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Automated detection of outbreaks of antimicrobial-resistant bacteria in Japan

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SUMMARY

Background: Hospital outbreaks of antimicrobial-resistant (AMR) bacteria should be detected and controlled as early as possible.
Aim: To develop a framework for automatic detection of AMR outbreaks in hospitals.
Methods: Japan Nosocomial Infections Surveillance (JANIS) is one of the largest national AMR surveillance systems in the world. For this study, all bacterial data in the JANIS database were extracted between 2011 and 2016. WHONET, a free software for the management of microbiology data, and SaTScan, a free cluster detection tool embedded in WHONET, were used to analyse 2015–2016 data of eligible hospitals. Manual evaluation and validation of 10 representative hospitals around Japan were then performed using 2011–2016 data.
Findings: Data from 1031 hospitals were studied; mid-sized (200–499 beds) hospitals accounted for 60%, followed by large hospitals (≥500 beds; 24%) and small hospitals (<200 beds; 16%). More clusters were detected in large hospitals. Most of the clusters included five or fewer patients. From the in-depth analysis of 10 hospitals, ~80% of the detected clusters were unrecognized by infection control staff because the bacterial species involved were not included in the priority pathogen list for routine surveillance. In two hospitals, clusters of more susceptible isolates were detected before outbreaks of more resistant pathogens.
Conclusion: WHONET-SaTScan can automatically detect clusters of epidemiologically related patients based on isolate resistance profiles beyond lists of high-priority AMR pathogens. If clusters of more susceptible isolates can be detected, it may allow early intervention in infection control practices before outbreaks of more resistant pathogens occur.

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Introduction

Antimicrobial resistance (AMR) is a global public health threat exposing patients to ineffective antibiotics. The World Health Organization (WHO) developed a global action plan to combat antimicrobial resistance, which was endorsed by the World Health Assembly in May 2015 [1]. The plan underscores the importance of strengthening AMR surveillance in healthcare settings, which is meant to help improve the detection and control of emerging bacterial resistance and outbreaks.

One of the largest AMR surveillance systems in the world, Japan Nosocomial Infections Surveillance (JANIS), was established by the Ministry of Health, Labour and Welfare (MHLW) in 2000. As of January 2018, there are 2000 hospitals voluntarily participating in the clinical laboratory JANIS module, which collects comprehensive routine bacteriological test results monthly online [2]. It generates not only national and regional AMR reports but also benchmarking data for each member hospital to guide and evaluate infection control practices.

Hospital outbreaks of AMR pathogens should be detected and controlled as early as possible. In Japan, some of the large hospitals with electronic medical records and hospital microbiology laboratories have adopted high-cost infection control systems with automated daily cluster-detection algorithms, yet the sensitivity and specificity of these alerts is poorly quantified. Recognizing that the monthly JANIS hospital-specific feedback reports are far from real-time, there is a need in all facilities for a validated low-cost cluster-detection tool to take prompt action against the rise of AMR, especially for resource-limited hospitals.

WHONET, software to manage and analyse microbiology data, has been distributed free-of-charge since 1989 by the WHO Collaborating Centre for Surveillance of Antimicrobial Resistance in collaboration with the WHO [3]. Nowadays, it is actively used in more than 120 countries worldwide to support local, national, and international surveillance initiatives. One core analytical feature of WHONET is the use of routine antimicrobial susceptibility test data to define multidrug-resistant strain phenotypes to support the geographic and temporal tracking of susceptible, resistant, and multidrug-resistant subpopulations. The integration of the free cluster-detection tool SaTScan may provide timely detection of AMR bacteria in clusters when applied to routine bacteriological tests [4].

Previous studies have demonstrated how WHONET-SaTScan can detect both previously identified and unrecognized outbreaks, in part through its consideration of pathogens beyond the list of specific priority AMR pathogens [5–7]. However, it also detects clusters of fully susceptible isolates and intrinsically or high-level resistance patterns, which are of less interest to infection control staff [7,8]. Moreover, whereas WHONET-SaTScan has been evaluated in several countries and settings, there are no publications thus far on its use in Asia [5–11]. Since the level of concern for AMR pathogens is different in each country, the algorithm of WHONET-SaTScan for identifying clinically meaningful clusters needs to be validated in regions within Asia. Furthermore, the scalability of WHONET-SaTScan data management steps is unclear because it has been applied to no more than 45 facilities in any one study to date [10].

