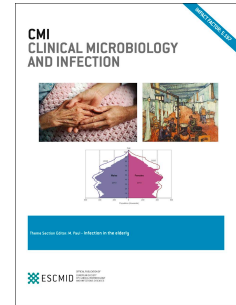


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Combined epidemiological and genomic analysis of nosocomial SARS-CoV-2 infection early in the pandemic and the role of unidentified cases in transmission

Luke B. Snell, Chloe L. Fisher, Usman Taj, Oliver Stirrup, Blair Merrick, Adela Alcolea-Medina, Themoula Charalampous, Adrian W. Signell, Harry D. Wilson, Gilberto Betancor, Mark Tan Kia Ik, Emma Cunningham, Penelope R. Cliff, Suzanne Pickering, Rui Pedro Galao, Rahul Batra, Stuart J.D. Neil, Michael H. Malim, Katie J. Doores, Sam T. Douthwaite, Gaia Nebbia, The COVID-19 Genomics UK (COG-UK) consortium



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TITLE

Combined epidemiological and genomic analysis of nosocomial SARS-CoV-2 infection early in the pandemic and the role of unidentified cases in transmission.

AUTHORS

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RUNNING TITLE: Genomic analysis of nosocomial SARS-CoV-2 in London

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ABSTRACT

Objectives. Analysis of nosocomial transmission in the early stages of the pandemic at a large multi-site healthcare institution. Nosocomial incidence is linked with infection control interventions..

Methods. Viral genome sequence and epidemiological data were analysed for 574 consecutive SARS-CoV-2 PCR-positive patients including 86 nosocomial cases during the first 19 days of the pandemic

Results. 44 putative transmission clusters were found through epidemiological analysis, which included 234 cases and all 86 nosocomial cases. SARS-CoV-2 genome sequence was obtained from 168/234 (72%) of these cases in epidemiological clusters, including 77/86 (90%) nosocomial cases. Only 75/168 (45%) linked, sequenced cases were not refuted by applying genomic data, creating 14 final clusters accounting for 59/77 (77%) sequenced nosocomial cases. Viral haplotypes from these clusters were enriched 1-14x (median 4x) compared to the community. Three factors implicated unidentified cases in transmission: i) community-onset or indeterminate cases were absent in 7/14 (50%) of clusters ii) 4 (29%) clusters had additional evidence of cryptic transmission. iii) In 3 (21%) clusters, diagnosis of the earliest case was delayed which may have facilitated transmission. Nosocomial cases decreased to low levels (0-2 per day) despite continuing high numbers of admissions of community-onset SARS-CoV-2 cases (40-50 per day) and before the impact of introducing universal face-masks or banning hospital visitors.

Conclusion. Genomics was necessary to accurately resolve transmission clusters. Our data supports unidentified cases, such as healthcare workers or asymptomatic patients, as important vectors of transmission. Evidence is needed to ascertain whether routine screening increases case ascertainment and limits nosocomial transmission.

KEY WORDS

SARS-CoV-2, nosocomial transmission, healthcare-associated infection, molecular epidemiology, whole genome sequencing

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China in December 2019[1], with over 4 million deaths having since been reported worldwide[2]. Cases in the UK increased rapidly during March 2020 leading to social distancing policies[3][4]. On March 23rd, legislation compelled the UK population to stay home with only limited exceptions. COVID-19 hospital admissions peaked 1 week later, around April 1st [5].

Nosocomial infection may account for 10-20% of all confirmed cases[6][7][8], with associated mortality of up to 30%[7]. Most SARS-CoV-2 transmission studies during the first wave utilised epidemiological analysis alone to identify outbreaks [9][10][11][12][13]. The main limitation with using epidemiology alone is that when point prevalence is high, for instance at 2.2% in London during April 2020[4], this increases the chance two people in epidemiological contact are independent cases. Furthermore, a wide incubation period of 2-14 days[14,15] means infections that arise several days after hospital admission may still have been acquired in the community.

Epidemiological data can be supplemented with SARS-CoV-2 genome sequence to aid analysis of transmission[16][17]. Genomic analysis is complicated during early stages of the pandemic due to low genetic diversity, with less than 200 mutations recognised by April 2020[18]. Thus two people infected with an identical strain may not be epidemiologically-linked.

This study combines epidemiological and genomic data to analyse clusters of nosocomial SARS-CoV-2 transmission during the first weeks of the pandemic before infection control policies had been formalised, and when community incidence was high[3][4]. Understanding nosocomial transmission would help set priorities for future infection control planning.

METHODS

Setting

Our institution comprises an acute hospital site (STH) admitting COVID-19 patients, an elective site including surgery and oncology (GUY), two long-stay community-care units and multiple dialysis units. Diagnostics and infection control policies were uniform across sites. Major infection control policies introduced during this time are shown in Figure 1. Wards are all multi-bedded with a small allocation of side rooms.

From March 13th only patients requiring admission and with cough, fever or shortness of breath were tested for SARS-CoV-2 infection, as per PHE recommendations. Inpatients developing these symptoms were tested before isolation in side rooms whilst awaiting results. Confirmed cases were cohorted in wards with other confirmed cases only. Very exceptionally, confirmed cases stayed on a non-COVID ward in a side room due to capacity issues. Neither asymptomatic individuals nor patients/staff exposed to known cases were routinely screened for infection.

SARS-CoV-2 whole genome sequencing

RNA extracts were processed using the ARTIC protocol v1.0 [19] and V3 primers set[20] using Oxford Nanopore Technology and the ARTIC bioinformatics pipeline v1.0[21]. Lineages were assigned using Pangolin [22] v1.1.14 with lineages v2020-05-19.

