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Effectiveness of rapid SARS-CoV-2 genome sequencing in supporting infection control for hospital-onset COVID-19 infection: multicenter, prospective study

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51   **Abstract**

52   **Background**

53   Viral sequencing of SARS-CoV-2 has been used for outbreak investigation, but there is limited
54   evidence supporting routine use for infection prevention and control (IPC) within hospital settings.

55   **Methods**

56   We conducted a prospective non-randomised trial of sequencing at 14 acute UK hospital trusts. Sites
57   each had a 4-week baseline data-collection period, followed by intervention periods comprising 8
58   weeks of 'rapid' (<48h) and 4 weeks of 'longer-turnaround' (5-10 day) sequencing using a sequence
59   reporting tool (SRT). Data were collected on all hospital onset COVID-19 infections (HOCIs; detected
60   ≥48h from admission). The impact of the sequencing intervention on IPC knowledge and actions, and
61   on incidence of probable/definite hospital-acquired infections (HAIs) was evaluated.

62   **Results**

63   A total of 2170 HOCI cases were recorded from October 2020-April 2021, corresponding to a period
64   of extreme strain on the health service, with sequence reports returned for 650/1320 (49.2%) during
65   intervention phases. We did not detect a statistically significant change in weekly incidence of HAIs
66   in longer-turnaround (incidence rate ratio 1.60, 95%CI 0.85-3.01; *P*=0.14) or rapid (0.85, 0.48-1.50;
67   *P*=0.54) intervention phases compared to baseline phase. However, IPC practice was changed in
68   7.8% and 7.4% of all HOCI cases in rapid and longer-turnaround phases, respectively, and 17.2% and
69   11.6% of cases where the report was returned. In a 'per-protocol' sensitivity analysis there was an
70   impact on IPC actions in 20.7% of HOCI cases when the SRT report was returned within 5 days.
71   Capacity to respond effectively to insights from sequencing was breached in most sites by the
72   volume of cases and limited resources.

73   **Conclusion**

74   While we did not demonstrate a direct impact of sequencing on the incidence of nosocomial
75   transmission, our results suggest that sequencing can inform IPC response to HOCIs, particularly
76   when returned within 5 days.

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81   **Clinical trial number**

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86   infection prevention and control; molecular epidemiology; SARS-CoV-2.

Introduction

88   Viral sequencing has played an important role in developing our understanding of the emergence
89   and evolution of the SARS-CoV-2 pandemic[1]. Sequencing technologies can now be used for local
90   outbreak investigation in near real-time, and this was implemented by some research centres for
91   evaluation of nosocomial transmission from the early stages of the pandemic[2]. It has been
92   demonstrated that sequencing can provide additional information on outbreak characteristics and
93   transmission routes in comparison to traditional epidemiological investigation alone[2-4]. However,
94   limited data are available on the feasibility of routine use of sequencing for infection prevention and
95   control (IPC), or on its direct impact on IPC actions and nosocomial transmission rates.

96   Throughout the pandemic, nosocomial transmission of SARS-CoV-2 has been a major concern[5], with
97   hospital-acquired infections (HAIs) accounting for more than 5% of lab-confirmed cases from March-
98   August 2020 in the UK[6] and representing 11% of COVID-19 cases within hospitals in this period[7].
99   HAIs also frequently occur within a very vulnerable population with high levels of mortality[6, 8, 9].
100   There is therefore an unmet need to develop interventions that can reduce the occurrence of
101   nosocomial transmission. The aims of this study were to determine the effectiveness of SARS-CoV-2
102   sequencing in informing acute IPC actions and reducing the incidence of HAIs when used
103   prospectively in routine practice, and to record the impact of sequencing reports on the actions of
104   IPC teams.

105   When this study was planned in the summer of 2020 there was imperfect knowledge regarding the
106   dominant mode of transmission of SARS-CoV-2[10] and it was not possible to predict the future
107   course of the pandemic. In conducting this study, substantial difficulties were encountered in
108   implementing the intervention and in responding effectively to any insights generated. As such, this
109   report serves as a record of the challenge of conducting research within a pandemic as well as being
110   a conventional study summary report.

111

Methods

113   We conducted a prospective multiphase non-randomised trial to evaluate the implementation and
114   impact of SARS-CoV-2 sequencing for IPC within 14 acute NHS hospital groups in the UK. All sites
115   were linked to a COG-UK sequencing hub, 13 were university hospitals and one a district general
116   hospital. We implemented a bespoke sequence reporting tool (SRT) intervention, developed and
117   previously evaluated for this study[11], and assessed the importance of turnaround time for
118   sequencing and reporting. The study included integral health economic and qualitative process
119   evaluation[12].

120   The study design comprised a planned 4-week baseline data-collection period, followed by
121   intervention periods defined by the time from diagnostic sampling to return of sequence data to IPC
122   teams, comprising 8 weeks of 'rapid' (<48 hours) turnaround sequencing and 4 weeks of 'longer' (5-
123   10 days) turnaround sequencing for each site. Target turnaround time was 48h from diagnostic
124   sampling to return of the SRT report during the 'rapid' sequencing phase, and 5-10 days for the

125   'longer-turnaround' phase. Eight sites implemented rapid' followed by 'longer-turnaround' phases
126   with five doing the opposite. One site did not implement longer-turnaround sequencing because
127   they considered it a reduction in their standard practice, comprising outbreak sequencing with
128   weekly meetings to discuss phylogenetic analyses; they nonetheless completed the baseline phase
129   of the study without use of the SRT or automated feedback to IPC teams on all HOCI cases. The order
130   of the intervention phases was pragmatically determined in some sites by the need to first run the
131   'longer-turnaround' phase to develop sample transport and sequencing procedures before
132   attempting the 'rapid' sequencing phase, and the ordering was decided in the remaining sites to
133   ensure a mixture of intervention phases over calendar time – there was no randomisation process in
134   deciding the order of study phases.

135   Data were recorded in all phases for all patients meeting the definition of: a hospital-onset COVID-19
136   infection (HOCI), i.e. first confirmed test for SARS-CoV-2 >48 hours after admission and without
137   suspicion of COVID-19 at time of admission. During the intervention phases, and for at least 3 weeks
138   prior to any intervention period to enable linkage to recent cases, participating sites aimed to
139   sequence all SARS-CoV-2 cases including both HOCI and non-HOCI cases.

140   The SRT aimed to integrate sequence and patient data to produce concise and immediately
141   interpretable feedback about cases to IPC teams via a one-page report. Sites were also able to apply
142   other methods (e.g. phylogenetics) to the sequence data generated, where this was part of their
143   usual practice. Guidance regarding IPC actions was not specified as part of this study. Sites were
144   expected to follow current national guidelines, which evolved throughout the course of the
145   pandemic. Sequencing data from healthcare workers (HCW) could be utilised in the SRT system, and
146   this was implemented by 8/14 sites. Whether this was done depended on availability of HCW
147   samples for each lab as staff testing was generally managed separately to patient testing. HCW
148   testing protocols followed national guidelines.

149   Data collection on patient characteristics and on implementation and impact of the intervention was
150   conducted using a central study-specific database. Ethical approval for the study was granted by NHS
151   HRA (REC 20/EE/0118), and the study was prospectively registered (ClinicalTrials.gov Identifier:
152   NCT04405934).

153   The primary outcomes of the study as defined in the protocol[13] were: (1) incidence of IPC-defined
154   SARS-CoV-2 HAIs per week per 100 currently admitted non-COVID-19 inpatients, and (2) for each
155   HOCI, identification of linkage to individuals within an outbreak of SARS-CoV-2 nosocomial
156   transmission using sequencing data as interpreted through the SRT that was not identified by pre-
157   sequencing IPC evaluation during intervention phases. The second outcome used all observed HOCI
158   cases as the denominator, and so represented the proportion of cases in which sequencing provided
159   information regarding potential transmission routes where none had been previously uncovered.

160   Secondary outcomes were: (1) incidence of IPC-defined SARS-CoV-2 hospital outbreaks per week per
161   1000 non-COVID-19 inpatients, (2) for each HOCI, any change to IPC actions following receipt of SRT
162   report during intervention phases, (3) any recommended change to IPC actions (regardless of
163   whether changes were implemented). There was considered to be an impact on IPC actions if this
164   was recorded for any of a number of pre-defined outcomes (e.g. enhanced cleaning, visitor and

165 staffing restrictions, provision of personal protective equipment), or if it was stated that the report
166 had effected any change to IPC practice on that ward or elsewhere within the hospital. The
167 proportion of HOCI cases for which IPC reported the SRT report to be 'useful' was added as a further
168 outcome.

169 To support standardisation across sites, 'IPC-defined SARS-CoV-2 HAIs' were considered to be all
170 HOCIs with ≥8 days from admission to symptom onset (if known) or sample date (i.e. UK Health
171 Security Agency definition of a probable/definite HAI[14]).

172 An IPC-defined SARS-CoV-2 hospital outbreak was defined as at least two HOCI cases on the same
173 ward, with at least one having ≥8 days from admission to symptom onset or sample date. Outbreak
174 events were considered to be concluded once there was a period of 28 days prior to observation of
175 another HOCI[14].

176 Further details of outcome definitions are given in Appendix 1.
177

178 ***Statistical analysis***
179
180 We used three approaches: intention-to-treat analysis to assess the overall impact of sequencing on
181 IPC activity and the incidence of HAIs, per protocol site-based analysis on a subset of high
182 performance sites, and pooled analysis to describe how turnaround time was related to impact on
183 IPC irrespective of study phase. Inclusion of sites in the per protocol analysis was based on the
184 proportion of sequence reports returned and speed of return in the rapid phase. Thresholds to
185 define this group were determined following review of the data but before analysis of outcomes.

186 Incidence outcomes were analysed using mixed effects negative binomial regression models, which
187 in this context correspond to Poisson regression with an additional overdispersion parameter. Data
188 for the first week of each intervention period, or in the first week of return to intervention following
189 a break, were considered transition periods and not considered as direct evidence regarding the
190 intervention effect. Analysis was conducted with calendar time divided into 'study weeks' running
191 Monday-Sunday. Models were adjusted for calendar time, the proportion of current inpatients that
192 were SARS-CoV-2 positive, as well as local community SARS-CoV-2 incidence for each study site,
193 using 5-knot restricted cubic splines [15]. Number of inpatients not positive for SARS-CoV-2 was
194 considered an exposure variable (defining 'person-time' at risk of nosocomial infection). Differences
195 between study phases were evaluated using adjusted incidence rate ratios.
196
197 The primary outcome of identification of SARS-CoV-2 nosocomial transmission using sequencing
198 data and secondary outcomes relating to changes to IPC actions and the 'usefulness' of SRT reports
199 were analysed using mixed effects logistic regression models, without covariable adjustment or
200 removal of cases from the first week of each intervention phase. Marginal proportions from fitted
201 models were reported for rapid- and longer-turnaround intervention phases, and differences in
202 outcomes between these phases were evaluated. If the SRT report was not returned this was
203 interpreted as a 'failure', i.e. no change to IPC action; however, we also present percentages for
204 these outcomes restricted to HOCIs where the SRT report was returned.
205

206 For both incidence and 'per HOCI' outcomes, we accounted for the structure of the data with
207 hierarchical exchangeable normally distributed random effects for each study site, and for each
208 study phase within each study site. Analyses were conducted using Stata V16, with figures generated
209 using the *ggplot2* package for R V4.0.

210
211

Results

213 A total of 2170 HOCIs were recorded for the study between 15 October 2020 and 26 April 2021.
214 These cases had median age of 76.7 (IQR 64.4-85.6) years, and 80% had at least one clinically
215 significant comorbidity (Table 1).

216 All 14 sites completed baseline and rapid sequencing intervention phases (Appendix 1—figure 1).
217 Thirteen sites completed the longer-turnaround sequencing intervention phase. 49.2% (650/1320)
218 SRT reports for HOCIs were returned in the intervention phases, with only 9.3% (123/1320) returned
219 within the target timeframes (Table 2). This figure was greater in the longer-turnaround phase at
220 21.2% (79/373) than in the rapid phase (4.6%; 44/947). The median turnaround time from diagnostic
221 sampling for reports returned was 5 days in the rapid phase and 13 days in the longer-turnaround
222 phase, substantially longer than the targets of 48 hours and 5-10 days, respectively. A detailed
223 breakdown of reporting turnaround times is reported separately[16].

224 Ordering the sites by proportion of cases with sequencing results returned and median turnaround
225 time during the rapid phase (Figure 1) identified no obvious clustering of highest versus lowest
226 performing sites. We therefore also carried out a 'per protocol' sensitivity analysis on the seven
227 highest performing sites; these sites returned ≥40% of SRTs within a median time from diagnostic
228 sample of ≤8 days within their rapid phase. The criteria for this analysis were decided after data
229 collection but prior to data analysis, as per the statistical analysis plan (SAP). However, we
230 acknowledge that the 'higher performing sites' did not meet the target turnaround time for
231 reporting in the rapid phase; criteria were therefore set to split the sites into upper and lower 50%
232 based on level of implementation.

233 We did not detect a statistically significant change in weekly incidence of HAIs in the longer-
234 turnaround (incidence rate ratio 1.60, 95%CI 0.85-3.01; *P*=0.14) or rapid (0.85, 0.48-1.50; 0.54)
235 intervention phases in comparison to baseline phase across the 14 sites (Table 3), and incidence rate
236 ratios were comparable in our 'per protocol' analysis. Similarly, there was only weak evidence for an
237 effect of phase on incidence of outbreaks in both intention-to-treat and 'per protocol' analyses, with
238 wide confidence intervals inclusive of no difference in incidence (Table 3).

