The epidemiology of hospital inpatient exposure to SARS-CoV-2:
A retrospective cohort study

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Abstract

Background

COVID-19 has posed a significant challenge to Infection and Prevention Control practices in UK hospitals. The epidemiology of nosocomial COVID-19 is not yet fully understood.

Methods

In this cohort study, all incidences of patient-to-patient exposure on non-COVID wards between October and December 2020 at a UK hospital trust were identified. Patient contacts were traced, and data collected on SARS-CoV-2 testing, length of stay and mortality outcome. Factors associated with acquiring infection, mortality and length of stay were investigated using multivariable regression and Cox proportional hazard modelling respectively.

Findings

575 patients were exposed across 24 clusters. 118 (19.5%) tested positive for SARS-CoV-2 within 14 days of exposure. Evidence of multiple introductions were found in four clusters and this was associated with a greater secondary attack rate (SAR). There was no detected transmission in 6 of the clusters.

Sharing a bay and spending a longer time on the ward with the index case were associated with acquiring infection (ORs of 3.8, 95% CI: 1.89, 7.74, and 1.08, 95% CI: 1.01, 1.15 respectively). Half of all secondary cases did not develop symptoms.

Patients acquiring symptomatic COVID-19 had four-fold increased odds of mortality. There was no difference in mortality between asymptomatic COVID-positive and COVID-negative patients.

Interpretation

Exposure to COVID-19 in hospital often, but not always, leads to transmission. This study highlights the large mortality risk associated with symptomatic nosocomial COVID-19 infection and is the first to describe factors that can be used to understand a contact's risk of developing infection post-exposure.

Funding

None

Research in context

Evidence before the study

On 17th January 2021, we searched PubMed for articles reporting on inpatient exposure to SARS-CoV-2 and factors relating to nosocomial transmission. Search terms included “COVID-19”, “SARS-CoV-2”, “nosocomial”, “inpatient” and “exposure”, with no language restrictions. The reference lists of the articles identified from this search were scrutinised to identify further relevant articles.

The COPE-Nosocomial study describes the level of nosocomial SARS-CoV-2 infection at a population level, as well as describing factors associated with nosocomial infection, which included a lower mortality rate in the authors’ primary analysis.

The majority of existing studies report on single clusters of SARS-CoV-2 outbreaks in hospitals or tend to focus on healthcare workers rather than patients. The secondary attack rate of nosocomial transmission is frequently defined in these single cluster reports. However, we found only one study that reported no secondary cases after an exposure. No studies robustly investigated risk factors for acquiring nosocomial SARS-CoV-2 after exposure.

Added value of this study

We present the largest review of in-hospital exposure to SARS-CoV-2 known to us at the time of writing. By tracing 575 patients exposed in 24 unique events we have attempted to describe the fundamental epidemiology of nosocomial SARS-CoV-2 infection after a known exposure.

It provides further evidence that infection is occurring within hospitals, but also captures the fact that several exposures led to no detectable infections, something largely missing from previous studies. In addition, the majority of index and secondary cases were not symptomatic at the time of their positive test which suggests that asymptomatic testing has an important role to play.

Detailed information on both index and secondary cases was available to investigate potential contributing factors. The factors selected in this study represent ones universally available to the Infection Prevention and Control teams and that are therefore generalisable across contexts. Multiple sources of infection were strongly associated with a larger overall outbreak size highlighting the importance of effective cohorting and screening procedures. Similarly, for individual patients, being in closer proximity to an index case and spending a longer time with them was associated with an increased likelihood of testing positive. Finally, this study confirms that nosocomial infection with SARS-CoV-2 places a significant mortality risk on those infected who develop symptomatic disease.

Implications of all available evidence

This study provides important insights into the epidemiology of hospital-acquired COVID-19 infection. There is now incontrovertible evidence that exposure to SARS-CoV-2 within hospital poses a serious risk of transmission and that it should be managed accordingly.

Moreover, it clearly highlights the large mortality risk that exists and the need to develop robust infection prevention and control practices as these deaths are potentially preventable.

