

Validation of a Real-Time Locating System for Contact Tracing of Healthcare Workers during the COVID-19 Pandemic in Singapore

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Abstract

Background: In early 2020, the 2019 coronavirus disease (COVID-19) emerged and resulted in community and nosocomial transmissions. Effective contact tracing for potentially exposed healthcare workers (HCWs) is crucial for the prevention and control of infectious disease outbreaks in the healthcare setting.

Objective: This study aimed to evaluate the comparative effectiveness of contact tracing through real-time locating systems (RTLS) and electronic medical records (EMRs) review at the designated hospital for COVID-19 response in Singapore, during the COVID-19 pandemic.

Methods: Over a two-day study period, all admitted COVID-19 patients, their ward locations, and the HCWs rostered to each ward, were identified to determine the total number of potential contacts between COVID-19 patients and HCWs. The number of staff-patient contacts determined by EMR reviews, RTLS-based contact tracing, and a combination of both methods were evaluated. The use of EMR and RTLS-based contact tracing methods were further validated by comparing their sensitivity and specificity against self-reported staff-patient contacts by HCWs.

Results: Of 796 potential staff-patient contacts (between 17 patients and 162 staff), 104(13.1%) were identified on both RTLS and EMR, 54(6.8%) by RTLS alone, 99(12.4%) by EMR alone, and 539(67.7%) not identified through either method. Compared to self-reported contacts, EMR reviews had a sensitivity of 47.2% and specificity of 77.9%, while RTLS had a sensitivity of 72.2% and specificity of 87.7%. Highest sensitivity was obtained by including all contacts identified by either RTLS or EMR (sensitivity 77.8%, specificity 73.4%).

Conclusions: RTLS-based contact tracing had higher sensitivity and specificity than EMR reviews. An integration of both methods provided the best performance for rapid contact tracing, although technical adjustments to the RTLS and increasing user compliance with wearing RTLS tags consistently remain necessary.

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Original Manuscript

Validation of a Real-Time Locating System for Contact Tracing of Healthcare Workers during the COVID-19 Pandemic in Singapore

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Abstract

Background:

In early 2020, the 2019 coronavirus disease (COVID-19) emerged and resulted in community and nosocomial transmissions. Effective contact tracing for potentially exposed healthcare workers (HCWs) is crucial for the prevention and control of infectious disease outbreaks in the healthcare setting.

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This study aimed to evaluate the comparative effectiveness of contact tracing through real-time locating systems (RTLS) and electronic medical records (EMRs) review at the designated hospital for COVID-19 response in Singapore, during the COVID-19 pandemic.

Methods:

Over a two-day study period, all admitted COVID-19 patients, their ward locations, and the HCWs rostered to each ward, were identified to determine the total number of potential contacts between COVID-19 patients and HCWs. The number of staff-patient contacts determined by EMR reviews, RTLS-based contact tracing, and a combination of both methods were evaluated. The use of EMR and RTLS-based contact tracing methods were further validated by comparing their sensitivity and specificity against self-reported staff-patient contacts by HCWs.

Results:

Of 796 potential staff-patient contacts (between 17 patients and 162 staff), 104(13.1%) were identified on both RTLS and EMR, 54(6.8%) by RTLS alone, 99(12.4%) by EMR alone, and 539(67.7%) not identified through either method. Compared to self-reported contacts, EMR reviews had a sensitivity of 47.2% and specificity of 77.9%, while RTLS had a sensitivity of 72.2% and specificity of 87.7%. The highest sensitivity was obtained by including all contacts identified by either RTLS or EMR (sensitivity 77.8%, specificity 73.4%).

Conclusions:

RTLS-based contact tracing had higher sensitivity and specificity than EMR reviews. An integration of both methods provided the best performance for rapid contact tracing, although technical adjustments to the RTLS and increasing user compliance with wearing RTLS tags consistently remain necessary.

Keywords:

Infectious disease; real-time locating systems; electronic medical records; COVID-19; contact tracing; healthcare workers; RFID

Introduction

In early 2020, the 2019 coronavirus disease (COVID-19) emerged in Wuhan, China, and resulted in community and nosocomial transmissions, infecting up to 3019 healthcare workers (HCWs) by 12 February 2020 [1].