239 We compared HOCI-level impacts of the sequence report between phases. Nosocomial linkage to
240 other individual cases, where initial IPC investigation had not correctly identified any such linkage,
241 was identified in 6.7% and 6.8% of all HOCI cases in the rapid and longer-turnaround phases,
242 respectively (OR for 'rapid vs longer-turnaround' 0.98, 95%CI 0.46-2.08; *P*=0.95) (Table 2) and in
243 11.4% and 12.6% respectively of cases where the report was returned. For 25 cases in the rapid and
244 five cases in the longer-turnaround phase phylogenetic trees were used for sequences with <90%
245 genome coverage, with three from the rapid phase showing previously unidentified linkage.

246 IPC practices were changed in 7.8% and 7.4% of all HOCI cases in the rapid and longer-turnaround
247 phases, respectively (OR for 'rapid vs longer-turnaround' 1.07, 0.34-3.38; *P*=0.90) and 17.2% and
248 11.6% respectively of cases where the report was returned. No one specific change to IPC action

249   dominated those recorded among the options included within study reporting forms (Appendix 1—
250   table 2). When restricted to higher performing sites (i.e. 'per protocol'), IPC practice was changed in
251   a greater proportion of all HOCI cases in the rapid (9.9%) in comparison to the longer-turnaround
252   (0.7%) sequencing phase (OR for 'rapid vs longer-turnaround' 15.55, 1.30-1.85; *P*=0.01) and 16.7%
253   and 1.1% respectively of cases where SRT reports were returned. The impact of phase on detecting
254   nosocomial linkage was similar.

255   IPC teams more commonly reported finding the sequence reports useful in the rapid sequencing,
256   303/428 (70.8%) compared to the longer-turnaround phase, 107/215 (49.8%) (although this
257   association was reversed on analysis within the multi-level mode specified, OR 0.82 rapid *vs* longer-
258   turnaround, 0.12-5.46; *P*=0.82), and the difference was more pronounced in the 'per protocol'
259   analysis (79.0 vs 27.2%, respectively; OR 3.44, 0.28-42.61; *P*=0.41). We explored this association
260   further using the actual time to return of the reports, going beyond the analyses prespecified in the
261   SAP (Figure 2). In the 'per protocol' analysis an impact on IPC actions was observed in 20.7%
262   (45/217) of HOCI cases in which the SRT report was returned within 5 days, but in very few cases
263   beyond this, with this trend less apparent when data from all sites were considered. Figure 2 also
264   displays a strong decline in reported usefulness of the SRT with increasing turnaround time, both
265   across all sites and in the 'per protocol' analysis. Sequence reports were considered useful in 79.1%
266   (182/230) of cases if returned within 5 days for all sites (169/216, 78%, in 'per protocol' analysis).
267   However, we note that many of the HOCI cases with SRT returned within 5 days were from a single
268   study site, and some sites did not seem to have clearly differentiated 'useful' SRT reports when
269   completing data collection (Appendix 1—figure 2 and Appendix 1—figure 3).

270   SRT reports suggested that 91.3% of HOCI patients had acquired their infection post-admission
271   (580/635, Table 2). In 91.9%, (589/641, Appendix 1—table 2) of cases the reports were interpreted
272   as supportive of IPC actions already taken. SRT reports also suggested post-admission infection in
273   the majority of indeterminate HAIs (diagnosed 3-7 days from admission) (176/223, 78.9%).

274   Our analysis models reveal important findings beyond the effect of the intervention. The analysis
275   model for the incidence of HAIs identified independent positive associations with the proportion of
276   current SARS-CoV-2 positive inpatients, the local community incidence of new SARS-CoV-2 cases
277   (which peaked in December 2020 to January 2021, Appendix 1—figure 4 and Appendix 1—figure 5),
278   and calendar time (modelled as 'study week'). Adding the proportion of local community cases that
279   were Alpha (lineage B.1.1.7) variant did not lead to a statistically significant improvement in model
280   fit (*P*=0.78). The observed weekly HOCI incidence rates varied substantially from 0 to 7.6 per 100
281   SARS-CoV-2 negative inpatients, with peaks aligning with those for local community incidence
282   (Appendix 1—figure 4).

283   From modelling outbreaks, positive associations were similarly found for both hospital prevalence
284   and community incidence of SARS-CoV-2 (Appendix 1—figure 5). The median number of HOCIs per
285   IPC-defined outbreak event was four, with the largest observed outbreak including 43 HOCIs
286   (Appendix 1—table 1).

287   Extensive qualitative analyses[17, 18] found high levels of acceptability for the SRT sequencing reports,
288   which supported decision-making about IPC activity (e.g. stand down some IPC actions or continue
289   as planned). In several sites the major barriers to embedding and normalising the SRT within existing
290   systems and processes were overcome. The SRT did provide new and valued insights into
291   transmission events, outbreaks and wider hospital functioning but mainly acted to offer
292   confirmation and reassurance to IPC teams. Critically, given the context of the study within the
293   pandemic timeline, the capacity to generate and respond to these insights effectively on a case-by-
294   case basis was breached in most sites by the volume of HOCIs, and the limits of finite human and
295   physical resource (e.g. hospital layout).

296   *Cost of SARS-CoV-2 genome sequencing*

297   The analysis of the SARS-CoV-2 genome sequencing in the 10 laboratories who performed the tests
298   for the sites included in the study showed that mean per sample costs were on average higher for
299   rapid (£78.11) versus longer-turnaround (£66.94) sequencing. (Appendix 1—table 4). Consumables
300   were the highest cost driver of the sequencing process accounting for 66% in rapid and 67% in
301   longer turnaround sequencing.
302
303   Several factors affected the costs of genome sequencing. There was a general tendency of increasing
304   returns to scale, with average per-sample costs of genome sequencing tending to decrease as the
305   batch size increases; cost per sample in reagents also depends highly on how many samples
306   are processed per batch. Another factor was the sequencing platform and protocols used:
307   some processes had been automated which reduced the hands-on input.
308

309

310   **Discussion**

311   This study constitutes the largest prospective multicentre evaluation study of viral whole genome
312   sequencing (WGS) for acute IPC investigation of nosocomial transmission conducted to date. The
313   study was run as part of routine practice within the NHS, and the challenges faced in implementing
314   the intervention reflected the context and barriers in winter 2020–2021 in the UK. We did not
315   demonstrate a direct impact of sequencing on the primary outcome of the incidence of HAIs, either
316   on full analysis or when restricted to the higher performing sites, and the overall proportion of cases
317   with nosocomial transmission linkage identified using sequencing that had been missed by IPC
318   investigation was <10% in the intervention phases. However, post hoc exploratory investigation
319   found that among sites with the most effective implementation of the sequencing intervention we
320   showed that feedback within 5 days of diagnosis allowed for maximal impact on IPC actions. IPC
321   teams, particularly in the 'per protocol' analysis, were almost all positive in their perception of the
322   utility of viral sequencing for outbreak investigation.

323   The study was undertaken during a period of extreme strain on the NHS, with hospitals described as
324   being "in the eye of a covid-19 storm"[19]. Sites reported that they lacked the additional resources, in
325   terms of staff and bed space, needed to respond effectively to insights generated by sequencing.
326   Furthermore, if the study were repeated now then IPC teams would have more evidence-backed
327   tools at their disposal, such as increasing respirator usage. As such, we do not believe that the null
328   result for the impact on incidence of nosocomial transmission should be taken as strong evidence for
329   a general lack of effectiveness of viral WGS for IPC.

330   Outbreak investigations are inherently complex and must take account of uncertainty regarding
331   transmission links, even in the presence of high-quality genomic data[20]. Interventions centred on
332   IPC practices often need to be evaluated at the hospital level in order to allow for impacts on
333   transmission across an institution as a whole[21], meaning that large multicentre studies are required
334   to generate high-quality evidence. Standardisation of data collection with complex structures across
335   multiple hospital sites is a considerable challenge. A review of IPC practice guidelines conducted
336   prior to the SARS-CoV-2 pandemic found that most recommendations were based on evidence from
337   descriptive studies, expert opinion and other low-quality evidence[22].

338   The use of viral WGS for public health surveillance has become firmly established in the UK for SARS-
339   CoV-2[23]. This enabled early detection of the increased transmissibility and health impact of the
340   Alpha variant[24] and subsequent monitoring of the Delta[25] and Omicron variants[26]. However, whilst

341 viral WGS for acute outbreak investigation has been shown for both SARS-CoV-2[2, 4, 27, 28] and other
342 viruses[29-31] to better identify sources of hospital acquired infections and transmission chains, its
343 impact on the management and outcome of nosocomial infection has not previously been
344 quantified. Our study provides a substantial body of evidence regarding the introduction of viral
345 WGS into hospital functioning, routine IPC practice, its potential usage for outbreak management
346 and the challenges that need to be overcome to achieve implementation across the UK.

347 There are several limitations that may have impacted on the results from this study. The study was
348 conducted between October 2020 and April 2021. In this period, the local community incidence for
349 the study sites ranged from <50 to >1200 weekly cases per 100,000 people. There were
350 corresponding large variations in the healthcare burden of COVID-19, with several sites recording
351 weeks when more than half of all inpatients were SARS-CoV-2 positive. High community infection
352 rates and associated increases in the incidence of HOCI cases contributed to difficulties for site
353 research teams in generating good quality viral sequences and reports for all HOCI cases within
354 target timeframes.

355 Our qualitative analyses also found that the capacity of sites to react to information generated by
356 the sequencing intervention was breached by the volume of HOCI and admitted COVID-19 cases
357 ('*we've been basically deluged*' IPC staff) in combination with the finite personnel resources and
358 limited physical space for isolation that was available ('*The trouble is when you have so many wards*
359 *going down and such a high prevalence of COVID, your actions are kind of the same regardless*' IPC
360 staff). It may therefore be more achievable to develop effective systems for rapid viral WGS and
361 feedback for endemic respiratory viruses at lower and more consistent levels, and more timely
362 reporting of results might be associated with greater impact on IPC actions. As well as acute changes
363 to IPC actions, there is the potential for routine pathogen sequencing to allow prospective IPC
364 practice and policies to be refined. This could enable a longer-term reduction in the incidence of
365 nosocomial infection at any given site, and such effects would be less dependent on turnaround
366 time of sequencing in any given case. However, the capacity of sites to make such informed
367 adjustments to IPC practice were limited during peaks in incidence of SARS-CoV-2 over the timescale
368 of the present study.

369 Planning this study and developing the data collection forms during the early stages of a novel viral
370 pandemic was challenging, as in the summer of 2020 there were still ongoing debates around the
371 primary mode of viral transmission and optimal IPC practice, and global supply chains for personal
372 protective equipment were strained. In the planning of an equivalent study now, there would be a
373 greater focus on adjustments to ventilation[32], air filtration[33] and respirator[34] usage. It would also
374 be possible to be more prescriptive and standardised regarding the recommended changes to IPC
375 practice in response to sequencing findings, with the potential that our improved knowledge and
376 available tools might facilitate a measurable impact on the incidence of nosocomial transmission.

377 The peak in SARS-CoV-2 levels in December 2020 to January 2021 corresponded to the rise of the
378 highly transmissible Alpha variant in the UK[24]. We did not find that the local prevalence of the Alpha
379 variant was associated with the incidence rate of HAIs, beyond any effect mediated by higher
380 community incidence. This matches the conclusions of a previously reported sub-study analysis using
381 data from our sites[35].

382 The study intervention made use of a bespoke sequence reporting tool[11]. The SRT combined both
383 patient-meta-data and sequencing data, providing a single-page, easily interpretable report for IPC
384 teams. It also facilitated standardisation of data collection across sites. Interestingly, while HOCIs
385 diagnosed 3-7 days after admission are generally excluded from assessments of nosocomial SARS-
386 CoV-2 infections[8], because of difficulty in distinguishing them from community-acquired infections,
387 the SRT reported the majority (78.9%) of these indeterminate HAIs as being hospital-acquired. This

388 confirms findings from a retrospective study using genomic linkage[27], and may reflect a shorter
389 incubation time for the Alpha variant compared to earlier variants[36] (although this remains
390 uncertain[37]), indicating that definitions used for monitoring and reporting may need to be kept
391 under active review. Variants with shorter incubation times would lead to a greater importance for
392 the rapidity of feedback in informing adjustments to IPC actions.

393 A number of limitations of the SRT were recognised, and work is ongoing to rectify these for future
394 studies. The SRT's probability calculations did not include patient and HCW movements. The SRT
395 gave feedback on cases that could plausibly form part of the same outbreak but did not identify
396 direct transmission pairs or networks, as has been done in other studies[20, 38]. HCW sequencing data
397 could not be incorporated at all sites dues to logistical and data management and access constraints.
398 Implementation of an improved tool with these features might help to better identify routes of
399 transmission within a hospital that could be interrupted, e.g. through changes to the management of
400 ward transfers for patients, isolation policies or identification of areas within the hospital linked to
401 high risk of transmission. Finally, samples with less than 90% genome coverage were not included
402 within the reporting system, despite the fact that they may still be useful for phylogenetic analyses.

