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# Point-of-care testing by healthcare workers for detection of meticillin-resistant *Staphylococcus aureus*, *Clostridioides difficile*, and norovirus

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## SUMMARY

**Background:** The feasibility of introducing three separate Cepheid GeneXpert® assays was assessed: Xpert SA Nasal Complete, Xpert *C. difficile*, and Xpert Norovirus for point-of-care testing (POCT) on a ward in a district general hospital.

**Aim:** To establish a seven-day/24 h POCT service for meticillin-resistant *Staphylococcus aureus* (MRSA), *Clostridioides difficile*, and norovirus operated solely by healthcare workers (HCWs).

**Methods:** The Cepheid GeneXpert assays performance characteristics were assessed by comparing the assays to traditional central laboratory methods in terms of clinical turnaround times, hands-on time, number of process steps, time to result and diagnostic accuracy. HCW feedback was collected to consider the potential added value of applying this technology to improve patient flow and clinical care.

**Findings:** In total 1170 tests were carried out over the 16-month study period. The assays significantly reduced hands-on time, process steps, and time to result for identification of all three micro-organisms. Overall agreement with central laboratory testing was >98% for all three assays. Staff members fed back that POCT had a positive impact in terms of clinical utility.

**Conclusion:** Xpert SA Nasal Complete for MRSA detection, Xpert *C. difficile*, and Xpert Norovirus can be used as POCT solely by HCWs in a ward setting. Each assay was used throughout a seven-day/24 h period with potential positive impact on bed management and patient care.

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## Introduction

Microbiology and virology diagnostic services play a key role informing infection prevention and control (IPC) strategies, antimicrobial stewardship, and clinical management. It has been estimated that diagnostic services support 80% of all

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diagnoses in all models of care [1]. Timely, accurate patient sample results are essential in order for this to occur. Traditional microbiology, however, is often culture-based and reportable results can sometimes take days to deliver [2]. Additionally there is a sustainability challenge in microbiology services due to reduced staffing, increasing costs, greater demand for services and a rising ageing population [3,4]. Centralization of laboratory services in some instances has been introduced to address these issues. However, concern has been reported that sample turnaround times may increase, due to batch processing of clinical specimens and the distance from patient care to laboratories increasing (increased specimen transport time) [5]. It has been reported however that good transport links and extended shift working in some centres can overcome these issues [4]. As clinical microbiology has entered a new era of molecular diagnostics, rapid point-of-care tests (POCTs) could be an alternative option to resolving some of these challenges. POCTs have been introduced to detect a number of pathogens such as human immunodeficiency virus (HIV), respiratory syncytial virus (RSV), influenza, group A streptococcus, and dengue [6]. The rapid turnaround times of POCTs are potentially beneficial for making decisions in a variety of clinical situations including antimicrobial stewardship and IPC strategies. Indeed a systematic review published in 2013 identified that POCTs for RSV and norovirus had the greatest impact upon IPC measures; however, at that time, issues still remained regarding test sensitivity, staff training, and the high costs of the tests [7]. The objective of this current study was to determine the feasibility of establishing a healthcare worker (HCW)-controlled POCT service for the detection of meticillin-resistant *Staphylococcus aureus* (MRSA), *Clostridioides difficile*, and norovirus using multiple separate assays on a rural district general hospital: Dr Gray's Hospital Elgin is 65 miles (90 min travelling time) from the microbiology/virology laboratory facilities provided at Aberdeen Royal Infirmary. The performance of each POCT assay was compared to baseline routine microbiology testing data in terms of hands-on time, number of process steps, time to result and diagnostic accuracy. A staff questionnaire was also used to gauge opinion on perceived benefits and acceptability of polymerase chain reaction (PCR)-POCTs.

## Methods

### Study design and microbiology methods

POCTs were performed in Dr Gray's Hospital, Elgin, which is a rural district general hospital in Scotland with 210 staffed beds, and no microbiology or virology laboratory facilities on site. A Cepheid GeneXpert® Rapid Molecular Diagnostic Platform (Cepheid, Sunnyvale, CA, USA) (Supplementary Figure S1) was situated on the stroke ward which has eight beds. This HCW-operated POCT evaluation study ran prospectively from October 16<sup>th</sup>, 2014 to January 18<sup>th</sup>, 2016. In total, 26 non-laboratory staff were trained to use the GeneXpert (healthcare assistants and qualified nursing staff). All staff received training from the company. Patient specimens, including nasal swabs (Copan, Brescia, Italy) for MRSA screening and faeces for norovirus and/or *C. difficile* testing, were routinely taken as part of patient care on Dr Gray's hospital wards and were transported to the Stroke ward by healthcare support workers.