Introduction

During the SARS-CoV-2 pandemic, one of the central dilemmas for healthcare workers and managers has been in determining how to control nosocomial transmission of the virus among vulnerable inpatient populations. Issues in detecting COVID-19 positive inpatients are compounded by potential asymptomatic transmission¹, and variable accuracy in testing methods².

Several studies have reported on outbreaks of COVID-19 in healthcare settings, some of which describe the secondary attack rate of nosocomial transmission after an outbreak and some that outline measures to control and prevent further spread. Most of these are reports of single outbreak clusters from single centres³⁻⁸. Other studies have described nosocomial infection at a population level, such as the COPE-Nosocomial Study, which found that 12.5% of COVID-19 infections were acquired in hospital, taking a cohort of patients from across multiple centres in the UK and Italy^{9,10}.

In the face of the ‘second wave’ in the UK, clinicians and hospital managers need targeted information to guide their responses to nosocomial outbreaks. Research into nosocomial spread needs to reflect the reality of the situation as it is experienced in clinical areas during the height of the pandemic: where multiple, evolving and often interconnected outbreaks exist within hospital sites. However, we have not found any examples of studies that report on all clusters of inpatient exposure to COVID-19 infection on non-COVID wards in a given timeframe¹¹. The intention of our study is to produce an accurate descriptive analysis of the nosocomial transmission within our local hospital trust over a given time period.

By describing the mechanics of nosocomial spread at a local level, which includes several clusters with no single identified source, we hope to identify factors that will be useful in predicting the severity of outbreaks before they unfold. We want to use the findings generated from our study as a tool to improve the informed containment of further nosocomial transmission.

Methodology

Study Design

This study was conducted at Brighton and Sussex University Hospitals NHS Trust (BSUH) in the United Kingdom, a large acute hospital trust split across two sites. At this trust, patients exposed to SARS-CoV-2 in hospital are prospectively recorded on the Infection Prevention and Control (IPC) database. The research questions described here were planned prior to data collection and additional required data was retrospectively collected.

All incidences of inpatient exposure between 1st October 2020 and 10th December 2020 were downloaded from the prospective database of SARS-CoV-2 exposure. In the study time period, the community case rate in Brighton and Hove ranged from 22 per 100,000 to 221.6 per 100,000¹².

Definitions

A **positive** result refers to laboratory confirmation of SARS-CoV-2 detection through the use of qRT PCR for the viral RNA-dependent RNA-polymerase. Patients with negative samples on qRT PCR were considered to be non-infected.

An **index case** (or **index**) was the first patient to be identified as positive for SARS-CoV-2 on the ward. An index is **“early”** if they test positive within 48 hours of entry onto the ward whereas if they test positive more than 48 hours into their ward admission they are described as **“late”**.

A **contact** was defined as any patient present on the ward between the timepoints below:

- 2 days before the index’s positive result **AND** index leaving the ward (Category 1, current Public Health England (PHE) guidance)
- 5 days before the index’s positive result **AND** index leaving the ward (Category 2)

If any contacts test positive for SARS-CoV-2 within 48 hours of their ward admission they are defined as a **co-index** as they could not have acquired infection on the ward.

Data Collection

The index cases were identified and extracted from this database on 10th December 2020. Contact tracing was performed using the integrated reporting tool of the hospital’s electronic bed management system (Medway, System C Healthcare Ltd.) as per the criteria outlined above. All patients traced were eligible for inclusion in the study. SARS-CoV-2 testing history, ward locations, physiological observations, co-morbidities, length of stay and mortality outcomes were extracted from the electronic records for all contacts. Symptomatic infection was defined as development of new, persistent cough, fever >37.5°C, hypoxia (SpO2 <94%, a decrease of 4% or a requirement for supplemental oxygen). For contacts discharged within 14 days of their exposure, there was limited data available on the development of symptoms and if they had not re-presented to hospital were assumed to have not developed significant symptoms. The Cycle Threshold (Ct) of the index cases RT-PCR was collected.

The validated Charlson Co-morbidity Index (CCI) score was calculated for each patient¹³. For any patients with unclear co-morbidities a second review was undertaken by another author and a decision made by consensus. For any patients that died, date of death was collected and censored by the completion of data collection on 5th February 2021 (maximum length of follow up 122 days).

No sample size calculation was performed as all reported cases of in-hospital exposure to SARS-CoV-2 at the time of data extraction were included. There was no missing data.