403 The study sites varied in their ability to process sequence and meta-data and generate and distribute
404 reports in a timely manner (Figure 1), and the targeted turnaround times for reporting were not
405 achieved at any of the sites for the majority of HOCIs in either the 'rapid' or 'longer turnaround'
406 phases. Sites that had established teams with existing genomics expertise and on-site sequencing
407 facilities were generally more successful at implementing the SRT into clinical practice[17]. There is a
408 need to focus on how sequencing and reporting processes can be integrated within local
409 infrastructure and tailoring of local processes to ensure clear chains of communication from
410 diagnostic labs through to the IPC team. Precisely understanding the barriers to achieving rapid
411 turnaround times is key to future IPC use of viral WGS and is currently being analysed in a follow-up
412 secondary analysis. Standardising and automating more of the SRT production pipeline will also help
413 reduce the implementation burden at sites.

414 The study covered a period in which a national vaccination programme was initiated for HCWs and
415 the elderly population in the UK, commencing with those ≥80 years from 8 December 2020. We had
416 planned to include data on the proportion of HCWs who had received at least one vaccine dose as a
417 variable in the analysis of incidence outcomes. This was subsequently not included because data
418 was only available from 10 sites, for which rollout of HCW vaccination was broadly consistent. As
419 such, any effect of HCW or patient vaccination on the incidence outcomes would form part of the
420 estimated association with calendar time.

421 With the sequencing technology now available and high levels of interest in viral genomics for public
422 health, there is the potential to incorporate viral WGS into routine IPC practice. Many publications
423 have already highlighted the utility of viral sequence data for changing IPC policy and auditing the
424 management of outbreaks[2, 4, 27-31]. We did not demonstrate an effect of our sequencing intervention
425 on our primary outcome of the incidence of HAIS, and there were challenges in the implementation
426 of the intervention. However, our study provides the first prospective evidence that with faster
427 turnaround times, viral sequences can inform ongoing IPC actions in managing nosocomial
428 infections; on post hoc exploratory analysis results returned within ≤5 days from sampling to result
429 changed the actions of IPC teams in around 20% of cases. The SRT, by rapidly combining sequence
430 and patient meta-data, was also better able than standard IPC definitions alone to distinguish
431 hospital and community acquired infections within a clinically relevant time scale. The difference in
432 the cost of rapid compared with longer-turnaround hospital sample sequencing is low relative to the
433 overall cost level at present (Appendix 1—table 4). Assuming SARS-CoV-2 sequencing for public
434 health purposes continues, the added cost of rapid sequencing for IPC purposes could potentially be
435 offset by the benefits accrued.

436   While we did not show an impact of sequencing on the numbers of HAIs or outbreaks, the evidence
437   that these correlated with the high community SARS-CoV-2 rates suggests that factors beyond the
438   control of IPC were influential. Our study nonetheless provides valuable evidence regarding the
439   implementation and utility of this technology for IPC, and potentially it will have a greater positive
440   impact on IPC practice outside of the burdens and resource constraints imposed by a pandemic.
441   Importantly for future research, we provide a wealth of data on why the study worked better at
442   some sites than others, and the challenges that would need to be overcome to make full use of viral
443   genome sequencing for IPC practice more widely. It remains to be demonstrated that viral
444   sequencing can have a direct impact on clinical outcomes such as the incidence of HAIs, and further
445   prospective studies with refined implementation of similar interventions are required to address
446   this.

447

469

470 **Data Sharing**
471 The fully anonymised datasets analysed during the study will be stored on a publicly available
472 repository. The COG-UK HOCI study to be shared on the UCL Data Repository data-sharing platform
473 so that the data may be reused by other researchers. This will include individual participant level
474 data, data dictionaries and the statistical analysis plan for this study. This will be done within 6
475 months of public reporting of results. Access through the data sharing platform requires submission
476 of a viable research plan for review.

477

484

485 **Supplementary files**

486 **Appendix 1**. Appendix containing further details of statistical analysis methods, and supplementary
487 figures and tables describing additional study data.

488 **Supplementary File 1.** List of COG-UK HOCI Investigators.

489   **Supplementary File 2.** Member list for the COVID-19 Genomics UK (COG-UK) consortium.

490

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613

614   **Figure 1** Plots of the median turnaround time against the percentage of HOCI cases with
615   SRT reports returned for the rapid (left panel) and longer-turnaround (right panel)
616   sequencing phases across the 14 study sites. The size of each circle plotted indicates the
617   number of HOCI cases observed within each phase for each site, with letter labels
618   corresponding to study site. The criteria for inclusion in our sensitivity analysis are displayed
619   as the green rectangle in the rapid phase plot, and sites on the longer-turnaround phase
620   plot are color-coded by their inclusion. In the rapid phase, SRT reports were returned for 0/4
621   HOCI cases recorded for Site H. Site N did not have a longer-turnaround phase, Site A
622   observed 0 HOCI cases and Sites D and E returned SRT reports for 0/1 and 0/2 HOCI cases,
623   respectively, in this phase.
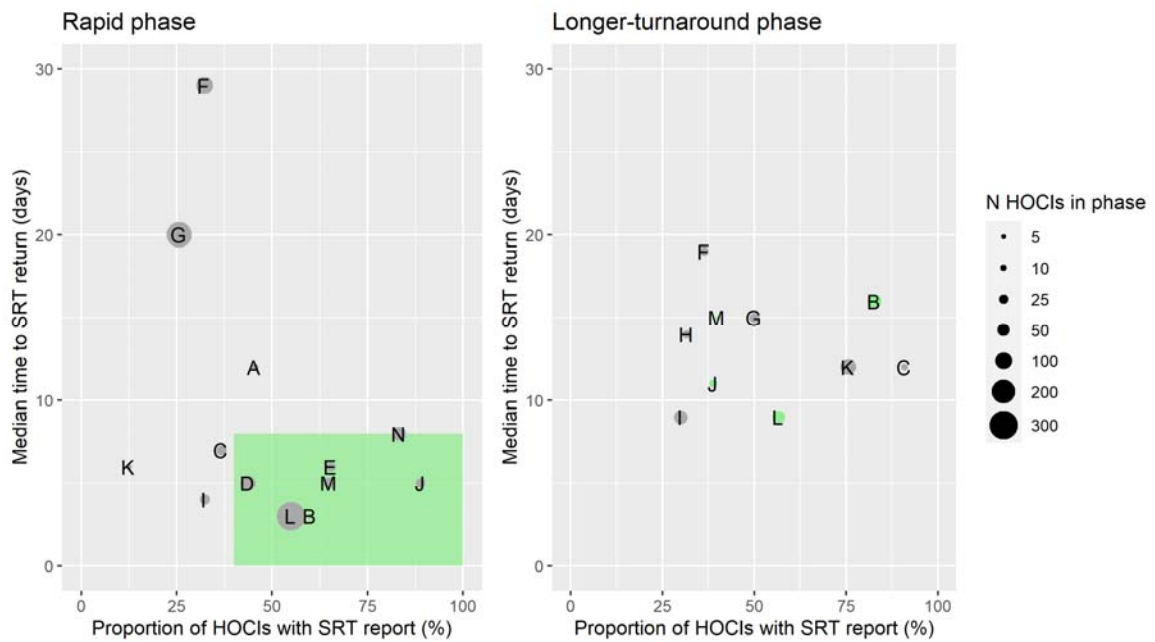
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626 **Figure 2** Plots of the proportion of returned SRT reports that had an impact on IPC actions ((a) and
627 (b)) and that were reported to be useful by IPC teams ((c) and (d)). Data are shown for all sites in (a)
628 and (c), and for the seven sites included in the 'per protocol' sensitivity analysis in (b) and (d). Results
629 are only shown up to turnaround times of ≤28 days, and grouped proportions are shown for ≥9 days
630 because of data sparsity at higher turnaround times. Error bars show binomial 95% CIs. "Yes" and
631 "No" outcomes for individual HOCI cases are displayed, colour-coded by rapid (red) and longer-
632 turnaround (blue) intervention phases and with random jitter to avoid overplotting. "Unsure"
633 responses were coded as "No" for (c) and (d).
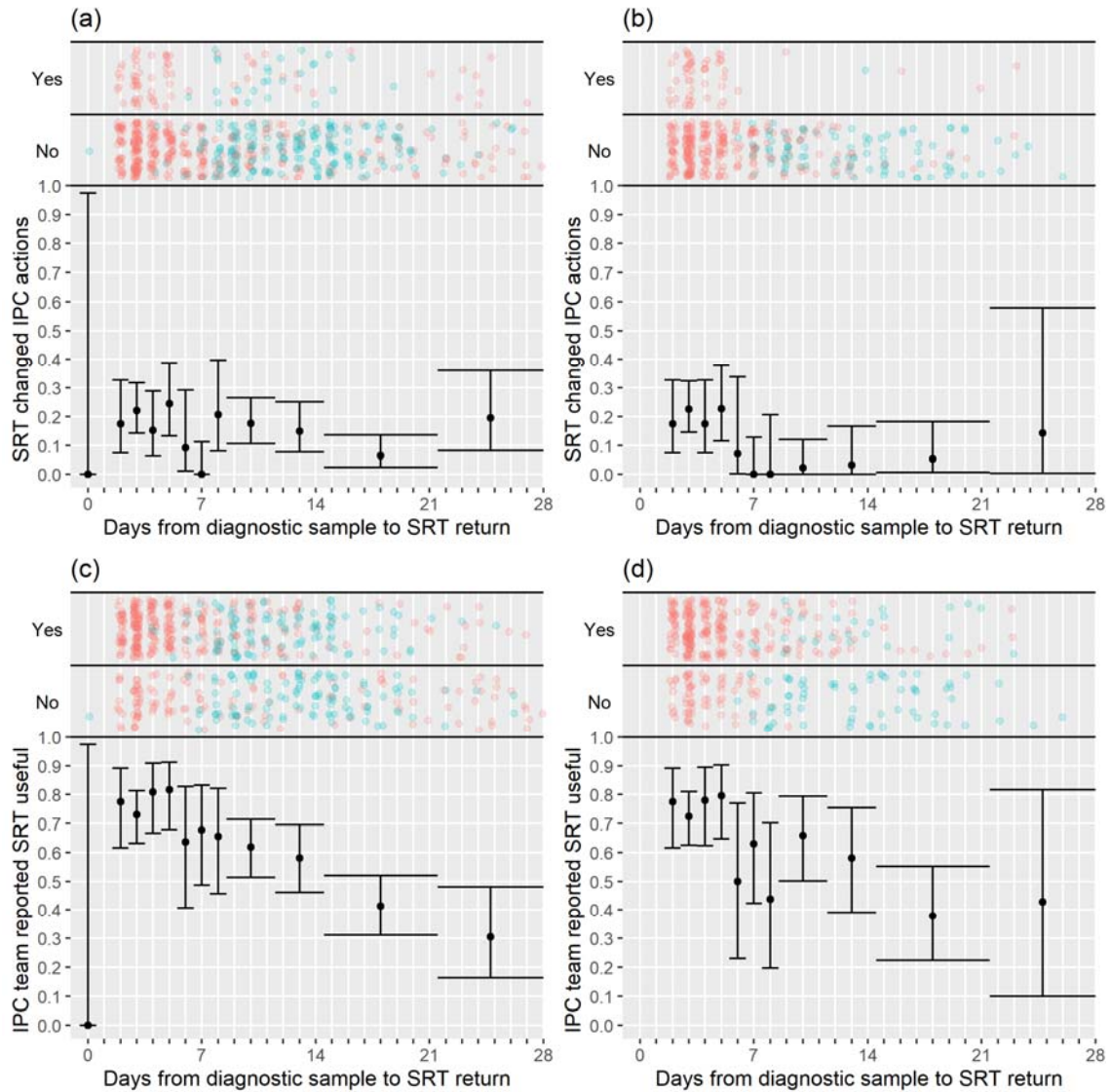
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636 **Table 1:** Demographic and baseline characteristics of the participants by study phase

Characteristic at screening	Study phase			
	Baseline	Longer-turnaround	Rapid	Total
N HOCI cases	850	373	947	2170
N HOCI cases per site, median (range); *N* sites	36 (1-207); 14	19 (0-86); 13	30.5 (4-297); 14	103.5 (40-451); 14
HAI classification, *n* (%)				
Indeterminate (3-7 days)	362 (42.6)	166 (44.5)	371 (39.2)	899 (41.4)
Probable (8-14 days)	236 (27.8)	121 (32.4)	270 (28.5)	627 (28.9)
Definite (>14 days)	252 (29.6)	86 (23.1)	306 (32.3)	644 (29.7)
Age (years), median (IQR, range)	77.5 (65.4-85.6, 0.4-100.5)	77.6 (64.6-86.7, 0.7-100.7)	76.4 (62.6-85.5, 0.6-103.5)	76.7 (64.4-85.6, 0.4-103.5)
Age ≥70 years, *n/N* (%)	589/850 (69.3)	240/373 (64.3)	598/947 (63.1)	1427/2170 (65.8)
Sex at birth: female, *n/N* (%)	457/850 (53.8)	177/372 (47.6)	460/947 (48.6)	1094/2169 (50.4)
Ethnicity, *n* (%)				
White	668 (78.6)	275 (73.7)	732 (77.3)	1675 (77.2)
Mixed ethnicity	9 (1.1)	6 (1.6)	8 (0.8)	23 (1.1)
Asian	46 (5.4)	26 (7.0)	34 (3.6)	106 (4.9)
Black Caribbean or African	36 (4.2)	18 (4.8)	46 (4.9)	100 (4.6)
Other	6 (0.7)	1 (0.3)	4 (0.4)	11 (0.5)
Unknown	85 (10.0)	47 (12.6)	123 (13.0)	255 (11.8)
Symptomatic at time of sampling, *n/N* (%)	167/739 (22.6)	58/322 (18.0)	106/659 (16.1)	331/1720 (19.2)
Significant comorbidity present, *n/N* (%)	650/776 (83.8)	260/323 (80.5)	574/757 (75.8)	1484/1856 (80.0)
Pregnant, *n/N* (%)	6/451 (1.3)	1/177 (0.6)	4/445 (0.9)	11/1073 (1.0)
Hosp. admission route, *n* (%)				
Emergency department	605 (71.2)	258 (69.2)	549 (58.0)	1412 (65.1)
Hospital transfer	59 (6.9)	21 (5.6)	51 (5.4)	131 (6.0)
Care home	3 (0.4)	0 (0)	0 (0)	3 (0.1)
GP referral	38 (4.5)	15 (4.0)	76 (8.0)	129 (5.9)
Outpatient clinic ref.	27 (3.2)	20 (5.4)	30 (3.2)	77 (3.5)
Other	42 (4.9)	9 (2.4)	48 (5.1)	99 (4.6)
Unknown	76 (8.9)	50 (13.4)	193 (20.4)	319 (14.7)