The following assays were used as per manufacturer's instructions: Xpert SA Nasal Complete for MRSA testing, Xpert *C. difficile* and Xpert Norovirus on the Cepheid GeneXpert rapid molecular diagnostic platform [8–10]. Xpert SA Nasal Complete detects sequences for the staphylococcal protein A (*spa*), the gene for meticillin/oxacillin resistance (*mecA*), and the staphylococcal cassette chromosome (SCC*mec*) inserted into the SA chromosomal attB site [8]. Xpert *C. difficile* detects sequences of the genes for toxin B (*tcdB*), binary toxin (*cdt*), and a point mutation associated with ribotype 027 [9]. A positive test for the toxin B target indicates that toxigenic *C. difficile* has been detected; the other two targets provide information about the presence of presumptive ribotype 027. Xpert Norovirus detects sequences for norovirus genotype I and genotype II [10]. The automated system consisted of an instrument, personal computer, and preloaded software for running tests and viewing the results. The system requires single-use disposable cartridges that hold the PCR reagents and host the PCR process. The assays contain a sample processing control (SPC) for adequate processing of the target bacteria and to monitor the presence of inhibitor(s) in the PCR reaction. Probe check control confirms dye stability, reagent rehydration, PCR tube filling in the cartridge and probe integrity. Results were reported as 'positive', 'negative', 'invalid', 'error', or 'no result'. 'Invalid' results could be due to failure of the SPC, PCR inhibition, or problems with the sample not being properly processed. 'Error' results indicated that there had been: a probe check control failure and the assay was aborted potentially due to improper filling of the reaction tube; reagent probe integrity problem; maximum pressure limits had been exceeded; or valve positioning error was detected. A 'no result' indicated that insufficient data had been collected, for instance, an operator had stopped a test that had been in progress [9]. The Cepheid testing was performed by an HCW and a preliminary result placed in the patient medical notes.

Patient specimens were sent to the central laboratory at Aberdeen Royal Infirmary for routine microbiology testing. The Infirmary has 900 staffed beds and complete range of medical and clinical specialties. Transport was by road, twice daily from Monday to Friday and once on Saturday (there was no routine sample transport on Sunday). Specimens were transported to Aberdeen at ambient temperature, where they were refrigerated upon arrival until processing by traditional microbiology methods seven days per week. For MRSA testing, nasal swabs were cultured on Brilliance™ MRSA Agar (Oxoid Ltd, Basingstoke, UK) and the coagulase test was carried out on isolated organisms using Prolex™ Staph Xtra Latex kit (Pro-Lab Diagnostics, Bromborough, UK). Formal bacterial identification was performed on the Vitek MS (bioMérieux, Marcy l'Etoile, France) and antibiotic sensitivity carried out by Vitek 2 (bioMérieux). Enzyme immunoassay (EIA) for glutamate dehydrogenase (GDH) followed by toxin testing (Meridian Bioscience, Cincinnati, OH, USA) was used for identification of *C. difficile* on faeces specimens as per national guidance [11].

*C. difficile* PCR was not used by the central laboratory as part of its *C. difficile* diagnostic tests and so direct comparison of POCT-PCR with an equivocal PCR method could not be undertaken. Laboratory detection of norovirus RNA (norovirus genotype I and genotype II) in patient faeces was carried out by TaqMan real-time reverse-transcriptase PCR as previously described [12,13].

