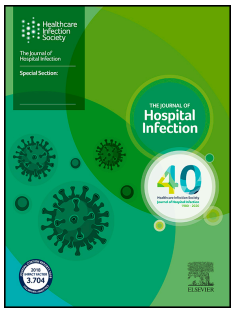
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



Getting to the Heart of In-hospital Transmission of SARS-CoV-2 with the Help of Whole Genome Sequencing

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- COVID-19, Super spreader event, hospital outbreak, PPE, Whole genome sequencing

Word count for Summary: 183

1. Summary:

We present an outbreak of 56 staff and patient cases of COVID-19 over a 31 day period in a tertiary referral unit, with at least a further 29 cases identified outside of the unit and the hospital by whole genome sequencing (WGS). We document transmission from staff-to-staff, staff-to-patients and patients-to-staff and show disruption of a tertiary referral service, despite implementation of nationally recommended control measures, superior ventilation and use of PPE. We demonstrate extensive spread from the index case, despite them spending only 10 hours bed bound on the ward in strict cubicle isolation and with an initial single target low level (CT=32) PCR test. This investigation highlights critical issues including how effectively and explosively SARS-CoV-2 can spread in certain circumstances. It raises questions about infection control measures in place at the time and calls into question the premise that transmissibility can be reliably detected using lower sensitivity rapid antigen lateral flow tests. We also highlight the value of early intervention in reducing impact as well as the value of WGS in understanding outbreaks.

2. Introduction

The first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wales was identified on 28th February 2020 [1]. Wales experienced two waves of the pandemic in 2020; spring and autumn/winter months. Infection rates triggered a firebreak lockdown in October. A full national lockdown followed in December.

Hospital transmission of SARS-CoV-2 has proved difficult to control, with healthcare associated infections (HCAI) troublesome throughout. Understanding factors contributing to hospital transmission is critical to containing spread.

This paper describes a super-spreading event, identified through WGS, spanning a 31-day period in autumn 2020, with extensive spread and disruption of a tertiary service despite minimal direct exposure to the primary case and an initial low level PCR result. We suggest this was the result of aerosol transmission in the absence of a specific aerosol generating procedure (AGP). Transmission occurred despite the use of recommended PPE, and questions the effectiveness of infection control measures in place at the time. Recommendations are made to reduce the risk of nosocomial spread of SARS-CoV-2. Transmission from patient to staff, staff to patient, patient to patient and staff to staff are exhibited and movement across and between sites through staff and patient intermediaries is identified.

3. Methods

Setting

A regional unit, receiving planned and unscheduled emergency admissions from a large rural and urban area. Reorganisation, including a separate “COVID free” / “green” area (Ward 4) with strict admission criteria, enabled ongoing management of circa 350 patients per month throughout the pandemic (See Supplementary Material S1).

Ventilation on the unit is higher specification than most wards (fig 5) reliably achieving four to six air changes per hour.

PCR testing

SARS-CoV-2 real-time PCR testing on all oro/nasopharyngeal swabs undertaken using approved CE marked assays. Different platforms used according to availability, capacity and urgency (Appendix A).

Genomic sequence generation and processing

All samples with a Ct ≤30 underwent sequencing at the Public Health Wales (PHW) Pathogen Genomics Unit (PenGU) following the ARTIC nCoV PCR protocol [2]. Amplicons generated were tagmented using Nextera XT library preparation kits, multiplexed for sequencing on MiSeq instruments using 2x250bp V2 kits and then processed using the ARTIC nCoV (pipeline re-implemented for use in automated environments using next flow). Sequences were uploaded to MRC CLIMB [3] [4] as part of the COG-UK sequence collation, management and processing system and analysed using an automated phylogenetics pipeline which assigns cases to a PANGO lineage [5] and a putative 'UK transmission group' using ancestral state reconstruction (F). The 'UK transmission group' effectively represents a group of cases from the UK which are phylogenetically related and are bounded by cases from elsewhere in the world, providing a system to enable the use of genomics data to exclude cases, or identify possible cases to include (method used to examine imports [6] and cluster growth [7]). The genomic lineage and transmission group assignments were then linked with epidemiological data for further analysis and interpretation.

Case finding and investigation

The outbreak was investigated by an outbreak team comprising ward staff, IP&C, Public Health doctors and a hospital epidemiologist in line with Health Board outbreak management guidelines. Screening (patients and staff) took place on day 10. Patient contacts were re-screened when a new case was identified. The outbreak was put together using real time epidemiology combined with use of WGS data, patient movement data, staff sickness and staff shift data, staff and patient screening and staff and patient COVID19 results. Data was collected in real time through staff interviews, on the ground epidemiological investigation and regular outbreak meetings (daily initially).

Patient laboratory results, contacts and ward movements were extracted from an infection prevention and control database and reporting system (ICNet).

Additional data was gathered from staff self-isolation databases, and patient medical records.

Case definition

1) Patient residing or staff member working on the affected wards during the outbreak period
2) PCR positive COVID-19 laboratory result during the outbreak period
3) Epidemiologically linked in place and time with another confirmed case
4) Sample falls within a single UK transmission group within PANGO Lineage B.1.1.311.

A 'confirmed case' was defined as satisfying criteria 2, 3 and 4 +/- criterion 1. A 'probable case' satisfied criteria 1, 2 and 3 with no WGS information.

National guideline categorisation was subsequently applied (table III) [8].

Exposed patient – contact with a positive outbreak case (preceding 14 days) and not symptomatic or PCR positive.

Exclusions:–

- Cases falling into a different lineage to B.1.1.311.
- Community Acquired Infection (CAI) not satisfying inclusion criteria above and WGS not available.

End of the outbreak – last WGS confirmed case identified on the affected unit.

Data storage and analysis

Data were stored on a secure PHW server. Analysis was conducted in STATA version 14.2 and R studio version 3.5.1. The outbreak investigation was conducted under the PHW establishment order © and did not require ethical approval. The Health Board's Joint Study Review Committee (JSRC) deemed the work exempt from requiring NHS Ethics review.

4. Results

Descriptive epidemiology

A total of 56 cases (21 (39%) patient and 35 (61%) HCW) met the case definition: 24/56 (43%) confirmed cases falling within the UK transmission group associated with the outbreak, and 32/56 (57%) probable cases. In total, 251 staff (with some pre-existing immunity from outbreaks in the first wave) were tested (table II). The epidemic curve shows three initial peaks; day 6, 10 and 14 (Fig. 2).

Genomic diversity

Wales has maintained active genomic surveillance of 20-30% of SARS-CoV-2 cases since the early pandemic. To understand the context of the outbreak cases, we used genomics to identify the UK transmission group of outbreak cases, identifying that this transmission group belonged to the Pango lineage B.1.1.311. B.1.1.311 was first reported in the UK in England during epi week 31, with cases identified in Scotland in week 33 and Wales in week 36 (in a geographically distinct Health Board (GD1)). The first case in the Health Board associated with this outbreak was P0, in week 40. In Wales between weeks 40 and 48, B.1.1.311 represented 2.3% of all cases and was the ninth most frequent lineage (210 sequenced cases in total). B.1.1.311 was predominantly associated with two locations - the outbreak Health Board (58 cases) and Health Board GD1 (54 cases). To place the occurrence of B.1.1.311 in outbreak cases with its occurrence more widely, we examined the prevalence of other lineages in the Health-board area at the same time. Between weeks 40 and 48 in the outbreak Health Board the overall dominant lineages were Pango lineages B.1.177 and its sub-lineages, which collectively accounted for over 75% of sequenced cases. In contrast B.1.1.311 (the outbreak lineage) was the seventh most prevalent lineage in the area as a whole at that time, the first case being P0 with most subsequent cases linked to P0.

The population level genomic surveillance clearly demonstrates that the outbreak lineage was distinct from the main contemporaneously circulating lineages in the community, and that there was limited community circulation of B.1.1.311. In addition, most community circulation was related to the hospital and some subsequent community cases were likely related to spill out from the hospital back into the community. The rare nature of the lineage at that time enabled reliable detection of outbreak cases, including retrospective identification of the index case (P0) (Figure 6, 7). No cases of B.1.1.311 were identified in the hospital prior to P0's admission (Figure 6). Only B.1.1.311 was identified on the ward during this period, whereas other viral lineages accounted for the vast majority of circulating virus in the community at the time (Fig 7). Eighteen additional cases of B.1.1.311 with no identified epidemiological link (most likely related) were subsequently detected (D18 - 86). Of the 29 confirmed linked cases with the outbreak lineage genotype, three were descendants with single nucleotide polymorphisms.

The outbreak

The outbreak, reconstructed using a combination of WGS and epidemiology (patient movement, staff rosters and date of onset of infection) is reported below.

Primary case (P0)

P0 was admitted to the COVID area of the Accident and Emergency (AE) department with a rib fracture following a fall. P0 was transferred to ward 1 (02:00h Outbreak Day 0), along a corridor providing access to wards 1, 2 and 4 while receiving oxygen (10L via a non-rebreather facemask). P0 was bed bound and isolated in an en-suite cubicle in a distal corner of a dead-end corridor, at the proximal end of ward 1, 100 metres from the first affected bay. A patient toilet is situated on the same corridor and a shower is nearby. Figure 1 provides the geographical layout. P0 remained in the cubicle for 10 hours with no direct contact with any other patient. At midday, P0 was transferred to the intensive care unit (ICU) whilst receiving oxygen (15L, non-rebreather facemask). Staff reported that the corridors were cleared (for both transfers) and no direct contact (≤2m) between P0 and any other patients or staff occurred.

P0's journey to and from the cubicle passed close (>2m <5m) to the desk area (Fig. 1, Fig 3), busy with staff and patients at lunchtime (exact details of those present unknown). Routine mask wearing around the desk was identified retrospectively, as suboptimal.

A throat swab (taken at 23:20 on day 0 tested positive for SARS-CoV-2 on the Aries platform in a single gene (N gene CT-32, ORF1a not detected) with the result returned after 30 hours. A repeat swab on day 1 (D1) was positive on the same platform, CT N gene 27, ORF1a 25.