Deduction of transmission clusters

Transmission clusters were deduced using combined epidemiological and genetic information. First, each case was classified based on time between admission and symptom onset, according to ECDC definitions[23]: community-onset (<3d), indeterminate (3-7d), probable nosocomial (8-14d) and definite nosocomial (>14d) cases. Epidemiological clusters required at least two cases, including a probable or definite nosocomial case, and all requiring an overlapping ward-stay during incubation period with another case. Incubation period was calculated as symptom onset minus 14 days [15] (or sample collection date, if symptom onset unknown). Viral haplotypes were then used to exclude cases differing by ≥ 2 SNPs, or by ≥ 3 SNPs in the secondary analysis. Finally, there were two clusters (GUY4 and GUY5) where nosocomial cases were linked manually on adjacent wards due to presence

of a specific SNP highly enriched compared to community haplotypes (see Supplementary Methods).

Choice of SNP threshold for excluding transmission

Previous literature discusses the probability of acquiring SNPs between cases based on the mutation rate of SARS-CoV-2, estimating a 24% chance of one new SNP and 4% of two new SNPs per generation (further in Supplementary Methods) [24]. Assuming all relevant cases were captured, for our 77 sequenced nosocomial cases one expects $0.04 \times 77 = 3.1$ cases to differ by ≥ 2 SNPs from their infection source. (see Supplementary Methods). Other published literature also supports the lower SNP exclusion threshold of ≥ 2 [16]. Notably however, one study found evidence that 2 SNP could occur in institutional outbreaks in 17 days [25].

Construction of phylogenetic tree

Maximum likelihood phylogenetic trees were derived using phangorn (v2.5.5) and plotted with ggtree (v.2.41) in R (v4.0.2). Trees were fitted separately according to Pangolin lineage assignment using a generalised time reversible (GTR) + $\Gamma(4)$ + I model.

Healthcare worker (HCW) symptomology and seroconversion

228 HCW were followed up from March 13th until June 10th 2020 for self-reported COVID-19 compatible symptoms and SARS-CoV-2 seroconversion. Sequential serum samples were collected every 1-2 weeks and tested using ELISA [27]. The median time between symptom onset and seroconversion in symptomatic HCW was used to infer infectious period for those asymptomatic. HCW absenteeism was retrieved from human resource records.

RESULTS

Clinical characteristics and epidemiology.

By March 31st there were 574 laboratory-confirmed cases (Supplementary Table S1). Most were admitted (483/574: 84%, Supplementary Table S2) with a median length of stay of 12 days (IQR: 5-27, Table 1).

New cases peaked between March 31st and April 8th, before falling steadily through April (Figure 1). The daily number of probable and definite nosocomial cases peaked earlier on March 23rd with 12 new cases. Nosocomial cases then rapidly declined to 0-2 cases per day during April (Figure 1) and none in the following 4 months (data not shown).

471 (82%) of the 574 SARS-CoV-2 positive patients were categorised based on ECDC definitions[23] as community-onset, with 59 (10%) definite nosocomial, 27 (5%) probable nosocomial, and 17 (4%) indeterminate cases. Demographics are shown in Table 1. The crude in-hospital mortality was 20%, highest in the definite nosocomial group (39%; 23/59).

541/574 cases were within the period for genomic analysis between March 13th and 31st. SARS-CoV-2 genome sequence was obtained from 380/541 (70%) cases, including 90% (77/86) of all probable and definite nosocomial cases and 72% (168/234) of cases placed into epidemiological clusters (Supplementary Table S4).

Linking epidemiology and genomics to define transmission clusters.

44 epidemiological clusters were formed involving 234 cases including all 86 nosocomial acquisitions, with a median of 6 patients per cluster (IQR 2-10) (Figure 2a-b; Supplementary Table S4). These 44 clusters were resolved into 14 final clusters where genomic data was available and did not refute epidemiological linkage. (Figure 2a, c Supplementary Table 5). These final clusters included 75 cases and 59/77 (77%) sequenced nosocomial cases.

These 14 final clusters are mapped onto the 44 epidemiology-only clusters to demonstrate the impact of introducing genomics (Figure 2b; Supplementary Table S4). Of the 168 sequenced cases in epidemiological clusters, only 75 (45%) were not refuted from being part of a plausible transmission

network with other sequenced cases in their epidemiological cluster (Figure 2b, Supplementary Table S4). 13 (30%) epidemiological clusters had at least two cases from different final clusters, indicating multiple contemporaneous transmission clusters within an epidemiologically-defined cluster (Figure 2b, Supplementary Table S4).

Genomic clusters from different SARS-CoV-2 lineage were further assessed using maximum likelihood phylogenetic trees (Figure 3, Supplementary Figure 1). This showed limited genetic diversity, with multiple community-onset cases showing genomic relatedness to nosocomial cases despite having no plausible epidemiological link. This illustrates the need for epidemiological linkage to postulate plausible transmission networks. No additional nosocomial cases could be linked to or excluded from existing clusters through review of the phylogenetic trees.

Differences in final clusters with less stringent exclusion criteria of ≥ 3 SNP

Next, we reapplied our clustering method with a less stringent SNP threshold for excluding cases of ≥ 3 SNPs. This identified three further cases possibly linked to existing clusters (Supplementary Table S6): case 84 (probable nosocomial) and case 135 (community-onset) to STH3; and case 359 (definite nosocomial) to STH1. Including them in final clusters would increase the proportion of sequenced nosocomial cases accounted for to 61/77 (79%).

Nosocomial cases not present in final clusters.

Eighteen remaining sequenced nosocomial cases (18/77; 23%) are not present in the final clusters. We reviewed the epidemiological clusters in which these eighteen remaining nosocomial cases were placed (Supplementary Table S7). In total, 265/344 (77%) of all cases in these epidemiological clusters were sequenced and none shared a viral haplotype within < 2 SNP of a remaining nosocomial patient, excluding them from being part of a transmission network. Instead, it is plausible that non-sequenced cases in these epidemiological clusters (79/344, 23%) or other unidentified cases (e.g. point-source infectors like HCW) could form a transmission cluster with our remaining nosocomial cases.

Originators of final transmission clusters, spatial distribution and enrichment of haplotypes.