637 HAI, hospital-acquired infection; HOCI, hospital onset COVID-19 infection; Hosp., hospital.

Table 2: Per hospital onset COVID-19 infection (HOCI) implementation and outcome summary by study intervention phase, overall and within the 7/14 sites included in the 'per protocol' sensitivity analysis

	All study sites			Sensitivity analysis	
	Study phase			**Study phase**	
	Longer-turnaround	Rapid	**Total**	Longer-turnaround	Rapid
N HOCI cases	373	947	1320	143	533
Implementation					
Sequence returned within expected timeline, *n* (%)*	229 (61.4)	377 (39.8)	606 (45.9)	81 (56.6)	204 (38.3)
Sequence returned within study period, *n* (%)*	277 (74.3)	596 (62.9)	873 (66.1)	98 (68.5)	347 (65.1)
SRT report returned within target timeline (10d for longer-turnaround, 2d for rapid), *n* (%)	79 (21.2)	44 (4.6)	123 (9.3)	35 (24.5)	44 (8.3)
SRT report returned within study period, *n* (%)	215 (57.6)	435 (45.9)	650 (49.2)	92 (64.3)	317 (59.5)
Time from sample to report return (days), median (IQR, range) [*n*]	13 (9-15, 0-36) [215]	5 (3-11, 2-84) [430]	9 (4-14, 0-84) [645]	13 (9-17, 6-29) [92]	4 (3-6, 2-64) [312]
Sequencing results					
SRT suggestive patient acquired infection post-admission, *n/N* (%)	196/212 (92.5)	384/423 (90.8)	580/635 (91.3)	85/92 (92.4)	287/311 (92.3)
SRT suggestive patient is part of ward outbreak, *n/N* (%)	151/212 (71.2)	260/423 (61.5)	411/635 (64.7)	65/92 (70.7)	202/311 (65.0)
Linkage identified not suspected at initial IPC investigation:					
All HOCIs in phase *n/N* (%†, 95% CI)	24/348 (6.8, 1.7-11.8)	46/915 (6.7, 2.0-11.3)	70/1263 (5.5)	11/139 (7.9, 3.4-12.4)	39/512 (7.6, 5.3-9.9)
When SRT returned *n/N* (%)	24/190 (12.6)	46/403 (11.4)	70/593 (11.8)	11/88 (12.5)	39/296 (13.2)
SRT excluded IPC-identified hospital outbreak, *n/N* (%)	14/213 (6.6)	27/428 (6.3)	41/641 (6.4)	9/92 (9.8)	25/310 (8.1)
Impact on IPC					
SRT changed IPC practice:					
All HOCIs in phase *n/N* (%†, 95% CI)	25/373 (7.4, 1.1-13.6)	74/941 (7.8, 2.4-13.2)	99/1314 (7.5)	1/143 (0.7, 0.0-2.1)	52/527 (9.9, 7.3-12.4)
When SRT returned *n/N* (%)	25/215 (11.6)	74/429 (17.2)	99/644 (15.4)	1/92 (1.1)	52/311 (16.7)
SRT changed IPC practice for ward, *n/N* (%)	13/215 (6.0)	31/429 (7.2)	44/644 (6.8)	0/92 (0.0)	28/311 (9.0)
SRT used in IPC decisions beyond ward, *n/N* (%)	12/215 (5.6)	45/428 (10.5)	57/643 (8.9)	1/92 (1.1)	27/310 (8.7)
IPC team reported SRT to be useful, *n/N* (%)					
Yes	107/215 (49.8)	303/428 (70.8)	410/643 (63.8)	25/92 (27.2)	245/310 (79.0)
No	67/215 (31.2)	71/428 (16.6)	138/643 (21.5)	50/92 (54.3)	57/310 (18.4)
Unsure	41/215 (19.1)	54/428 (12.6)	95/643 (14.8)	17/92 (18.5)	8/310 (2.6)
HCW absence on ward					
Prop. HCWs on sick leave	0.09 (0.00-	0.13 (0.07-	0.13 (0.04-	0.09 (0.00-	0.13 (0.08-

| due to COVID-19, median (IQR, range) [*n*] | 0.15, 0.00-0.30) [49] | 0.29, 0.00-1.00) [162] | 0.27, 0.00-1.00) [321]‡ | 0.15, 0.00-0.30) [49] | 0.29, 0.00-1.00) [143] |

HCW, healthcare worker; IPC, infection prevention and control; IQR, interquartile range; Prop., proportion; SRT, sequence reporting tool. *As recorded by site, not based on recorded date or availability on central CLIMB server. †Estimated marginal value from mixed effects model, not raw %, evaluated on intention-to-treat basis with lack of SRT report classified as 'no'. ‡Includes data for baseline phase: 0.13 (0.00-0.30, 0.00-0.88) [110].

646 **Table 3:** Incidence outcomes by study intervention phase, overall and within the 7/14 sites
647 included in the 'per protocol' sensitivity analysis

	Study phase			IRR† (95% CI, *P*)	
	Baseline	Longer-turnaround	Rapid	Longer-turnaround vs baseline	Rapid vs baseline
All sites					
n HOCI cases	850	373	947	—	—
n IPC-defined HAIs	488	207	576	—	—
Weekly inc. of IPC-defined HAIs per 100 inpatients, mean (median, IQR, range)* [primary outcome]	1.0 (0.5, 0.0-1.4, 0.0-5.6)	0.7 (0.3, 0.0-0.7, 0.0-7.6)‡	0.6 (0.3, 0.0-0.8, 0.0-5.3)‡	1.60 (0.85-3.01; 0.14)	0.85 (0.48-1.50; 0.54)
n IPC-defined outbreak events	129	33	114	—	—
Weekly inc. of IPC-defined outbreak events per 1000 inpatients, mean (median, IQR, range)*	2.7 (1.1, 0.0-4.1, 0.0-23.0)	0.8 (0.0, 0.0-1.0, 0.0-8.9) ‡	0.7 (0.0, 0.0-0.0, 0.0-8.9) ‡	1.09 (0.38-3.16; 0.86)	0.58 (0.24-1.39; 0.20)
n IPC+sequencing-defined outbreak events	—	40	133	—	—
Weekly inc. of IPC+seq. -defined outbreak events per 1000 inpatients, mean (median, IQR, range)*	—	1.1 (0.0, 0.0-1.5, 0.0-13.4) ‡	0.9 (0.0, 0.0-1.4, 0.0-7.6) ‡	—	—
Sensitivity analysis					
n HOCI cases	290	143	533	—	—
n IPC-defined HAIs	179	91	337	—	—
Weekly inc. of IPC-defined HAIs per 100 inpatients, mean (median, IQR, range)* [primary outcome]	0.3 (0.0, 0.0-0.3, 0.0-3.0)	0.3 (0.0, 0.0-0.0, 0.0-3.4)‡	0.4 (0.0, 0.0-0.3, 0.0-5.3)‡	2.21 (0.82-5.92; 0.10)	1.75 (0.75-4.08; 0.16)
n IPC-defined outbreak events	58	14	55	—	—
Weekly inc. of IPC-defined outbreak events per 1000 inpatients, mean (median, IQR, range)*	1.1 (0.0, 0.0-1.3, 0.0-12.9)	0.3 (0.0, 0.0-0.0, 0.0-5.7) ‡	0.4 (0.0, 0.0-0.0, 0.0-8.9) ‡	0.83 (0.14-4.93; 0.80)	0.46 (0.11-1.86; 0.21)
n IPC+seq.-defined outbreak events	—	14	67	—	—
Weekly inc. of IPC+seq. -defined outbreak events per 1000 inpatients, mean (median, IQR, range)*	—	0.3 (0.0, 0.0-0.0, 0.0-5.7) ‡	0.5 (0.0, 0.0-0.0, 0.0-7.6) ‡	—	—

648
649 HAI, hospital-acquired infection; HOCI, hospital onset COVID-19 infection; IPC, infection prevention and
650 control; IQR, interquartile range; IRR, incidence rate ratio; seq., sequencing.
651 IPC-defined HAIs are considered to be 'probable' or 'definite' HAIs. *Descriptive data over all week-long
652 periods at all study sites. †Adjusted for proportion of current inpatients at site that are COVID-19 cases,
653 community incidence rate and calendar time (as displayed in Appendix 1—figure 5 and Appendix 1—figure 6
654 for all sites). ‡Not including data from the first week of each intervention period, or in the week following any
655 break in the intervention period.

Appendix 1

Methods

Sample size estimation

There was uncertainty in the number of HOCIs that would be identified at each site during each of the intervention periods, with the rapid sequencing phase being 8 weeks' duration. We assumed there may be an average of 10 HOCIs/week per site during this intervention period, a total of 80 per site. Within a typical site this would allow us to estimate the proportion of HOCIs with genotypic linkage to another case(s) not detected by IPC processes with minimum precision of +/- 9.4%. Similarly we would be able to estimate the proportion of HOCIs where an action is taken that would not have occurred without sequencing within +/-9.4%, with a pooled estimate of key proportions across the 14 sites implementing rapid sequencing within +/- 6.5% assuming an intra-cluster correlation coefficient of 0.05.

Comparing the proportion of HOCIs with genotypic linkage to another case(s) not detected by IPC processes between rapid testing and delayed testing phases across all sites, the study aimed for at least 80% power to detect a percentage point difference of 11% (two-sided test with alpha=0.05, considering proportions of 55.5% vs 44.5% which would be associated with minimum power for a difference of this magnitude).

For the outcome of weekly incidence of IPC-defined HOCIs, using an approximate Normal distribution for weekly counts there was 86.7% power to demonstrate a reduction from 12 IPC-defined HOCIs per week in the baseline phase to 10 per week during the rapid testing phase across all sites, under 5% significance level two-tailed testing. However, these calculations correspond to a variance of 12 for weekly counts based on the Poisson distribution, but the presence of over-dispersion of weekly counts would lead to a lower power to detect a difference. Using an overdispersion parameter of 0.82 based on retrospective analysis of data from Sheffield and Glasgow (dataset as described by Stirrup et al.[10]) resulted in 81% power to detect a reduction in mean weekly incidence from 12.5 to 10.

Planned secondary outcomes dropped from formal analysis

We did not carry out formal statistical analysis for the following planned secondary outcomes:

- Weekly incidence of IPC+sequencing-defined SARS-CoV-2 hospital outbreaks, measured as incidence rate per week per 100 non-COVID-19 inpatients, during each phase of the study based on case report forms.

- The number of healthcare worker (HCW) periods of sickness/self-isolation as assessed as a proportion of the number of staff usually on those wards impacted by HOCI cases, for all phases of the study.

42   The first of these was dropped prior to analysis because of incomplete sequencing coverage of HOCI
43   cases in the intervention phases – it was not felt that this would add useful information given the
44   level of sequencing achieved and the null results for other incidence outcomes. The second was
45   dropped (again prior to any statistical analysis) because of low levels of data completion at most of
46   the study sites. Data collection on HCW absence was discontinued whilst the study was ongoing in
47   order to reduce the administrative burden for sites and due to difficulties in accessing this data for
48   research staff (with staff data being recorded on separate systems to patient data).

49   We also omitted specific reporting of the secondary outcome of 'Ideal changes to IPC actions
50   following receipt of sequencing report'. This was because no recommended changes to IPC actions
51   were recorded that were also recorded as 'not implemented'. As such, this outcome was identical to
52   'changes to IPC actions following receipt of sequencing report'.