## Data management and analysis

Cepheid assay results and traditional testing information were collected from the Cepheid GeneXpert rapid molecular diagnostic platform and laboratory information management system (LIMS) respectively. As part of this, two sets of data were collected, the first involving 12 months of baseline data reflecting pre-existing testing methods from 2013 to 2014, the second including test phase evaluation data collected for the duration of the POCT during 2014–2016. Baseline and evaluation data were directly compared. Data included sample collection date/time; date/time samples were received in the laboratory, patient location code, ward, test start date, test start time, final results, report date and time to identify the clinical turnaround times (CTATs), i.e. time from sample taken to report available to the clinician. Clinical and laboratory data were analysed in Microsoft Excel. Standard formulae were used to calculate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence interval (CI) [14]. HCW feedback was gained at the end of the study to inform acceptability, bed management, and patient care. Caldicott guardian approval was gained from NHS Grampian in order to enable appropriate information sharing and to protect the confidentiality of patients, and the study was approved by the Clinical Effectiveness Unit in NHS Grampian.

## Results

Overall 1170 samples underwent Cepheid GeneXpert assay testing. Figure 1 demonstrates the number of results which were reported as 'positive', 'negative', 'invalid', 'no result' or 'error'. There was a significant reduction in CTATs from baseline (before PCR-POCT) to test phase (introduction of PCR-POCT) for all three organisms. For MRSA the median CTATs for traditional methods was 44 h compared to 3 h for POCT ( $P < 0.05$ ), for *C. difficile* median CTATs for traditional methods was 84 h compared to 3 h for POCT ( $P < 0.05$ ), and for norovirus median CTATs for traditional methods was 54 h compared to 3 h for POCT ( $P < 0.05$ ) (Supplementary Figure S2). Each assay greatly reduced hands-on time, number of process steps, and time to result (Table I). Analysis of the Cepheid GeneXpert rapid molecular diagnostic platform user data identified that specimens were tested over a 24 h period for all assays (Supplementary Figures S3–S5).

### Xpert SA Nasal Complete

In total, 688 POCTs for MRSA detection were completed during the evaluation period, of which 605 had concomitant bacterial culture (see Figure 1 for exclusions). The Cepheid was positive in 17 samples; 10 were culture positive (true positive) and seven culture negative.  $C_T$  values for the seven false-positive Cepheid samples are shown in Supplementary Table S1. Overall in 598 out of 605 samples (98.8%) there was concordance with the central laboratory result. Xpert SA Nasal Complete sensitivity for MRSA was found to be 100% (95% confidence interval (CI): 65.55–100), specificity 98.82% (95% CI: 97.48–99.48), PPV 58.82% (95% CI: 33.45–80.57) and NPV 100% (95% CI: 99.19–100) compared with reference standard MRSA detection by culture methods.

### Xpert *C. difficile*

In all, 257 POCTs were carried out using the Xpert *C. difficile* assay, of which 195 had a concomitant GDH test (see Figure 1 for exclusions; note that in the initial stage of the evaluation the laboratory had not yet implemented *C. difficile* testing as per national guidance and that 30 specimens were tested by methods other than GDH). In total there were 170 specimens tested which were negative by GDH and Xpert *C. difficile* (Xpert *C. difficile* true negative). Seventeen samples were positive by POCT-PCR and laboratory GDH. There were six instances in which Xpert *C. difficile* was negative yet the specimen was positive by GDH, which may be explained by the presence of non-toxicogenic *C. difficile*. There were two cases in which the Xpert *C. difficile* was positive, but laboratory-based GDH negative (considered discrepant). Overall agreement was 99.0%.