First peak

Six days following P0's admission (D7), two HCWs from ward 1 (S1, S2) and one patient from ward 2 (P1) became symptomatic. Epidemiological investigation revealed that P1 was ambulatory, frequently visited the desk area and used the toilet and shower adjacent to P0's cubicle (Fig. 1) on the morning that P0 was on the ward.

Amongst initial healthcare worker cases, only S1 directly cared for P0, using recommended PPE (fluid repellent surgical face mask (FRSM), visor, gown and gloves). Two other staff members caring for P0 wore FFP3 masks, in breach of national guidelines, and were not infected.

A further three staff (S5, S6, S8 on D8) and two patients (P2 on D8, P9 on D9) became symptomatic and tested positive. P9 was mobile and known to use the toilet and shower adjacent to P0's cubicle and likely contracted infection directly from P0 (although acquisition from another early patient or staff case cannot be excluded). P2 was immobile in a bed opposite P1.

P1 had very low CT values (16, 17 and 14) and was likely highly infectious. P1 had onset of symptoms on D6 (infectious from day four), had a positive swab taken on D7, reported on D8. P1 is the proposed source of onward transmission to Bay O, ward 2 and a neighbouring hospital. P1 was resident on Bay O D1 to D6, on ward 2 D6 to D8 (transferred following a procedure), and in a neighbouring hospital from D8. Among these exposed locations, there were five cases in Bay O (3/7 resident in the bay on day four to six including P2), five in ward 2 (3/10 resident on the ward day six to eight, including P5), and 10 (7 patient and 3 staff) in the neighbouring hospital.

Of the four staff initially infected that did not provide direct care for P0, two (S6, S8) worked shifts when P0 was on the ward. Two did not (S2, S5). In the intervening period, none of these four staff worked a shift with any of the other early-infected staff during their infectious period (table I). S6 and S8 likely acquired infection from P0. S2 and S5 provided close care for patients in all ward bays including P1 and P2 and likely acquired infection from them.

Subsequent infections

Subsequent infections are shown in *figure 2*. The spread of infection around the unit is depicted in figures 3 and 4, showing patient cases in bays O and M and ward 2 from day 10 to 15 and in bay B from day 19. Spread to bay M is likely to have occurred primarily through secondary patient intermediaries - P5 (likely infected from P1) and / or P9 (likely infected from P0). Bay B is used for closer patient monitoring and patients are consequently less mobile. Despite being closest to the desk, only two cases were acquired here later in the outbreak (D19). P9 was the likely source of introduction to bay B.

Secondary cases prevented:

There were no secondary cases on ward 3. Five patient cases were identified through screening, all had transferred from wards 1 and 2 shortly prior to testing positive and were rapidly retrieved back to ward 1.

There were no documented transmission events following transfer of P0 to ITU.

Staff Infections

High numbers of staff cases (N=31) were identified. Potential risk areas for staff-to-staff transmission included a break room, changing room, kitchen facilities and the desk, although none could be categorically implicated because of overlapping exposure risks. The break room was closed and end of shift changing (where social distancing could not be guaranteed) was controlled.

Four ward 4 staff (S15, S23, S26, S28) tested positive during the outbreak (one definite and three probable cases). Two likely acquired infection during shifts on ward 1, three to seven days prior to symptom onset. The other two had no direct link to ward 1 but with no identified patient transfer to ward 4 and no patient cases, spread was likely due to contact with infected staff or were incidental cases. Twenty-two staff tested negative on screening.

Spread of infection by staff:

Epidemiological data supports introduction of the outbreak genotype to geographically separate wards via staff, despite use of nationally recommended PPE.

Seven cases (five patients and two staff) were identified on ward 5, with a descendent of the virus infecting the index case (single nucleotide polymorphism – B.1.311 sub-lineage 1). There were no patient transfers between wards 1 and 5. The first descendent virus case was identified in a staff member (S13) on D11. S13 worked on both ward 1 and 5 (pre-symptomatic transmission likely). On D15, another ward 1 staff member (S6) tested positive with the descendent virus.

Further hospital spread

Movement of a patient from ward 5 (prior to recognition of infection on the ward) led to another three WGS linked cases on a geographically separate ward (ward 6). One other staff case with no identified link was also detected.

A descendent virus of B.1.1.311 sub-lineage 1 with a minor polymorphic change (B.1.1.311 sub-lineage 1.1) was subsequently detected in the hospital. This cluster of six patient and two staff cases, including three patient and one staff case from ward 7, are also likely linked to the original outbreak, although an exact route of transmission has not been determined.

Overall 85 cases were identified, with 56 on the unit (Table II), representing the absolute minimum as uncaptured linked cases undoubtedly exist.

Potential transmission in spite of appropriate PPE:

See Appendix B.

At least three staff members were infected whilst wearing recommended PPE, two caring for P0 and one for P1.

An A&E staff member (S4) developed symptoms and tested positive for the outbreak genotype five days after transferring P0 to ward 2. S4 had limited contact with P0 (facilitating the transfer), did not examine or have very close face-to-face contact. No breach in PPE occurred. S4 did not have contact with other staff or patients on the outbreak unit and no known contacts outside work. S1 directly cared for P0, had no reported breaches in PPE use and developed symptoms six days after. Two other staff members caring for P0 wore FFP3 masks, in breach of national guidelines, and were not infected.

On D7, P1 underwent an Echocardiogram. Five days later (D11), the cardiac physiologist developed symptoms and tested positive for the outbreak genotype. The cardiac physiologist known for meticulous compliance with PPE and adherence to social distancing, was not based in the outbreak unit, their household contacts tested negative and no contact with other individuals with the outbreak genotype was identified. They did not experience any PPE breach during the procedure, but did recall the patient coughing.

Whilst it is not possible to completely exclude transmission through other routes, the timing of their infections combined with the rare outbreak genotype in the hospital make alternative explanations very unlikely.

Control measures

Appendix C outlines control measures introduced on the afternoon of D8 when results first became available.

Discussion

The combination of sequencing data and descriptive epidemiology has enabled the identification of transmission routes during the course of this extensive outbreak. The data demonstrates rapid and widespread transmission across a defined ward area to both patients and staff, despite use of recommended control measures. Transmission occurred despite a high initial CT Value in P0 and lack of direct contact with cases, including transmission to three staff with known limited contact and full compliance with PPE. This single patient case gave rise to at least three secondary clusters totalling at least 85 cases, including at least 10 in another hospital.

5.1. Super-spreading event

This outbreak is typical of a super-spreader event, with explosive early growth and sustained transmission in later stages [9]. Stochastic transmission and the 20:80 rule (20% of infected individuals causing 80% of infections [10] [11]) need to be considered when assessing effectiveness of control measures. Control measures should be designed to prevent super-spreading events as they are responsible for the majority (80%) of transmission events and measures that control these more explosive transmission events will likely also control the other 20% of transmissions as well.

5.2. Transmission greater than that expected by droplet spread (Supplementary Material S2)

The spread of infection from P0 is surprising because of the very short stay on ward 1, admission directly into an en-suite cubicle at the proximal end of the ward and lack of direct contact with most cases (P1, P9, S6, S8) infected in the early phase of the outbreak. The epidemiological data and witness histories support the desk and / or corridor area as the most likely place of transmission. P0 passed through at a busy time, ambulatory patients (P1 & P9) were using the toilet and shower and mask wearing in this area was retrospectively identified as suboptimal (although all infected staff members reported wearing masks at the time of transfer). Transmission probably occurred through exposure to contaminated air over distances in the region of three to five metres (greater than that expected by droplet spread). No aerosol generating procedure (AGPs) took place to account for this. Fomite transmission is also possible but less likely (no shared facilities).

5.3. Person to person spread: (see Supplementary Material S2)

Sequential onset of infection around the ward is consistent with person-to-person spread. Infection was first established in bay O and ward 2 and subsequently spread to bay M then bay B. Exact events leading to infection in these latter areas cannot be precisely defined but timing fits with introduction of infection via patient intermediaries. The relative sparing of bay B suggests that lack of mobility may have been partially protective.

A single airborne event affecting the whole ward simultaneously is not supported (infection initially skipped the nearest bay (Bay B, Fig. 3) and proximal bays and ward 4 were spared (Fig. 1)).

Finally, spread to other wards occurred through patient and staff intermediaries, likely during the pre-symptomatic or minimally symptomatic infectious period.

Limiting patient movement and improved staffing levels (reducing the need to cover other ward areas) would both reduce the risk of spread.

5.4. Transmission in spite of recommended PPE

The outbreak highlights transmission of COVID-19 in spite of strict adherence with recommended PPE (Appendix B).

Numerous groups including the British Society of Echocardiography [12] challenged the PPE recommendations [12]. However, PPE availability is linked to national guidelines, making it unfeasible for hospitals to deviate from recommendations in certain settings, particularly as deviation in one area would require change in many areas, on the grounds of similar risk.

No documented transmission events occurred following the transfer of P0 to ITU, where staff routinely wear PPE suitable for AGPs, including FFP3 masks.

5.5. Factors contributing to hospital spread

The outbreak demonstrated factors contributing to spread across two hospitals (Appendix D); patient movement, staff working across multiple areas (inadequate staffing levels), the built environment (close patient proximity, shared facilities, limited ventilation) and the inability of deployed control measures to prevent transmission.

Other potential factors identified included incomplete adherence to PPE and localised breakdown in social distancing, often related to inadequate facilities (changing / break rooms).

Incomplete adherence to PPE occurs due to complacency, fatigue and poor fit / comfort of PPE [13] [14]. FRSM are imperfectly fitting with a gender bias [13], creating risk through droplet, aerosol and fomite transmission.

Reduction in transmission could be achieved through improved PPE design, use of higher specification masks (FFP3 or N95) (as evidenced by lack of transmission on ITU), and improvements in hospital design (improved ventilation, increased spacing, individual facilities, improved facilities for breaks and changing).