Analytic methods

Contacts that were exposed in multiple clusters and tested positive within 14 days of more than one exposure were excluded from the analysis as the location of their infection could not be ascertained.

The primary outcome for each contact was whether they developed COVID-19 infection as defined as a positive test within 14 days of their exposure. Secondary attack rates (SARs) were calculated for the entire cohort and each cluster using the number of secondary cases and the total number of contacts. Sub-group analysis was then conducted to explore the impact of index factors (i.e., time on ward prior to positive test) and contact factors (i.e., proximity). The associations between those factors and the secondary attack rate and time delay between index and contact positive results were investigated using mixed effects regression modelling (full statistical methods in supplementary materials). Cluster was considered a random effect in all regression analyses.

The time that had elapsed since the index's last inpatient negative PCR test was calculated. If no tests had been conducted as an inpatient prior to the positive result, time since admission was used instead.

The association between COVID-19 infection and the outcomes of mortality and hospital length of stay were investigated using a Cox proportional hazards model with shared frailty and a negative binomial regression model for overdispersed data, respectively (both incorporating clustering, supplementary materials).

Data was initially extracted into Microsoft Excel, manipulated in R(v1.2.5033) using dplyr(v1.0.2) and visualised with ggplot2(v3.3.2). The statistical analysis packages coxme (v2.2.16) and geepack(v1.3.2) were downloaded and installed into R.

Results have been reported as per the STROBE guidelines on the reporting of observational studies¹⁴. A statistical analysis plan was developed pre-analysis and reviewed by a statistician.

As a study of healthcare-associated infections, this investigation is exempt from requiring ethical approval under Section 251 of the NHS Act 2006 (see also the NHS Health Research Authority algorithm, available at <https://www.hra-decisiontools.org.uk/research/>, which confirms that no formal ethical approval is required). Local approval was granted for this study.

Results

In the studied time period, 24 incidences of patient-to-patient in-hospital exposure to SARS-CoV-2 were identified on 17 wards (each incidence referred to as a cluster hereafter). 58% (14/24) occurred on Site A and 83.3% (20/24) on the more modern ward (type 1). These clusters were caused by exposure to 22 index cases. Two of the index cases were identified as indexes in two separate clusters.

Using the Public Health England definition of an exposure (Category 1 in the methodology) 586 unique hospitalised patients were identified as being exposed to an index. This comprised 624 individual exposure episodes as 34 patients were exposed twice with a further 2 patients exposed on 3 occasions. Demographic and clinical information for all patients are included in Table 1.

Analysis of index cases

In this study, 22 index patients were identified as linked to 24 clusters. The mean time from hospital admission to positive test for index patients was 7.8 days (95% CI: 4.2, 11.4) with 13.6% (3/22) defined as “Definite Hospital Acquired COVID-19 infection” as per PHE. The maximum time from hospital admission to positive test was 33 days. On average, indexes had spent 5.6 days (95% CI: 2.8, 8.5) on the ward before testing positive.

42% (10/24) of index cases are defined as “early” as they tested positive within 2 days of their ward admission. 7 of the “early index cases” (27.3% of all indexes) had their positive PCR samples collected before their admission onto the ward. However, one of them is an index into two clusters (2 and 15). Of the 6 unique patients, one was tested in the community due to COVID-19 symptoms, 2 were tested as part hospital inpatient surveillance (both moved wards shortly after) and 3 were tested on admission to hospital as per trust guidance. None of these cases had their results back before arriving onto the ward.

The remaining 14 index cases tested positive more than 2 days into their admission and are “late index cases”. 78.6% (11/14) of “late index cases” were identified as SARS-CoV-2 positive on routine surveillance tests. The remainder (3/14) were tested after developing symptoms. “Late index cases” were tested at a median of 5.6 days after their ward admission (range 2.5 to 23.3 days) and 100% of them had previously had a negative SARS-CoV-2 PCR during their admission.

In total, 16 index patients had undergone previous inpatient testing and 37.5% (6/16) had their positive result within 5 days of their last test. Two were previously tested with a rapid SARS-CoV-2 test on admission with the remainder undergoing conventional RT-PCR.

