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

Rhys D. Wenlock*, Matija Tausan, George Stoyle, Holly Hendron, Oscar Buchanan, Zachary Tait, Bethany Whittle, Samuel McInerney, Jessica Blackaby, Andrew Davies, Martin Still, Catherine Sargent

University Hospitals Sussex NHS Foundation Trust, Eastern Road, Brighton, BN2 5BE, UK

ARTICLE INFO

Article history:
Received 8 July 2021
Accepted 2 September 2021
Available online 4 September 2021

SUMMARY

Background: Exposure to SARS-CoV-2 was widespread in hospitals during 2020. The risk of infection after in-hospital exposure has not yet been quantified and effective strategies to prevent it remain unclear.

Methods: All incidences of patient-to-patient exposure to SARS-CoV-2 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, symptoms, and outcomes. Factors associated with acquiring infection and mortality were investigated.

Results: Of 575 patients exposed, 118 (19.5%) tested positive within 14 days of their exposure, with secondary attack rates (SAR) ranging from 0 to 72%. 68.6% (81/118) of secondary cases had not been in the same bay as the index case. For exposed patients, sharing a bay with the index case and having spent longer on the ward with them 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). 71% of secondary cases tested positive while asymptomatic and 94.6% had tested negative earlier in their admission.

Conclusions: This is the first study to describe the outcomes of a cohort of patients exposed to COVID-19 in hospital. Exposure to COVID-19 in hospital commonly leads to transmission that is not confined to the index case's bay. This study confirms that asymptomatic testing is important and suggests that an increased frequency of testing may be beneficial. Moreover, we provide factors that can be used to identify the contacts at the greatest risk of acquiring infection.

© 2021 The Authors. Published by Elsevier Ltd on behalf of The Healthcare Infection Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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 transmission [1], and variable accuracy in testing methods [2].

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 centres [3–8]. 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 future potential waves 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 timeframe [11]. The intention of our study is to produce an accurate descriptive analysis of the nosocomial transmission within our local hospital trust over a given period.

By describing the 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 the Brighton site of University Hospitals Sussex NHS Foundation Trust in the United Kingdom. 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.

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 on the 1st October 2020 to 221.6 per 100,000 on the 10th December 2020 [12].

Existing Infection Prevention and Control measures

At the time of the study several measures to prevent hospital-acquired SARS-CoV-2 were operational:

- Staff were required to wear surgical gloves, a fluid-resistant surgical face mask and a plastic apron when interacting with any patients. Those items were to be changed between each patient.
- When a COVID-19 positive case was found on a non-COVID-19 ward, they were transferred to a different area.
- After exposure to a COVID-19 positive patient, exposed patients would be isolated in a side room if available for 14 days (unless discharged). Otherwise, they remained with other exposed patients until transfer was possible.

Definitions

A positive result refers to laboratory confirmation of SARS-CoV-2 detection by qRT PCR for the viral RNA-dependent RNA-polymerase.

The index case (or index) was the first patient to test positive for SARS-CoV-2 on a ward with no connection to previous ward cases (indicating a new source of infection).

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

- two days before the index’s positive result AND index leaving the ward (current Public Health England (PHE) guidance)

A cluster refers to the group of patients who shared the ward with the index case (and were exposed to SARS-CoV-2 as per the definition of contact above). It comprises index cases, contacts, and if present, secondary cases. A cluster was designated each time an index case is identified.

Secondary cases were defined as patients developing a positive SARS-CoV-2 test within 14 days of their exposure to an index case.

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

Each ward cared for 15–25 patients, and were comprised of bays (single rooms shared by four-six patients) and side rooms (single occupancy rooms).

Data collection

The index cases were identified and extracted from the 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 any of the following: development of new, persistent cough, fever >37.5°C or 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 were assumed to have not developed significant symptoms if they had not re-presented to hospital (they were however included fully in the analysis). The Cycle Threshold (Ct) of the index cases RT-PCR was collected.
The validated Charlson Co-morbidity Index (CCI) score was calculated for each patient [13]. 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 analyses were 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 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 over-dispersed 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 studies [14]. A statistical analysis plan was developed pre-analysis and reviewed by a statistician.

University Hospitals Sussex NHS Foundation Trust approved the study. Similarly, as a study of healthcare-associated infections, this investigation is exempt from requiring ethical approval under Section 251 of the NHS Act 2006 (confirmed by the NHS Health Research Authority algorithm, available at https://www.hra-decisiontools.org.uk/research/, which notes that no formal ethical approval is required).

Results

Index cases

In the studied period, 24 incidences of patient-to-patient in-hospital exposure to SARS-CoV-2 occurred (Figure 1). These clusters were caused by exposure to 22 index cases. Two of the index cases were identified as indexes in two separate clusters.

Seven out of 22 (32%) index patients tested positive on their first test of the admission with six asymptomatic at the time of the positive SARS-CoV-2 PCR. The remainder of the index cases had tested negative earlier in their admission and subsequently tested positive on routine inpatient surveillance testing (n = 15). Eighty percent (12/15) of them were asymptomatic at the time and 40% (6/15) had their positive result within five days of their last test (Figure 1).