### Xpert Norovirus assay, of which 155 had a concomitant norovirus laboratory PCR

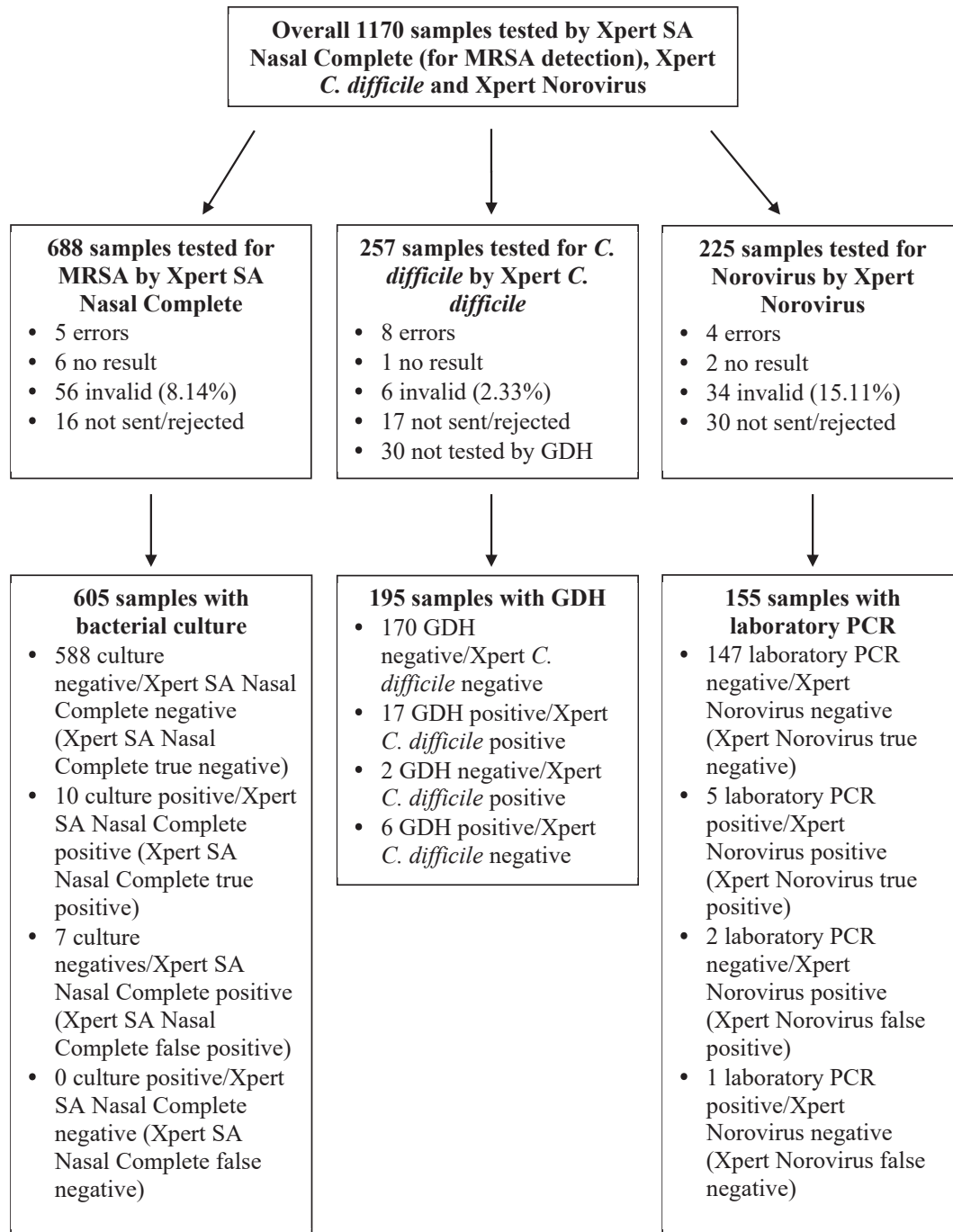
In total 225 POCTs were completed during this evaluation period using the Xpert Norovirus, of which 155 had a concomitant norovirus laboratory PCR (see Figure 1 for exclusions). Xpert Norovirus was positive in seven cases; five were confirmed by laboratory PCR (Xpert Norovirus true positives) and two were negative by laboratory PCR (Xpert Norovirus false positives). Xpert Norovirus was negative in 148 cases; 147 were negative by laboratory PCR (Xpert Norovirus true negative) and one case was positive by laboratory PCR (Xpert Norovirus false negative). Overall in 152 out of 155 samples (98.1%) there was concordance with the central laboratory result. Xpert Norovirus sensitivity was 83.33% (95% CI: 36.48–99.12), specificity 98.66% (95% CI: 94.74–99.77), PPV 71.43% (95% CI: 30.26–94.89) and NPV 99.32% (95% CI: 95.73–99.96) compared to reference-standard detection by laboratory PCR method.

### Evaluation of HCWs' perceptions

Eleven members of staff who regularly operated the GeneExpert gave feedback on their experiences. They responded to a series of statements (Table II). HCWs rated their answers from 1 (strongly disagree) to 5 (strongly agree). Overall staff reported that the tests were easy to perform, giving faster results. They identified that, out of the three Cepheid GeneExpert assays, the use of Xpert Norovirus was most favourable in improved bed management whereas the use of Xpert SA Nasal Complete was most favourable in improved patient care.

