cases were identified in the care home. A timeline of the movement of the discharged patient is shown in Figure 3.

The discharged patient, care home cases and hospital inpatients were infected with a virus of high genetic similarity, with at least one SNP difference between the consensus genomes (Figure A2, see online supplementary material). Patient timeline and sequencing data suggest that transmission may have occurred during the first hospital admission, so the introduction of SARS-CoV-2 following the first discharge to CH1 cannot be ruled out. Additional sequences that clustered together with CH1 sequences were from the community, but these cases had positive tests after the discharged patient and residents, suggesting that SARS-CoV-2 had already been introduced to the care home.

Discharge episodes inconclusive

For 10 of 41 discharge episodes, the result was inconclusive as to whether a patient discharged from hospital introduced an outbreak into the care home. For three episodes, no sequence data were available. The remaining seven episodes were sequenced but the consensus genome displayed insufficient diversity to investigate the source of introduction (Figure A4,

see online supplementary material). Cluster analysis showed limited diversity from background data, with many cases clustering to sequences from around the world (USA, Mexico, Australia), although they were unlikely to be linked. Therefore, in these cases, it is difficult to investigate the source of introduction as infection could have been acquired from either the community or hospital. For two of these episodes, there was evidence of no onward transmission in the care home, and there were five discharges to care homes which already had an outbreak.

Discussion

For the first epidemic wave, the question regarding the introduction of SARS-CoV-2 into care homes by patients discharged from hospital has long remained unanswered. This study has shown that hospital introduction could not be ruled out following discharge to care homes for 11 of 787 discharge episodes. In 10 discharge episodes, the result was inconclusive based on limited sequencing information or low genetic diversity of SARS-CoV-2. For one discharge episode, a genomic, time and location link to hospital inpatients was identified. Most outbreaks were therefore likely to be introduced by other sources.

CIVET was used to investigate care home outbreaks and sources of introductions; this tool has been used to study cluster analysis for outbreaks previously [20,21]. CIVET enabled the comparison of sequences within the care home and with background data to identify possible community or hospital genetically related cases. The mutation rate of SARS-CoV-2 was estimated to be approximately two mutations per month on average during the pandemic period [22]. Therefore, in this study, cases within 14 days were classified as potentially linked if the consensus genomes differed by at least one SNP, in agreement with other studies [14,23—25]. The study findings agree with others suggesting that there were single and multiple clusters in the first epidemic wave [9,14].

It was possible to rule out most hospital discharges as potential sources of introduction of SARS-CoV-2 into care homes based on the clinical review and the infectious period lasting <14 days [16,26]. If SARS-CoV-2 was introduced into a care home at hospital discharge, one would expect to see positive cases in the care home within 14 days. As found in the present study, Hamilton *et al.* showed that most patients discharged from hospital were not infectious at the time of discharge [7].

The addition of WGS analysis enabled hospital discharge episodes to be ruled out as sources of SARS-CoV-2 introduction into care homes as these episodes had a consensus genome that clustered with sequences from an outbreak already in the care home or community cases. Most episodes were positive prior to or within 2 days of hospital admission, so the discharged patient likely acquired the virus from the outbreak in the care home before hospital admission. However, they could still have been infectious when discharged to the care home. These episodes were ruled out on the basis that SARS-CoV-2 had already been introduced into the care home. The prevalence in the community was likely very high during the first epidemic wave, as no vaccines were available at the time. A large study by Emerson *et al.* showed that care home outbreaks were not associated with hospital discharge, and this agrees with the present finding of likely introduction from other sources [27]. The sequencing data from most care homes show clusters of care home cases with background community cases rather than hospital cases, indicating that community introduction was far more likely. Other studies have shown that most infections in care homes are community acquired [7,10].

For one discharge episode, CIVET revealed two hospital inpatient sequences within the same cluster as CH1 sequences. Further review of patient timelines showed that the discharged patient was located on the same ward as two inpatients with a consensus genome of high similarity. It is known that direct contact between individuals is a key factor in transmission [28]. As there was evidence of the discharged patient being the link between cases in the hospital and cases in the care home, hospital introduction could not be ruled out. Van Den Besselaar *et al.* also suggested the introduction of SARS-CoV-2 into a care home by a patient discharged from hospital using WGS data, where clustering was found between cases in residents and a hospital outbreak [8].

For 10 discharge episodes, it was not possible to assess whether SARS-CoV-2 was introduced to a care home by a patient discharged from hospital as the results were inconclusive. Low genetic diversity among positive cases during the first epidemic wave is well known because SARS-CoV-2 has only emerged recently in the human population [29,30]. Therefore, WGS could not add any further information to these investigations, as the introduction could have come from any source. Five discharge episodes were not the first positive case identified in the care home. However, it was possible there could have been multiple introductions, so these episodes could not be ruled out for discharge introduction.

A limitation of this study is that some patients discharged from hospital were not tested for COVID-19 due to limited availability of testing at the early stages of the pandemic. However, those that were symptomatic or had clinical suspicion of COVID were tested. It is possible that asymptomatic-positive patients discharged from hospital could have introduced SARS-CoV-2 to care homes, as suggested by Jeffery-Smith *et al.* [23]. The present study relates to a period before vaccines were introduced, and when asymptomatic infection was less likely in older generations compared with younger generations [31]. There has been evidence of asymptomatic infections in care home residents, and this led to the recommendation for regular screening [3,6,32,33]. However, in these outbreaks, there are nearly always symptomatic cases, which suggests that if SARS-CoV-2 is introduced into this population, there will be a symptomatic case. Additionally, cases which were initially thought to be asymptomatic were, in fact, pre-symptomatic, as they developed symptoms after testing [3,33]. Many of the episodes that were not tested at hospital discharge in the present study were discharged to care homes with no reported cases [5].

Identifying all positive care home residents is a challenge as data systems can have poor data quality, and it remains unlikely that all hospital discharges to care homes in the period have been captured. Another limitation is the number of cases unable to be sequenced due to low RNA input for sequencing or because residents were missed. The analysis is incomplete for some outbreaks, and it is possible that multiple introductions may not have been identified. However, not every case is needed to rule out the introduction of SARS-CoV-2 into care homes from patients discharged from hospital, as shown in the present study.

This study highlights the importance of utilizing a combined approach of epidemiology and WGS to tackle investigations of sources for SARS-CoV-2 outbreaks. WGS can add another layer to investigations by revealing similarities and differences between consensus genomes. This information can link or rule out cases which would otherwise remain concealed. Understanding how SARS-CoV-2 was introduced can help to prevent further outbreaks in a very vulnerable population, and identify areas to improve infection control.

In conclusion, this study found that most outbreaks in care homes in the first wave were not sourced by patients discharged from hospital. Infection control strategies should focus on all admissions and sources into the care home when faced with a novel emerging virus without a vaccine. This study has shown that, for future outbreaks, it is possible to combine clinical and sequencing information to investigate the source of virus introduction.

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Conflict of interest statement
None declared.

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Appendix A. Supplementary data

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