In this study, we aimed to develop a framework for AMR outbreak detection improving upon the past limitations of WHONET-SaTScan, by applying the algorithm to ~1000 hospitals all around Japan, which required the development of new data management and automation tools, and by manually evaluating and validating the clusters detected by WHONET-SaTScan in 10 representative hospitals.

Methods

Preparation of the dataset

All data fields were extracted between January 2011 and December 2016 from the JANIS database, which stores both culture-positive and -negative test diagnostic and surveillance sample results (but does not store data on antimicrobial usage). The bacterial code list of JANIS includes codes for the bacterial subtypes meticillin-resistant *Staphylococcus aureus* (MRSA), meticillin-susceptible *S. aureus* (MSSA), and vancomycin-resistant enterococci (VRE), considering the use of selective media without antimicrobial susceptibility testing (AST) results. The results for oxacillin and vancomycin were imputed for the MRSA/MSSA and VRE codes, respectively.

The recoding of JANIS data to WHONET format was conducted using a newly created 'JANIS to WHONET data parser' followed by WHONET's BacLink data import module. Two-step filtering was then carried out using WHONET macros. First, inpatient samples were selected to focus on outbreaks in the hospital. Second, the first isolate per patient per species per 30 days, regardless of specimen type and resistance profile, was included to avoid counting repeat isolates. The filtered data were saved as a file for each hospital, separately.

Antimicrobial resistance profiles of the pathogens

The organisms and antimicrobials for the resistance profile (combination of antimicrobial susceptibility test results) were selected from the antibiograms included in the JANIS annual 2016 report. The antimicrobials were narrowed down to a core set for *S. aureus*, *Enterococcus* spp., *Escherichia coli* as a representative for Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. by selecting the drug most frequently tested among the class or generation. Drugs with resistance rates >50% or <0.1% were excluded from the core set considering their value for defining meaningful resistance profiles. Cotrimoxazole for *S. aureus* and cefazoline for *E. coli* were also excluded because of the unreliability of the minimum inhibitory concentration values reported to JANIS. The isolate was considered 'resistant' when categorized as 'intermediate' or 'resistant' according to the Clinical and Laboratory Standards Institute (CLSI) guideline M100-S27 [12].

SaTScan and cluster detection

The batch version of the SaTScan software implemented within WHONET was used to detect clusters of patients from whom isolates of the same bacterial species with identical resistance profile were isolated [10]. SaTScan uses scan statistics, which offer a relatively simple approach to determining whether the number of cases reported for a certain period is excessive [13]. Note that it is not designed to detect longitudinal trends but detects statistically significant short-term clusters suggestive of outbreaks meriting immediate

response. In this study, the statistical significance of a cluster was evaluated by Monte Carlo hypothesis testing, in which the expected number of cases was estimated with the space–time permutation algorithm based on the observed historical data [14]. The simulated prospective mode of WHONET-SaTScan, an iterative series of prospective analyses conducted over the length of the study period, uses previous data as a historical baseline for comparison. The statistical likelihood that observed clusters are due to chance alone is expressed in terms of a recurrence interval, which is the inverse of the *P*-value [10]. A recurrence interval threshold of 60 days was used for this study to detect clusters that one could expect to see by chance alone at most six times a year for further examination and validation. We selected this threshold to prioritize reduction of false-negative results for detecting detrimental events such as outbreaks. The other parameters for the analysis were chosen from previous studies; the baseline (the number of days of historical data prior to the day of analysis) was set at 365 days, maximum cluster detection window of 60 days (SaTScan simultaneously searches for statistical clusters of 1, 2, 3, and up to 60 days' duration), and 999 Monte Carlo simulations for calculating recurrence intervals [5,7–10].

There is no definitive minimum number of cases required to define an outbreak; however, three cases in the same unit within one month is widely used by infection control practitioners, especially for MRSA [15]. Based on that, the minimum number of cases for cluster detection was set at three within a month, although a cluster that is a statistically significant signal does not necessarily correspond to a real outbreak.

The analyses were implemented as a series of WHONET macros conducted iteratively separately for each hospital. Using an in-house post-processing Perl script, we excluded clusters in which measured antibiotics in the resistance profile were fully susceptible, AST results were not reported, breakpoints were not defined by the CLSI, or combinations of the above. Moreover, clusters of *Enterococcus faecium* merely resistant to ampicillin and/or levofloxacin, and *Enterobacter cloacae* and *E. aerogenes* merely resistant to cefmetazole were excluded because of high or intrinsic resistance [12].