## Discussion

This study provides evidence that rural hospitals without microbiology or virology laboratories can improve their CTATs for MRSA, *C. difficile*, and norovirus by using POCT methods. One strength of the study is that testing was solely conducted by HCWs rather than by laboratory-trained staff, as has been the case in previous studies [15,16]. The most common test carried out was SA Nasal Complete, which had a sensitivity of 100.00% for MRSA detection, similar to findings from previously reported POCT studies [17–21]. The PPV in our study was low



**Figure 1.** Results of Xpert SA Nasal Complete, Xpert *C. difficile*, and Xpert Norovirus Tests and central laboratory tests performed. MRSA, methicillin-resistant *Staphylococcus aureus*; GDH, glutamate dehydrogenase; PCR, polymerase chain reaction.

(58.82%) and may reflect the low prevalence of MRSA in the patient population tested. Discordant screening tests have been described before, and, although we did not detect any false-negative PCR results, we did identify seven patients with positive MRSA results on the Cepheid SA Nasal Complete which were subsequently culture negative by traditional methods. This could be explained by the following: low-level colonization, antibiotic use, opsonizing antibody to *S. aureus*, poor sampling, or non-viable organisms from the specimen [18]. In a

previous study, in POCT-positive/culture-negative MRSA cases there was no evidence of MRSA infection or colonization in these patients for a year post procedure [20]. Potential unintentional consequences of false-positive MRSA identification include inappropriate isolation, decolonization, and potential prescriptions of anti-MRSA-targeted antimicrobials.

The Xpert Norovirus proportionately had the most confirmatory samples that were not sent or rejected by the laboratory. It also had the highest proportion of invalid results



**Table I**  
Comparison of Xpert SA Nasal Complete, Xpert *C. difficile*, and Xpert Norovirus assay testing with central laboratory testing

Target	Molecular method	Hands-on time (h:min:s)	No. of process steps	Time to result (h:min:s)	Central laboratory test	Hands on time (h:min:s)	No. of process steps	Time to result (h:min:s)
MRSA	Xpert SA Nasal Complete	0:00:30	11	1:07:00	Culture	0:06:30	30	24:00:00
<i>C. difficile</i>	Xpert <i>C. difficile</i>	0:00:30	11	1:04:00	GDH/toxin	0:48:00	106	4:08:00
Norovirus	Xpert Norovirus	0:00:30	11	1:04:00	Laboratory PCR	0:0:30	17	3:12:00

MRSA, methicillin-resistant *Staphylococcus aureus*; GDH, glutamate dehydrogenase; PCR, polymerase chain reaction.

**Table II**  
Average scores of healthcare worker feedback on use of Xpert SA Nasal Complete, Xpert *C. difficile*, and Xpert Norovirus assays and impact on clinical utility

Statement	Xpert SA Nasal Complete	Xpert <i>C. difficile</i>	Xpert Norovirus
The test was easy to perform	4.50	4.36	4.22
The technology means I am more likely to send specimens	3.88	3.27	3.50
I like the idea of carrying out the test on the ward	3.88	3.73	3.44
I like the idea of carrying out the test myself	3.88	3.82	3.44
Testing is an acceptable part of my job	3.75	3.64	3.44
The technology gives me faster results	4.62	4.80	4.78
The technology improves bed management	3.75	4.22	4.25
The technology improves patient care	4.40	3.67	3.67

Healthcare workers rated their answers from 1 (strongly disagree) to 5 (strongly agree).

and was found to be the least easy test to perform. Invalid results occur when the sample is not properly processed, PCR is inhibited, or the sample is not properly collected (e.g. too much stool in the sample can often result in invalid results) [10]. Moreover, the fact that users found this Xpert Norovirus the least easy to perform may have resulted in improper processing and a high proportion of invalid results. The sensitivity of the Xpert Norovirus was 83.33% and PPV 71.43%, lower values than previously reported [22,23]. There is no established reference-standard nucleic acid amplification test (NAAT) for norovirus testing and the variation in Xpert Norovirus performance may reflect the different comparator laboratory PCR used in these studies. Interestingly authors from a previous study concluded that the POCT Xpert Norovirus assay in their hands may have been more reliable than laboratory PCR in detecting norovirus [23]. They therefore proposed that caution should be taken when using laboratory PCR as a comparator.

