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Evaluating the cost implications of integrating SARS-CoV-2 genome sequencing for infection prevention and control investigation of nosocomial transmission within hospitals

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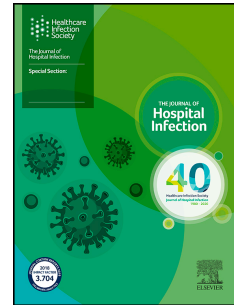
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2 **infection prevention and control investigation of nosocomial transmission within**  
3 **hospitals**

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44 **Abstract**

45 **Objectives:** The COG-UK hospital-onset COVID-19 infection (HOI) trial evaluated the  
46 impact of SARS-CoV-2 whole genome sequencing (WGS) on acute infection, prevention, and  
47 control (IPC) investigation of nosocomial transmission within hospitals. We estimated the cost  
48 implications of using the information from the sequencing reporting tool (SRT), used to  
49 determine likelihood of nosocomial infection in IPC practice.

50 **Methods:** We conducted a micro-costing approach for SARS-CoV-2 WGS. Data on IPC  
51 management resource use and costs were collected from interviews with IPC teams from 14  
52 participating sites and used to assign cost estimates for IPC activities as collected in the trial.  
53 Activities included IPC specific actions following a suspicion of healthcare-associated infection  
54 (HAI) or outbreak, as well as changes to practice following the return of data via SRT.

55 **Results:** The mean per sample costs of SARS-CoV-2 sequencing was estimated at £77.10  
56 for rapid and £66.94 for longer turnaround phases. Over the 3 months interventional phases,  
57 the total management cost of IPC-defined HAIs and outbreak events across the sites was  
58 estimated at £225,070 and £416,447, respectively. Main cost drivers were bed-day lost due  
59 to wards closures because of outbreaks followed by outbreak meetings and bed-day lost due  
60 to cohorting contacts. Actioning SRTs, the cost of HAIs increased by £5,178 due to  
61 unidentified cases and the cost of outbreaks lowered by £11,246 as SRTs excluded hospital  
62 outbreaks.

63 **Conclusions:** Although, SARS-CoV-2 WGS adds to the total IPC management cost,  
64 additional information provided could balance out the additional cost, depending on identified  
65 design improvements and effective deployment.

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79 **Key words:** COVID-19; cost; healthcare-associated infection; infection prevention and  
80 control; micro-costing; SARS-CoV-2.

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## 83 Introduction

84 Over 5% of laboratory-confirmed cases of severe acute respiratory syndrome coronavirus 2  
85 (SARS-CoV-2) in the UK between March and August 2020 were healthcare-associated  
86 infections (HAIs) [1] with a risk that remained high [2] even during the second wave of the  
87 pandemic [3] that began in the autumn and peaked in mid-January 2021.

88 HAIs can affect both patients and healthcare workers to the detriment of patient care. It is  
89 important to detect and manage HAIs rapidly to prevent both complications and further  
90 transmission to patients and staff [4]. Costs of HAIs have important implications for hospitals,  
91 patients, and healthcare funders. The associated economic burden of HAIs is vast, resulting  
92 in longer hospital stays, higher treatment costs, intensive care unit stays and bed closures  
93 [5,6]. The containment and control of HAIs costs substantial funds and resources, especially  
94 when left undetected [7].

95 The implementation of targeted infection prevention and control (IPC) measures relies on IPC  
96 teams (IPCTs) using epidemiological data. Using time-to-symptom onset from admission for  
97 inpatients as a detection method potentially misses a considerable proportion of HAIs [8].  
98 Rapid identification and investigation of HAIs is important for suppression of SARS-CoV-2, but  
99 the infection source for hospital onset coronavirus (COVID-19) infections cannot always be  
100 readily identified based only on epidemiological data [9].

101 SARS-CoV-2 whole genome sequencing (WGS) can provide valuable information on virus  
102 biology, transmission, and population dynamics [10,11]. When linked with epidemiological  
103 data and on a short timescale (days), genomic data can support epidemiological investigations  
104 of potential HAIs, avoiding disruption to services. The additional benefits to the hospital and  
105 patients could be wards opening, unnecessary screenings avoided, reduced cleaning regimes  
106 and domestic staff cleaning input [12].

107 Several health economic studies have demonstrated that the use of WGS in bacterial  
108 pathogens to assist hospital IPCTs can lead to reduced transmission and infection rates and  
109 lower overall costs [13,14].

110 Between October 2020 and April 2021, a prospective non-randomised trial of SARS-CoV-2  
111 WGS at 14 acute UK hospital trusts was conducted to evaluate whether the use of rapid WGS  
112 of SARS-CoV-2, supported by a novel probabilistic reporting methodology, could inform IPC  
113 practice within NHS hospital settings (COG-UK hospital-onset COVID-19 infection (COG-UK  
114 HOI) study) [15]. A SARS-CoV-2 WGS data report was delivered to the NHS site's IPCTs,  
115 planned as either within 24–48 hours of the sample from the patient being confirmed as  
116 positive for SARS-CoV-2 (rapid phase) or within 5–10 days (longer turnaround phase) [16].  
117 The results are described in detail elsewhere [17].