7/14 (50%) cases include a community-onset or intermediate case that plausibly served as the

potential originator of the cluster. (Figure 2c; Figure 4, Supplemental Figure 2).

7/12 (58%) of hospital clusters were contained within single wards and 5/12 (42%) spread across ≥ 2 wards (Supplemental Figure 3). In-depth ward movement data available in Figure 4 and Supplementary Figure 2.

The validity of these 14 final clusters was supported by calculating haplotype enrichment compared to community sequences reported in COG-UK CLIMB database [26] of between 1 and 14-fold (median 4-fold) (Figure 2c, Supplementary Table S5).

Non-sequenced community-onset cases are unlikely to be originators of clusters

We assessed whether non-sequenced cases could have originated clusters which contained no community-onset or indeterminate cases by reviewing non-sequenced cases present in the same epidemiological cluster (Supplementary Table S8). We excluded cases as potential originators if i) they were symptomatic after the first nosocomial case (or sampling date was later, if symptom onset not known), or ii) viral haplotype differed by ≥ 2 SNP or iii) if cases were not community-onset or indeterminate. Only 2/8 (25%) of the clusters without originators could have potentially been originated by a non-sequenced community-onset case with epidemiological linkage (case 50 or case 187 cluster GUY4; case 62 for cluster GUY5).

Delayed identification of cases may have contributed to transmission in 5 clusters

Conversely, where community-onset or indeterminate cases were found as possible originators, earlier testing after symptom onset could have identified possible originators in 3 clusters (Supplementary Figure 2). For example case 34 in STH2 was symptomatic for 3 days before sample collection; case 90 in STH3 for 5 days, and case 277 in GUY1 for 6 days. Additionally, other cases were tested several days after symptom onset possibly facilitating onward transmission; for instance case 173 in STH2, case 160 in GUY1, case 295 in GUY3 and case 471 in GUY5.

Evidence of cryptic transmission in 4 clusters

Four clusters had other evidence of cryptic transmission: Clusters GUY1 and GUY2 involved different wards in the same building with an identical viral haplotype that was highly enriched compared with

community haplotypes, suggesting these clusters are linked by cryptic transmission. GUY4 and GUY5 both similarly involve neighbouring wards with high enrichment of viral haplotype. Of note, these neighbouring wards share multiple HCW, including allied health professionals, cleaners, and visiting clinicians. These HCW plausibly may have served as vectors for cryptic transmission between wards.

Representation of HCW in transmission networks

HCW were not offered SARS-CoV-2 testing when developing COVID-19 compatible symptoms, instead self-isolating. As such, only 20 SARS-CoV-2 sequences from HCW were available. Three (3/20) HCW were sufficiently similar to plausible link to our final clusters. The infectious diseases team undertook contact tracing, identifying on which wards they worked and for which patients they cared during the period of acquisition. One HCW (case 280) had cared for a nosocomial case (case 61) within cluster STH1, becoming symptomatic 5 days later. Case 280 can therefore be added to cluster STH1, however is unlikely to be the originator of this cluster.

Given HCW were not routinely tested we used HCW absenteeism due to COVID-19 related sickness or isolation as a marker for COVID-19 infection. Across the period, 337 working days were lost due to HCW COVID-19 related absenteeism across the nine main wards implicated in our hospital clusters (Supplementary Table S9), averaging 1.9 lost working days per ward each day.

From a hospital-wide cohort of 228 HCWs we collected information on COVID-19 compatible symptoms and judged seroconversion to SARS-CoV-2 IgG every 1-2 weeks (Supplementary Figure 4, Supplementary Table S10). 43/228 (19%) seroconverted to SARS-CoV-2 IgG with 13/43 (30%) being asymptomatic. Supplementary Figure 4 presents the predicted period of peak HCW infectiousness based on a combination of ± 2 days from date of symptom onset or seroconversion where asymptomatic. The rapid rise in HCW infectiousness is predicted to occur between March 16th and 25th, overlapping with incidence of nosocomial cases.

DISCUSSION

Applying epidemiological and genomic data described 14 transmission clusters, accounting for the vast majority of sequenced nosocomial cases. Only a minority of sequenced cases were not refuted from being part of a plausible transmission network with other sequenced cases in their epidemiological cluster, and multiple contemporaneous clusters were found within clusters formed by epidemiology alone, emphasising the importance of applying genomic data for transmission analysis. Haplotypes in these 14 final clusters were enriched 1-14 fold compared with the surrounding community, which increases confidence that they are true nosocomial clusters - an assessment which has not been used in other genomic studies of nosocomial transmission. Our final clusters contained a similar proportion of the probable (18/25, 72%) and definite (41/52, 79%, χ^2 $p=0.8$) sequenced nosocomial cases, increasing confidence that probable nosocomial cases are genuine nosocomial acquisitions.

In addition, our analysis adds to the literature on SNP thresholds for analysis of nosocomial transmission. Importantly, relaxing the SNP threshold did not cause clustering of community-onset cases where transmission is unlikely to have occurred. We permitted epidemiological contact during previous admissions given the 14 day incubation time of SARS-CoV-2, which is not considered in published definitions of nosocomial cases [23]. Five patients in 3 clusters were epidemiologically linked during a previous admission (Supplementary Figure 2).

Overlapping ward-stays allow epidemiological linkage by inferring risk of exposure between cases. More granular information not available through our hospital computer systems may improve epidemiological linkage, for instance a live bed state to determine the exact bed allocation and movements of patients between departments. This would allow environmental risk factors for acquisition to be identified, such as multi-bedded rooms, shared bathrooms, and air changes.

The presence of cryptic transmission and the absence of plausible originators in half of clusters suggests unidentified cases are involved in transmission, most likely HCWs or minimally/asymptomatic patients. Even in clusters where a plausible originator is present, it is still possible an unidentified case (e.g. HCW) is responsible for introducing infection - however this is less parsimonious. Cryptic transmission may also represent transmission in non-ward areas not covered

by our epidemiological data. Lack of routine screening of patients and HCW, along with poor recognition of milder, yet relevant symptoms early in the pandemic such as anosmia and upper respiratory coryzal illness, may have facilitated transmission as cases were missed. Our data suggests routine screening of staff and patients may be beneficial to improve case ascertainment.