In the short-term, education on behaviour change targeting strict compliance with PPE and infection, prevention and control measures is critical.

5.6. Prevention of spread

Early intervention (Appendix E), including swift retrieving or isolating exposed patients, successfully prevented spread to ward 3 and other areas.

6. Conclusion:

We describe a hospital outbreak super-spreading event demonstrating the extreme difficulty in containing SARS-CoV-2. This extensive outbreak, triggered by a patient with very limited opportunity to transmit infection, had a devastating impact on a tertiary service and occurred despite recommended control measures.

The outbreak demonstrates how the healthcare environment can be very conducive to spread. We recommend reducing transmission risk through constant reinforcement of IPC guidance, developing a culture that endorses compliance, improving the design of healthcare settings (better spacing, ventilation, reduction in shared facilities for staff and patients, reduced patient movement) and adequate staffing levels (with some redundancy to support compliance in times of system stress).

The report highlights the value of WGS in excluding and identifying related cases when supported by epidemiological investigation. It also demonstrates how early and rapid response to infections with careful management of recent and future transfers / discharges can prevent spread.

Finally, this outbreak questions the protection afforded by FRSM against the transmission of SARS-CoV-2. Improvements in the design, fit and effectiveness of PPE are required. The findings from this outbreak contribute to the growing body of evidence on this topic.

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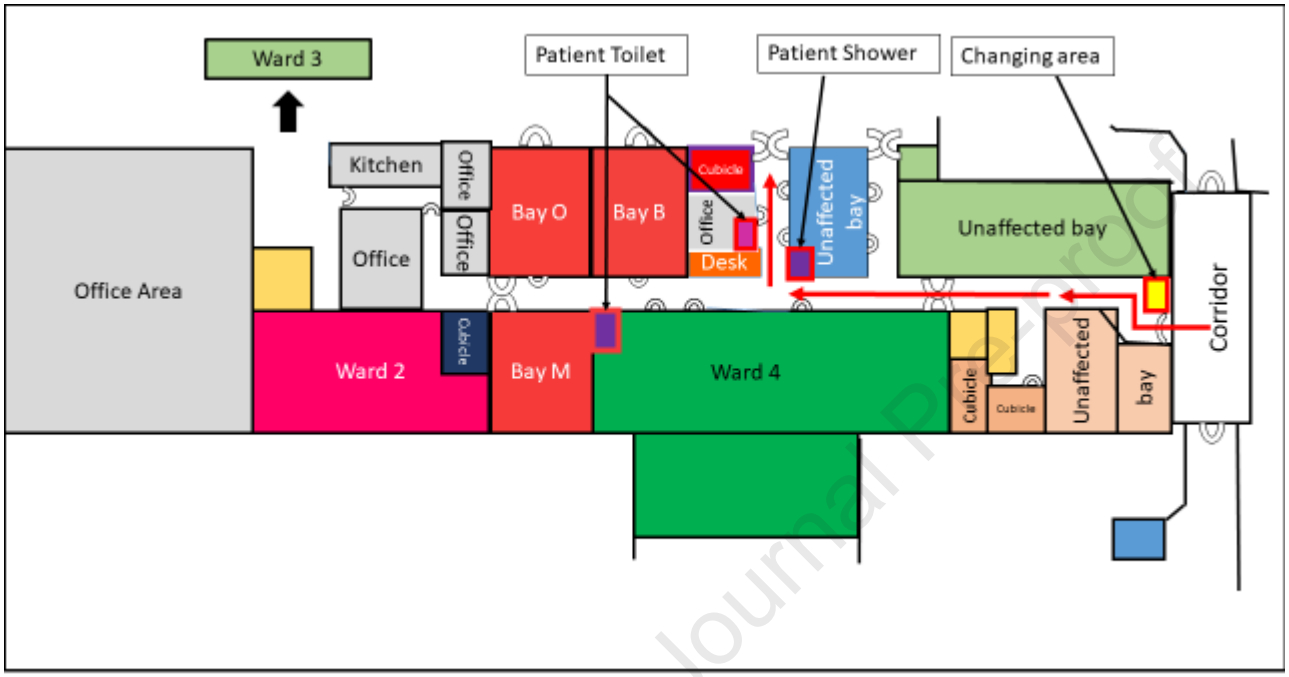
Figure 1: Ward 1 area floor plan with the index case's pathway outlined.



Key

→ = P0 admission route

➡ = Direction to ward 3

Figure 2: the epidemiological curve of confirmed outbreak cases by type of infection and ward of sample collection (N=90)

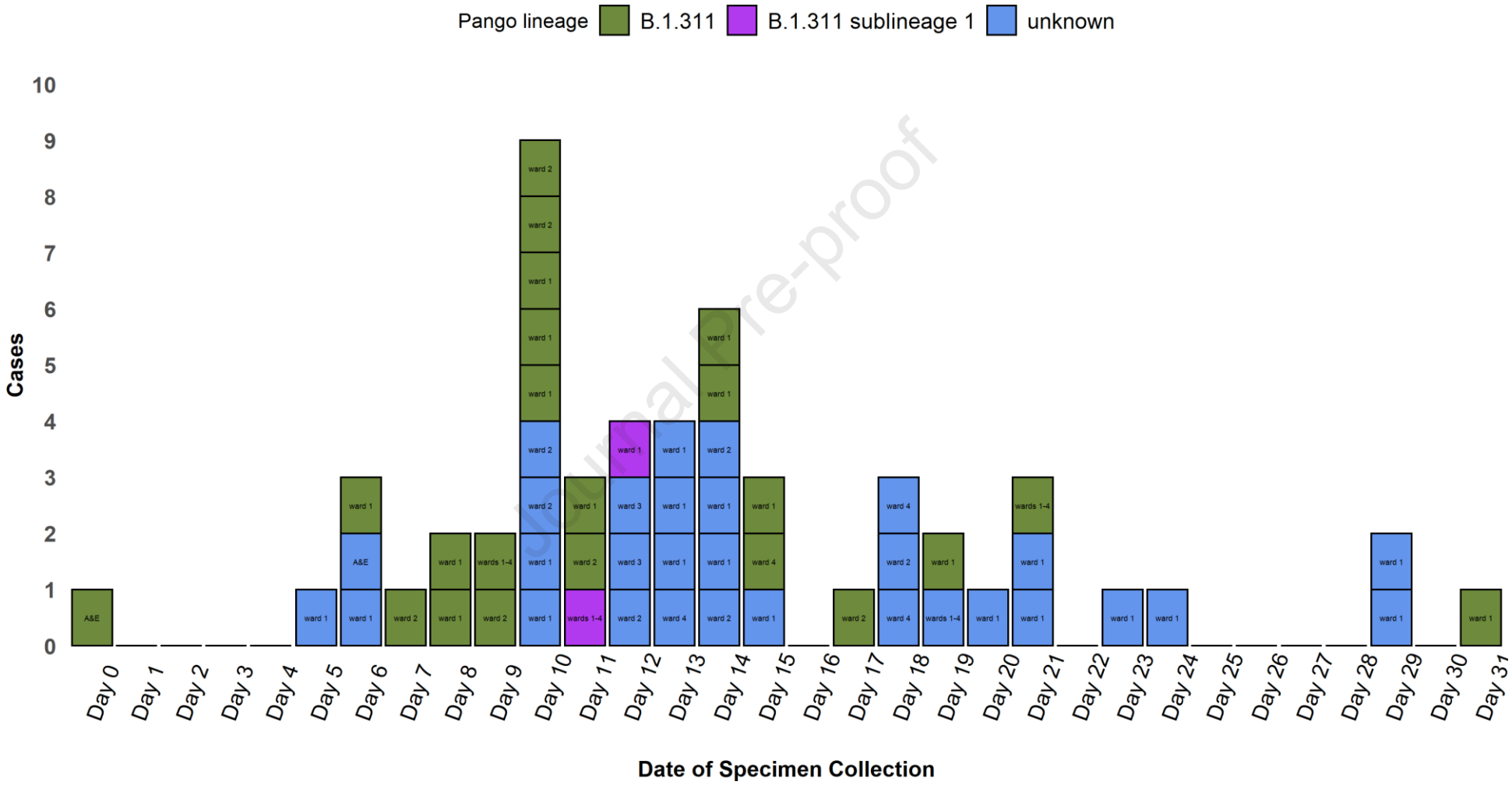
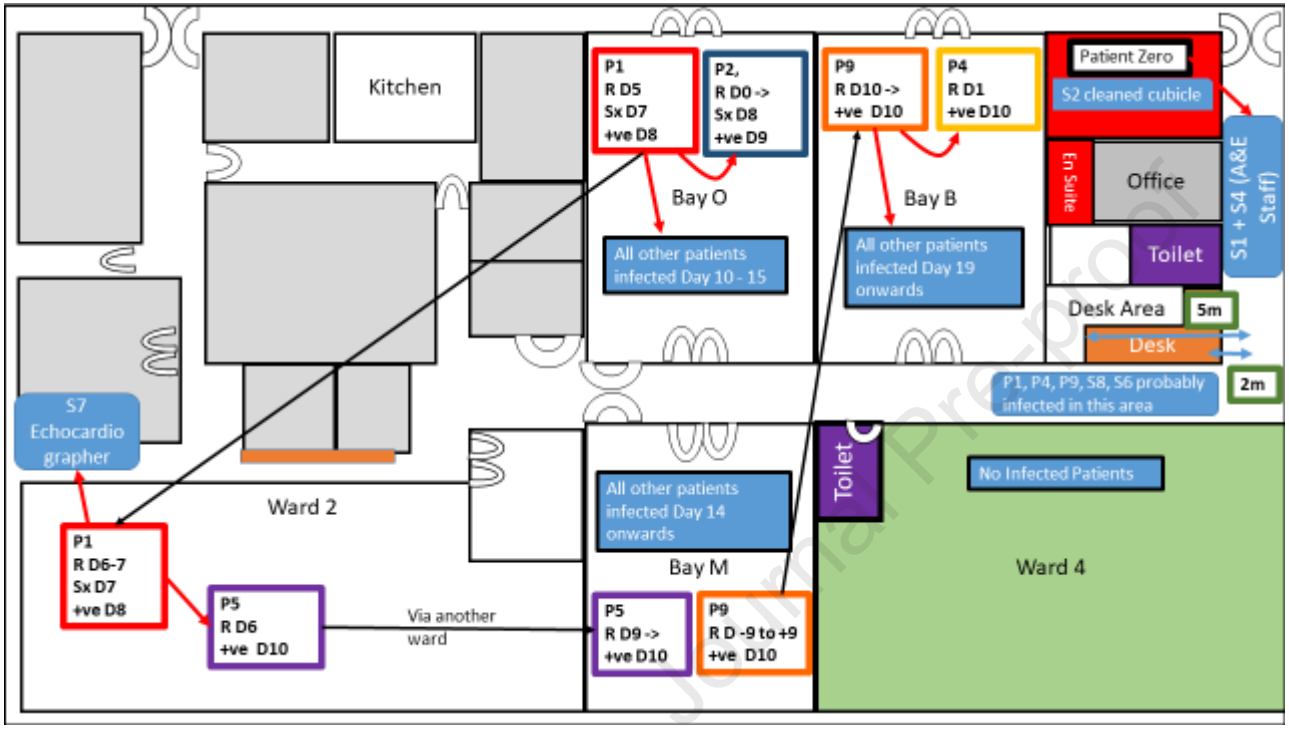