118 The aim of this study is to determine the cost impact of integrating SARS-CoV-2 WGS as part  
119 of the IPC management plan.

120

## 121 Methods

122 Hospital-onset COVID-19 infection (HOI) cases were defined as inpatients with first positive  
123 SARS-CoV-2 test or symptom onset >48 hr after admission, without suspicion of COVID-19  
124 at admission. The novel sequence reporting tool (SRT) combines epidemiological and WGS  
125 data to provide a rapid assessment of the probability of HAI among HOI cases and to identify  
126 outbreak events, with a concise automated 1-page summary generated for circulation to  
127 IPCTs [9]. For this study, data were collected on the cost of IPCTs training to interpret the

128 SRT, cost of SARS-CoV-2 sequencing and cost of intensity of IPC management. Information  
129 on local IPC activities performed in response to HOCl cases obtained from the IPC teams at  
130 each site included: IPC team staff time (infection control resource use required to review each  
131 new case and ensure that the necessary precautions were in place), transmission-based  
132 precautions (including isolation), ward/bay/ bed closures, provision of protective clothing (e.g.,  
133 gloves, eye protection, protective apron/gown, FFP-3 masks, face shields), environmental  
134 decontamination (supplies used, and time required for cleaning). Additionally, patient level  
135 data during the trial's interventional phases were recorded using Case Report Forms (CRFs).  
136 To highlight the impact of SARS-CoV-2 WGS on IPC activities in COG-UK HOCl study, we  
137 estimated the costs combining both sources of resource use information.

138 Within the COG-UK HOCl study, SRTs were returned in 45.9% and 57.6% of HOCl cases,  
139 and within the target timeline in 4.6% in the rapid phase and 21.2% in the longer turnaround  
140 phase [17,18].

141 Therefore, costs were also estimated assuming that SRTs were actioned, and the IPC  
142 activities and resource use allocation was altered to reflect the output on the SRT. However,  
143 the number of SRTs returned during the target timeline was very small for both intervention  
144 phases, and therefore IPC teams could not change the management plan based on the SRT  
145 output. To this was also added a notable number of patients with missing data. Therefore, to  
146 eliminate these limitations, in this analysis approach we assumed that all SRTs (irrespective  
147 of the return time) were returned within the rapid phase target timeline.

148 Costs were estimated from the hospital perspective over the duration of the intervention  
149 phases (8 weeks of rapid phase and 4 weeks of longer turnaround phase).

150

### 151 **SARS -CoV-2 genome sequencing**

152 A data collection form developed [Supplementary Table A1] using the structure of a  
153 cancer/rare disease genome sequencing model [19] assisted with collection of resource use.  
154 Due to the pressure to which the laboratories were subjected because of the high volume of  
155 samples and limited human resources, we were unable to obtain precise testing pathway for  
156 genome sequencing in each laboratory. Most of the steps in the genome sequencing protocol  
157 in the cancer/rare disease genome sequencing model (using the HiSeq 4000 (Illumina Inc.,  
158 San Diego, CA)) were similar to those followed for SARS-CoV-2 WGS and therefore this  
159 approach was considered as appropriate to use in our study. However, the data collection  
160 form was adapted to the SARS-CoV-2 genome sequencing protocol with the help from an  
161 expert in genomic sequencing at one of the participating laboratories in the study. Also,  
162 laboratories had the freedom to modify the structure of the collection form if needed. Direct  
163 costs were estimated by micro-costing (a cost estimation method that involves direct  
164 enumeration of the cost of each resource required) to cost the SARS-CoV-2 WGS using  
165 information from laboratories using a bottom-up approach [20].

166 Data on resource use included the average staff time for each activity and salary data, use of  
167 equipment and consumables. Other infrastructure required to set up a sequencing laboratory  
168 such as general equipment, staff training and national laboratory accreditations were  
169 excluded, as they were already in place from the start of the pandemic. Pieces of equipment  
170 were already in place for the Covid-19 Genomics UK (COG-UK) Consortium [21] sequencing  
171 work and this study carries on with this. Many laboratories now do some sequencing and as  
172 such do have Illumina HiSeq or Oxford Nanopore (ONT, Oxford Nanopore Technologies  
173 Limited, UK) sequences in place. Fixed assets such as equipment are being worn down, and  
174 therefore we included equipment cost depreciation calculation. Equipment usage was

175 recorded by assigning a lifespan to each piece of equipment provided by the laboratory staff.  
176 The equipment cost was then weighted by the percentage of time that a piece of equipment  
177 was used for genome sequencing.