Importantly, nosocomial cases declined before any possible impact from universal surgical mask use by HCWs or banning of hospital visitors. This may be due to falling infection rates in the community after implementation of non-pharmacological measures, effectively social distancing, decreasing transmission to admitted patients in hospitals. Interestingly community infections were predicted to peak around the same time as social distancing was introduced [4], with nosocomial cases beginning to fall around 7 days after this point, consistent with a delay of 5-7 days for incubation.

Moreover, nosocomial cases declined even whilst admission of community-onset cases continued to rise. This suggests that infection control measures can be effective at preventing transmission from admitted cases to other patients by rapid diagnosis, isolation and use of personal protective equipment. Community-onset cases may have passed peak viral shedding (often first 4 days of illness[29]) upon admission to hospital, with admission being a median of 7 days after symptom onset in our cohort. Instead, we hypothesise that infection is often introduced into the hospital by HCW or patients who are minimally/asymptomatic, who remain unidentified.

In summary, this study supports the role of genome sequencing in SARS-CoV-2 outbreak investigation. In addition, the presence of cryptic transmission and the implication of unidentified cases suggests routine screening of both HCW and patients may be valuable. It will be important to assess whether interventions such as universal mask use and intermittent screening limit nosocomial transmission.

TRANSPARENCY DECLARATIONS

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Ethics. Favourable opinion to conduct this work was granted by the North West Preston Research Ethics Committee (Reference 18/NW/0584) The COVID-19 Genomics UK (COG-UK) consortium study protocol was approved by the Public Health England Research Ethics and Governance Group (reference: R&D NR0195).

Conflict of interest. The authors declare that they have no competing interest

Access to data. The dataset(s) supporting the conclusions of this article are available in the Supplementary Materials. **Acknowledgements:** None.

Contribution. LBS, CLF, JDE, ARA designed the study, participated in dry and wet laboratory, performed analysis and drafted the manuscript. UT curated metadata and performed epidemiological analysis of outbreaks. CLF AA-M, TC, AWS, HDW, GB performed nanopore sequencing. BM provided epidemiological data. SP, RPG, SJDN, MHM, KJD provided supervisory support. EC, MTKI, PRC, RB, STD and GN managed patient samples including PCR testing. COG-UK curated and maintained the CLIMB database, and provided input into manuscript. All authors approved the final manuscript.

FIGURE and TABLE LEGENDS

FIGURE 1 Epidemiological description of cases diagnosed during the first wave. On the left hand y-axis, the grey bar chart displays new cases over time between March 10th and April 31st. Over the same period the right hand y axis shows incidence of nosocomial cases (maroon line). Overlaid is 5 key dates in public policy and infection control (A) March 13th; testing recommended for all inpatients with cough and fever; use of aprons, gloves and surgical face masks for interactions with confirmed/suspected cases. (B) March 16th; strong government advice for social distancing; (C) March 23rd; implementation of national lockdown (D) March 25th; exclusion of hospital visitors (E) March 28th; mandatory use of surgical masks for all patient interactions under 2 metres.

FIGURE 2a) Haplotype representations of the fourteen clusters that emerge after applying the process depicted in part a) to epidemiological and viral genetic data (see Methods). Clusters are named after the hospital site they occur in (leftmost column). Cluster haplotype lineages are shown in black (second column from left). Cluster haplotypes are depicted (rightmost column) with a "1" in a given position indicating the presence of the SNP relative to the reference genome shown above in vertical text, and a "." indicating its absence (wild-type sequence). Cluster rows are coloured based loosely on the similarity of the cluster haplotypes to one another. This same colour scheme is used to represent specific clusters in subsequent figures.

FIGURE 2b) Epidemiological clusters 4-33, including cases where $n > 2$ (Supplementary Table S6) are coloured according to how many of their patients belong to a combined epidemiological plus genomics cluster, with the colour indicative of the viral haplotype (Figure 2a). Patients with viral haplotypes not found in any combined cluster are coloured grey, and those patients for which sequence was unavailable are shown in black. Epidemiological cluster number is shown on the x-axis. Epidemiological cluster 1-3 are not displayed due to their large size.

FIGURE 2c) Combined epidemiological plus genomic clusters from the acute and elective hospital sites. Clusters are coloured according to viral genomic haplotype (Figure 2a). Clusters are shown broken down into PHE patient nosocomial categories, with different shapes indicating the different categories. Enrichment of the cluster viral haplotype frequency in our study dataset vs. the frequency

in the community (Supplementary Table S7, Methods) is shown on top of each cluster column.

FIGURE 3 - Phylogenetic tree (left panel) for sequences with Pangolin lineage assignment B.1. Tree tips are labelled with patient ID, color-coded according to transmission cluster assigned in our combined epidemiological and genomic investigation. Symbols at the tree tips are displayed according to community-acquired or nosocomial infection classifications. Sequence sample dates are plotted in line with the tree tips using the same symbols in the right-hand panel; admission periods prior to the sample date for each patient are also displayed in this plot as horizontal lines

FIGURE 4 - Pictorial representation of ward stays and movements for patients within cluster GUY1. Each row represents a different case. Patient ID, designation, lineage and SNP variants are marked. Ward movements between March 1st to 31st are displayed. Different wards are by given colours. Where there is >1 ward stay on one day, the longest ward stay is represented. The sample collection date is marked with an 'x'. Symptom onset, where known, is marked with a cross '□'. Time periods outside of the acquisition period are shaded.

TABLE 1 Demographics of the 574 cases diagnosed by the diagnostic lab until March 31st, separated by community-onset, indeterminate, probable nosocomial, and definite nosocomial infections.