53

54   Coding of primary and secondary outcomes
55   Primary outcome 1
56   *Incidence of IPC-defined SARS-CoV-2 HAIs*
57   In order to standardise this measure across sites, 'IPC-defined SARS-CoV-2 HAIs' were considered to
58   be all HOCIs with an interval of ≥8 days from admission to symptom onset (if known) or sample date
59   (i.e. those meeting the PHE definition of a probable or definite HAI[13]). Incidence was expressed 'per
60   100 non-COVID-19 inpatients per site per week', and was evaluated for study baseline and
61   intervention phases.
62

63   Primary outcome 2
64   *Identification of SARS-CoV-2 nosocomial transmission using sequencing data*
65   For each HOCI case during the intervention phases, the occurrence of this outcome was defined as
66   positive where the following two answers had been recorded in the Hospital Transmission section of
67   the relevant clinical reporting form (CRF04):
68

69   "Is sequencing report suggestive that patient is part of a hospital outbreak (i.e. involving ≥2
70   patients or HCWs in the hospital)?: Yes"
71   &
72   "If yes, was linkage to one or more of these patients suspected at initial IPC investigation?:
73   No"
74

75   The occurrence of this outcome was considered to be negative if the following answer was recorded:
76

77   "Is sequencing report suggestive that patient is part of a hospital outbreak (i.e. involving ≥2
78   patients or HCWs in the hospital)?: No"
79

80   Or if the following combination was recorded:
81

82   "Is sequencing report suggestive that patient is part of a hospital outbreak (i.e. involving ≥2
83   patients or HCWs in the hospital)?: Yes"

84   &
85   "If yes, was linkage to one or more of these patients suspected at initial IPC investigation?:
86   Yes"
87
88   The outcome will be considered missing if either the first question was not answered, or if the first
89   question was answered 'Yes' and the second question was not answered or was answered
90   'unknown'.
91
92   The outcome was also be considered negative if the viral sequence and sequence report had not
93   been returned during the period of study data collection.
94
95   This outcome was only be evaluated for study sequencing intervention periods.
96

97   **Secondary outcome 1**
98   *Incidence of IPC-defined SARS-CoV-2 hospital outbreaks*
99   An IPC-defined SARS-CoV-2 hospital outbreak was defined as the occurrence of at least two HOCI
100   cases on the same ward, with at least one having an interval of ≥8 days from admission to symptom
101   onset (if known) or sample date, and with the outbreak event considered to be concluded if there
102   was a gap of 28 days before the observation of another HOCI case[13]. This was evaluated using the
103   ward location recorded at patient registration into the study (CRF01) for HOCI cases, cross-checked
104   against patient movement data to confirm location at diagnostic sampling. Outbreak events were
105   considered to have occurred on the date of diagnosis of the first HOCI case. This outcome was be
106   evaluated for study baseline and intervention phases.
107

108   **Secondary outcome 2**
109   *Changes to IPC actions following receipt of sequencing report*
110   For each HOCI case, the occurrence of this outcome was defined as positive if 'Yes' is the answer to
111   either of the following two questions in the 'Sequencing report impact on IPC team' section of
112   CRF04:
113   "Overall, did the sequencing report change IPC practice for this ward?"
114   And/or
115   "Has the sequencing report information been used in IPC decisions beyond this patient's
116   ward?"
117   And/or, if any specific changes to IPC practice were recorded on CRF04.
118
119   The occurrence of the outcome was considered negative if at least one of these questions was
120   answered 'No' and neither is answered 'Yes', and it was considered missing if neither were
121   answered.
122
123   This outcome was only evaluated for study sequencing intervention periods.
124

125   **Secondary outcome 3**
126   *Ideal changes to IPC actions following receipt of sequencing report*
127   A binary outcome was defined for each HOCI patient. This was based on the value of Secondary
128   Outcome 3, but was additionally be defined as positive (whether Secondary Outcome 3 was negative

129 or missing) if an 'increase' or 'decrease' that was not implemented was recorded for any of the
130 actions in the 'other recommended changes to IPC protocols' section of CRF04.
131
132 This outcome was only evaluated for study sequencing intervention periods.
133

134 **Secondary outcome 4**
135 *Incidence of IPC+sequencing-defined SARS-CoV-2 hospital outbreaks*
136 An IPC+sequencing-defined SARS-CoV-2 hospital outbreak was defined as the occurrance of at least
137 two HOCI cases on the same ward that form a genetic cluster with maximum viral sequence pairwise
138 SNP distance of 2 between each individual included and their nearest neighbour within the cluster.
139 This was evaluated using the ward location recorded at patient registration into the study (CRF01),
140 with HOCI cases sorted into outbreak groups using the lists of close sequence matches on unit-ward
141 as returned by the SRT and recorded in CRF03.
142
143 Outbreak events were considered to have occurred on the date of diagnosis of the first HOCI case.
144 This outcome was evaluated for study sequencing intervention periods for all sites.
145

146 **Secondary outcome 5**
147 *HCW sickness*
148 The proportion of HCWs on sick leave due to COVID-19 was calculated using the 'Current staffing
149 levels on ward' section of CRF02. Analysis was performed using the first available data within each
150 IPC-defined SARS-CoV-2 hospital outbreak (as per secondary outcome 1), so as to provide a measure
151 of the level of staff absence at the start of each outbreak. This outcome was evaluated for study
152 baseline and intervention phases.
153
154

155 **Changes with respect to the statistical analysis plan (SAP)**
156 It was planned that the cumulative proportion of HCWs vaccinated at each site for each study week
157 would also be included as a covariate for the analysis models of incidence outcomes. However, this
158 was dropped because these supplementary data could not be obtained from four sites (and one site
159 was only able to provide partial data). Where available, the data showed the rollout of HCW
160 vaccination to be broadly consistent across sites. As such, any effect of HCW vaccination on the
161 incidence outcomes would be incorporated into estimates of variation in relation to calendar time.

162 Local community incidence was not included within the SAP, but was added as an adjustment factor
163 for incidence models because within-hospital prevalence of patients admitted for SARS-CoV-2 did
164 not correlate perfectly with local incidence (e.g. due to triage of COVID-19 patients to different
165 hospitals).

166 The proportion of HOCI cases in which the sequencing report feedback was considered to be 'useful'
167 was added as a Secondary Outcome.

168 It was stated in the SAP that "We will conduct sensitivity analyses excluding study sites and/or
169 periods with suboptimal implementation of the trial intervention, both in terms of overall
170 population sequencing coverage for HOCIs and the turnaround time for sequence reports being
171 returned to IPC teams. The exact criteria for this will be decided amongst the study team before any
172 analysis has been conducted". This forms the basis for the 'per protocol' analyses presented. It was
173 not possible to prespecify the exact criteria. After data collection for the study had been completed

174   it became clear that none of the sites had met target turnaround times for sequence reporting in the
175   intervention phases, and so it was decided to set criteria to select the 50% 'higher performing' sites.

176   It was stated in the SAP that "If the target turnaround time for sequence generation and reporting is
177   missed for a substantial proportion of HOCI cases in each of the intervention phases, then results
178   [for Impact on IPC actions] will also be reported separately for the subset of cases for which the
179   intervention was implemented within the target timeframe." Because the proportion of HOCI cases
180   with SRT report returned within the target timeframe was low for the rapid intervention phases, we
181   instead reported the association of this outcome with turnaround time more generally.

182   The SAP did not state that unadjusted estimates would be reported for the incidence rate ratios for
183   HAIs and outtbreaks, but these have been added for completeness in response to the comments of a
184   Reviewer (Appendix 1—table 5).

185   Weekly incidence rates for outbreak events are displayed as '/1000 inpatients' rather than '/100
186   inpatients' to improve display.

187

Small sample correction
188

189   The topic of small sample corrections for cluster randomised and other cluster-structured studies
190   (e.g. stepped wedge trials) with outcomes that are not normally distributed is an area of ongoing
191   active research. To our knowledge, there do not exist any studies regarding appropriate corrections
192   for clustered data when analysing an outcome with negative binomial distribution. However, when
193   calculating P-values and confidence intervals for the primary and secondary outcomes we will use a
194   t-distribution with 12 or 13 degrees of freedom (n clusters – n relevant parameters) in order to
195   ensure that there is not an inflated type-1 error rate. This correction has shown appropriate
196   characteristics in simulation studies of analyses of binary outcomes using mixed effects models and
197   generalised estimating equations[34, 35].

198

Decision regarding continuation of study into final phase
199

200   A decision regarding the final phase of the study (Period 4) was planned for April 2021, with the
201   options being: ending of the study at Period 3, a further phase of rapid sequencing at each site or a
202   further phase of 'baseline' date collection without use of the SRT. A recommendation regarding this
203   decision was made by the study investigators and agreed with the TSC-DMC. The decision was
204   determined by the course of the epidemic and the progress of vaccination among key risk groups,
205   and by the quantity of data collected by the end of Period 3. The decision was not based on any
206   interim evaluation of the effect of the sequencing intervention under investigation on the incidence
207   of nosocomial infection.

208   A decision was made to stop the study at the end of Period 3 because the total sample size was close
209   to that projected for the study, and few new HOCI cases were being recorded at this point in time.

210

Further details for incidence model specification
211

212   The primary outcome of incidence of SARS-CoV-2 HAIs was analysed using a mixed effects negative
213   binomial regression model. This acts as an extension of a Poission regression model, with an
214   additional parameter allowing for overdispersion (for a Poission model the variance is the always the
215   mean for any given combination of covariables and conditional on random effect terms). The

216   negative binomial regression model is a generalised linear model, which uses a log-link function for
217   the expectation of the outcome variable. In our analysis we used nested independent normally
218   distributed random effects for each study site, and for each study phase within each study site,
219   which were incorporated into the 'linear predictor' for the expectation of the outcome variable as
220   for other forms of linear mixed effects model. The variance of the two random effects components
221   of the model were estimated within the maximum likelihood estimation for the model.

222   The command used in Stata to run this model was of the form:

223   menbreg n_HAIs i.study_phase_analysis prop_cov_sp_* study_week_sp_* community_inc_sp_*,
224   exposure(exposure_pw) || site_anon: || study_phase:, irr dispersion(constant)

225   Where the dataset under analysis included one row per study week at each site, with the variables
226   defined as:

227   n_HAIs: Number of HAIs observed at each sites in each study week

228   study_phase_analysis: Intervention phase for each study week, with separate categories for the first
229   week of each intervention phase at each site (to allow for 1 week to pass before potential impact on
230   incidence of HAIs)

231   prop_cov_sp_*: Spline basis variables for proportion of inpatients who were SARS-CoV-2 positive at
232   each site in each study week

233   study_week_sp_*: Spline basis variables for adjustment for calendar time

234   community_inc_sp_*: Spline basis variables for local community incidence for each site in each
235   study week

236   exposure_pw: person-weeks of SARS-CoV-2 negative inpatients at each site for each study week (i.e.
237   sum of patient-time at-risk for nosocomial SARS-CoV-2 infection)

238   site_anon: anonymised site label

239   study_phase: Intervention phase for each study week

240

241   **Qualitative analyses**

242   An exploratory, qualitative process evaluation using iterative programme theory employed semi-
243   structured interviews with 39 diverse healthcare professionals between December 2020 and June
244   2021. Participants were purposive sampled from 5/14 sites. Data collection and analysis (deductive
245   and inductive thematic analysis) focussed on the programme theory: intervention acceptability;
246   contextual dependencies; issues of fidelity/adaption; insights into local implementation; and effects
247   on outcomes.

Results

248

249 **Appendix 1—figure 1:** Flow diagram of study site enrolment and intervention
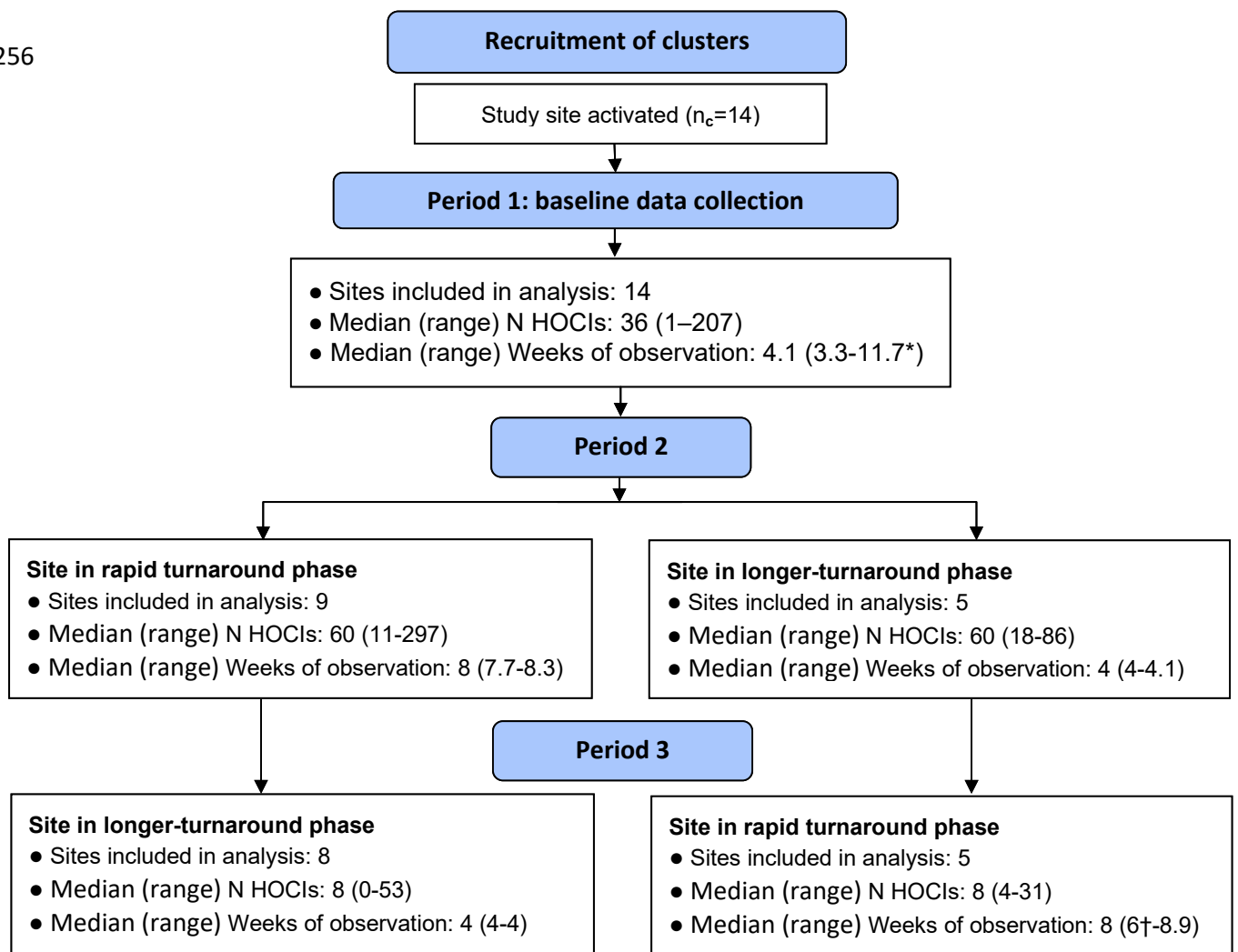250 implementation

251

252 *Baseline phase extended for one site due to a complete lack of HOCI cases during first few
253 weeks of study period and omission of longer-turnaround sequencing phase.
254 †Rapid sequencing phase truncated at one site due to cessation of enrolment at all sites.