Figure 3: Spread of infection across Wards 1 and 2



Key:

P1	=	patient case 1 etc.
S1	=	Staff case 1 etc.
Patient zero	=	index case
R	=	Days of outbreak when patient was resident in that bay (e.g. D6 = day 6 of outbreak)
Sx	=	Day of onset of symptoms
+ve	=	Day of positive test
→	=	Movement of patient
→	=	Likely transmission
↔	=	Distance

* Desk area sometimes used by patients for phone calls. Phone situated at the desk end closest to Bay B.

Figure 4: Network diagram of confirmed outbreak patient and staff cases in the first two weeks of the outbreak

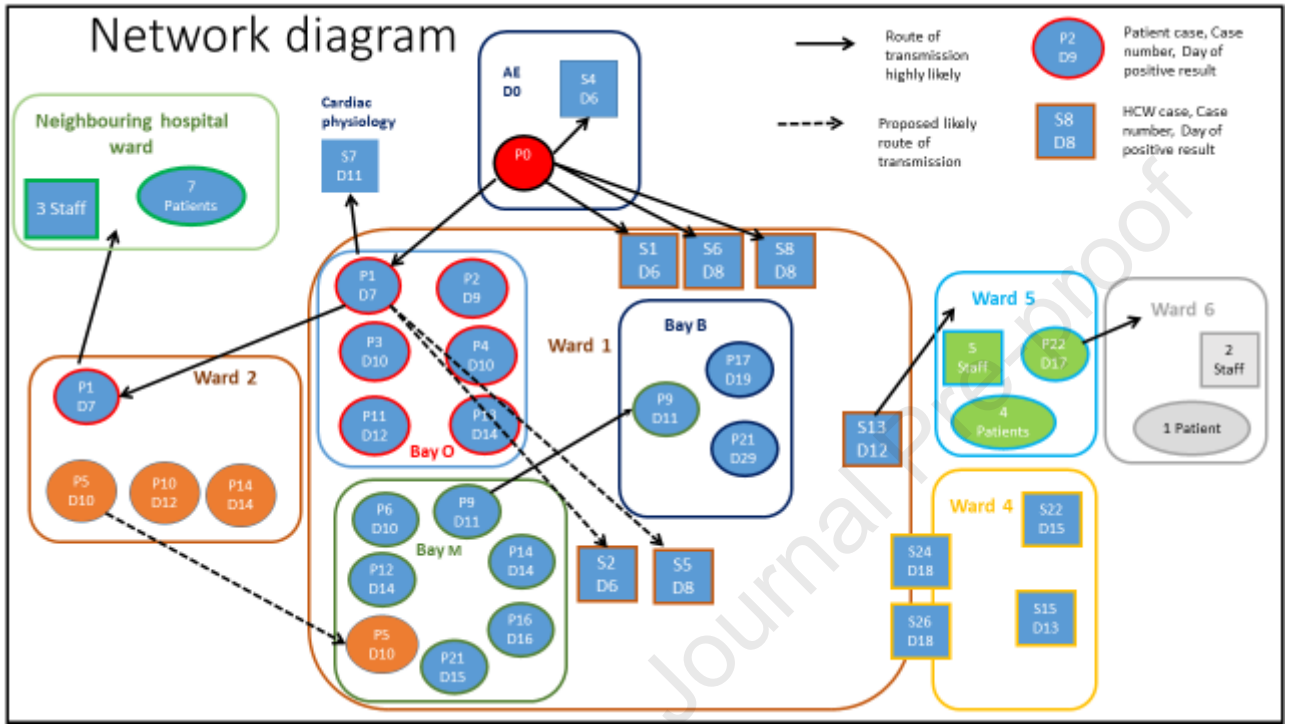


Fig 5: Air flow across the Unit:

All air extracted from the area is deposited outside. No air is recirculated. Air from the cubicle is extracted outside and does not pass into any of the other bays. Airflow on the ward moves from the central area to the periphery in a clean to less clean directional design. All wards and bays have extraction units and as such, ventilation on the unit is of a higher specification than most wards in the hospital. This gives standard recommended air change rates for a ward area (four to six air changes per hour (ACH)), which are significantly lower than a theatre or high dependency unit.

Figure 6: The number of sequenced cases belonging to Pango Lineage B.1.1.311 in the nations of the UK (A) and within Wales (B).

Case P0 was the first sequenced case from the Health Board of interest.

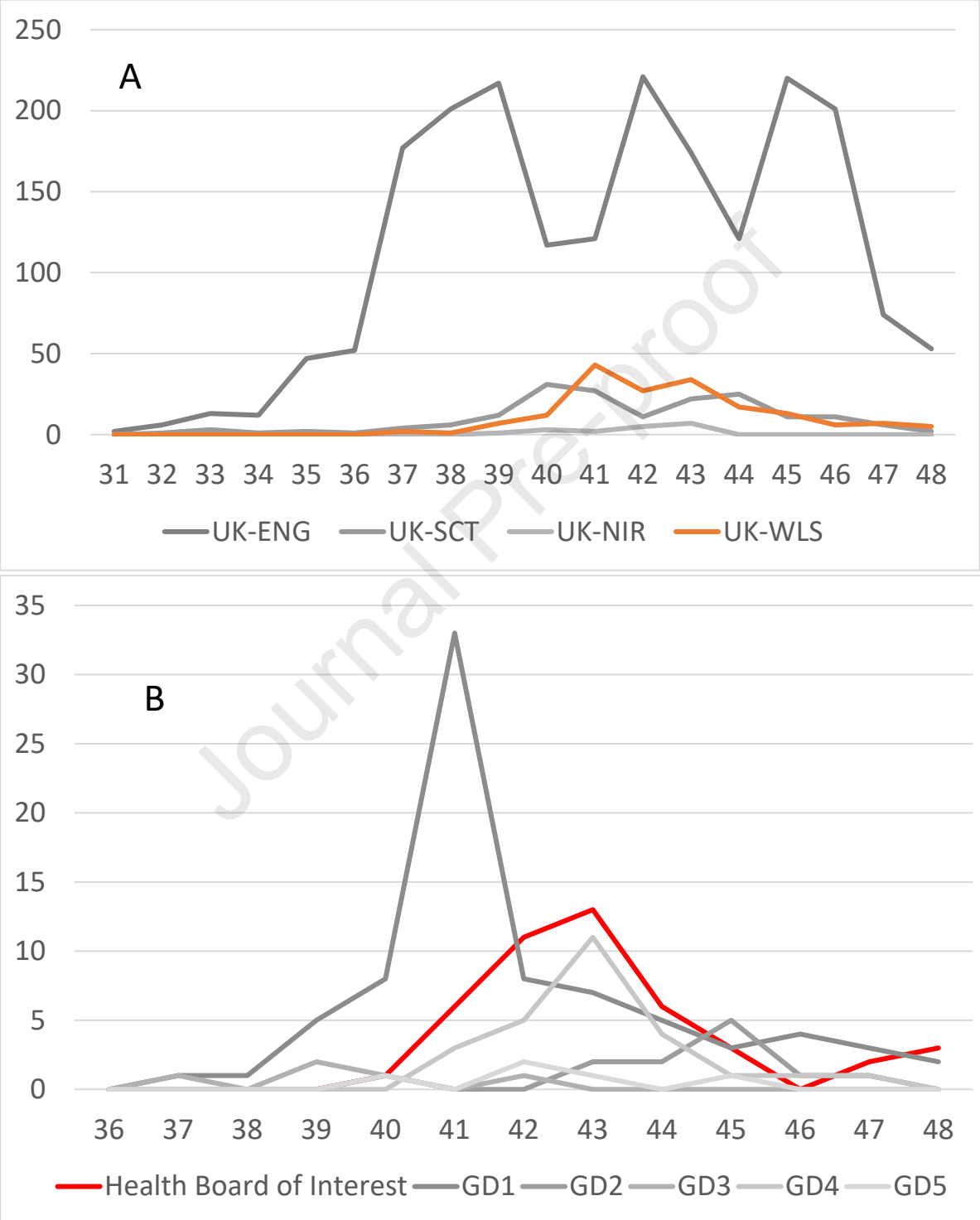


Figure 7: Top ten PANGO lineages in the Health Board of interest from epi week 40 to week 48, 2020. B.1.1.311 (outbreak strain) shown in red. Demonstrating that the outbreak strain was not a predominant strain, that the outbreak strain was not detected in the community prior to the hospital outbreak. Most of the cases below are known linked cases to the outbreak