SUPPLEMENTARY FIGURE AND TABLE LEGENDS

SUPPLEMENTARY FIGURE 1A-D Phylogenetic tree (left panel) for sequences with different Pangolin lineage assignments. Tree tips are labelled with sequence identification numbers, color-coded according to transmission cluster assigned in our combined epidemiological and genomic investigation. Symbols at the tree tips are displayed according to community-acquired or nosocomial infection classifications. Sequence sample dates are plotted in line with the tree tips using the same symbols in the right-hand panel; admission periods prior to the sample date for each patient are also displayed in this plot as horizontal lines.

SUPPLEMENTARY FIGURE 2 Ward movement diagrams for the combined clusters formed through epidemiological and genetic analysis. Each row represents one patient's movements. Lineage, case classification and haplotype are shown. Ward stays are shown coloured by different ward location, with time on the horizontal axis. Where a patient is on two wards in one day, the ward with the longest stay is represented. The symptom onset date is marked with '□' and the sample collection date with an 'x'. Timepoints outside the possible acquisition period are shaded in gray. Wards where known COVID-19 cases are cohorted are coloured in blue. Outpatient wards are represented in grey.

SUPPLEMENTARY FIGURE 3 3D spatial representation of St. Thomas' Hospital (a) and Guy's Hospital (b) is shown with wards where transmission of clusters STH1-5 and GUY1-7 occurred (see Supplemental Figure 2) are coloured according to viral genetic haplotype (Figure 2b). The numbers in the ward indicate the number of patients from the given cluster inside that ward during their incubation period (as defined in Figure 2a).

SUPPLEMENTARY FIGURE 4: Epidemiological description of cases diagnosed during the first wave. On the left hand y-axis, the grey bar chart displays new cases over time between March 10th and April 31st. Over the same period the right hand y axis shows incidence of nosocomial cases (orange line) and, the proportion (%) of screened HCW with confirmed infection reporting symptom onset (black line) with peak period of infectivity ± 2 days (dashed black line), with IgG seroprevalence of HCW (green). Overlaid is 5 key dates in public policy and infection control (A) March 13th; testing recommended for all inpatients with cough and fever. (B) March 16th; strong government advice for social distancing; (C) March 23rd; implementation of national lockdown (D) March 25th; exclusion of hospital visitors (E) March 28th; mandatory use of surgical masks for all patient interactions under 2 metres.

SUPPLEMENTARY TABLE 1 Number of tests performed, number of positive tests, number of new cases, combined number of probable and definite nosocomial cases, and number of community viral sequences submitted to CLIMB, all by date from March 9th to March 31st.

SUPPLEMENTARY TABLE 2 For each patient, symptom onset (column B), hospital admission or outpatient encounter date (column C) during which first positive SARS-CoV-2 samples is taken.

Sample collection date and time (column D) is given, with time between symptom onset and admission (column E) or admission/encounter and sample collection date (column F). The admission/encounter is categorised (column G) as either 'outpatient', 'A&E' where samples are taken in the emergency room when the patient is not admitted, and 'Inpatient' where the patient is admitted during that encounter. Column H categorises patients as either as per the NHS England and ECDC definitions of nosocomial infection[23]. Column I shows whether viral sequence for the isolate was successfully obtained..

SUPPLEMENTARY TABLE 3: Epidemiological clusters with ward of overlaps and patients within the cluster. Clusters must contain at least one probable or nosocomial infection (see Methods). Sorted from largest cluster to smallest.

SUPPLEMENTARY TABLE 4: Epidemiological clusters separated into those that isolates that were not sequenced successfully, genetic haplotypes without genetic similarity to other sequenced individuals, and by haplotypes that form clusters with other cases (GUY1 to GUY7, STH1 to STH5, INB, IND)

SUPPLEMENTARY TABLE 5: Final transmission clusters using a permitted pairwise SNP distance of 1. with associated hospital site, ward, ward type, lineage and case numbers. Overall number of each case classification for the clusters is given in column G. Seed haplotype is given, with SNP variants from the seed haplotype also reported. The final three columns show the calculation of the hospital enrichment factor; the number of sequences with the seed haplotype from the sequenced isolates from hospital, the number of community samples with this haplotype submitted to CLIMB, and the enrichment factor which is the ratio of these two numbers.

SUPPLEMENTARY TABLE 6: Final transmission clusters using a permitted pairwise SNP distance of 2.

SUPPLEMENTARY TABLE 7: Analysis of unresolved sequenced nosocomial cases that are absent from final transmission clusters. The proportion of cases sequenced in the epidemiological clusters where these unresolved sequenced nosocomials are present is presented.

SUPPLEMENTAL TABLE 8: Epidemiological clusters that contribute to combined epi + genetic

cluster without community-onset or indeterminate cases are assessed to see whether they could contain non-sequenced cases that may serve as originators to the cluster. Cases are deemed not to represent a potential non-sequenced originator if they are a probable or definite nosocomial case, diagnosed after the start of the cluster, or if they do not share significant genome similarity with other cases in the cluster. Epidemiological cluster information is used from Supplementary Table 3 and 4.

SUPPLEMENTARY TABLE 9: HCW absenteeism. HCW numbers and total hours lost to COVID-19 related isolation or illness is presented for the 9 main wards involved in outbreaks during the study period

SUPPLEMENTARY TABLE 10 Cumulative incidence of HCW IgM and IgG seroconversion by week, beginning on Mar 13th until Jun 12th. Total number sampled (n=228)

SUPPLEMENTARY TABLE 11: Genomic sequence of viral isolates from cases. Sequence only included if sequenced successfully with >90% coverage at 8x depth. GISAID accession ID, lineage, haplotype, coverage and N positions for each genomic sequence displayed.

SUPPLEMENTARY TABLE 12: Patient ward movements. Every encounter or ward stays in the 14 days prior to the first positive test is given, with start and end date. Each row represents a different encounter or ward stay. Ward stays are arranged by ascending patient number and in chronological order.