255

256

257 **Appendix 1—figure 2** Plots of the proportion of returned SRT reports that had an impact on IPC
258 actions by study site. Results are only shown up to turnaround times of ≤28 days, and grouped
259 proportions are shown for ≥9 days because of data sparsity at higher turnaround times. Error bars
260 show binomial 95% CIs. "Yes" and "No" outcomes for individual HOCI cases are displayed, colour-
261 coded by rapid (red) and longer-turnaround (blue) intervention phases and with random jitter to
262 avoid overplotting.

263

264
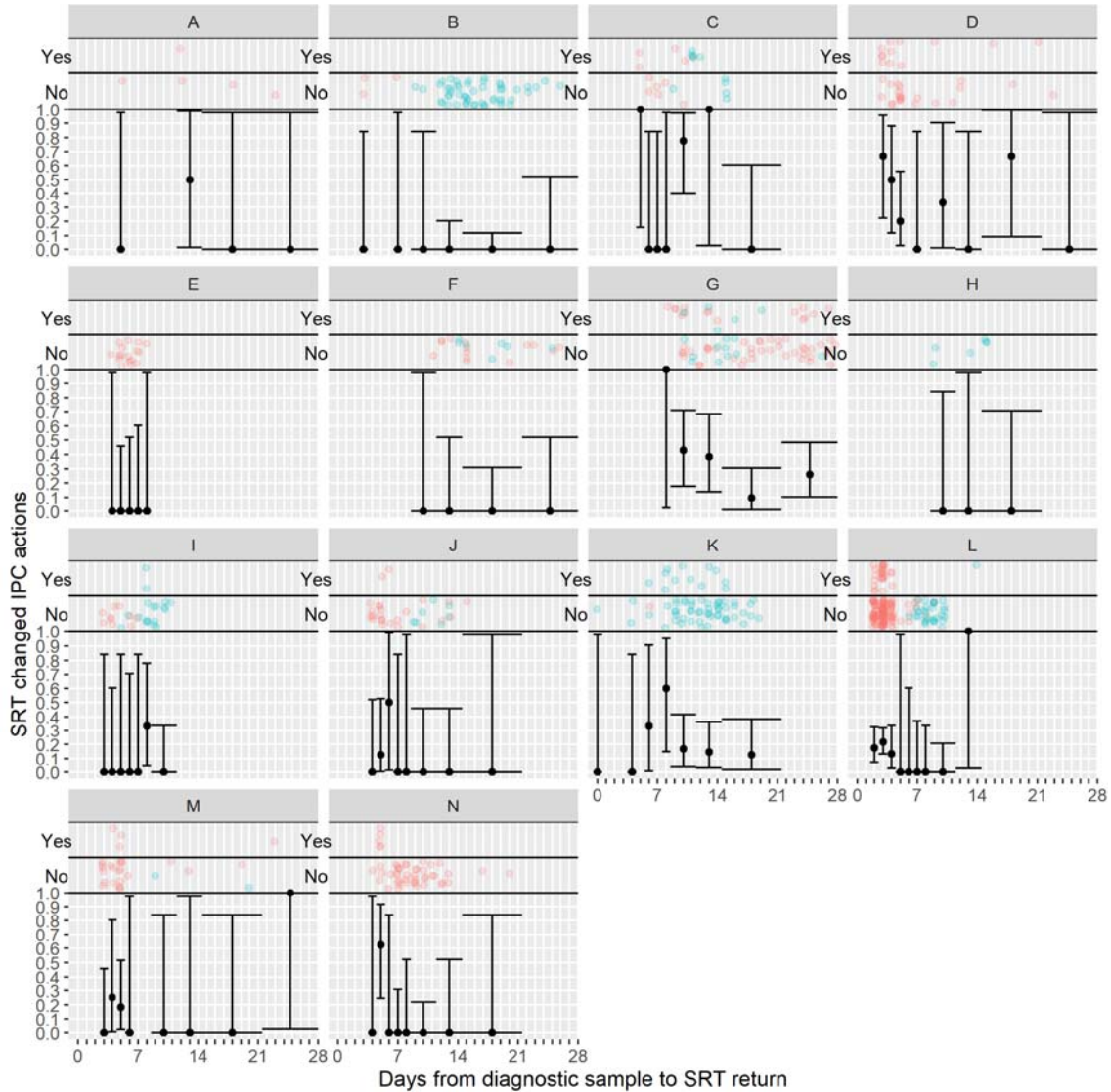
Appendix 1—figure 3 Plots of the proportion of returned SRT reports that were reported to be
266   useful by IPC teams by study site. Results are only shown up to turnaround times of ≤28 days, and
267   grouped proportions are shown for ≥9 days because of data sparsity at higher turnaround times.
268   Error bars show binomial 95% CIs. "Yes" and "No" outcomes for individual HOCI cases are displayed,
269   colour-coded by rapid (red) and longer-turnaround (blue) intervention phases and with random jitter
270   to avoid overplotting. "Unsure" responses were coded as "No"
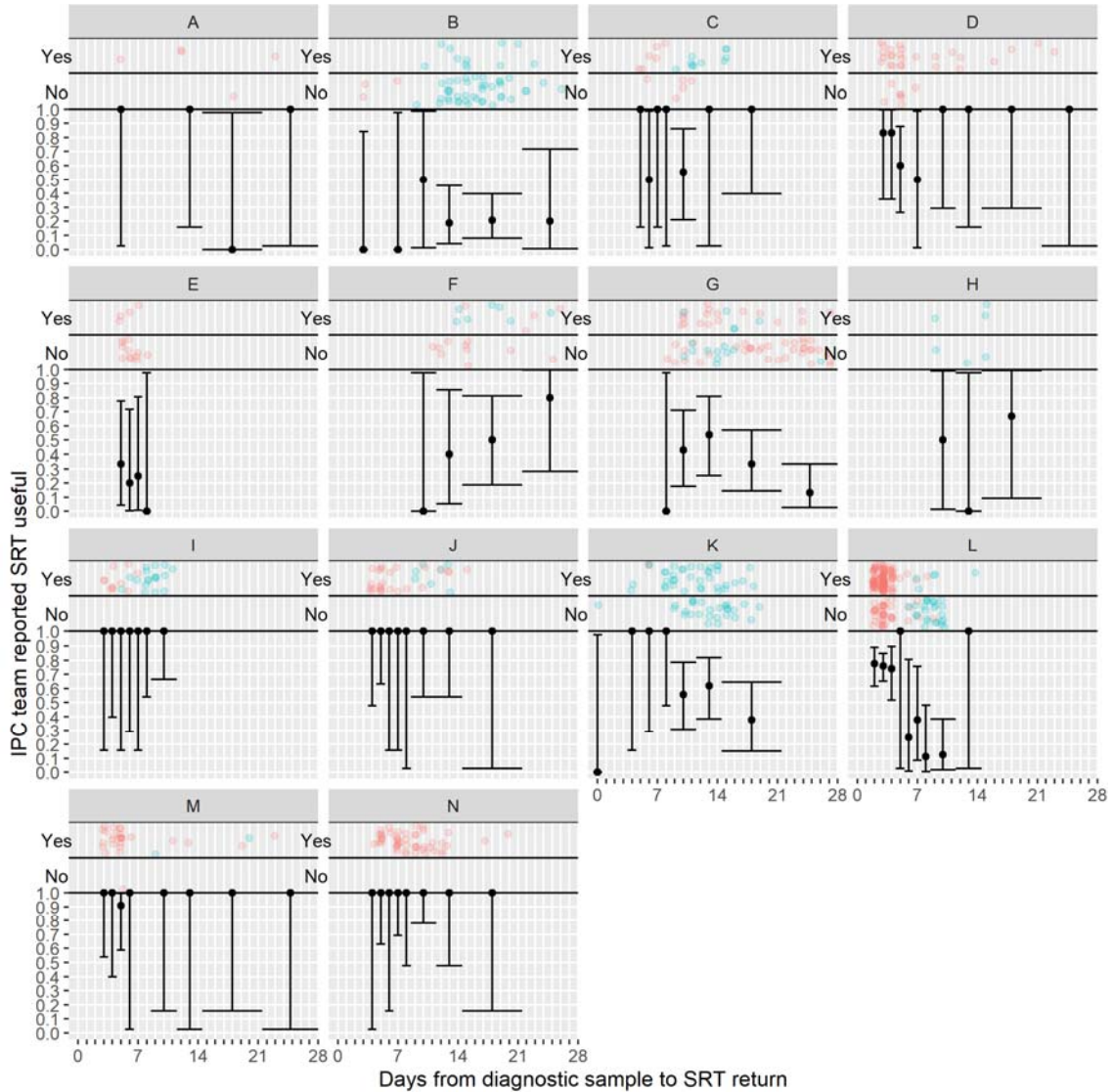
271
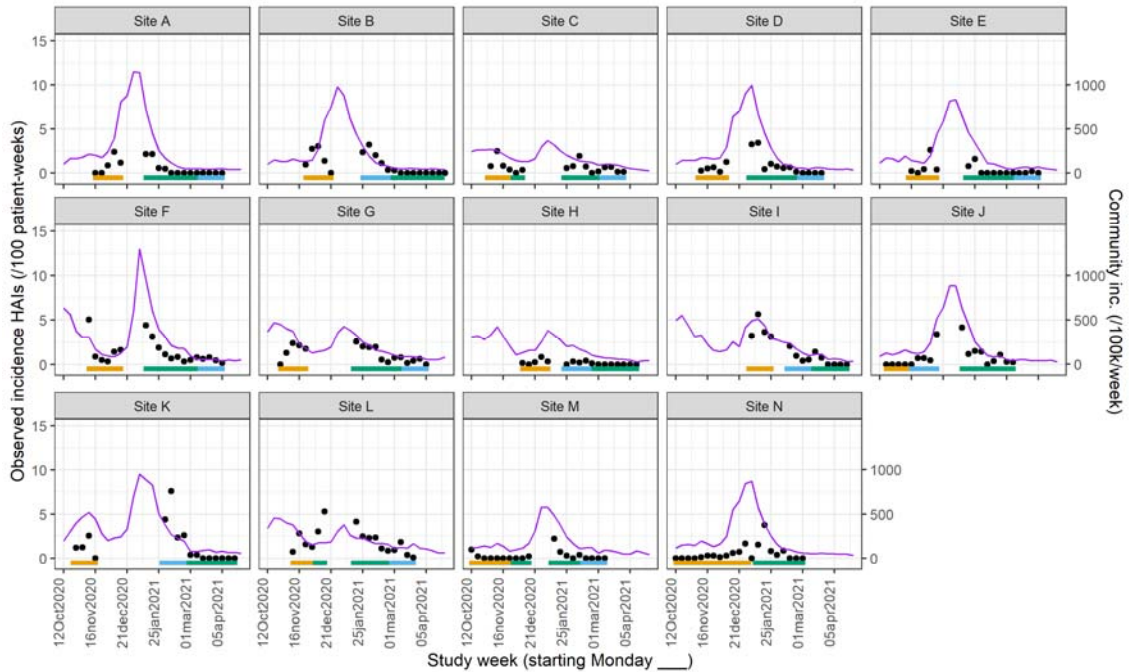272   .