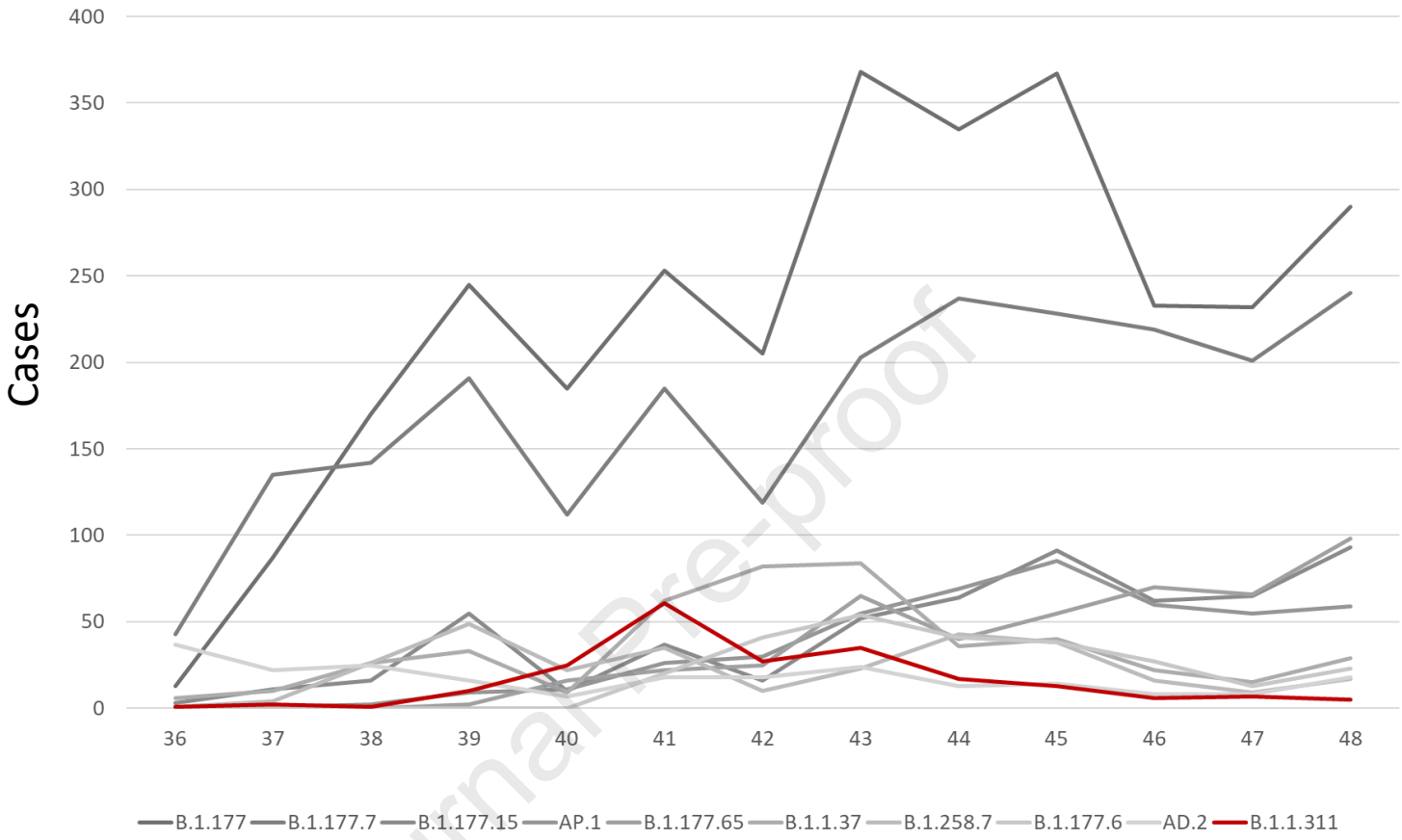


Table I:

Day	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
S1 **Day 6**	**Night** **Contact with**	*Night*			*	*		

	patient zero							
S2 **Day 7**	*Late*			*Night* *Handover S5 & S8*	*Night* *Handover S6*	*	*	
S5 **Day 8**			*Early* *Handover S6*		*Early* *Handover S2. Works shift S8*		*	*Early**
S6 **Day 8**	**Night** **Contact with patient zero**	*Night* *Handover S5*	*Night*			*Early*	*Early**	*
S8 **Day 8**	Early	*Late* *Handover S1 & S6*			*Early* *Handover S2. Works shift S5*		*	*Early**

Red font – contact with patient zero

Italics – significant contact with other potentially incubating staff member unlikely (i.e. other staff member unlikely to be infectious at the point of contact)

Italics and underlined – no contact with other potentially incubating staff member

Green font – too close to onset day for contact to be relevant

*** - likely onset of infectiousness**

Table II: Breakdown of staff testing and patient positives by ward area

	Outbreak unit					Other ward areas	
Ward/Dept	**No. Referred For Testing**	**Negative**	**Positive**	**Not Tested**	**Patients**	**Staff**	**Patients**
Ward 1	77	60	16	1	16		
Ward 2	36	28	8	0	5		
Ward 3	41	39	0	2	0		
Ward 4	27	22	4*	1	0		
Domestics	10	10	0	0	NA		
Doctors	58	49	3	6	NA		
Medical Students	7	7	0	0	NA		
Other staff	NA	NA	4**	NA	NA		
Ward 5						2***	5***
Ward 6						2***	1***
Ward 7						1****	3****
Other areas						2#	3****
Other Hospital						3	7
Total	256	215	35	10	21	10	19

NA Not applicable

***** 2 acquired during shifts on ward 1

****** 3 that provided care to the entire unit and one staff member that transferred the patient from A&E.

*** B.1.1.311 sub-lineage 1

**** B.1.1.311 sub-lineage 1.1

[#] One B.1.1.311 sub-lineage 1 and one B.1.1.311 sub-lineage 1.1

Overall 84 cases were identified, 56 on the unit (Table II). There are likely other linked cases not captured by WGS, so cases reported here represent the minimum.

Table III:

Definition	Days post admission of positive test
Definite HAI*	>14 days
Probable HAI	8-14 days
Indeterminate	3-7
CAI**	< 48 hours

* Healthcare acquired infection (HAI)

**Community acquired infection (CAI)

Acknowledgements

We thank all partners and contributors to the COG-UK consortium who are listed at https://www.cogconsortium.uk/about/. T.R.C. acknowledges support from the MRC, which funded computational resources used by the project (grant reference MR/L015080/1). T.R.C. acknowledges support from Supercomputing Wales, which is partially funded by the European Regional Development Fund (ERDF) via Welsh Government. The project was also supported by specific funding from Welsh Government, which provided funds for the sequencing and analysis of a subset of the Welsh samples used in this study, via Genomics Partnership Wales. The sequencing of samples was funded by COG-UK, and this analysis utilised software provided by members of the COG-UK consortium. COG-UK is funded by the Medical Research Council (MRC) part of UK Research & Innovation (UKRI), the National Institute of Health Research (NIHR) and Genome Research Limited, operating as the Wellcome Sanger Institute.

Appendix A – PCR assays used

Assays used include an in house assay (E gene), the Cepheid GeneXpert (N2 gene and E gene), Luminex Aries (ORF1ab gene and N gene), Genmark Eplex (N gene), Seegene Starlet (E gene, RdRP gene, N gene), Roche (ORF1ab gene, and E gene), Perkin Elmer (ORF1ab gene, and N gene) and the Bosphore (ORF1ab gene, and E gene). The majority were processed on the Seegene.

Appendix B Transmission in spite of appropriate PPE

Case 1

S1 directly cared for P0, using recommended PPE (fluid repellent surgical face mask (FRSM), visor, gown and gloves). There were no reported breeches in PPE use. S1 developed symptoms six days after caring for P0. Two other staff members caring for P0 wore FFP3 masks, in breach of national guidelines, and were not infected.

Case 2

On day seven P1 underwent an Echocardiogram. Five days afterwards, the cardiac physiologist developed symptoms and tested positive for the outbreak genotype on day 11. The cardiac physiologist known for meticulous compliance with PPE and adherence to social distancing was not based in the outbreak unit, their household contacts tested negative and no other contact with individuals with the outbreak genotype was identified. During the procedure, the PPE as recommended by national guidelines was worn (FRSM, visor, apron, gloves). The cardiac physiologist did not experience any breach in PPE during the procedure but did recall that the patient was coughing.

Case 3

An A&E staff member (S4) developed symptoms and tested positive for the outbreak genotype five days after transferring P0 to ward 2, whilst wearing PPE in line with national guidelines (FRSM, visor, apron, gloves). S4 had limited contact with P0 (facilitating the transfer), did not examine or have very close face-to-face contact. No breach in PPE occurred. S4 did not have contact with any other staff or patients on the outbreak unit and no known contacts outside of work. Given the timing of the infection and the rare nature of the outbreak genotype, it is likely that transmission occurred during patient transfer and in spite of appropriate PPE.

Appendix C – Outbreak control measures

- Screening of staff and patients, on wards 1 and 2 (day 9), ward 3 (day 10), ward 4 (day 14)
- Identifying and managing recent discharges (in the preceding 7 days) from the ward – all were swabbed and placed in isolation or retrieved back to the ward.
- Cohorting of positive and exposed patients in different bays
- Closure of wards 1 and 2 to new admissions
- Establishing an alternative area for admissions to maintain the tertiary service
- Flagging of health records of all patients with possible exposure risk
- Adopting a low threshold for swabbing exposed patients with repeat screening of bays when deemed appropriate

- Notifying recently discharged patients and flagging their health records to optimise management in the event of re-admission.
- Notifying, screening and isolation of patients recently transferred from wards 1 and 2 to other hospitals
- Reinforcing compliance with infection control guidelines
- Careful management of all discharges and transfers to reduce the risk of further spread.
- Managing end of shift changing where social distancing was not always maintained
- Closing a small break room where social distancing could not be guaranteed

Appendix D – Factors identified as contributing to spread

- Patient movement*
- Staff working across multiple areas**
- The built environment (close proximity of patients with shared facilities in areas of limited ventilation)
- The inability of currently deployed control measures to prevent transmission
- Incomplete adherence to PPE
- Breakdown in social distancing measures in certain areas (changing rooms and break rooms)***
- Low staffing levels****

*Frequent patient movement was necessary for the operation of this tertiary centre with a high dependency unit. Risks from movement can be reduced by isolation on arrival, frequent testing and risk-based management, but the low availability of testing capacity (at that time) and isolation facilities limits the use of these measures.