178 Resource quantities and costs were categorised into steps representing the logical flow of  
179 activities for sequencing. These steps included sample reception, purification of viral  
180 ribonucleic acid (RNA), library preparation, bioinformatics, reporting/delivery of report and data  
181 archiving. The resources used were linked to their associated unit costs. Unit cost data was  
182 extracted from laboratories purchasing records where possible or, if not available, from  
183 commercial laboratory equipment suppliers. Costs specified in other currencies were  
184 converted to British pounds (£) based on the average exchange rate at the time of data costing  
185 for analysis (\$1.41 to £1.00, as for 15 June 2021).

186 Information on staff salaries was extracted from national salary scales for NHS staff and from  
187 universities salary scales for the year 2021 for university staff. The midpoints of salary ranges  
188 were used. Costs were examined per batch and then divided by batch size to enable  
189 comparisons on a per-sample basis.

190 The costing methods described by Drummond were followed for the analysis [22].

191 Microbiology and IPC teams attended training sessions with an expert in genomic sequencing  
192 interpretation on how to use the SRT to report nosocomial SARS-CoV-2 transmissions to  
193 hospital IPCTs.

194 In addition to genome sequencing, our study made use of the full set of available hospital- and  
195 community-obtained SARS-CoV-2 viral sequences, with associated meta-data, to enable the  
196 generation of the SRT report for the participants in the intervention phases. We used SARS-  
197 CoV-2 viral sequences generated by the Covid-19 Genomics UK (COG-UK) Consortium  
198 (formed in March 2020 to deliver SARS-CoV-2 genomic surveillance and analysis to inform  
199 public health policy and to support the establishment of a national pathogen sequencing  
200 service). We also made use of the community sequences from Wellcome Sanger Institute (a  
201 centralised service for large-scale genome sequencing of samples from diagnostic services in  
202 parts of the UK that are not covered by the COG-UK regional sequencing labs) [23] as they  
203 were readily available.

204 We were unable to cost the Wellcome Sager Institute sequenced samples, therefore we  
205 applied the estimated mean per-sample cost of rapid and longer turnaround for each  
206 laboratory to the number of sequences requested (regardless of their origin, COG-UK, or  
207 Sanger Institute) for each site to facilitate identification of individuals as part of a SARS-COV-  
208 2 transmission network. This allowed us to estimate the cost necessary to set up a hypothetical  
209 surveillance dataset system necessary for our study, in other words how much it would have  
210 cost if this system did not exist, and we had to create it.

211

## 212 **Infection Prevention and Control management**

213 Sites followed current national guidelines, which developed and evolved throughout the  
214 course of the pandemic. Hospital policy and clinical processes were already adapted to  
215 prevent nosocomial transmission of SARS-CoV-2. IPC management plan following a  
216 suspicion of HOI considered in our analysis included IPC actions following a suspicion of  
217 HAIs/outbreaks, as well as changes (if any) to these actions following the return of the SRT  
218 (**Supplementary Figure A1**). A series of variations and changes to the local IPC guidance  
219 occurred throughout the study because of the increase in the number of cases. The description

220 of the IPC actions below reflects the closest possible image of the undertaken activities during  
221 the study time.

### 222 ***Management of (suspected) HOCl***

223 If capacity allowed, COVID-19 positive cases were moved to a COVID-19 ward; contacts were  
224 moved to side rooms (if available), or if there were many patients on the ward, the ward was  
225 closed and contacts cohorted. The IPC nurses performed contact tracing of contacts of a  
226 positive case stayed/ cohorted in their respective bays/ wards. Previous contacts to the  
227 positive case were called to the wards in which they were currently, and a plan put in place for  
228 isolation. Where there was a suspicion of transmission within a ward an incident management  
229 team (IMT) was convened. At the height of the pandemic at some sites these meetings were,  
230 at most, 15 minutes with as many relevant people as possible. If a ward was to be closed, IPC  
231 nurses contacted the ward daily until there were 14 days since the last positive case. Where  
232 possible any discharge plans were prioritised.

233 The additional measures of isolation precautions included transmission-based precautions  
234 including provision of protective clothing. Type FFP2 surgical mask, single use plastic apron,  
235 and single use gloves were used as standard personal protective equipment (PPE) when  
236 caring for patients as per National infection prevention and control manual [24], with enhanced  
237 PPE when aerosol-generating procedures (AGPS) were carried out (e.g., surgical masks were  
238 worn with FFP3 respirators). In addition to this for a period during the January 2021 peak in  
239 incidence, FFP3 was advised for AGPS in the low-risk pathway also.