273

274 **Appendix 1—figure 4:** Weekly incidence of HAIs at each site (●), with (a) proportion of all
275 inpatients SARS-CoV-2 +ve and (b) local community incidence of SARS-CoV-2 +ve tests also
276 plotted on the y-axis (purple line). Horizontal bars show the duration of study phases
277 (orange: baseline; blue: longer turnaround; green: rapid).
278
279 (a)
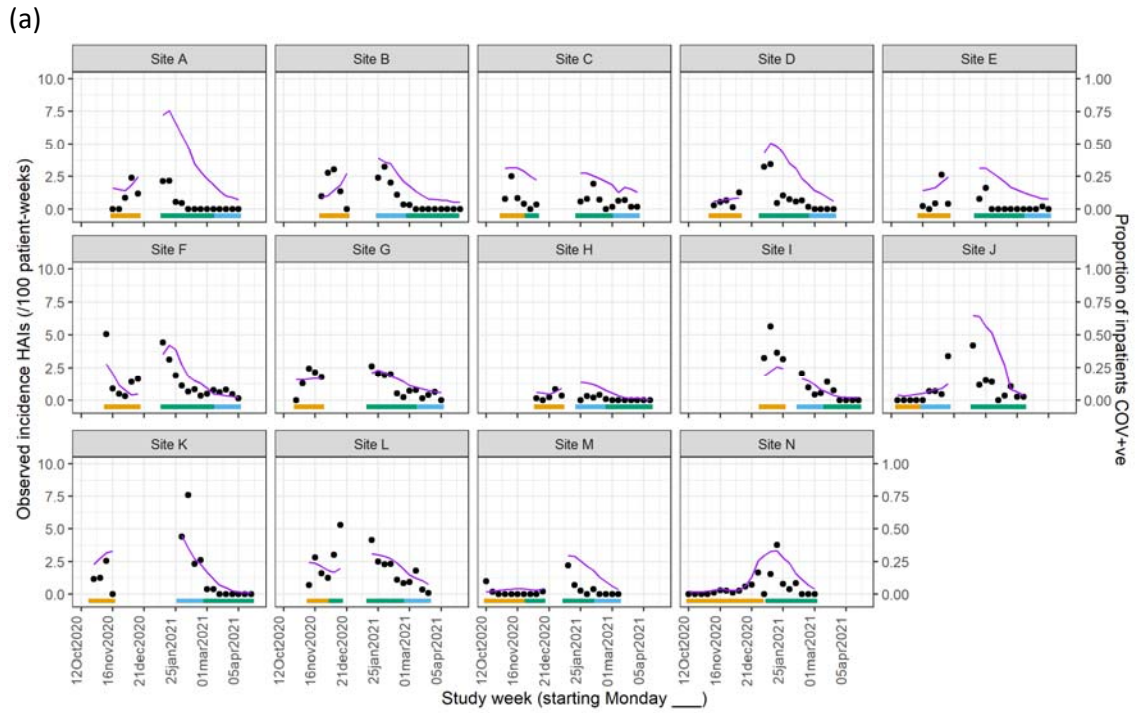
280
281 (b)

282
283

284 **Appendix 1—figure 5:** Adustment variables for analysis of weekly incidence of IPC-defined HAIs
285 per 100 inpatients, as described in Table 3. Incidence rate ratios are displayed relative to the median
286 for (a) calendar time expressed as study week from 12th October 2020, (b) proportion of inpatients
287 with positive SARS-CoV-2 test and (c) local community incidence of SARS-CoV-2 (government
288 surveillance data weighted by total set of postcodes for patients at each site). The spline curves
289 shown are estimated simultaneously within the final analysis model, and show how these factors
290 have independent contributions to the prediction of the incidence rate for HAIs. The associations for
291 each covariable indicated by model parameter point estimates are shown as solid lines, with 95%CIs
292 shown as dashed lines. Adjustment for (c) was not pre-specified in the SAP, but adding this variable
293 to the model was associated with a statistically significant improvement in fit (P =0.01). The
294 proportion of community-sampled cases in the region that were found to be the Alpha variant on
295 sequencing was also considered, but adding this as a linear predictor did not lead to a statistically
296 significant improvement in model fit (P=0.78).
297
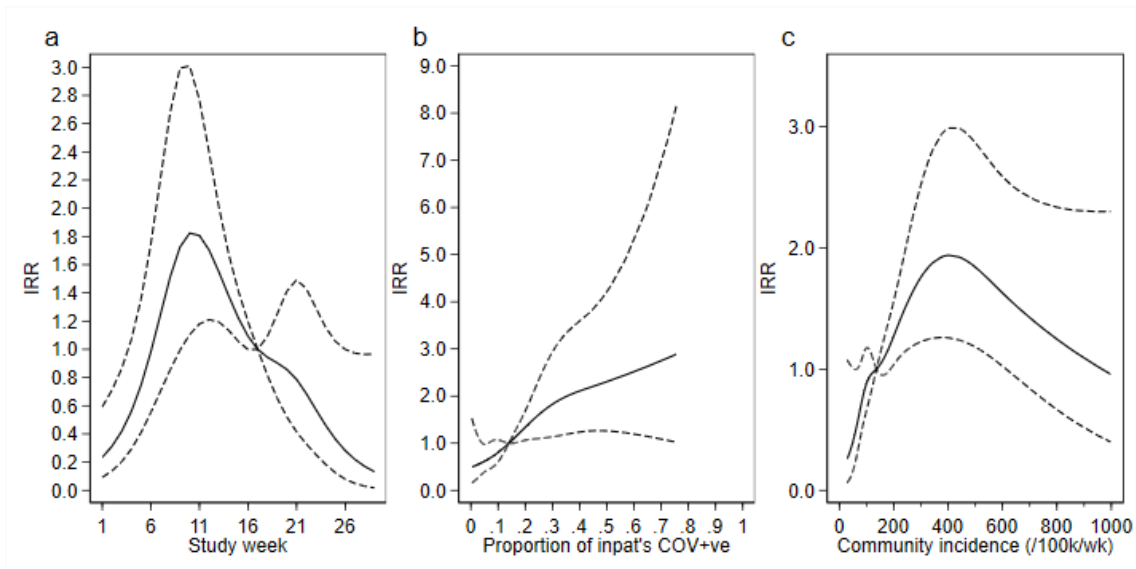
298

299

300　**Appendix 1—figure 6:** Adustment variables for analysis of weekly incidence of IPC-defined
301　outbreak events per 100 inpatients, as described in Table 3. Incidence rate ratios are displayed
302　relative to the median for (a) calendar time expressed as study week from 12th October 2020, (b)
303　proportion of inpatients with positive SARS-CoV-2 test and (c) local community incidence of SARS-
304　CoV-2 (government surveillance data weighted by total set of postcodes for patients at each site).
305　The spline curves shown are estimated simultaneously within the final analysis model, and show
306　how these factors have independent contributions to the prediction of the incidence rate for
307　outbreaks. The associations for each covariable indicated by model parameter point estimates are
308　shown as solid lines, with 95%CIs shown as dashed lines. Adjustment for (c) was not pre-specified in
309　the SAP, but adding this variable to the model was associated with a near-statistically significant
310　improvement in fit (*P*=0.05) and was included for consistency with the analysis of individual HAIs.
311　The proportion of community-sampled cases in the region that were found to be the Alpha variant
312　on sequencing was also considered, but adding this as a linear predictor did not lead to a statistically
313　significant improvement in model fit (*P*=0.80).
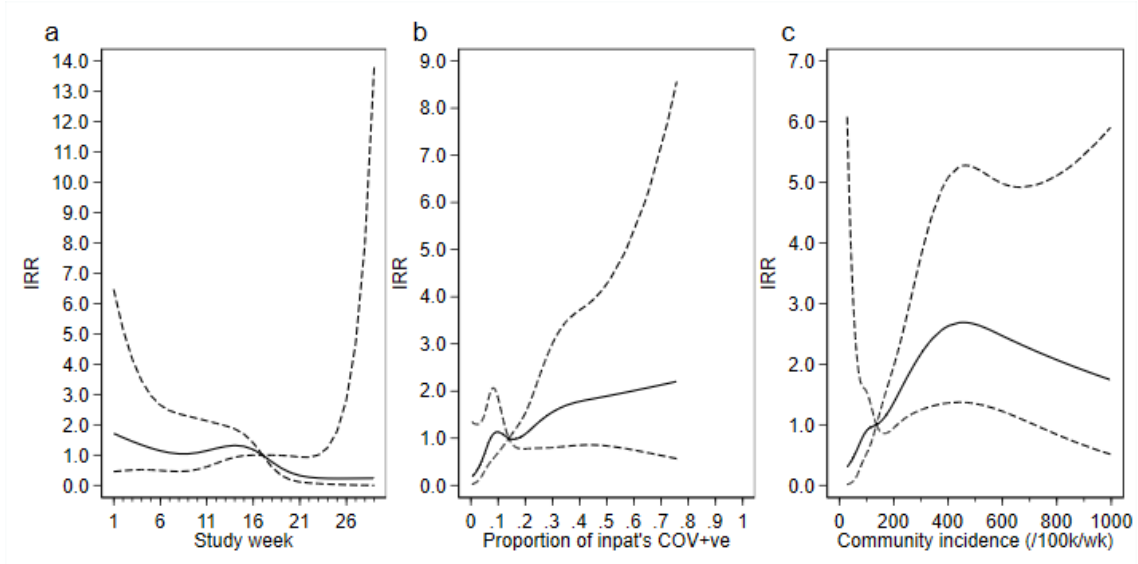
314
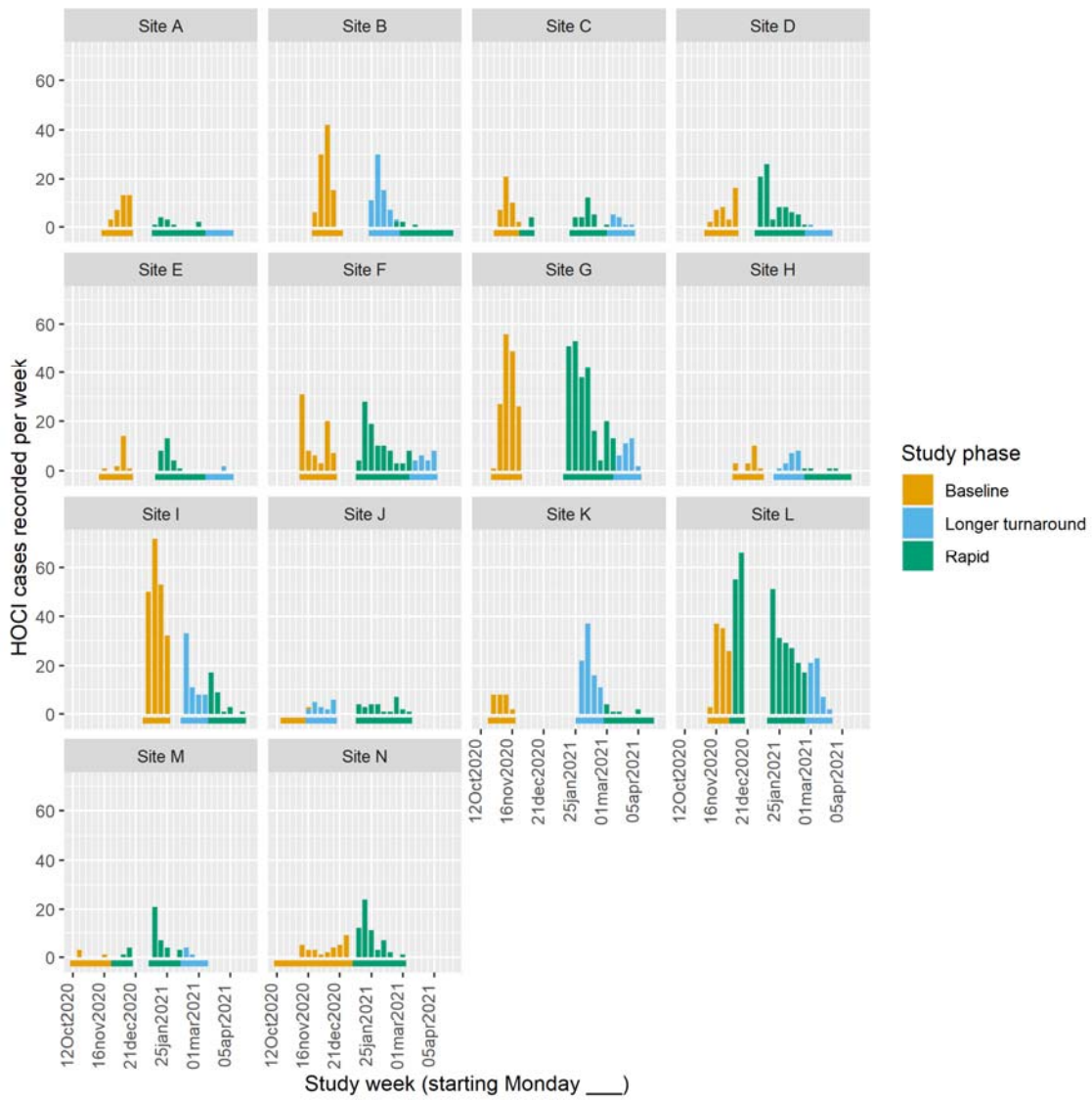315
316

317 **Appendix 1—figure 7:** Weekly counts of enrolled HOCI cases by date of positive test return
318 for each site, color-coded by intervention phases. Horizontal bars show the duration of
319 study phases.
320

321
322

323   **Appendix 1—table 1:** Per outbreak event outcomes by study intervention phase

	Study phase			
	Baseline	Longer-turnaround	Rapid	**Total**
IPC-defined outbreak events				
n outbreak events	129	33	114	276
n/N (%) of HOCI cases part of outbreak event	682/850 (80.2)	314/373 (84.2)	763/947 (80.6)	1759/2170 (81.1)
Number of HOCIs per outbreak event, median (IQR, range)	5.0 (3-8, 2-43)	5.0 (3-9, 2-24)	4.0 (2-7, 2-31)	4.0 (2-8, 2-43)
Prop. HCWs on sick leave due to COVID-19, median (IQR, range) [*n*]	0.13 (0.00-0.35, 0.00-0.50) [13]	0.05 (0.00-0.18, 0.00-0.30) [7]	0.20 (0.08-0.33, 0.00-0.89) [14]	0.13 (0.00-0.31, 0.00-0.89) [34]
IPC+sequencing-defined outbreak events				
n outbreak events	—	41	135	176
n/N (%) of HOCI cases part of outbreak event	—	292/373 (78.3)	705/947 (74.4)	997/1320 (75.5)
Number of HOCIs per outbreak event, median (IQR, range)	—	5.0 (2-8, 2-23)	3.0 (2-6, 2-29)	3.0 (2-7, 2-29)
For first HOCI in outbreak:				
SRT changed IPC practice, *n/N* (%*, 95% CI)	—	4/41 (10.4, 0-21.0)	19/133 (14.9, 6.6-23.2)	23/174 (13.2)
SRT changed IPC practice for ward, *n/N* (%)	—	2/35 (5.7)	6/82 (7.3)	8/117 (6.8)
SRT used in IPC decisions beyond ward, *n/N* (%)	—	2/35 (5.7)	10/82 (12.2)	12/117 (10.3)
IPC team reported SRT to be useful, *n/N* (%)				
Yes	—	20/35 (57.1)	51/82 (62.2)	71/117 (60.7)
No	—	9/35 (25.7)	15/82 (18.3)	24/117 (20.5)
Unsure	—	6/35 (17.1)	16/82 (19.5)	22/117 (18.8)
SRT would ideally have changed IPC practice, *n/N* (%*, 95% CI)	—	4/41 (9.8)	19/133 (14.3)	23/174 (13.2)

324   HCW, healthcare worker.

325   *Estimated marginal value from mixed effects model, not raw %, evaluated on intention-to-
326   treat basis with lack of SRT report classified as 'no'.