**Our data shows both the effectiveness of having a dedicated workforce in reducing the risk of transmission and also that transmission from one ward to another can occur via staff. Having adequate staffing to facilitate more limited cross-ward cover would reduce the risk of spread.

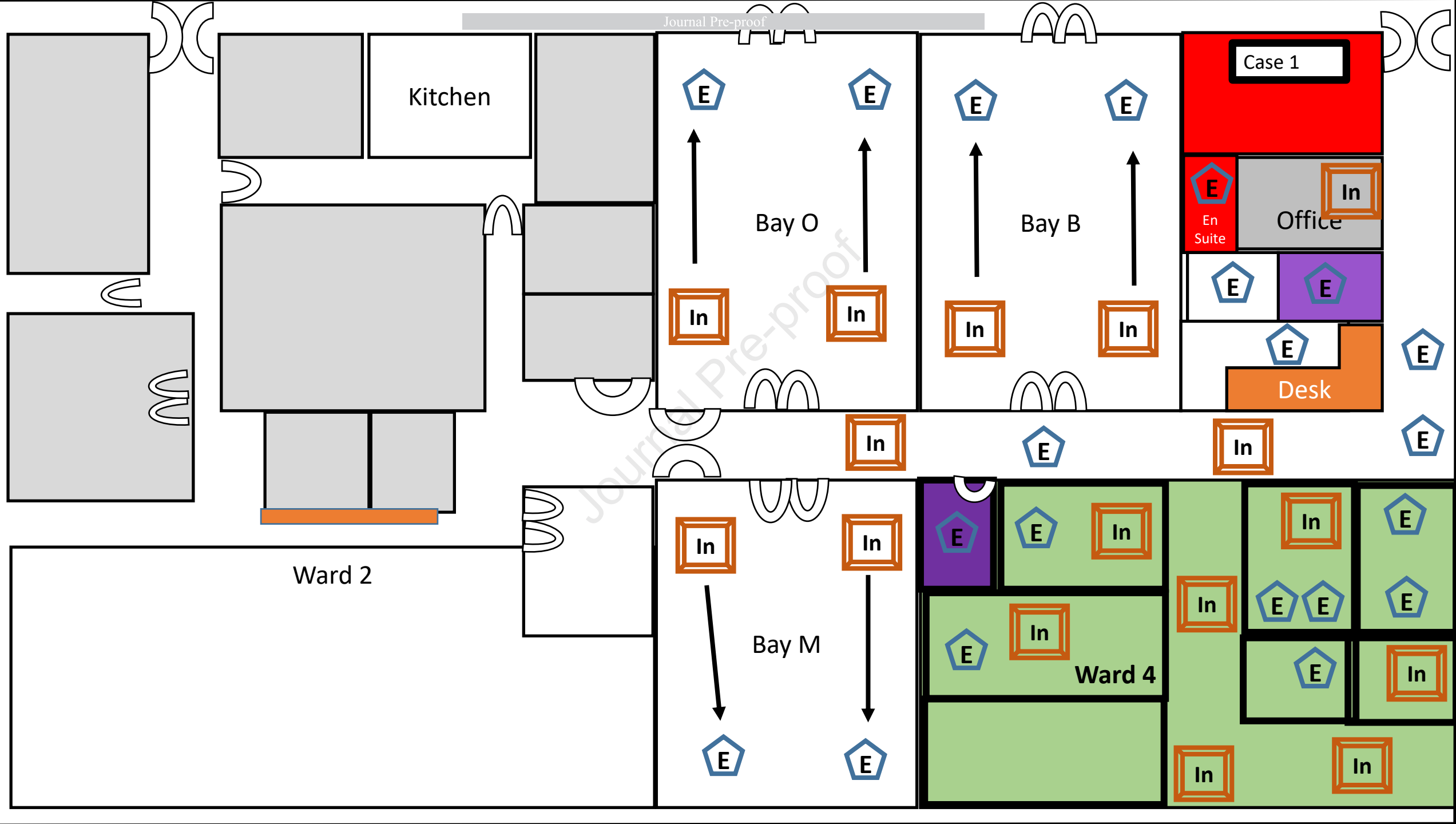
***Staff changing at the end of a shift was identified as a potential source of spread. Staff wearing scrubs in work and changing prior to leaving for fear of transporting the infection home was a routine feature of the pandemic. However, a lack of suitable changing facilities often resulted in staff changing in rooms with poor ventilation, where social distancing could not be maintained. Providing larger more appropriate changing facilities would reduce risk. This also highlights the risk of unintended consequences as wearing of scrubs likely increased risk of transmission.

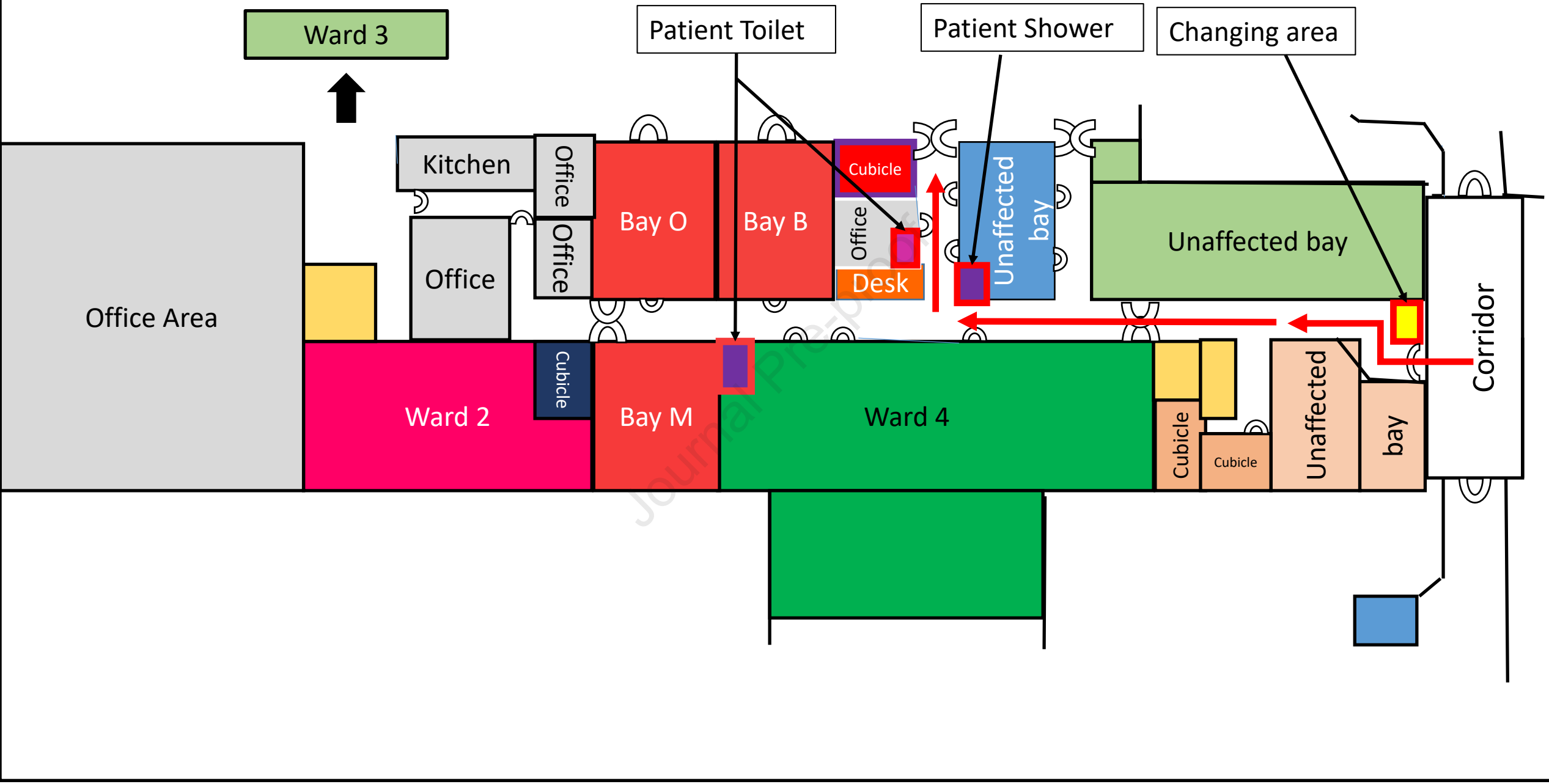
Similarly, there are no adequate break facilities on the ward areas resulting in staff congregating in small poorly ventilated areas on the ward in order to rehydrate and take sustenance. Future hospital designs should take into account the need for staff on long shifts to be able to take breaks in safe and adequately spaced and ventilated environments.