240 Enhanced cleaning already in place from the beginning of pandemic was continued.

### 241 ***Outbreak management plan***

242 When an outbreak was suspected daily outbreak meetings were held (if capacity permitted).

243 If a ward was closed, patients were notified, and were then screened. The frequency with  
244 which the screenings were performed differed at each site: every day, twice a week, every 4  
245 days (once a week) and, in a high risk setting every 48 hours (three times a week). Since  
246 most sites reported a frequency of three times a week (for a period of two weeks or until  
247 discharge or transfer to other hospital), this was used as the best estimate for the purpose of  
248 the calculation. Frequency of follow-up Reverse Transcription-Polymerase Chain Reaction  
249 (RT-PCR) screening would be decided by the IMT. Staff were encouraged to take part in  
250 lateral flow device (LFD) screening or weekly RT-PCR screening as indicated by national  
251 guidance for their area. All outbreak areas required enhanced cleaning (decontamination,  
252 terminal decontamination) including curtain change prior to re-opening.

253

### 254 **Sensitivity analysis**

255 Sensitivity analysis was performed to assess how changes in key variables would affect costs.  
256 Parameters that were varied included the cost of per-sample sequencing, SRT report training  
257 and frequency of screenings.

258

## 259 **Results**

### 260 **Cost of SARS-CoV-2 genome sequencing**



261 There were 11 laboratories performing sequencing for the COG-UK HOCl study. One site did  
262 not implement the longer turnaround phase because they considered it a reduction in their  
263 standard practice. The total cost of performing SARS-CoV-2 WGS in intervention phases for  
264 all sites included in the study was £86,546. The analysis of the SARS-CoV-2 WGS showed  
265 that the mean per sample costs were on average higher for rapid (£77.10) versus longer  
266 turnaround (£66.94) sequencing (**Table I**). The cost of sequencing was influenced by the  
267 different platforms used by laboratories, the staff who performed the sequencing and the  
268 consumables used. Consumables were the highest cost driver of the sequencing process,  
269 accounting for 66% in rapid and 67% in longer turnaround phases.

270 There were three training sessions (via Teams) offered by an expert in genomic sequencing  
271 interpretation on how to use/read/interpret the SRT output. Invitations to all three sessions  
272 were sent out to all sites so that as many staff as possible could participate. Some of the sites  
273 also ran self-directed genomics and bioinformatics training sessions. One site participated in  
274 the development of the SRT and therefore no further training needed. Total cost of  
275 implementation of SRT training was £2,898 (range £10 to £542). The total cost at each site  
276 depended on the number/qualification of staff and number of attendances (**Supplementary**  
277 **Table A2**).

278 There were meetings organised to discuss SRT outputs once they were returned to decide if  
279 further changes to IPC management plans were needed. Various professionals attended the  
280 meetings and the frequency and duration varied between sites. The total cost of these  
281 meetings was £8,840 (range £115 to £1,752). Subsequent meetings (121 occasions, total cost  
282 £2,040, range £113 to £715) were provided (phone/online) by a COG-UK HOCl Expert  
283 Sequence Group (expert sequence interpretation team, subset of the Study Team) when  
284 needed to discuss SRTs' results and to provide guidance on best practice (**Supplementary**  
285 **Table A2**). Thus, the total cost of implementation of SRT across all sites in COG-UK HOCl  
286 study was estimated at £100,324.

287 A total of 11,475 SARS-CoV-2 genome sequences were obtained for the genomic  
288 comparison on the SRTs. The total cost of SARS-CoV-2 genome sequencing data requested  
289 for matching with the SRT outputs representing here the (hypothetical) cost necessary to set  
290 up a surveillance dataset system necessary for our study was estimated at £712,007.

291

## 292 **Cost of Infection Prevention and Control management**

293 A total of 1,320 HOCl cases in the interventional phases were recorded for the COG-UK HOCl  
294 study. IPC nurses spent a total of 1,298 hours to perform contact tracing, resulting in a total  
295 cost of £52,549. RT-PCR screening following suspicion of a HOCl was performed in 2,100  
296 contacts resulting in a total cost of £31,500. IPC management resource use is presented in  
297 **Table II**.

298 Over the 3 months interventional phases, the total IPC management cost of IPC-defined HAI  
299 (n=783 [17]) and IPC-defined outbreak events (n=147 [17]) across the sites was estimated at  
300 £225,070 and £416,447, respectively (**Table III**). The main cost drivers were mainly bed-day  
301 lost due to wards closure because of outbreaks (£205,923), followed by outbreak meetings  
302 (£161,988) and bed-day lost due to cohorting contacts (£144,935) (**Supplementary Figure**  
303 **A2**).

304 Assuming that returned SRTs were actioned, this had an impact on costs as returned SRTs  
305 showed that there were 5.5% (n=70 [17]) linkages identified by the SRT but not suspected at  
306 initial IPC investigation that increased HAI management cost by £5,178. Also, returned SRTs

307 excluded 6.4% (n=41 [17]) of IPC-identified hospital outbreaks which led to a reduction in the  
308 outbreaks management cost by £11,246. (Table III).