327   Odds ratio of SRT changed IPC practice for 'rapid *vs* longer-turnaround' phases 1.54 (95% CI 0.37-
328   6.44; *P*=0.52).

329 **Appendix 1—table 2:** Descriptive summary of impact of sequencing on IPC actions implemented during study intervention phases, as recorded
330 on pre-specified study reporting forms

	Study phase					
	Longer-turnaround sequencing			Rapid turnaround sequencing		
N HOCI cases	373			947		
Review of IPC actions already taken	*Support*	*Refute*	*Missing*	*Support*	*Refute*	*Missing*
SRT results support or refute IPC actions already taken*	200/213 (93.9)	7/213 (3.3)	2	389/428 (90.9)	9/428 (2.1)	7
Changes to IPC practice following SRT	*To enhanced*	*To routine*	*No change*	*To enhanced*	*To routine*	*No change*
Change to cleaning protocols on ward	2/185 (1.1)	0/185 (0.0)	183/185 (98.9)	7/341 (2.1)	0/341 (0.0)	334/341 (97.9)
	To greater	*To fewer*	*No change*	*To greater*	*To fewer*	*No change*
Change to visitor restrictions	1/186 (0.5)	0/186 (0.0)	185/186 (99.5)	1/340 (0.3)	0/340 (0.0)	339/340 (99.7)
	To 'cohort nursing'	*To 'other restrictions'*	*No change*	*To 'cohort nursing'*	*To 'other restrictions'*	*No change*
Change to staffing restrictions on ward	0/186 (0.0)	1/186 (0.5)	185/186 (99.5)	0/336 (0.0)	1/336 (0.3)	335/336 (99.7)
	Increase	*Decrease*	*No change*	*Increase*	*Decrease*	*No change*
Hand hygiene audit frequency	1/185 (0.5)	0/185 (0.0)	184/185 (99.5)	10/335 (3.0)	0/335 (0.0)	325/335 (97.0)
IPC staff visits to ward	1/185 (0.5)	0/185 (0.0)	184/185 (99.5)	14/335 (4.2)	0/335 (0.0)	321/335 (95.8)
Assessment of alcogel stocks	0/185 (0.0)	0/185 (0.0)	185/185 (100.0)	2/335 (0.6)	0/335 (0.0)	333/335 (99.4)
Assessment of soap stocks	0/185 (0.0)	0/185 (0.0)	185/185 (100.0)	2/334 (0.6)	0/334 (0.0)	332/334 (99.4)
Assessment of aseptic non-touch technique compliance	0/185 (0.0)	0/185 (0.0)	185/185 (100.0)	8/335 (2.4)	0/335 (0.0)	327/335 (97.6)
Assessment of PPE supply	1/185 (0.5)	0/185 (0.0)	184/185 (99.5)	9/336 (2.7)	0/336 (0.0)	327/336 (97.3)
Availability of doffing and donning buddy	0/185 (0.0)	0/185 (0.0)	185/185 (100.0)	1/333 (0.3)	0/333 (0.0)	332/333 (99.7)
IPC signage assessment	1/185 (0.5)	0/185 (0.0)	184/185 (99.5)	12/336 (3.6)	0/336 (0.0)	324/336 (96.4)
IPC signage implementation	1/185 (0.5)	0/185 (0.0)	184/185 (99.5)	11/336 (3.3)	0/336 (0.0)	325/336 (96.7)
Training on IPC procedures	0/185 (0.0)	0/185 (0.0)	185/185 (100.0)	8/336 (2.4)	0/336 (0.0)	328/336 (97.6)

331 Data shown as *n* or *n/N* (%). Overall impact on IPC actions per HOCI case is given in Appendix 1—table 1. *Sites could select 'yes' or 'no' for both
332 'support' and 'refute', as these were entered as separate data items.

Appendix 1—table 3: Descriptive summary of impact of sequencing on IPC actions implemented during study intervention phases, only including the first HOCI in each IPC+sequencing-defined outbreak event, as recorded on pre-specified study reporting forms	**Study phase**					
	Longer-turnaround sequencing			Rapid turnaround sequencing		
N HOCI cases	41			135		
Review of IPC actions already taken	*Support*	*Refute*	*Missing*	*Support*	*Refute*	*Missing*
SRT results support or refute IPC actions already taken*	30/35 (85.7)	3/35 (8.6)	0	71/82 (86.6)	5/82 (6.1)	2
Changes to IPC practice following SRT	*To enhanced*	*To routine*	*No change*	*To enhanced*	*To routine*	*No change*
Change to cleaning protocols on ward	1/34 (2.9)	0/34 (0.0)	33/34 (97.1)	1/70 (1.4)	0/70 (0.0)	69/70 (98.6)
	To greater	*To fewer*	*No change*	*To greater*	*To fewer*	*No change*
Change to visitor restrictions	0/34 (0.0)	0/34 (0.0)	34/34 (100.0)	1/70 (1.4)	0/70 (0.0)	69/70 (98.6)
	To 'cohort nursing'	*To 'other restrictions'*	*No change*	*To 'cohort nursing'*	*To 'other restrictions'*	*No change*
Change to staffing restrictions on ward	0/34 (0.0)	1/34 (2.9)	33/34 (97.1)	0/70 (0.0)	1/70 (1.4)	69/70 (98.6)
	Increase	*Decrease*	*No change*	*Increase*	*Decrease*	*No change*
Hand hygiene audit frequency	0/34 (0.0)	0/34 (0.0)	34/34 (100.0)	3/70 (4.3)	0/70 (0.0)	67/70 (95.7)
IPC staff visits to ward	0/34 (0.0)	0/34 (0.0)	34/34 (100.0)	5/70 (7.1)	0/70 (0.0)	65/70 (92.9)
Assessment of alcogel stocks	0/34 (0.0)	0/34 (0.0)	34/34 (100.0)	2/70 (2.9)	0/70 (0.0)	68/70 (97.1)
Assessment of soap stocks	0/34 (0.0)	0/34 (0.0)	34/34 (100.0)	2/70 (2.9)	0/70 (0.0)	68/70 (97.1)
Assessment of aseptic non-touch technique compliance	0/34 (0.0)	0/34 (0.0)	34/34 (100.0)	3/70 (4.3)	0/70 (0.0)	67/70 (95.7)
Assessment of PPE supply	0/34 (0.0)	0/34 (0.0)	34/34 (100.0)	3/70 (4.3)	0/70 (0.0)	67/70 (95.7)
Availability of doffing and donning buddy	0/34 (0.0)	0/34 (0.0)	34/34 (100.0)	1/70 (1.4)	0/70 (0.0)	69/70 (98.6)
IPC signage assessment	0/34 (0.0)	0/34 (0.0)	34/34 (100.0)	4/70 (5.7)	0/70 (0.0)	66/70 (94.3)

IPC signage implementation	0/34 (0.0)	0/34 (0.0)	34/34 (100.0)	4/70 (5.7)	0/70 (0.0)	66/70 (94.3)
Training on IPC procedures	0/34 (0.0)	0/34 (0.0)	34/34 (100.0)	4/70 (5.7)	0/70 (0.0)	66/70 (94.3)

333 Data shown as *n* or *n/N* (%).Overall impact on IPC actions per HOCI case is given in Table 2. *Sites could select 'yes' or 'no' for both 'support' and
334 'refute', as these were entered as separate data items.

335 **Appendix 1—table 4**: Per-sample costs of SARS-CoV-2 genome rapid and longer turnaround sequencing

336

Laboratories	Lab 1	Lab 2	Lab 3	Lab 4	Lab 5	Lab 6	Lab 7	Lab 8	Lab 9	Lab 10	
Rapid turnaround sequencing											
Sequencing platform	Illumina MiSeq	Nanopore MinION/ GridiON	Nanopore GridiON	Nanopore GridiON	Nanopore GridiON	Nanopore MinION/ GridiON	Nanopore GridiON	Nanopore GridiON	Illumina MiSeq	Illumina MiSeq	Mean
Batch size	**24**	**24**	**24**	**96**	**24**	**24**	**24**	**24**	**96**	**96**	
Equipment	£45.11	£26.06	£19.34	£4.38	£12.38	£24.66	£11.99	£11.26	£5.91	£6.13	£16.72
Consumables	£69.14	£54.56	£87.07	£31.11	£79.06	£28.84	£62.09	£46.02	£14.37	£39.63	£51.19
Staff	£6.11	£20.25	£24.66	£7.93	£11.16	£5.66	£12.16	£8.45	£2.20	£3.45	£10.20
Total per-sample cost	**£120.36**	**£100.87**	**£131.07**	**£43.43**	**£102.60**	**£59.17**	**£86.23**	**£65.73**	**£22.48**	**£49.21**	**£78.11**
Total cost (including overheads calculated at 20%)	**£144.43**	**£121.04**	**£157.28**	**£52.11**	**£123.12**	**£71.01**	**£103.48**	**£78.88**	**£26.97**	**£59.05**	**£93.74**
Longer-turnaround sequencing											
Sequencing platform	Illumina MiSeq	Nanopore MinION/ GridiON	Nanopore GridiON	Nanopore GridiON	Nanopore GridiON	Nanopore MinION/ GridiON	Nanopore GridiON	Nanopore GridiON	Nanopore MinION	Illumina MiSeq	Mean
Batch size	**24**	**24**	**24**	**96**	**24**	**24**	**24**	**96**	**24**	**96**	
Equipment	£40.60	£22.15	£17.02	£3.94	£11.88	£22.44	£11.27	£2.81	£2.54	£5.76	£14.04
Consumables	£61.53	£48.56	£77.49	£27.69	£70.36	£25.67	£55.26	£11.51	£33.75	£35.27	£44.71
Staff	£4.95	£15.19	£16.52	£2.78	£2.23	£4.53	£12.04	£8.45	£11.85	£3.32	£8.19
Total per-sample cost	**£107.08**	**£85.89**	**£111.03**	**£34.41**	**£84.48**	**£52.65**	**£78.56**	**£22.77**	**£48.13**	**£44.34**	**£66.94**
Total cost (including overheads calculated at 20%)	**£128.50**	**£103.07**	**£133.24**	**£41.29**	**£101.38**	**£63.18**	**£94.28**	**£27.33**	**£57.76**	**£53.21**	**£80.32**

337 **Appendix 1—table 5:** Incidence outcomes by study intervention phase with unadjusted
338 incidence rate ratio (IRR)

	Study phase			IRR[†] (95% CI, *P*)	
	Baseline	Longer-turnaround	Rapid	Longer-turnaround vs baseline	Rapid vs baseline
All sites					
n HOCI cases	850	373	947	—	—
n IPC-defined HAIs	488	207	576	—	—
Weekly inc. of IPC-defined HAIs per 100 inpatients, mean (median, IQR, range)* [primary outcome]	1.0 (0.5, 0.0-1.4, 0.0-5.6)	0.7 (0.3, 0.0-0.7, 0.0-7.6)‡	0.6 (0.3, 0.0-0.8, 0.0-5.3)‡	0.49 (0.21-1.19; 0.12)	0.47 (0.21-1.08; 0.07)
n IPC-defined outbreak events	129	33	114	—	—
Weekly inc. of IPC-defined outbreak events per 100 inpatients, mean (median, IQR, range)*	0.3 (0.1, 0.0-0.4, 0.0-2.3)	0.1 (0.0, 0.0-0.1, 0.0-0.9)‡	0.1 (0.0, 0.0-0.0, 0.0-0.9)‡	0.25 (0.10-0.66; 0.005)	0.23 (0.10-0.54; 0.001)

339
340 HAI, hospital-acquired infection; HOCI, hospital onset COVID-19 infection; IPC, infection prevention and
341 control; IQR, interquartile range; seq., sequencing.
342 IPC-defined HAIs are considered to be 'probable' or 'definite' HAIs. *Descriptive data over all week-long
343 periods at all study sites. †Without adjustment for proportion of current inpatients at site that are COVID-19
344 cases, community incidence rate and calendar time. ‡Not including data from the first week of each
345 intervention period, or in the week following any break in the intervention period.