Contacts

Five hundred and eighty-six patients were identified as being exposed to an index case. This comprised 624 individual exposure episodes as 34 patients were exposed twice with a further two patients exposed on three occasions (Figure 1). Demographic and clinical information for all patients is included in Table I.

Table I

Demographic and clinical details of the clusters, index cases and secondary cases

| 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 (%)a

| Community | Indeterminate | Probable | Definite |
|-----------|---------------|----------|----------|
| 6 (27)    | 9 (41)        | 4 (18)   | 3 (14)   |

| Index Type (%) |
|----------------|
| Early | Late |
| 10 (42) | 14 (58) |

Previous Negative SARS-CoV-2 test during admission

| Yes | No |
|-----|----|
| 16  | 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 (%)b

| Positive | 118 (19 - 5) |
| Negative | 487 (80 - 5) |

No. of contacts with confirmed negative outcome (%)c

| 113 (23 - 2) |

Public Health England Definitions of Hospital-acquired COVID-19 infection (n=118) (%)d

| Community | Indeterminate | Probable | Definite |
|-----------|---------------|----------|----------|
| 0         | 36 (30 - 5)   | 37 (31 - 4) | 45 (38 - 1) |

Length of stay, median days (IQR) 31 (21 - 8, 43 - 6)

---

a Community = Positive test within 48 hours of admission; Indeterminate = Positive test 2–7 days after admission, Probable = Positive test 8–14 days into admission. Definite = Positive test more than 15 days into admission.
b Infection outcome (n=605) for each unique exposure episode.
c Proportion of negative infection outcomes (n=487) with a negative PCR 7–14 days post-exposure.
d Community = Positive test within 48 hours of admission; Indeterminate = Positive test 2–7 days after admission, Probable = Positive test 8–14 days into admission. Definite = Positive test more than 15 days into admission.
**Cluster-level analysis**

One hundred and eighteen secondary cases were identified, an overall secondary attack rate (SAR) of 19.5% (95% CI: 16.5, 22.8).

Ninety-five point eight percent (113/118) of secondary cases had a negative test earlier in their admission, 70 (61.9%, n=113) had a negative test in the last 7 days, and 8.0% (9/113) had had a negative result in the prior two days (Figure 1).

The median SAR 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 was large variation between the clusters, with six of the single source clusters having 0 secondary cases (Figure 2).

In multivariable analysis, multi-source exposure was associated with a larger SAR than single source exposure (OR 4.1, 95% CI: 1.13, 15.1). However, the index being symptomatic rather than asymptomatic (OR 1.24, 95% CI: 0.32, 4.48) and each day the index was on the ward prior to positive test had no discernible effect on the SAR (OR 1.07, 95% CI: 0.99, 1.16).

When considering the location of exposure relative to the index case, the secondary attack rate was greatest in the index bay at 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%) 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).

**Patient-level analysis**

In multivariable analysis of the single source clusters (Table II), being in the same bay as the index rather than elsewhere on the ward was associated with an increased risk of developing infection (OR 3.80, 95% CI: 1.89, 7.74). Similarly, each day spent on the ward with the index increased the odds of infection by 8% (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) after their last contact with the index case and 90% had tested positive by 8.7 days.

The majority of secondary cases tested positive while they were asymptomatic (71.2%, 84/118) with half of secondary cases (46.6%, 55/118) remaining asymptomatic throughout (Figure 1).

**Outcomes**

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

---

**Table II**

Multivariable regression analysis of the factors that influence whether a secondary case tests positive

| Variable                                      | Secondary cases (n=87) | Negative contacts (n=429) | Adjusted odds ratio | 95% confidence interval |
|-----------------------------------------------|------------------------|---------------------------|---------------------|-------------------------|
| In the same bay as the index, % (no.)         |                         |                           |                     |                         |
| Length of time shared with the index, median days (IQR) |                         |                           |                     |                         |

**Figure 2.** The secondary attack rate per cluster by source type.
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). 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 6.2, 4) days although this ranged from 0.4 to 503 days. For secondary cases the median length of stay was 26 (IQR 15, 40) days compared to 10 (IQR 4, 19) for the contacts who remained negative. 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 in length of stay.

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 events [11]. 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 one in four of the clusters reported here resulted in no detected secondary cases. However, it is important to note that only 23.2% of “negative contacts” had a negative PCR result in the 7–14 days after their exposure and as such secondary cases may have been missed.

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 not [17]. 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.

Most index cases had previously undergone testing in hospital, with some being tested within five days of their positive result. 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. However, it is significant that many secondary cases had not been exposed in the bay, but were elsewhere on the ward (with three 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 continues [19].

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.

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. The absence of this information has implications when considering the large number of secondary cases found outside of the index cases bay (were staff the drivers of beyond-bay transmission?). Thirdly, as already alluded to, a large proportion of contacts did not undergo post-exposure routine surveillance testing and therefore we may be underestimating the true impact of nosocomial COVID-19. Fourthly, our definition of symptomatic case, although necessarily strict due to the availability of data, likely missed mild infections (note that anosmia was not included). This may in part explain why half of secondary cases were asymptomatic and the high mortality rate observed. Finally, during the timeframe studied here, it is likely that most if not all of the cases were infected with the original (pre-alpha) variant of SARS-CoV-2, which is less transmissible.