309 The increased HAIs management cost was driven by the increased bed-day lost due to  
310 cohorting contacts and enhanced cleaning in the wards of cohorted contacts, and the  
311 reduction of outbreaks management cost was due to reduction in ward closures and  
312 unnecessary outbreak meetings.

313

### 314 **Sensitivity analysis**

315 The results of the sensitivity analysis (Supplementary Table A3) showed that changes in per-  
316 sample cost of sequencing had a notable impact on the base case costs. If laboratories used  
317 the platforms and protocols that generated the lowest per-sample sequencing costs in both  
318 interventional phases, this would decrease the total sequencing cost to £49,233, representing  
319 -57% change. If laboratories used the platforms and protocols that generated the highest per-  
320 sample sequencing costs in both interventional phases, this would increase the total  
321 sequencing cost to £164,418, representing 90% change.

322 If by implementing SRT in the IPC management plan, there would be no need for additional  
323 genomics/ bioinformatics training, this would generate a reduction of 55% in the training cost  
324 (£1,606.21 vs. £2,898.26). As sites reported different frequency of patients screening, different  
325 approaches were tested in the sensitivity analysis. Increasing patients screening to daily in  
326 the COG-UK HOCl study would increase the total cost to £7,905 (vs. £3,563 base case - 3  
327 times a week), while screening patients twice per week or once a week would decrease the  
328 total cost to £1,380 or £2,430, respectively.

329

### 330 **Ethics**

331 Clinical trial registration/ClinicalTrials.gov Identifier: NCT04405934.

332 Human subjects: Ethical approval for the study was granted by NHS HRA (REC 20/EE/0118).  
333 The need for consent from individual participants was waived because the study involved a  
334 hospital-level intervention that did not directly affect the clinical management of individual  
335 participants once diagnosed with a SARS-COV-2 infection.

336

### 337 **Discussion**

338 Our study estimated the cost implications of integrating SARS-CoV-2 WGS in IPC  
339 investigation of HAIs within hospitals. Although, the total cost is high, this would be scaled-  
340 down if we consider at per-hospital cost. The analysis was not conducted at per-hospital cost  
341 as, due to high workload and lack of human resources, some sites were not able to produce  
342 good quality data. Sequencing adds to the total IPC management cost, but our study was able  
343 to identify areas in which, if it were implemented, costs could be reduced especially by correct  
344 identification of transmission and outbreaks. Even conducted in extreme workload conditions,  
345 our study can reinforce the conclusion of another study about the need for additional detection  
346 methods added to epidemiological data which will conduct to avoiding missing HAIs [8]. The  
347 strength of costing WGS is that we obtained information on components included in  
348 sequencing cost estimates, so we were able to calculate the actual cost of genome  
349 sequencing per-sample, in contrast to the standard commercial price. The strength of the IPC  
350 management cost analysis was the use of multiple sites, so the findings could be potentially

351 considered representative for UK decision making in public health. Also, data on resource  
352 use collected from the interviews with IPCTs reflect the real-world IPCT activities in preventing  
353 HAls within hospitals.

354 However, there are several factors that could affect the costs. It was very difficult to isolate  
355 costings specifically when sequencing for the COG-UK HOCl project was ongoing alongside  
356 large-scale community sequencing with COG-UK. Some companies offered reduced costs to  
357 COG-UK members (e.g., cheaper flow cells with ONT). In general, laboratories processing a  
358 high volume of samples are likely to achieve a lower per-sample cost than laboratories  
359 processing fewer samples [25]. For our study, the time pressure during the peak period did  
360 not always allow for batching of samples and therefore, depending upon sample numbers and  
361 the required turnaround the pathway adopted was adapted. To ensure rapid turnaround,  
362 laboratories had to run libraries with small batches, which cost the same as a library with a  
363 large batch, increasing the per-sample cost. Some laboratories used both Oxford Nanopore  
364 Technologies and Illumina HiSeq sequencing platforms, during the peak of the last wave  
365 occurring within study.