Analysis of contacts

586 patients were exposed to SARS-CoV-2 on 624 occasions during the study period. 36 patients were exposed more than once with 7 subsequently excluded from further analysis as they tested positive within 14 days of more than one exposure.

Consequently, 579 patients were exposed in 609 unique exposure episodes. 122 tested positive with 4 “co-indexes” identified as they tested positive within 48 hours of their ward admission (clusters 4, 9, 11 and 14). For all 4 clusters with co-index cases, there was insufficient overlap between the index and co-index for any transmission to have occurred between them (further detail in supplementary materials). This is evidence of multiple introductions of SARS-CoV-2 into those clusters and those clusters are thus classified as “multi-source”.

118 secondary cases were identified, an overall secondary attack rate of 19.5% (95% CI: 16.5, 22.8). Secondary cases tested positive for SARS-CoV-2 a median of 11.8 days (IQR: 6.6, 18.7) into their hospital admission and a median of 10.5 days after ward admission (IQR: 6.0, 15.9).

95.8% (113/118) of secondary cases had a negative test earlier in their admission, 70 (61.9%, n=113) had one in the last 7 days, and 8.0% (9/113) had had a negative result in the prior two days. Only 23.2% (113/487) of negative contacts had returned negative SARS-CoV-2 testing in the 7-14 days after their exposure (confirmed negatives).

The median secondary attack rate was 13.1% (IQR 0, 24.1) for single source clusters compared to 37.5% for multi-source clusters (IQR 31.6, 44.6). However, there is large variation between the clusters, with 6 out of 22 (27.2%) of the single source clusters having 0 secondary cases (Figure 1).

In multivariable analysis, multi-source exposure was associated with a larger SAR (OR 4.1, 95% CI: 1.13, 15.1). The Ct value of the index had a statistically significant but small effect on the SAR (OR 1.10, 95% CI 1.01, 1.26) whereas the index being symptomatic (OR 1.24, 95% CI: 0.32, 4.48) and the length of time the index was on the ward prior to positive test did not (OR 1.07, 95% CI: 0.99, 1.16).

31.4% (37/118) of secondary cases had been in the same bay as an index, however, the majority of secondary cases (66.1%, 78/118) were individuals who were present on the same ward (not in the specific bay). Additionally, 3 secondary cases were in side-rooms on the ward at the time of their exposure.

However, despite this, the overall secondary attack rate was greatest in the index bay 29.8% (95% CI: 22.5%, 38.4%), with SARs of 17.4% (95% CI: 14.2%, 21.2%) and 9.1% (95% CI: 3.1%, 23.6%) observed for the patients exposed in other non-index bays and in side-rooms respectively. Similar findings were observed for both single and multi-source exposures (supplementary materials). Secondary cases shared the ward for a median of 4.6 days (IQR 2.7, 7.2) with the index, compared to 1.5 days for those not testing positive (IQR 1.0, 3.7).

In multivariable analysis of the single source clusters, being in the same bay as the index was associated with an increased risk of developing infection (OR 3.80, 95% CI: 1.89, 7.74) as was the length of time a contact shared the ward with the index (OR 1.08, 95% CI: 1.01, 1.15).

After a single-source exposure, secondary cases tested positive a median of 3.23 days (95% CI: 1.7, 3.8) post-contact with the index and 4.5 days (95% CI: 2.3, 5.8) after the index tested positive. For multi-source clusters, those times were 4.50 days (95% CI: 3.73, 8.03) and 6.0 days (95% CI: 4.0, 9.8) respectively (Figure 2). 90% of the secondary cases in single source clusters were identified within 8.7 days of the end of their exposure to the index case (Figure 2).

The majority of secondary cases tested positive while they were asymptomatic (71.2%, 84/118) with 35.7% (30/84) of those going on to develop symptoms. Approximately half of secondary cases (46.6%, 55/118) did not develop symptoms.

After multivariable analysis of the single source clusters (n=20), each day spent with the index reduced the time to the secondary case's positive result by 3 hours (95% CI: -5.2, -1.1) with being exposed outside of the bay increasing the time by 1.6 days (95% CI: 0.28, 3.0).