Contact tracing is used to identify individuals potentially exposed to infectious diseases, and is crucial for the prevention and control of infectious disease outbreaks [2, 3]. HCWs face high risks of infectious diseases due to a large amount of time spent interacting with patients and their co-workers [4, 5]. HCWs had 14 to 18 person-contacts in a typical work shift in the general wards, with nurses having the longest duration of physical contact with patients [6]. As contacts in healthcare settings tend to be close, any exposure to an infectious patient would require immediate contact tracing and contact management. Failure to identify potentially exposed contacts puts other patients and HCWs at greater risk of infection [7].

Conventional contact tracing methods are limited by their cost and reliability. Continuous direct observation has been considered as the gold standard method for accurately quantifying contact time (including activities and locations of interest), but intensive human resource requirements render the method cost-ineffective and impractical for large-scale projects [8]. Self-reporting methods, such as activity diaries and interviews, have been used as alternatives to direct observation due to their lower intensity on human resource demands [6, 8], but they are also time-consuming and subject to reporting biases that compromise the accuracy of the data collected [9, 10]. Another commonly used method for contact tracing is data extraction from administrative and clinical databases such as electronic medical records (EMR) [8, 11]. Although this method overcomes some of the problems with cost and reliability, it is also time-consuming and limits the capture of patient contact episodes to only care providers who can make inputs in the EMR [8, 12].

Technological advances such as real-time locating systems (RTLS) have shown promises in overcoming the barriers to conventional methods of contact tracing [13, 14]. In recent years, healthcare institutions have been increasingly exploring the use of RTLS to establish contacts within healthcare premises [12, 13, 15]. One type of RTLS technology is radiofrequency identification (RFID) tracking. RFID tracking requires the user to wear an RFID tag which continuously sends wireless signals to sensors (RFID readers) installed at various locations in the hospital [16]. The RFID technology can provide an accurate gauge of HCWs' movements and their interactions with patients and co-workers [15]. This capability is useful for hospital contact tracing during an infectious disease outbreak.

While many studies have been conducted on community-based contact tracing measures using digital technology, fewer articles have focused on technology for hospital-based contact tracing for healthcare workers. During the COVID-19 pandemic, we evaluated the comparative effectiveness of contact tracing through RTLS and the conventional method of identifying

contacts from EMRs, and validated them against self-reporting of contacts by HCWs.



Methods

Setting

This study was performed in the setting of the COVID-19 pandemic occurring in Singapore, at the National Centre for Infectious Diseases (NCID), the designated hospital for COVID-19 response. Singapore identified its first COVID-19 case on January 23, 2020, and by February 19, 2020, had a total of 84 cases reported nationally [17]. Of these, the NCID had managed 65 cases. The study was conducted over two days from February 25, 2020, 0000hrs to February 26, 2020, 2359hrs. NCID is a 330-bed purpose-built facility for the management of emerging infectious diseases. The NCID building was outfitted with RTLS technology, and location trackers were installed in all ward areas. All staff working within the building had been provided with RTLS tags which were routinely carried during work. The tags also served as access cards to the NCID building and inpatient wards.

Real-time Locating Systems Technology

Staff wearing RTLS tags could be located within the NCID wards and inpatient rooms. All inpatient rooms were fitted with RTLS location exciters and wireless access points (AP). Whenever a tag passed a location exciter in an inpatient room, it would receive a low-frequency signal and transmit a radio-frequency signal to the AP, where the location triangulation technology would decipher the signals and determine the exact location of the RTLS tag.

Electronic Medical Records System

NCID also used an EMR system to capture clinical encounters of all inpatients. Staff providing clinical care were issued with personal accounts for making entries into patients' clinical notes for their clinical assessments, medication orders, laboratory and radiological tests, and charting of vital signs.

Participants

We included all medical and nursing staff who could have a contact with a COVID-19 positive patient isolated in the general wards of NCID during the two-day study period as participants. Inpatients with a laboratory-confirmed diagnosis of COVID-19 infection were identified through the hospital's laboratory information system, and on-duty medical and nursing staff from duty rosters.

We excluded staff who did not have access to the hospital EMR system, did not have a working RTLS tag associated with their identity, or did not have a sufficiently charged RTLS tag that could be reliably detected by the location trackers. We ensured these by checking all staff that were on the roster for any movement records captured on RTLS in the week preceding the two

days of the study, and we excluded those whose identity could not be found on the RTLS (i.e. they were not issued a tag) or did not register any movement record (i.e. they were not using the tag, or their tags had not been charged).