366 Per-sample cost could also be underestimated as we did not include equipment acquisition  
367 and maintenance costs. In general, capital costs are usually seen as a one-off expenditure.  
368 The inclusion of fixed costs can confound an analysis with a short time horizon because they  
369 overstate the variable costs. When we consider cost estimation over longer time horizons, all  
370 costs are variable; however, with shorter time horizons and narrower perspectives, here  
371 hospital perspective, fixed costs are generally excluded from the evaluation because they  
372 create no opportunity cost [26,27]. Specific for our study, pieces of equipment were already in  
373 place for the COG-UK Consortium sequencing work. This study carries on with this.  
374 Therefore, we considered that the inclusion of fixed costs can confound an analysis with a  
375 short time horizon by overstating the costs that can be varied over time. Many laboratories  
376 now do some sequencing and as such do have Illumina or Nanopore sequences in place.  
377 Including purchase cost of equipment would have been more appropriate if we had information  
378 of the annual number of sequences performed at each site. Because our analyses considered  
379 only the number of sequences performed for this study, adding the capital cost would have  
380 significantly raised the cost per-sample. Fixed assets such as equipment are being worn down,  
381 and therefore we included equipment cost including depreciation calculation. However,  
382 registering institutional overheads at the cost of object level can be very difficult and we  
383 couldn't collect this data at each hospital. Including the cost of overheads in our estimates by  
384 assuming that these costs were equal to certain percentage of the total cost of testing implied  
385 that the overheads that are attributable to sequencing are proportional to the overall cost of  
386 sequencing. This assumption may not hold, given that consumables accounted for a large  
387 proportion of sequencing costs.

388 Surveillance is conducted to facilitate better control of diseases and lead to public health  
389 actions such as outbreak detection; it also facilitates the assessment of the magnitude,  
390 burden, and trends of disease. Setting up a sequencing platform can be a difficult and costly  
391 task. Our study showed that if we had to create a structure of wider reference set of hospital-  
392 and community-obtained SARS-CoV-2 viral sequences necessary for the  
393 genomic/epidemiological comparison on the SRTs, the associated cost (£712,007) would  
394 have been high. However, this value was estimated using the methods described, without  
395 having estimates of the cost of sequencing samples generated by the Wellcome Sanger  
396 Institute.

397 Given the interest in genomic sequencing, the data on potential benefits in the context of  
398 health care policy is timely. One difficulty is that various infection control measures are

399 complementary to one another, as well as being alternatives. The activities described as being  
400 part of the IPC management reflect the closest possible image of the undertaken activities  
401 however, there was a great deal of variation of practices based on operational challenges.  
402 The extremely high number of hospitalised patients during the peak in SARS-CoV-2 levels  
403 between December 2020 and January 2021 made IPCTs act quickly based on the local  
404 protocols already existing at each Trust. However, the capacity to respond on a case-by-case  
405 basis was breached in most sites by the volume of HOICs, and the limits of finite human and  
406 physical resource [28].

407 Specific data for cost analysis was not collected as part of the trial. Instead, we used the  
408 patient-level data from the COG-UK HOIC study [15] and built in the cost estimates using  
409 information provided by the IPCTs on resources used. Hospitals followed national guidance  
410 and local protocols. IPCTs stated that prevention and control measures were already in place  
411 since the beginning of the pandemic. Therefore, we do not know to what extent the return of  
412 the SRTs had influenced the costs. If the SRT was returned within 10-13 days (longer  
413 turnaround), the information provided regarding the patients' status may have been outdated  
414 so that the patients have benefited from the IPC specific protective measures and may have  
415 no longer been contact of or a positive case. However, IPCTs acknowledged that the  
416 maximum utility of SRT (especially with a rapid turnaround) was when there was a possibility  
417 of an error of judgment regarding the suspicion of HAI/outbreak, but especially in detecting  
418 patients contact of a positive case that was no longer in its vicinity and which could have  
419 spread the infection among other wards.

420 There are several ways through which the SRT implementation could lead to a reduction in  
421 costs. New efficient, optimised, and inexpensive strategies for WGS are under evaluation [29-  
422 31]. A more robust and user-friendly reporting tool could reduce the extent to which  
423 bioinformatic support and training sessions are needed as well as dedicated meetings  
424 convened to read/ interpret the output of the SRT. If SRTs become part of the IPC  
425 management plan, particularly if linked to electronic patient records and reporting, these  
426 meetings could be integrated into the IPC routine meetings, and the time staff dedicated to  
427 these meetings could be used to deliver other IPC activities.

428 We did not collect any measure of effectiveness as part of the cost impact analysis. The SRT  
429 gave feedback on cases that could form part of the same outbreak but did not identify direct  
430 transmission pairs or networks [17]. Therefore, a report tool that overcomes these limitations  
431 could have increased capacity to identify transmission routes and prevent the need for  
432 isolation measures and contact precautions through IPC activities interrupting the  
433 transmission (averted cases). Our study nonetheless provides valuable evidence regarding  
434 the implementation and utility of SRT for IPC management plan, and potentially it will have a  
435 greater positive impact on IPC practice outside of the burdens and resource constraints  
436 imposed by a pandemic. Assuming SARS-CoV-2 sequencing for public health purposes  
437 continues, the added cost of rapid sequencing for IPC management could potentially be offset  
438 by the benefits accrued, a cost-avoidant strategy for achieving a sustained decrease of SARS-  
439 CoV-2 transmission throughout hospitals. If the use of sequencing overcomes all the barriers  
440 (high cost of implementation, the lack of available protocols and guidelines, lack of  
441 infrastructure and capacity lack of bioinformatician availability and output interpretation)  
442 highlighted in the main study [17] and qualitative study [28], it can potentially justify the  
443 investment and running costs. As well as changes to IPC activities, there is the potential for  
444 routine genome sequencing to allow IPC practice and policies to be refined.

