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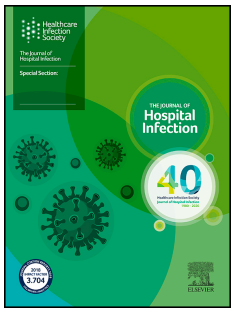

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Evaluating the cost implications of integrating SARS-CoV-2 genome sequencing for infection prevention and control investigation of nosocomial transmission within hospitals

Monica Panca[1], James Blackstone[1], Oliver Stirrup[2], Maria-Teresa Cutino-Moguel[3], Emma Thomson[4], Christine Peters[5], Luke B Snell[6], Gaia Nebbia[6], Alison Holmes[7], Anu Chawla[8], Nicholas Machin[9], Yusri Taha[10], Tabitha Mahungu[11], Tranprit Saluja[12], Thushan I de Silva[13], Kordo Saeed[14], Cassie Pope[15,22], Gee Yen Shin[16], Rachel Williams[17], Alistair Darby[18], Darren L Smith[19], Matthew Loose[20], Samuel C Robson[21], Kenneth Laing[22], David G Partridge[23], James R Price[7], Judith Breuer[24]

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Abstract

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

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

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

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

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

Introduction

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

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

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

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

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

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

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

Methods

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

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

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

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

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

SARS -CoV-2 genome sequencing

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

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

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

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

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

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

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

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

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

Infection Prevention and Control management

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

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

Management of (suspected) HOCI

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

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

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

Outbreak management plan

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

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

Sensitivity analysis

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

Results

Cost of SARS-CoV-2 genome sequencing

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

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

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

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

Cost of Infection Prevention and Control management

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

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

Assuming that returned SRTs were actioned, this had an impact on costs as returned SRTs showed that there were 5.5% (n=70 [**17**] linkages identified by the SRT but not suspected at 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 HOCI 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

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

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

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

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

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

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

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

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

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

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

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

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

Author contributions

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

Transparency declaration

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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	
RAPID TURNAROUND (N=947)												
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
Total per-sample cost	**£120.36**	**£100.87**	**£131.07**	**£43.43**	**£102.60**	**£59.17**	**£86.23**	**£65.73**	**£22.48**	**£49.21**	**£66.94**	**£77.10**
LONGER TURNAROUND (N=373)												
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
Total per-sample cost	**£107.08**	**£85.89**	**£111.03**	**£34.41**	**£84.48**	**£52.65**	**£78.56**	**£22.77**	**£48.19**	**£44.34**		**£66.94**

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

Resource use	Unit cost	IPC activities in COG-UK HOCI	IPC activities assuming SRT actioned	Difference
HOCI management				
IPCN contact tracing for each HOCI case (hours)	£41	1298	1298	0
Contacts screening (number of screens)	£15	2100	2100	0
HAIs				
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
OUTBREAKS				
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

Resource use:

- 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 HOCI case visited by IPC nurses taking 1 hour.

- 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.

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

Type of costs	IPC activities in COG-UK HOCI study	IPC activities assuming SRT actioned	Difference
HAIs			
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
	£225,070	£230,248	**£5,178**
OUTBREAKS			
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
	£416,447	£405,201	**-£11,246**

Cost estimations:

- *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 type of ward patients were on) were retrieved retrospectively from the hospital's patient costing system for each HOCI case and ranged between £125.44 and £4,697.61 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 number of days patients were on the closed ward until 14-day period
- Average salary for IPC nurse per hour was estimated at £28
- Contact tracing cost was estimated at £41 per case
- 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.
- Isolation costs were calculated at £39 per day (**Supplementary Table A4 and Supplementary Table A5**)

- 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)