Outcomes

By the end of data collection, 28.0% of secondary cases had died (33/118) compared to 13.3% (61/457) of those not infected. Patients developing symptomatic COVID-19 infection were more likely to die (41.2%, 26/63) than those infected asymptotically (12.7%, 7/55).

Accounting for co-morbidities, in a Cox proportional hazard model with shared frailty the hazard ratio for death after acquiring symptomatic COVID-19 infection in hospital was 4.0 (95% CI: 2.4, 6.6). The majority of that effect was observed within the first 30 days after exposure (Figure 6). Acquiring asymptomatic COVID-19 infection was not associated with increased mortality (HR 0.76, 95% CI 0.34, 1.70).

The median length of stay for contacts was 12.2 (IQR 6,24) days although this ranged from 0.4 to 503. For secondary cases the median length of stay was 26 (IQR 15, 40) days compared to 10 (IQR 4,19) for the negative contacts. After multivariable analysis accounting for co-morbidities, COVID-19 infection was associated with 2.3 times longer length of stay (95% CI: 1.9, 2.8). There was no significant difference between symptomatic and asymptomatic COVID-19 infection.

Extended Tracing

A second iteration of contact tracing was performed using the Category 2 definition and included patients who had contact with the index in the 5 days prior to the index testing positive. A further 89 contacts were identified with 11 of them testing positive for SARS-CoV-2.

Discussion

It has been well-documented that COVID-19 spreads efficiently, and with severe consequences, in healthcare settings. However, most of the literature either reports upon single outbreaks or use hospital-wide definition based approaches that do not identify exposure events¹¹. Understanding the epidemiology of hospital-acquired COVID-19 infection is central to protecting patients and restarting essential services as case numbers decrease. To our knowledge, this study is the first attempt to systematically describe the outcomes of patients exposed to COVID-19 in hospital. We have not sought to do so by explaining the underlying transmission dynamics but rather by observing the events that occur after an exposure.

Our analysis shows that exposure to SARS-CoV-2 in hospital often, but not always, results in secondary transmission to other patients. It is possible that the current literature may be subject to a degree of publication bias as the majority of publications thus far describe large outbreaks^{7,8,15,16}. It is significant therefore that 1 in 4 of the clusters reported here resulted in no detected secondary cases.

On four occasions, there was evidence for multiple introductions of SARS-CoV-2 onto the wards by “co-index cases” and this was strongly associated with a larger secondary attack rate (SAR). However, contrary to previous studies the presence of symptoms in the index case and the length of exposure were not¹⁷. This is likely explained by the fact that our definition of “Index Case” is purposefully non-specific and not definitively describing the initial infection source. This was a conscious decision given that it can be difficult, or even impossible, to identify the true source of infection and therefore we have sought to use clear, easily measurable and practical definitions to aid in IPC decision making.

The majority of the index cases had previously undergone testing in hospital, with some being tested within 5 days. This suggests that there may be opportunities to identify index

cases sooner with an increased frequency of testing. Similarly, approximately half of secondary cases did not develop classical COVID-19 symptoms and therefore symptomatology should not be relied on to detect those becoming infected after exposure counter to current PHE guidance (as of 10th February 2021)¹⁸.

Moreover, for an individual patient, their risk of acquiring COVID-19 increased if they shared the same bay as the index case and for a longer period of time. However, it is significant that the majority of secondary cases had not been exposed in the bay, but rather were just on the ward (with four cases in side-rooms). This poses difficult questions with regards to the exact mode of transmission of SARS-CoV-2 in-hospitals as the fomite, droplet, aerosol debate continues¹⁹. For those who did acquire COVID-19 infection, both being in the same bay as the index and having spent more time with the index was associated with an earlier positive test.

Patients who developed COVID-19 infection after exposure had two-fold increased odds of mortality and stayed in hospital for twice as long. The increased burden of mortality was solely in those patients developing symptomatic COVID-19 infection who had a four-fold increased risk of death. There was no difference in mortality between asymptomatic COVID-positive and COVID-negative patients suggesting that the effect on mortality is driven directly by COVID-19 rather than by indirect effects of lengthier hospitalisation.