445 Even if the results of our study appear in a period in which they seem to be no longer relevant,  
446 they may nevertheless contribute to inform health systems in their effort to quickly discover

447 ways to minimise the impact of a potential epidemic or pandemic. The cost of WGS is likely to  
448 fall over time as more competitors enter the market for next-generation sequencing (NGS)  
449 platforms, NGS is applied to more pathology disciplines and medical laboratories achieve  
450 greater economies of scale vis a vis NGS. Although we took advantage of the measures  
451 implemented in the COVID-19 pandemic to measure the impact of sequencing, the study was  
452 intended to derive generalisable conclusions about the potential cost benefit of sequencing for  
453 IPC. We consider important that our study reflect a real picture of the costs associated with  
454 what will likely become a major part of diagnostics in the future as well as its utility for other  
455 pathologies and future pandemic preparedness. The utility of sequencing or lack of it will  
456 ultimately determine how often it is used in clinical settings; therefore, understanding its full  
457 costs and cost-effectiveness will be critical as payers make decisions about reimbursement.

458 Future research should target cost analyses in the context of IPC program evaluations,  
459 involving random assignment. Including cost analyses in the context of randomised trials could  
460 produce unbiased cost estimates. Also, the impact on effects and on health care workers as  
461 transmission vectors could be estimated.

462

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464 OS, Judith B, James B, and MP designed the COG-UK HOCl study; contributors of the  
465 Infection Prevention and Control (IPC), laboratories and costing department teams provided  
466 data; MP performed the analysis and drafted the manuscript; and all authors reviewed and  
467 agreed on the final version for submission.

468

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1 Table I Per-sample costs of SARS-CoV-2 genome rapid and longer turnaround sequencing

Laboratories	Lab 1	Lab 2	Lab 3	Lab 4	Lab 5	Lab 6	Lab 7	Lab 8	Lab 9	Lab 10	Lab 11	
<b>RAPID TURNAROUND (N=947)</b>												
Sequencing platform	Illumina MiSeq	Nanopore MinION/ GridiON	Nanopore GridiON	Nanopore GridiON	Nanopore GridiON	Nanopore MinION/ GridiON	Nanopore GridiON	Nanopore GridiON	Illumina MiSeq	Illumina MiSeq	Illumina MiSeq	Mean
Batch size	24	24	24	96	24	24	24	24	96	96	24	
Equipment	£45.11	£26.06	£19.34	£4.38	£12.38	£24.66	£11.99	£11.26	£5.91	£6.13	£14.04	£16.48
Consumables	£69.14	£54.56	£87.07	£31.11	£79.06	£28.84	£62.09	£46.02	£14.37	£39.63	£44.71	£50.60
Staff	£6.11	£20.25	£24.66	£7.93	£11.16	£5.66	£12.16	£8.45	£2.20	£3.45	£8.19	£10.02
<b>Total per-sample cost</b>	<b>£120.36</b>	<b>£100.87</b>	<b>£131.07</b>	<b>£43.43</b>	<b>£102.60</b>	<b>£59.17</b>	<b>£86.23</b>	<b>£65.73</b>	<b>£22.48</b>	<b>£49.21</b>	<b>£66.94</b>	<b>£77.10</b>
<b>LONGER TURNAROUND (N=373)</b>												
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	£33.81	£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
<b>Total per-sample cost</b>	<b>£107.08</b>	<b>£85.89</b>	<b>£111.03</b>	<b>£34.41</b>	<b>£84.48</b>	<b>£52.65</b>	<b>£78.56</b>	<b>£22.77</b>	<b>£48.19</b>	<b>£44.34</b>		<b>£66.94</b>

2

1 **Table II IPC management resource use and unit costs following HOCl identification for two analysis scenarios: 1) IPC activities in COG-**  
 2 **UK HOCl study, and 2) IPC activities assuming SRTs were actioned**