Acknowledgements

The authors would like to thank Professor Stephen Bremner at Brighton and Sussex Medical School for advice and guidance on the statistical analyses. Similarly, we would like to thank the Virology Department at UHSx for their support. An evidence search of “Epidemiology of inpatient exposure to COVID-19” was completed by Lucy Sinclair on 22nd February 2021 as part of the Brighton and Sussex Library and Knowledge service. Finally, we are deeply grateful for the compassion and professionalism displayed by the healthcare workers while caring for patients over the last 12 months.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Funding

None.
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.infpip.2021.100173.

References

[1] Pollock AM, Lancaster J. Asymptomatic transmission of covid-19. BMJ 2020;371:1–2.

[2] Watson J, Whiting PF, Brush JE. Interpreting a covid-19 test result. BMJ 2020;vol. 369(May):1–7 [Internet] Available from: https://doi.org/10.1136/bmj.m1808.

[3] Harada S, Uno S, Ando T, Iida M, Takano Y, Ishibashi Y, et al. Control of a Nosocomial Outbreak of COVID-19 in a University Hospital. Open Forum Infect Dis 2020;7(12):1–9.

[4] Wee LE, Conceicao EP, Sim XYJ, Aung MK, Tan KY, Wong HM, et al. Minimising intra-hospital transmission of COVID-19: the role of social distancing. J Hosp Infect 2020. https://doi.org/10.1016/j.jhin.2020.04.016 [Internet]: Available from:.

[5] Wong SCY, Kwong RTS, Wu TC, Chan JWM, Chung HK, Lee SY, et al. Risk of nosocomial transmission of coronavirus disease 2019: an experience in a general ward setting in Hong Kong. J Hosp Infect 2020.

[6] Taylor J, Rangaiah J, Narasimhan S, Clark J, Alexander Z, Manuel R, et al. Nosocomial COVID-19: experience from a large acute NHS Trust in South-West London. J Hosp Infect 2020;(xxxx). https://doi.org/10.1016/j.jhin.2020.08.018 [Internet] Available from:.

[7] Lessells R, Moosa Y, De Oliveira T. Report into a nosocomial outbreak of coronavirus disease 2019 (COVID-19) at Netcare St. Augustine’s Hospital, 37; 2020.

[8] Schwierzeck V, König JC, Kühn J, Mellmann A, Correa-Martínez C, Omar H, et al. First reported nosocomial outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a pediatric dialysis unit. Clin Infect Dis. 2:1–21.

[9] Carter B, Collins J, Barlow-Pay F, Rickard F, Bruce E, Verduri A, et al. Nosocomial COVID-19 infection: examining the risk of mortality. The COPE-Nosocomial Study (COVID in Older PEople). J Hosp Infect 2020;(July).

[10] Khan KS, Reed-Embleton H, Lewis J, Saldanha J, Mahmud S. Does nosocomial COVID-19 result in increased 30-day mortality? A multi-centre observational study to identify risk factors for worse outcomes in patients with COVID-19. J Hosp Infect [Internet 2021;107:91–4. https://doi.org/10.1016/j.jhin.2020.09.017. Available from:.

[11] Abbas M, Robalo Nunes T, Martischang R, Zingg W, Iten A, Pittet D, et al. Nosocomial transmission and outbreaks of coronavirus disease 2019: the need to protect both patients and healthcare workers. Antimicrob Resist Infect Control [Internet 2021;10(1):1–13. https://doi.org/10.1186/s13756-020-00875-7. Available from:.

[12] GOV.UK Coronavirus Data. https://coronavirus.data.gov.uk/search?postcode=BN2+5BE.

[13] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–83.

[14] Cuschieri S. The STROBE guidelines. Saudi J Anaesth 2019 Apr;13(Suppl 1):S31–4.

[15] Jewkes SY, Zhang Y, Nicholl DJ. Nosocomial spread of COVID-19: lessons learned from an audit on a stroke/neurology ward in a UK district general hospital. Clin Med 2020;20(S):e173–7.

[16] Ramanathan K, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, et al. Nosocomial infection with SARS-cov-2 within departments of digestive surgery. 2020 (January):19–21. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7127800/pdf/main.pdf.

[17] Marks M, Millat P, Ouchi D, Roberts C, Alemay A, Corbacho-Monné M, et al. Transmission of COVID-19 in 282 clusters in Catalonia, Spain: A cohort study. medRxiv 2020;3099(20):1–8.

[18] GOV.UK Coronavirus Data. https://coronavirus.data.gov.uk/search?postcode=BN2+5BE.

[19] Jones JR, Qureshi ZU, Temple RJ, Larwood JPJ, Greenhalgh T, Bourouiba L. Two metres or one: what is the evidence for physical distancing in covid-19? BMJ 2020;370:m3223.