Study Design

The study was divided into two parts. In the first part of the study, we compared two methods of contact tracing for medical and nursing staff who had come into contact with a confirmed COVID-19 patient over the study period – the conventional method of reviewing EMRs versus the extraction of staff records from the RTLS system. For EMR reviews, we extracted names of all physicians and nurses who had come into contact with patients based on entries into the EMR. Records included medical and nursing notes, as well as documentation of patients' vital signs. For extraction of staff records from the RTLS system, we used location-based tracking to identify all individuals picked up by the appropriate location tracker in a specific airborne infection isolation room to which each COVID-positive patient was admitted. We used a highly sensitive cut-off of at least 1 second, i.e. as long as a staff's RTLS tag was picked up by the location tracker in a specific room, we considered that the staff had been in contact with the patient admitted into that room.

For each patient-day (a 24-hour period from 0000 to 2359hrs for each specific COVID-19 patient), we counted the total number of unique staff-patient contacts identified using EMR-based and RTLS-based contact tracing methods. For staff with multiple contacts with the same patient in the same day, we included only the first contact episode. We then classified them into contacts identified through both methods, and contacts identified via either one of the two methods. We constructed two-by-two tables for each patient-day, and aggregated these tables. We reported on the total number of contacts identified by the two methods, the proportion identified on both methods, and the proportions identified on either one of the two.

In the second part of our study, we attempted to validate both methods against self-reporting by doctors and nurses. For this part of the study, we restricted our analysis only to COVID-19 patients who had been admitted into two wards in NCID on February 25, 2020. We identified all possible contacts of a patient by looking at the rostered medical and nursing staff for a given ward. We then separately used both the EMR review as well as the RTLS staff record extraction methods, as detailed above, to identify all medical and nursing staff who had come into contact with each COVID-19 positive patient. For the self-reporting method, we contacted all physicians and nursing staff rostered to those wards by phone and asked them if they had physically entered the airborne infection isolation room (not just the anteroom) of each COVID-19 patient. This was done on the day after the day of interest, to reduce recall bias. Our hospital protocol requires all staff managing patients with COVID-19 to don full personal protection equipment (including fit-tested N95 mask, gowns, gloves, and goggles/face shield) during their encounter with patients. This is strictly enforced in the wards by both the ward nursing manager and senior doctors. As such, these staff were not in danger of being quarantined or reprimanded for not following protocol. We therefore expected these self-reports to be truthful.

For each patient-day, we constructed two two-by-two tables: one comparing the performance of the EMR review method against self-reported contacts (i.e. its comparative ability to correctly identify staff-patient contacts and non-staff patient contacts), and the other comparing the RTLS method against self-reported contacts. Tables for all patient-days were then aggregated. We used the aggregated tables to calculate the sensitivity (proportion of staff-patient contacts correctly identified) and specificity (proportion of non-staff patient contacts correctly identified) of both methods separately. In addition, we also created three logistic regression models with the dependent variable being self-reported contacts: Model 1 where the only independent variable was EMR detection, Model 2 where the only independent variable was RTLS detection, and Model 3 containing both variables as independent variables. We then used the likelihood ratio test to compare the goodness of fit of these models.

We further considered the sensitivity and specificity of using both methods concurrently, using either an “RTLS or EMR” approach or an “RTLS and EMR” approach to detect staff-patient contacts.

Results

RTLS versus EMR-based Contact Tracing

Our study included 17 COVID-19 inpatients warded at NCID on 25 and 26 February 2020, housed in single airborne infection isolation rooms across six isolation wards. From the ward duty rosters, a total of 212 (30 medical and 182 nursing) staff were rostered for duty in these six wards over the study period. We excluded 50 (5 medical and 45 nursing) staff due to tag-related issues, and the remaining 162 (25 medical and 137 nursing) staff were included in our study. In total, based on the ward location of each patient and the number of staff rostered to each ward over the two-day study period, 796 potential staff-patient contacts were identified between these 17 inpatients and 162 staff.

Table 1 compares the number of contacts identified on RTLS with those identified on EMR for 34 patient-days. Of 796 potential staff-patient contacts, 104 (13.1%) were identified on both RTLS and EMR, 54 (6.8%) by RTLS alone, 99 (12.4%) by EMR alone, and 539 (67.7%) not identified through either method. Within the total of 257 staff-patient contacts identified, RTLS identified 158 (61.5%) of them, while EMR identified 203 (79.0%). However, it is not possible to determine whether the contacts were identified accurately or not.