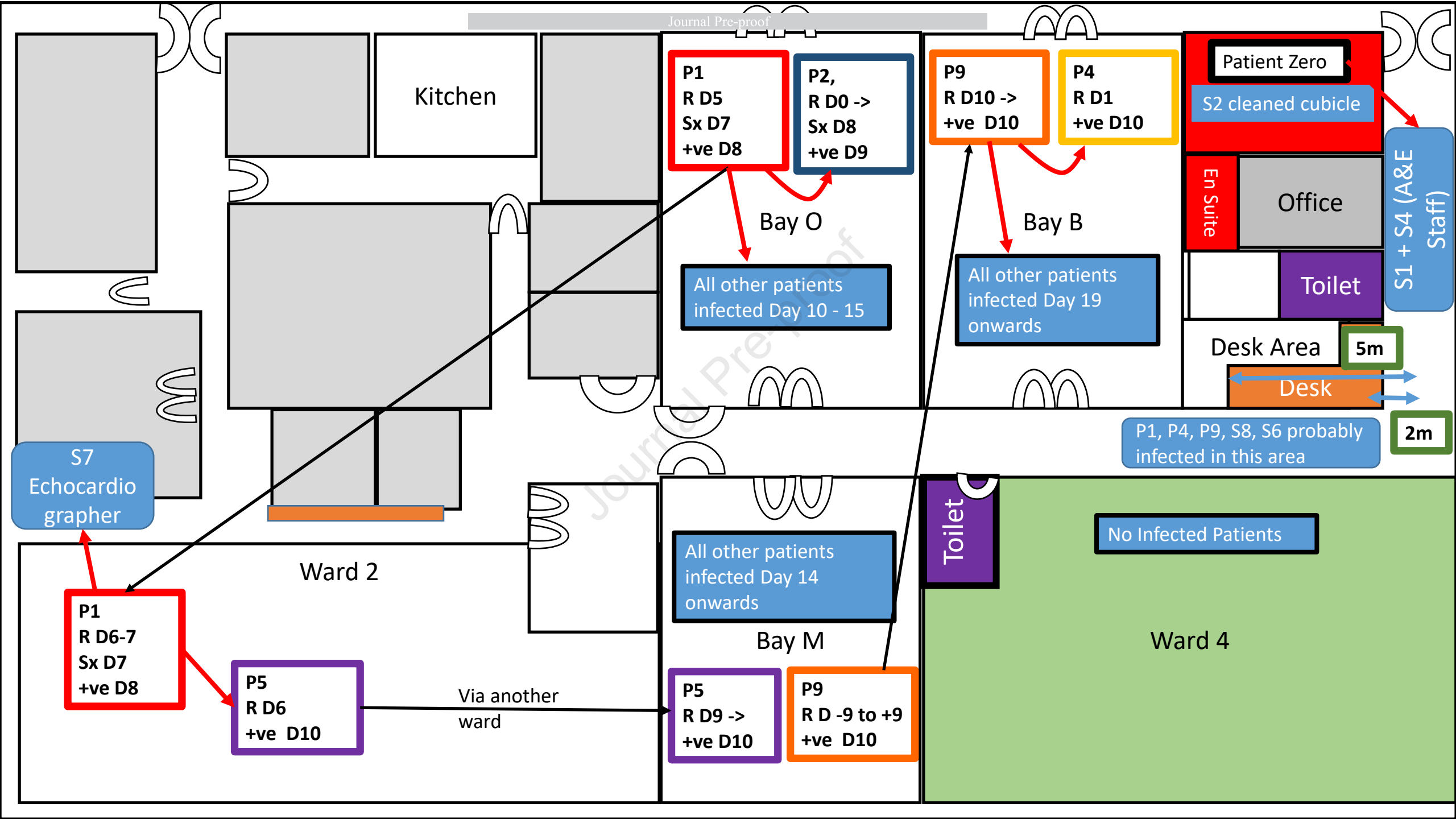
****Low levels of staffing with no redundancy create situations of risk during periods of system stress and limit time available for breaks compounding the problems highlighted above. Adequate staffing with some redundancy to cope with periods of strain is critical from a safety and infection control perspective.

Appendix E – Measures introduced to contain spread

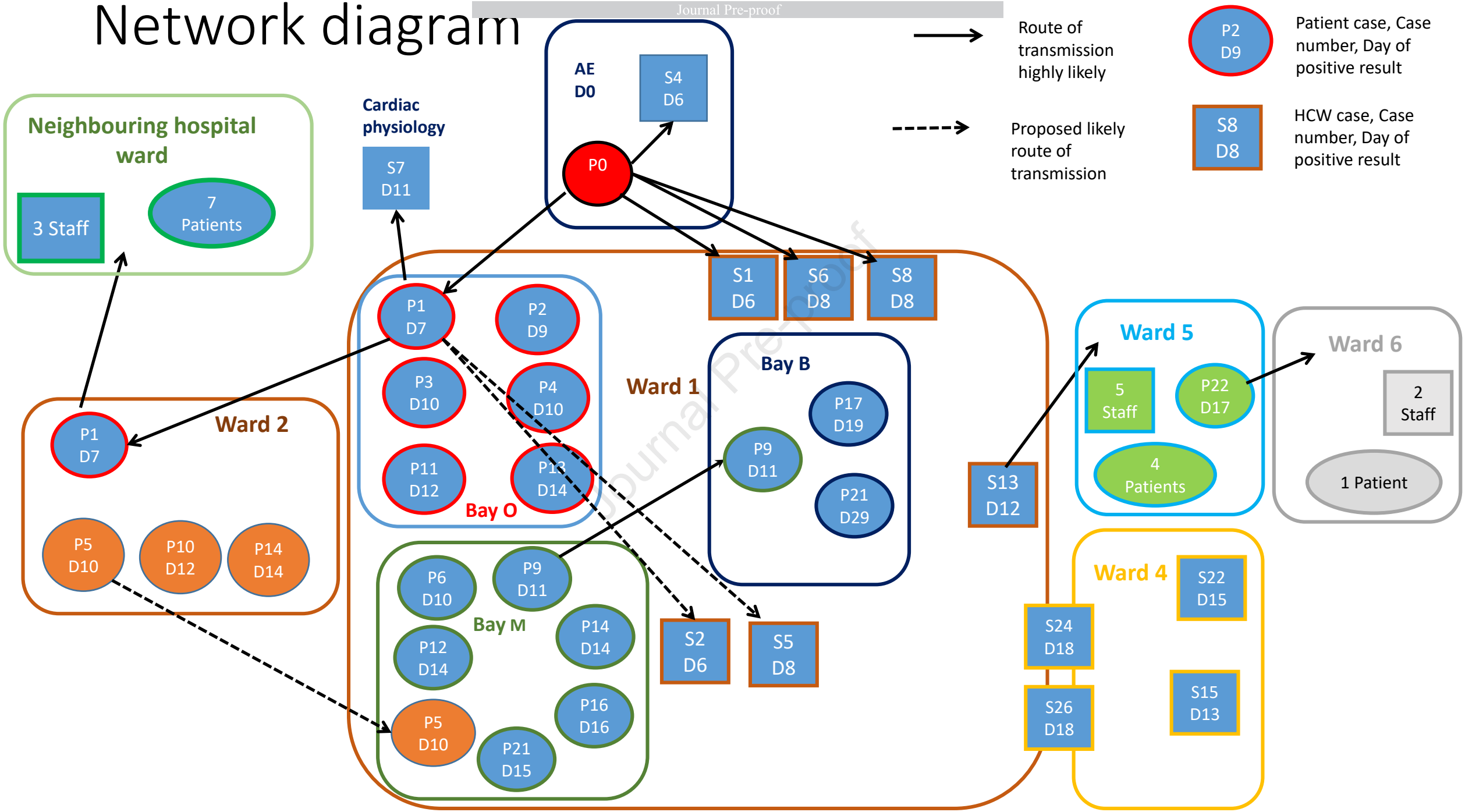
- swabbing of all patients in a ward area
- retrieving recently transferred patients from linked but geographically separate wards.
- Identifying all patients in the “at risk” area as “exposed” and managing them appropriately. This includes high vigilance for symptoms, a low threshold for testing and keeping them isolated from other non-exposed patients for 14 days. Where feasible screening patients following the exposure (e.g. day 3, 5 and 10) is recommended to detect infected individuals sooner and pick up asymptomatic carriers.
- Closing the wards to admissions and discharges. This was very effective in preventing further spread of the infection.
- Carefully planning all future discharges to reduce the risk of onward transmission.
- Reinforcing preventative measures. Reinforcement on the ward and across the site in response to this outbreak likely contributed to a reduction in the number of subsequent transmission events although the exact effect of this action is not measurable.
- Operating a “COVID free” pathway with a dedicated workforce. The implemented “COVID free” pathway in ward 4 prevented the spread of infection to patients on this ward despite the very close proximity of the affected wards.