The optimal laboratory diagnosis for *C. difficile* infection has been an area of controversy for many years. Direct cell cytotoxicity assay and toxigenic culture were the first two diagnostic *C. difficile* tests available, but a major drawback with these methods is the long turnaround times. EIAs with rapid turnaround time followed and were developed to detect toxins and GDH or a combination of these [24,25]. In the last 20 years advances in molecular methods for *C. difficile* diagnosis have been made. Various companies have developed automated and semi-automated NAATs that use PCR or loop-mediated isothermal amplification of DNA for testing *C. difficile* in stool, a significant number of which have been approved by the US Food and Drug Administration [26]. NAAT or PCR testing is less common in the UK for *C. difficile* screening. The comparator screening test used for *C. difficile* in this study

was GDH by EIA, which the laboratory adopted at the initial stages of the evaluation.

A limitation of our study is that we did not directly compare this assay to another equivalent PCR method to detect *C. difficile*. However, the UK national guidance does advise that *C. difficile* diagnosis should be based on using GDH EIA or NAAT to screen samples [11]. A molecular diagnosis of *C. difficile* will require confirmation with a sensitive toxin EIA test (or a cytotoxin assay) as molecular testing for *C. difficile* only detects genes associated with toxigenic *C. difficile*. As a proof-of-concept study we have shown that POCT-PCR, used solely by HCWs, could be used as an alternative screening test to laboratory GDH for *C. difficile* detection. A recent feasibility study focusing on the assessment of Cepheid GeneXpert for diagnosis of *C. difficile* on three wards and two intensive care units (ICUs) in a city hospital operated by laboratory technicians found an overall agreement with central laboratory testing to be 98.1% and the median turnaround time was 1.85 h for Xpert *C. difficile* results compared to 18 h for the central laboratory test [16]. Likewise our study showed good agreement with laboratory testing (99.0% agreement) and the use of Xpert *C. difficile* assay reduced CTATs; in our case the median CTAT for *C. difficile* detection using traditional methods (GDH and toxin) was 84 h and this decreased to 3 h using POCT-PR ( $P < 0.05$ ). Faster CTATs are also reported in our HCW feedback.

In general, staff who gave feedback on their experience of using POCT were receptive to this technology and responded that it allowed for more effective bed management and improved patient care. This supports previous reports that when a patient's sample has undergone POCTs the patient is three times more likely to be immediately discharged compared to patients who only had their samples tested by traditional microbiology methods [15]. The use of POCTs has the

potential to meet healthcare deliverables such as streamlining of health technology, equity of access, sustainability, reducing antibiotic prescribing, and achieving quality overall in healthcare [27–29]. At the time of the evaluation only two Scottish microbiology laboratories offered a seven-day/24 h service and we have shown that POCT can be used to assist in delivering results for MRSA, *C. difficile*, and norovirus in a hospital that does not have onsite testing facilities. If the POCT technology were to be rolled out routinely we would advise that it would need to be sustained with increased resource for staff and IT systems. In our study the GeneXpert system was not interfaced to LIMS and therefore Cepheid tests could not be ordered from the LIMS and results could not be transferred electronically to this system. GeneXpert results were also not transferred to other systems such as bed management systems and IPC systems such as ICNet. With the threat of antimicrobial resistance there are also calls for novel approaches to be undertaken in terms of new diagnostics with recommendations for investment in POCTs to assess the appropriateness of diagnosis and treatment [30]. It is outwith the scope of the study to undertake a formal cost-benefit/effectiveness study. Consumable costs per test for rapid, molecular technology are high relative to traditional methods; however, the associated benefits can only be appreciated when a whole-hospital approach is taken (including benefits such as reduced turnaround times, improved bed-days, reduced transport costs, etc.). Indeed POCTs may be of greatest value in hospitals with no microbiology/virology diagnostic services on site, as outlined in this study. With this in mind and considering low sensitivity and delayed results of traditional culturing, it is paramount that we continually develop and make use of the rapidly emerging technological advances in the field of real-time diagnostics in order to deliver the very best standards of healthcare.

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### Conflict of interest statement

K.T. has been in receipt of Cepheid USA research money and gave a presentation at a Cepheid-sponsored symposium. The authors declare no other potential conflicts of interest.

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## Appendix A. Supplementary data

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