Table 1. Summary of possible contacts identified by RTLS and EMR over 34 patient-days

	Detected by RTLS	Not detected by RTLS	Total
Detected by EMR	104 (13.1%)	99 (12.4%)	203
Not detected by EMR	54 (6.8%)	539 (67.7%)	593
Total	158	638	796

Validation of RTLS-based and EMR-based contact tracing

For our validation study, we evaluated staff-patient contacts for 10 confirmed COVID-19 patients in two wards (5 in Ward A and 5 in Ward B). A total of 36 staff (6 medical and 30 nursing staff) were rostered to Ward A, and 30 staff (6 medical and 24 nursing staff) to Ward B during the one-day validation study period. Of these, 8 (1 medical and 7 nursing) staff from Ward A and 2 (both nursing) staff from Ward B were excluded due to staff tag-related issues. We hence included 28 staff from Ward A and 28 staff from Ward B in our study. This gave a total of 280 potential staff-patient contacts.

In general, EMR review produced more records of staff than staff detected in RTLS ($P<.001$). The overall observed agreement between RTLS and EMR was 80.8%.

Table 2 compares the performance of RTLS staff records against self-reported contacts. Of 280 potential staff-patient contacts, 36 (12.9%) were self-reported as having occurred. Of these, 26 contacts were traced by RTLS, giving a sensitivity of 72.2%. Of 244 self-reported non-staff patient contacts, 214 were accurately identified by RTLS, giving a specificity of 87.7%. The positive predictive value was 46.4% while the negative predictive value was 95.5%.

Table 2. Comparison of the performance of RTLS-based contact tracing against self-reported contacts with COVID-19 patients.

	Detected by RTLS	Not detected by RTLS	Total
Contacts by self-report	26 (72.2%) ^a	10 (27.8%)	36
Non-contacts by self-report	30 (12.3%)	214 (87.7%)	244
Total	56	224	280

^a Percentages calculated are according to row values.

Table 3 compares the performance of EMR review against self-reporting by staff. Of 36 self-reported staff-patient contacts, 17 were identified by EMR review, giving a sensitivity of 47.2%. Of 244 staff-patient contacts not reported by the staff, 190 were identified by EMR review, giving a specificity of 77.9%. The positive predictive value was 23.9%, while the negative predictive value was 90.9%.

Table 3 Comparison of the performance of EMR-based contact tracing against self-reported contacts with COVID-19 patients. Percentages calculated are according to row values.

	Detected by EMR	Not detected by EMR	Total
Contacts by self-report	17 (47.2%)	19 (52.8%)	36
Non-contacts by self-report	54 (22.1%)	190 (77.9%)	244
Total	71	209	280

^a Percentages calculated are according to row values

Among the logistic regression models, Model 3 performed significantly better than Model 1 ($P<.001$) although not differently from Model 2 ($P=0.84$) (Table 4). These results suggest that RTLS was better than EMR in identifying self-reported contacts. This is consistent with our results showing the higher sensitivity and specificity of RTLS than EMR, when compared with self-reported contacts.

Table 4. Coefficients of three logistic regression models for EMR, RTLS and both methods

	Model 1 (EMR detection only)	Model 2 (RTLS detection only)	Model 3 (both EMR and RTLS detection)
EMR detection	1.15 (0.43-1.87)	-	-0.10 (-1.01-0.82)
RTLS detection	-	2.92 (2.40-3.74)	2.96 (2.04-3.88)

Likelihood ratio test	Model 3 vs Model 1: $P < .001$	Model 3 vs Model 2: $P = .84$	-
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Coefficients of three logistic regression models with self-reported contact as the dependent variable, and likelihood ratio test results comparing nested models. Model 1 contains EMR detection as the only independent variable, Model 2 contains RTLS detection as the only independent variable; Model 3 contains both EMR detection and RTLS detection as independent variables. Values in brackets denote 95% confidence intervals. EMR = electronic medical records; RTLS = real-time locating systems.

Table 5 shows the overall performance of combining RTLS with EMR-based contact tracing. By using an 'or' strategy and considering staff-patient contacts to have truly occurred if they were traced on either RTLS or EMR review, the sensitivity increased to 77.8% (28/36) but this came at a cost of a lower specificity of 73.4% (179/244). On the other hand, if we used an 'and' strategy, and considered staff-patient contacts to have truly occurred if they were traced on both RTLS and EMR, the sensitivity decreased to 41.7% (15/36) while the specificity increased to 92.2% (225/244).