Resource use	Unit cost	IPC activities in COG-UK HOCl	IPC activities assuming SRT actioned	Difference
<b>HOCl management</b>				
IPCN contact tracing for each HOCl case (hours)	£41	1298	1298	0
Contacts screening (number of screens)	£15	2100	2100	0
<b>HAIs</b>				
Bed-days lost due to cohorting contacts*		202	206	4
One off patient screening (no of screens)	£15	87	89	2
One off staff screening (no of screens)	£15	47	49	2
Incident Management meeting (no of meetings)	£414	11	11	0
Change PPE audit (no of audits)	£39	32	33	1
Enhanced cleaning contacts cohort wards (no of wards)	£70	73	75	2
Report suspicion of HAI to Health Authorities (no of wards)	£14	73	75	2
<b>OUTBREAKS</b>				
Daily outbreak meeting (hours)	£502	323	315	-8
Bed-days lost due to wards closed*		287	279	-8
Enhanced patient screening 3x/week (no of screens)	£15	238	232	-5
Enhanced staff screening 3x/week (no of screens)	£15	140	137	-3
Twice daily decontamination on closed wards (no of wards)	£70	40	39	-1
Reopening wards after 14 days isolation-terminal cleaning (no of wards)	£95	40	39	-1

3 Resource use:

- 4
- 5
- 6
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- The process of contact tracing takes approx.1.5 hours of IPC nurse time per case.
  - Incident management team (IMT) meeting usually takes up to 1 hour.
  - All cases of suspected transmission were reported to health authorities via the outbreak reporting tool. This would take approx. 30 mins of lead IPC nurse time per ward.
  - Closed wards because of the HOCl case visited by IPC nurses taking 1 hour.

- 8
- 9
- 10
- 11
- Closed wards were contacted daily until there were 14 days since the last positive case; this process could take approx. 30 mins of IPC nurse time if there were no new cases, or approx. 1 hour if there were new cases.
  - Outbreak meeting (daily) would last from 30 mins to over 1 hour.
  - When wards were carrying out 4 daily screens, these were reviewed by the IPC nurses; this takes approx. 30 mins of IPC nurse time per ward.

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1 **Table III Total cost of IPC activities following HOCl identification for two analysis scenarios 1) IPC activities in COG-UK HOCl study,**  
 2 **and 2) IPC activities assuming SRTs were actioned**

Type of costs	IPC activities in COG-UK HOCl study	IPC activities assuming SRT actioned	Difference
<b>HAIs</b>			
Bed-days lost due to cohorting contacts*	£144,935	£148,131	£3,196
One off patient screening	£1,305	£1,342	£37
One off staff screening	£705	£728	£23
Incident Management meeting	£4,554	£4,691	£137
Change PPE audit	£1,250	£1,291	£41
Enhanced cleaning contacts cohort wards	£71,336	£73,055	£1,720
Report suspicion of HAI to Health Authorities	£986	£1,009	£24
	<b>£225,070</b>	<b>£230,248</b>	<b>£5,178</b>
<b>OUTBREAKS</b>			
Daily outbreak meeting	£161,988	£157,928	-£4,060
Bed-days lost due to wards closed*	£205,923	£199,949	-£5,974
Enhanced patient screening 3x/week	£3,563	£3,481	-£81
Enhanced staff screening 3x/week	£2,100	£2,054	-£46
Twice daily decontamination on closed wards	£39,088	£38,099	-£989
Reopening wards after 14 days isolation-terminal cleaning	£3,786	£3,690	-£96
	<b>£416,447</b>	<b>£405,201</b>	<b>-£11,246</b>

3 Cost estimations:

- 4 • \*Healthcare Resource Groups (HRGs) [32] was used to predict patients' length of stay and total hospital cost using the hospital tariff. Bed day costs (depending on the  
 5 type of ward patients were on) were retrieved retrospectively from the hospital's patient costing system for each HOCl case and ranged between £125.44 and £4,697.61  
 6 in rapid phase and £126.35 and £4,696.61 in longer turnaround phase. The number of individual bed-days lost because of room/ beds closed was counted by the  
 7 number of days patients were on the closed ward until 14-day period
- 8 • Average salary for IPC nurse per hour was estimated at £28
- 9 • Contact tracing cost was estimated at £41 per case
- 10 • Cost of IPCT (site lead and senior IPC nurse) routine activities (review IPC measures and checklist, visiting wards, and review cases) were estimated at £69 per hour.
- 11 • Isolation costs were calculated at £39 per day (**Supplementary Table A4 and Supplementary Table A5**)

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- Cost of IMT meetings was estimated at £414 for an hour. This would be usually attended by IPC nurses, IPCTs, ward nurses and medical staff, domestic supervisor, clinical services manager, estates representatives, health and safety and occasionally occupational health staff and the press office.
  - Cost of outbreak meeting was estimated at £502. This would be usually attended by Directors of Infection Prevention and Control (DIPC) and attended by IPCT / directorate staff / senior medical staff / microbiology/ virology staff.
  - Cleaning costs were estimated based on IPCT communication at £67 per clean (based on £9/hour cleaner and £2.40/Chlor-Clean per clean) for routine cleaning and £70 for enhanced cleaning. One curtain change was costed at £27 (included in terminal cleaning).
  - Cost of screening was estimated at £15 per RT-PCR test (IPCT communication)