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Foundation Trust, 75 Centre for Clinical Infection & Diagnostics Research, St. Thomas' Hospital and King's College London, 76 Department of Infectious Diseases, King's College London, 77 Guy's and St. Thomas' Hospitals NHS Foundation Trust, 78 Centre for Clinical Infection and Diagnostics Research, Department of Infectious Diseases, Guy's and St Thomas' NHS Foundation Trust, 79 Princess Alexandra Hospital Microbiology Dept. , 80 Cambridge University Hospitals NHS Foundation Trust, 81 East Kent Hospitals University NHS Foundation Trust, 82 University of Kent, 83 Gloucestershire Hospitals NHS Foundation Trust, 84 Department of Microbiology, Kettering General Hospital, 85 National Infection Service, PHE and Leeds Teaching Hospitals Trust, 86 Cambridge Stem Cell Institute, University of Cambridge, 87 Public Health Scotland, 88 Belfast Health & Social Care Trust, 89 Health Services Laboratories, 90 Barking, Havering and Redbridge University Hospitals NHS Trust, 91 Royal Free NHS Trust, 92 Maidstone and Tunbridge Wells NHS Trust, 93 University of Brighton, 94 Kings College London, 95 PHE Heartlands, 96 Imperial College London, 97 Department of Infection Biology, London School of Hygiene and Tropical Medicine.

	Overall		Community		Indeterminate		Probable nosocomial		Definite nosocomial	
Cases (n)	574		471	82%	17	3%	27	5%	59	10%
In-hospital mortality	114	20%	81	17%	4	24%	6	22%	23	39%
Inpatients	483	84%	380	81%	-		-		-	
Length of stay (IQR)	12 (5-27)		9 (4-16)		19 (11-24)		23 (21-30)		53 (36-94)	
Sex										
Female	251	44%	208	44%	4	24%	9	33%	30	51%
Male	323	56%	263	56%	13	76%	18	67%	29	49%
Median age (IQR)	61 (48-76)		58 (45-73)		73 (61-80)		75 (69-81)		73 (61-82)	
Ethnicity										
Known	455	79%	377	80%	10	59%	18	67%	50	85%
White	230	51%	174	46%	5	50%	14	78%	37	74%
BAME	225	49%	203	54%	5	50%	4	22%	13	26%
Pregnant	13	2%	13	3%	0	0%	0	0%	0	0%
Charlson score (IQR)	2 (1-5)		1 (0-3)		5 (4-6)		5 (4-6)		5 (4-6)	
Hypertension	257	45%	203	43%	7	41%	17	63%	30	51%
Congestive cardiac failure	28	5%	13	3%	1	6%	4	15%	10	17%
Myocardial infarction	19	3%	12	3%	1	6%	2	7%	4	7%
Diabetes mellitus	168	29%	138	29%	3	18%	9	33%	18	31%
End organ damage	38	7%	28	6%	3	18%	3	11%	4	7%
Renal impairment	111	19%	87	18%	4	24%	6	22%	14	24%
Mild	49	9%	34	7%	3	18%	3	11%	9	15%
Moderate	7	1%	5	1%	0	0%	1	4%	1	2%
Severe	54	9%	47	10%	1	6%	2	7%	4	7%
Dementia	50	9%	31	7%	2	12%	4	15%	13	22%
COPD	46	8%	30	6%	3	18%	3	11%	10	17%
Immunosuppression	35	6%	24	5%	0	0%	3	11%	8	14%
HIV/AIDS	2	0%	2	0%	0	0%	0	0%	0	0%
Solid tumor	71	13%	45	10%	6	35%	6	22%	14	24%
Localised	53	9%	36	8%	3	18%	4	15%	10	17%
Metastatic	18	3%	9	2%	3	18%	2	7%	4	7%
Haematological malignancy	14	2%	4	1%	2	12%	2	7%	6	10%
Lymphoma	7	1%	1	0%	2	12%	1	4%	3	5%
Leukaemia	7	1%	3	1%	0	0%	1	4%	3	5%

TABLE 1

TABLE 1 Demographics of the 574 cases diagnosed by the diagnostic lab until March 31st, separated by community-onset, indeterminate, probable nosocomial, and definite nosocomial infections.