Table 5. Comparison of two different approaches to combining EMR and RTLS data against self-reported contacts with COVID-19 patients.

	Contact tracing using an 'or' strategy		Contact tracing using an 'and' strategy		Total
	Detected by EMR or RTLS	Not detected by EMR or RTLS	Detected by EMR and RTLS	Not detected by EMR and RTLS	
Contacts by self-report	28 (77.8%)	8 (22.2%)	15 (41.7%)	21 (58.3%)	36
Non-contacts by self-report	65 (26.6%)	179 (73.4%)	19 (7.8%)	225 (92.2%)	244
Total	93	187	34	246	280

^a Percentages calculated are according to row values.

Discussion

Timely and accurate hospital contact tracing is vital for staff and patient safety and to prevent nosocomial transmission of infectious diseases. Our study demonstrated that RTLS-based contact tracing had higher sensitivity and specificity than EMR-based contact tracing, compared to self-reporting by staff.

The performance of EMR reviews was surprisingly poor, with low sensitivity of 47% and moderate specificity less than 78%. This was likely related to clinical operational processes, where the staff performing clinical documentation for the patient might not be the same one entering the patient's room. This is especially so in the context of a busy airborne infection isolation ward, where staff may split up the workload in performing practical procedures (which would require the donning and doffing of PPE, and time interacting with patients to perform clinical procedures) and administrative tasks (including clinical documentation). A lack of clarity was likely present in documenting which specific staff had performed certain

tasks. Moreover, staff-patient contacts not required as part of routine reports, or which did not significantly affect clinical care of the patient, may not have been documented.

Consequently, although EMR review detected more staff-patient contacts than RTLS over our two-day study period, many of the staff would have either been false positive or false negative contacts. The inability to accurately contact trace staff may lead to false alarms or false reassurances when evaluating risk exposure to an infectious patient.

The RTLS-based contact tracing method performed better than EMR reviews, with moderate sensitivity of 72% and high specificity of 88%. While we did not specifically measure time taken for each method, it was estimated that RTLS data extraction took about 2 to 3 minutes per patient, while EMR record reviews took about 20 minutes per patient. These findings are comparable to previous studies validating the accuracy and ease of RFID technology in quantifying human contact episodes [12, 18, 19]. Chang et al. validated the accuracy of RFID tag readers (>80%) in detecting proximity events in the intensive care unit by comparing data obtained from direct observation [19], and demonstrated sensitivities ranging from 73.8% to 90.9%, as well as specificities ranging from 83.8% to 98.0%, for the technology used, with better performance for invasive events. Lucet et al. found no difference in the interaction duration between HCWs and tuberculosis patients in airborne isolation, when comparing records obtained from RFID network sensors, direct observations and interviews [18]. Hellmich et al. showed that the use of RFID technology in the emergency department generated twice as many contacts compared with the conventional method of EMR review during a pertussis outbreak, and each RTLS data query took less than 5 minutes, compared to the 30-60 minutes per EMR review [12].

For the purposes of accurately identifying as many staff in contact with an infectious patient as possible, a high test sensitivity is desired. Based on our study, RTLS-based contact tracing would be able to obtain most of the contacts with exposure to a COVID-19 case. Sensitivity would increase slightly by integrating EMR-based contact tracing methods (at slight compromise to specificity). Presently, this might be the most practicable solution to obtaining contacts quickly. Further verifications with staff would be required to capture the most accurate list of staff contacts requiring follow-up and intervention.

Aside from staff-patient contacts, there is also potential to use RTLS technology to determine staff-staff contacts as well, by using the RTLS data to analyse which staff who were in the same pre-demarcated zones at the same time. This has important practical applications in the event that a HCW is identified as a confirmed case of an infectious disease, and contact tracing of exposed staff is required.

The results obtained in our study were partially limited by implementation-related challenges of the RTLS system. RTLS electronic tags held by each staff would need to be detected by the correct location exciter when the staff moved from one demarcated zone to another. Careful calibration of the technology by the developers was necessary to optimise contact tracing

results.