Studies have now demonstrated that there is not an increased mortality risk associated with hospital-acquired COVID compared to community-acquired COVID when controlling for age and co-morbidities^{9,10}. Our findings are in agreement with that, but here we are specifically highlighting the potentially preventable burden of mortality that exists for patients who are exposed to COVID-19 in hospitals.

This study adds to the understanding of nosocomial COVID-19 infection but does have several limitations. Firstly, the evidence presented is purely epidemiological and as such we are unable to definitively confirm shared transmission between index and secondary cases in the clusters. Secondly, no information was available on the level of staff infection during these clusters. Thirdly, as already alluded to, a large proportion of contacts did not undergo post-exposure routine surveillance testing and we may be underestimating the true impact of nosocomial COVID-19. Finally, during the timeframe studied here, it is likely that the majority of the cases were infected with older (non-B.1.1.17) variants of SARS-CoV-2, which are thought to be less transmissible.

Contributor Statement

Rhys D Wenlock - conceptualisation, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualisation, writing – original draft, writing – review & editing, and data verification. Matija Tausan - conceptualisation, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualisation, writing – original draft, writing – review & editing, and data verification. George Stoye - conceptualisation, data curation, investigation, methodology, writing – original draft, and writing – review & editing. Holly Hendron - conceptualisation, data curation, investigation, methodology, writing – original draft, and writing – review & editing. Oscar Buchanan - conceptualisation, data curation, investigation, methodology, writing – original draft, and writing – review & editing. Zachary Tait - conceptualisation, data curation, investigation, methodology, writing –

original draft, and writing – review & editing. Bethany Whittle - conceptualisation, investigation, methodology, writing – original draft, and writing – review & editing. Samuel McInerney - conceptualisation, data curation, investigation, methodology, writing – original draft, and writing – review & editing. Jessica Blackaby - conceptualisation, investigation, methodology, writing – original draft, and writing – review & editing. Andrew Davies - data curation, resources, writing – original draft, and writing – review & editing. Martin Still - data curation, resources, writing – original draft, and writing – review & editing. Catherine Sargent - conceptualisation, methodology, project administration, resources, supervision, validation, visualisation, writing – original draft, writing – review & editing.

Data Sharing

A complete de-identified patient dataset will be available to researchers on request. Individuals wanting access to the data should send a request to r.wenlock@nhs.net.

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Clusters (n=24)	
Site	
A	14
B	10
No. of wards	17
Source Type	
Single	20
Multi	4
Index Cases (n=22)	
No. of clusters per patient	
1	20
2	2
Public Health England Definitions of Hospital-acquired COVID-19 infection (%)	
Community	6 (27)
Indeterminate	9 (41)
Probable	4 (18)
Definite	3 (14)
Index Type (%)	
Early	10 (42)
Late	14 (58)
Previous Negative SARS-CoV-2 test during admission	
Yes	16
No	6
Traced contacts (n=579)	
No. of "Co-indexes"	4
No. of unique patients	575
No. of exposures per patient	
1	546
2	28
3	1
Age, years (IQR)	75.7 (63.0, 85.2)
Charlson Co-Morbidity Score, median (IQR)	5 (3-6)
Sex (%)	
Male	287 (50.1)
Female	286 (49.9)
Infection Outcome (%) ^a	
Positive	118 (19.5)
Negative	487 (80.5)
No. of contacts with confirmed negative outcome (%) ^b	113 (23.2)
Public Health England Definitions of Hospital-acquired COVID-19 infection (n=118) (%)	
Community	0
Indeterminate	36 (30.5)
Probable	37 (31.4)
Definite	45 (38.1)
Length of stay, median days (IQR)	31 (21.8, 43.6)

^a Infection outcome (n=605) for each unique exposure episode. ^b Proportion of negative infection outcomes (n=487) with a negative PCR 7-14 days post-exposure.

Table 1 – Demographic and clinical details of the clusters, index cases and secondary cases

Figure 1 – The secondary attack rate per cluster by source type.

Figure 2 – Cumulative event plot demonstrating the time from end of contact with the index to positive result, by source type for all contacts (n=605).

Figure 3 – Survival plots for unique patients exposed to COVID-19 in hospital. Red is symptomatic infection, yellow asymptomatic infection, blue COVID-19 negative. Shaded area represents 95% confidence intervals.