Figure 1

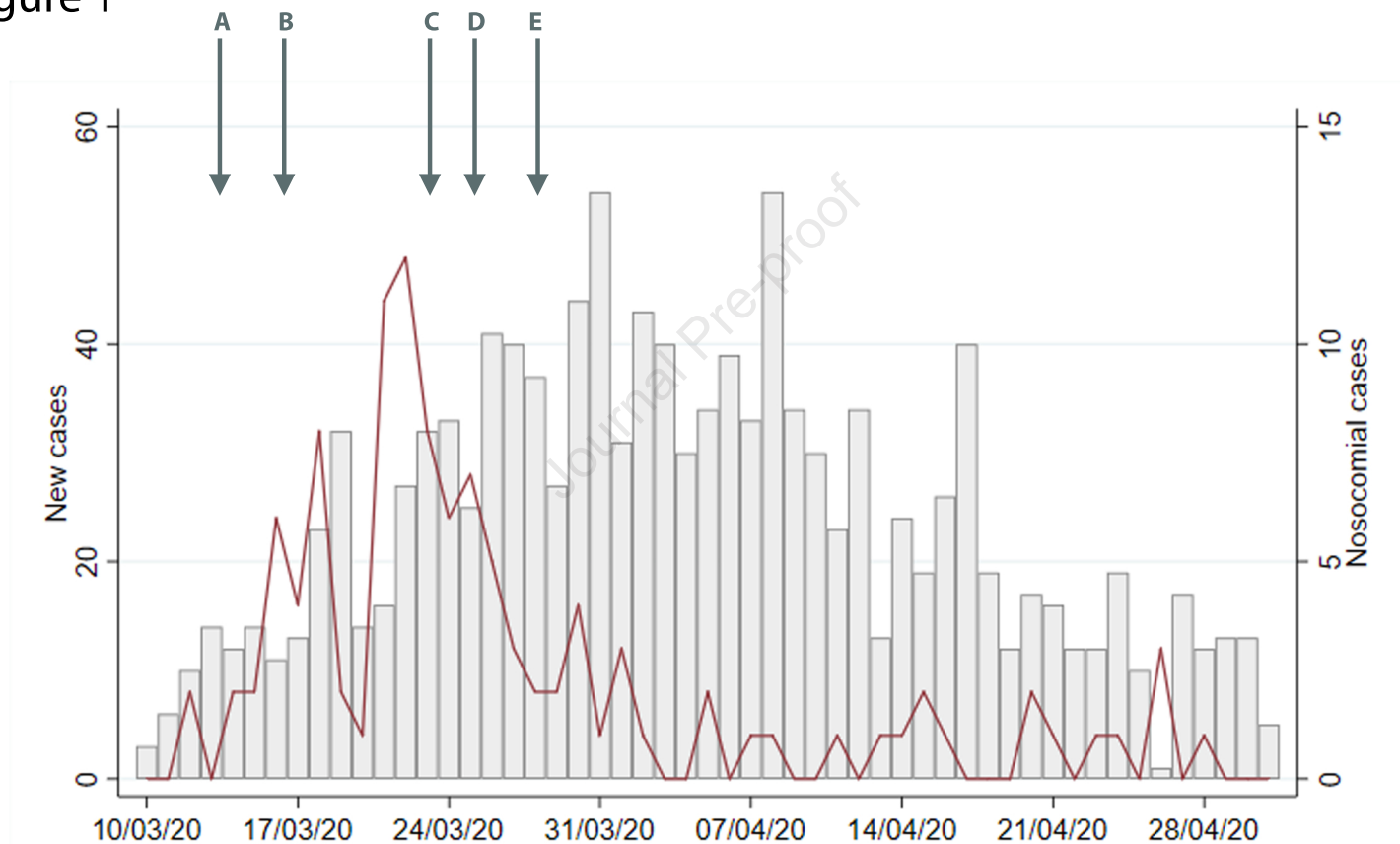
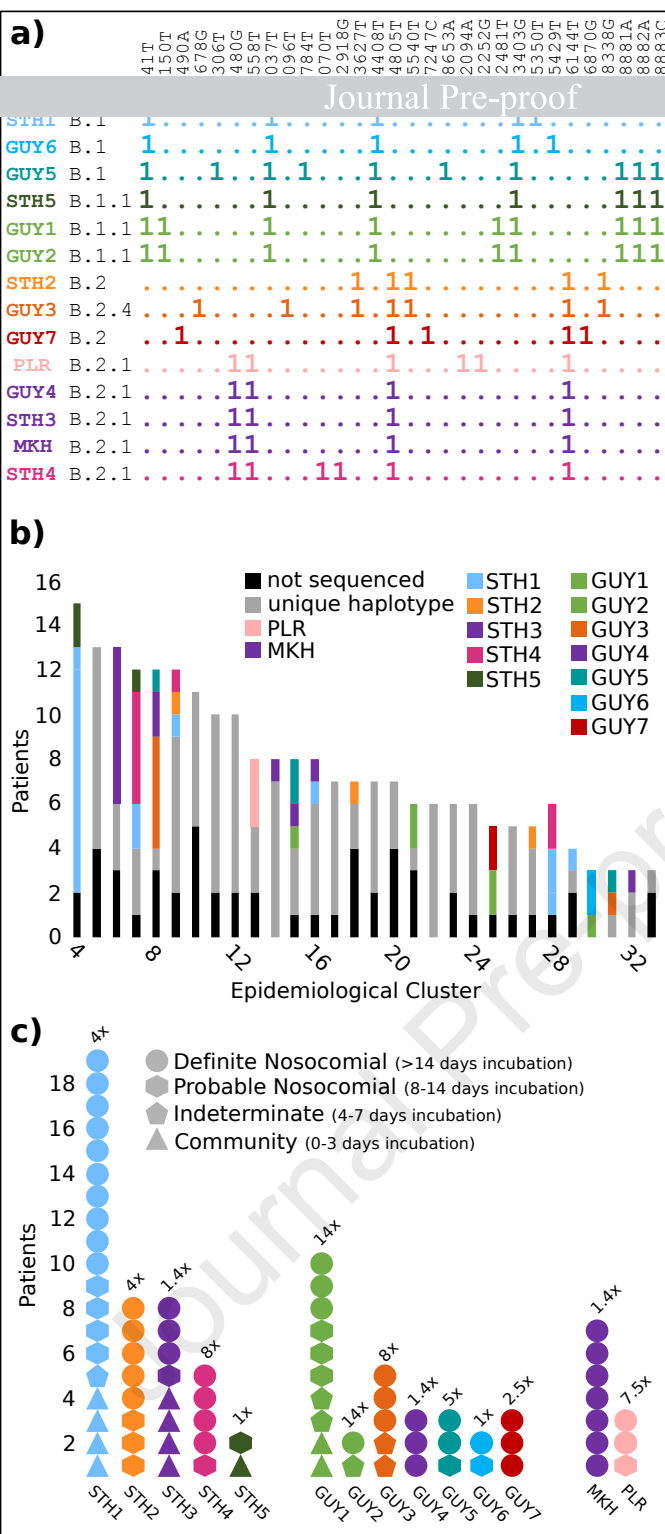
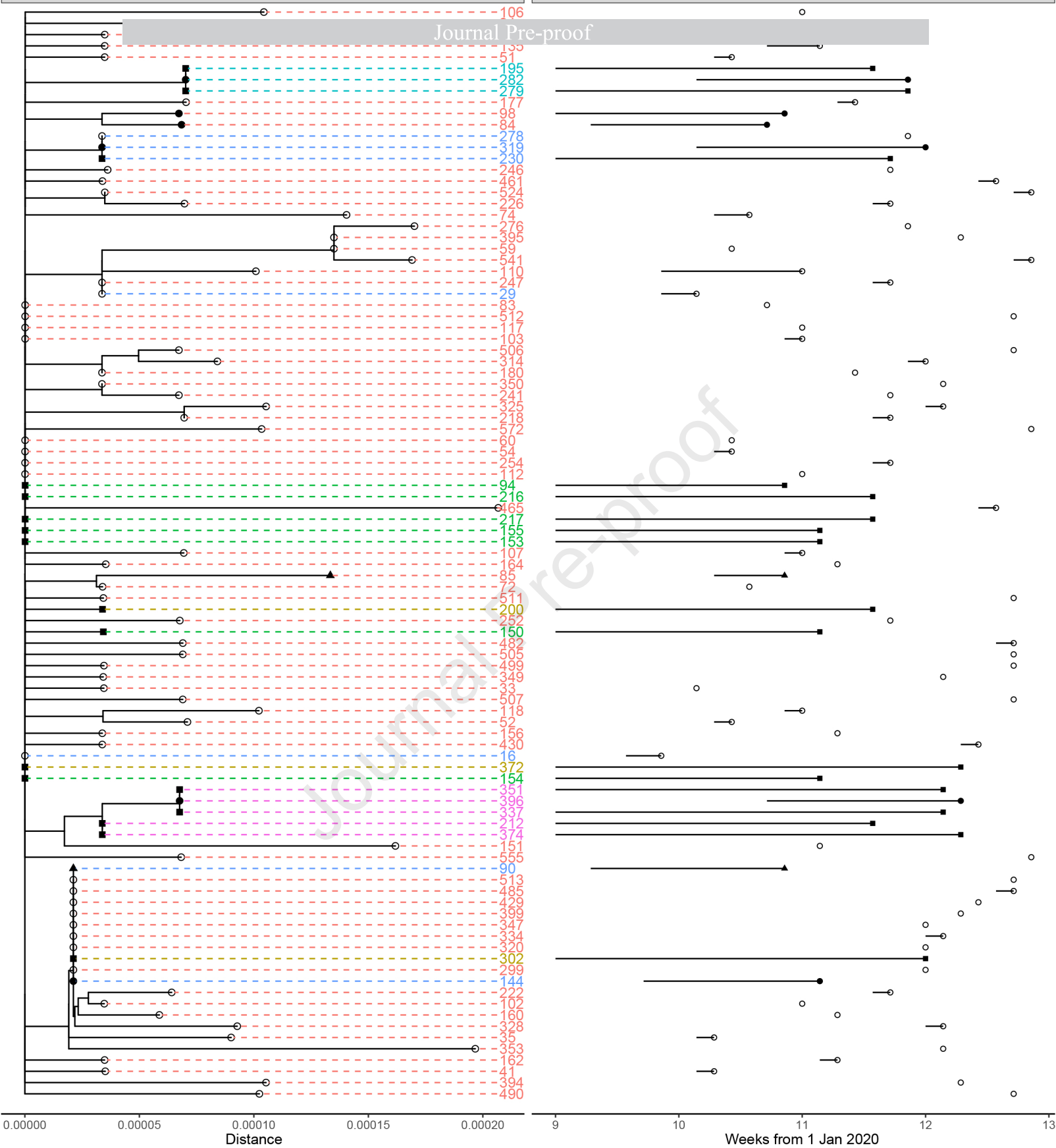