We also observed that a sizeable proportion of staff needed to be excluded from our study due to staff tag-related issues. This was partly because in the setting of the COVID-19 outbreak, some nursing staff had to be rapidly redeployed to augment the manpower at NCID, and consequently not all had RTLS tags readily available for them. Furthermore, issues related to staff acceptance of RTLS technology, compliance with carrying the tag consistently during routine work, and technical issues such as proper tag association and regular charging of the battery, might have also been present. Key principles for gaining user acceptance of such technology include clearly conveying the purpose and intended uses of the technology, and ensuring that individual electronic tags were practically convenient to use [13]. Although efforts have been made to ensure that staff were aware of the importance of contact tracing, and to integrate door access into a single tag for convenient use, some staff still failed to have fully-charged working tags. Further studies are needed to evaluate the knowledge, attitudes, practices and behaviours of HCWs towards RTLS technology.

While direct observation and self-reporting methods have been regarded as having a “higher” standard to accurately determine duration of contact time between staff and patients, as well as the nature of interaction (e.g. multiple brief episodes versus few episodes of prolonged contact) [6, 8], such methods are not practically implementable for extended periods of time, due to heavy manpower and time requirements (e.g. the need for research staff to observe HCWs, or to get HCWs to complete self-reported diaries, for an entire shift of 8 to 10 hours per day [6]). Other forms of technology, such as closed circuit television monitoring (CCTV), have also been used for risk exposure assessment for HCWs movements in an outbreak setting [20, 21]; however, these are potentially time- and labour-intensive.

Studies validating the accuracy of RFID technology have found no difference in the interaction duration between HCWs and tuberculosis patients when comparing records obtained from RFID network sensors, direct observations and interviews [18], and in the detection of proximity events in the intensive care unit by comparing data from direct observation [19]. We believe that the RTLS system, when properly implemented, would be a pragmatic means of capturing all staff-patient contact episodes in a similar fashion, to facilitate the rapid contact management of HCWs.

Strengths

This was a pragmatic study carried out in an outbreak setting, and hence offers a “real-world” perspective on the usefulness of EMR- and RTLS-based contact tracing methods. The study team employed a systematic and standardised means of carrying out the contact tracing methods and phone conversations with HCWs to ensure accurate capture of data. Furthermore, our study’s findings add to the limited information on the comparative effectiveness of RFID technology and conventional methods for contact tracing. Most studies on RTLS have been

confined to the measurement of human contact duration in healthcare settings [5, 22, 23].

Limitations

For RTLS-based contact tracing, we had only used location-based tracking to determine contacts but did not assess for the proximity of the contacts. Nevertheless, we reason that staff entering the isolation room would likely have needed to be in close contact with the patient (within 2m) to perform their clinical duties, and this was hence a reasonable means of determining close contacts of the patient. Regarding our chosen standard of self-reported contacts by HCWs, information bias was possible as staff were required to recall their movements from a shift that had already been completed. We sought to minimise errors in recall by contacting them one day after their working shifts and corroborating with other colleagues on the team. Our study period was short due to resource challenges faced by the study team which was concurrently involved in outbreak management work during the COVID-19 pandemic. Notwithstanding this, we believe our study methodology was robust and our observations remain valid in our evaluation of a novel technology under actual outbreak conditions.

Conclusions

In conclusion, we have demonstrated that RTLS-based contact tracing had higher sensitivity and specificity than EMR-based contact tracing, when compared with self-reported contacts. An integration of both methods appeared to provide the best performance for rapid contact tracing during the COVID-19 pandemic, with a sensitivity of 78% and a specificity of 73%. Technical adjustments and increasing user compliance are necessary to further improve the effectiveness of the RTLS system for contact tracing purposes.

Article information

Abbreviations

AP: Access point

COVID-19: 2019 coronavirus disease

EMR: Electronic Medical Record

HCW: Healthcare worker

NCID: National Centre for Infectious Diseases, Singapore

RFID: Radiofrequency identification

RTLS: Real-time locating systems

Consent for publication

All authors reviewed and approved the final version of the manuscript prior to submission.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

HJH conceived the study, analysed and interpreted the data, and drafted the manuscript with inputs from all authors. ZXZ assisted with acquiring and interpreting study data, and drafting the manuscript. ZH assisted with interpreting study data and drafting the manuscript. AAH assisted with analysing and interpreting study data, and provided inputs for the manuscript. WL conceived the study, assisted with acquiring, analysing and interpreting study data, and provided inputs for the manuscript. AC conceived the study, provided overall direction and planning for the study, analysed and interpreted the data, and critically revised the manuscript.

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Supplementary Files

Other materials for editor/reviewers onlies