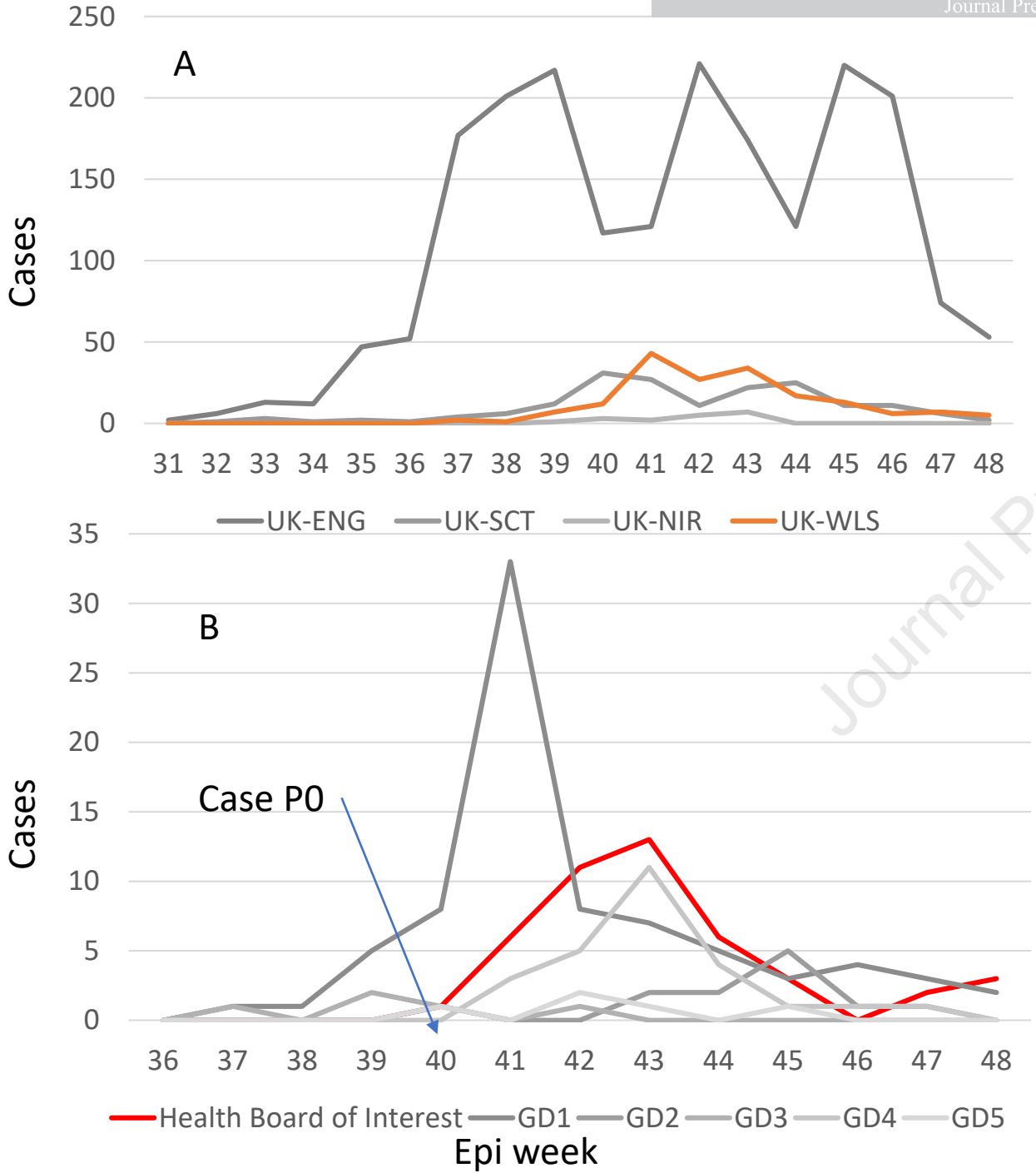






Network diagram





A

Figure X: Showing the number of sequenced cases belonging to Pango Lineage B.1.1.311 in the nations of the UK (A) and within Wales (B). Case P0 (indicated) was the first sequenced case from the lineage in the Health board of Interest

B

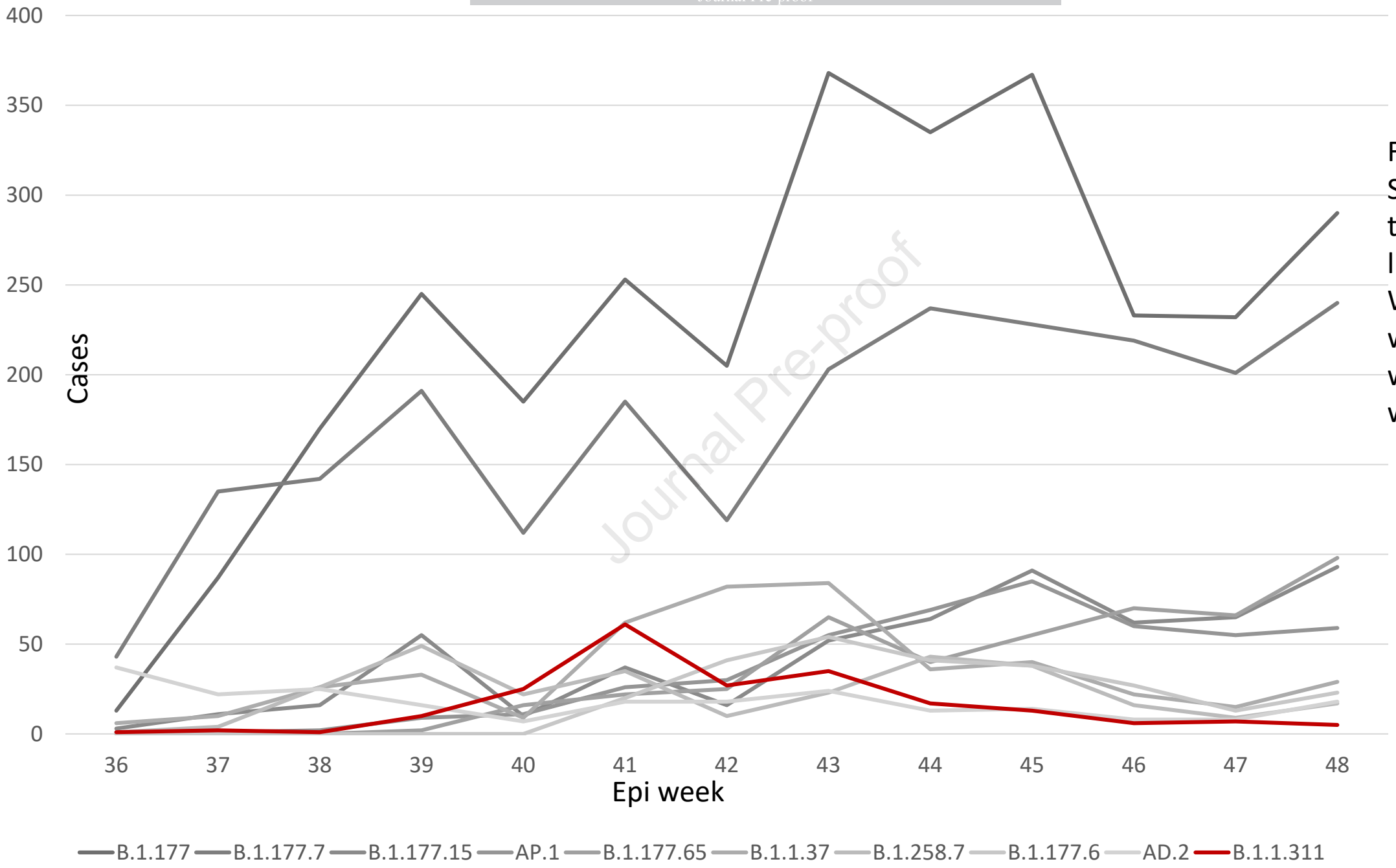


Figure X: Showing top ten PANGO lineages in Wales by epi week from week 36 to week 48, 2020

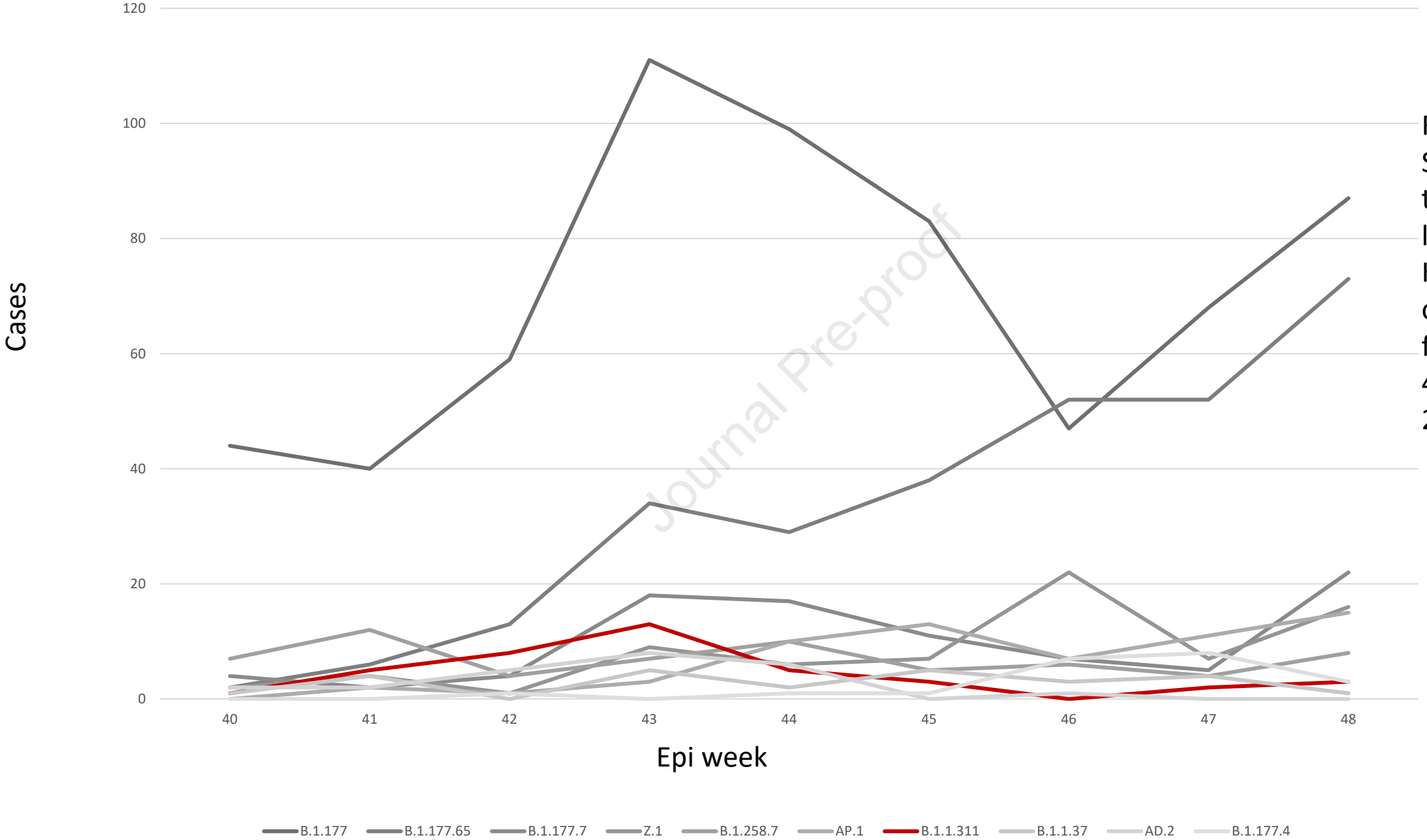


Figure X: Showing top ten PANGO lineages in the Health Board of Interest from epi week 40 to week 48, 2020