Figure 2



ID	Designation	Lineage	C241T	C1150T	C3037T	T2978C	C14408T	A22481T	A23403G	TTA28062T	G28881A	G28882A	G28883C	March																														
														1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
169	Indet noso	B.1.1	x	x	x		x	x	x		x	x	x	March 1-6: Grey	March 15: PVG	March 17: †	March 20: x	March 21: LHF	March 22: PEK	March 23-31: Blue																								
199	Prob noso	B.1.1	x	x	x		x	x	x		x	x	x	March 1-8: Grey	March 8: PVG	March 20: †	March 21: x	March 22: LHF	March 23: PEK	March 24-31: White																								
256	Def noso	B.1.1	x	x	x		x	x	x		x	x	x	March 1-10: AMS	March 17: HK	March 18: AMS	March 20: †	March 23: x	March 24: HND	March 25: PEK	March 26-31: Blue																							
277	Comm	B.1.1	x	x	x		x	x	x		x	x	x	March 1-10: Grey	March 10: OP	March 13: PVG	March 17: †	March 22: EDI	March 23: x	March 24: MAD	March 25-31: Blue																							
309	Def noso	B.1.1	x	x	x	x	x	x	x		x	x	x	March 4: PVG	March 7: IC9	March 8: PVG	March 11: LHR	March 13: IC9	March 15: PVG	March 16: A09	March 18: LHR	March 20: †	March 21: x	March 22: PEK	March 23-31: Blue																			
355	Prob noso	B.1.1	x	x	x		x	x	x		x	x	x	March 1-12: Grey	March 13: PVG	March 16: AMS	March 23: x	March 24: HN	March 25: PEK	March 26-31: Blue																								
356	Indet noso	B.1.1	x	x	x		x	x	x		x	x	x	March 1-14: Grey	March 16: A41	March 17: AMS	March 23: x	March 24: PEK	March 25-31: Blue																									
434	Def noso	B.1.1	x	x	x		x	x	x	x	x	x	x	March 1-10: Grey	March 11: CAN	March 12: IC9	March 13: CAN	March 22: AMS	March 28: †	March 29: x	March 30: CAN	March 31: Blue																						
551	Prob noso	B.1.1	x	x	x		x	x	x		x	x	x	March 1-16: Grey	March 17: DFW	March 21: CAN	March 28: LHF	March 29: †	March 30: x	March 31: D	March 22-27: Blue																							



Cluster

- ✗ -None identified
- ✗ GUY4
- ✗ MKH
- ✗ PLR
- ✗ STH3
- ✗ STH4

Case classification

- Community
- Definite Nosocomial
- ▲ Indeterminate
- Probable Nosocomial

Figure 3