Selection and investigation of hospitals nationwide and the 10 hospitals for site visits

In 2014, the breakpoint panels in most hospitals shifted to those conforming with CLSI M100-S22 and later [12]. Therefore, the all-hospital analyses were limited to 2015–2016, using the 2015 data as the baseline to detect clusters of 2016 data. Since medical ward data comprise a voluntary data field in JANIS, only hospitals with ward completeness ≥95% were included in the analysis. The analysis was further restricted to hospitals that were aggregated in the JANIS annual 2016 report because their datasets had previously undergone thorough validation. For each hospital, using an in-house Java program, descriptive statistics used in the JANIS annual report were calculated, such as the number of patients from whom each major bacterial species was isolated. The distribution of statistics stratified by hospital sizes was examined using JMP Pro version 13 (SAS Institute, Cary, NC, USA).

Ten hospitals were selected: three large (≥500 beds), four mid-sized (200–499 beds), and three small (<200 beds), to examine whether infection control staff were aware of the clusters suggested by SaTScan, whether the clusters detected by SaTScan were of clinical interest to facility staff, and whether there were additional known clusters that SaTScan did not detect. The hospitals visited were selected from those included in the nationwide analysis, at least one each from the nine regions in Japan. For these 10 hospitals, all data between 2011 and 2016 were analysed, using the first year as the baseline data for the detection of clusters. A combination of infection control doctors/nurses and microbiology technologists was interviewed during the hospital visits. The facility staff provided information on microbiological investigation in their hospital and how they defined and controlled the outbreaks that occurred during the study period in addition to the verification of the SaTScan results.

Ethical concerns

Patient identifiers are de-identified by each hospital before data submission to JANIS. The study protocol was approved by the Ethics Committee of National Institute of Infectious Diseases (approval number 817) and Brigham and Women's Hospital Partners Human Research Committee (approval number 2017P000279).

The 10 hospitals selected for site visits were asked to provide the opportunity for opt-out for the patients during the study period, and each hospital decided whether to request review and approval by their ethics committee. Prior to visiting the hospitals, we sent them the list of isolates and asked them how they responded to each cluster to avoid provision of personally identifiable information during the visit.

Results

Nationwide analysis

Among 8442 hospitals nationwide, 1471 hospitals (17.4%) submitted data both in 2015 and 2016, and 1046 hospitals (71%) had at least 95% of ward names filled. The analysis was restricted to 1031 hospitals aggregated in the JANIS 2016 annual report (Table I). Most of them were mid-sized (618, 60%), followed by large (246, 24%), and small (167, 16%). Comparison of the number of specimens per 100 beds revealed that large hospitals obtained more specimens than mid-sized hospitals, and mid-sized hospitals obtained more than small hospitals, for any type of specimen. Similarly, the comparison of the number of patients with each pathogen per 100 beds revealed that large hospitals had more patients with pathogens than mid-sized and small hospitals. Even though the top two pathogens were *S. aureus* and *E. coli* for all hospitals, large hospitals generally had more *S. aureus*, whereas small hospitals generally had more *E. coli*.

Clusters detected with WHONET-SaTScan in the 1031 hospitals are presented in Table II. There were more hospitals with clusters in large hospitals (190/246, 77.2%) than mid-sized (418/618, 67.6%) and small hospitals (86/167, 51.5%). The most frequently detected pathogen as a cluster was *S. aureus*, followed by *E. coli* and *Klebsiella pneumoniae* for all hospital sizes. Most clusters (1389/1588, 87.5%) included five or fewer patients for all pathogens, regardless of hospital size. The duration of each cluster was mostly (1150/1588, 72.4%) ≤30 days, depending on the organism (Table III). For the top two

Table I
Characteristics of 1031 hospitals in 2016

Characteristic	Large hospitals ($N = 246$)	Mid-sized hospitals ($N = 618$)	Small hospitals ($N = 167$)
No. of specimens/100 beds (median, IQR)			
Respiratory	406.8 (291.3–581.1)	252.0 (166.3–390.5)	196.8 (120.0–301.6)
Urine	177.9 (121.1–258.4)	124.6 (83.1–181.5)	92.4 (50–158)
Stool	93.4 (57.1–174.5)	58.9 (33.6–92.9)	33.3 (14.6–57.3)
Blood	538.3 (387.4–710.2)	328.1 (191.8–489.6)	151.7 (70–301)
CSF	21.6 (12.8–33.1)	7.5 (2.3–16)	0.7 (0–4.5)
Others	319.6 (193.2–456.3)	142.5 (91.5–214.5)	68.7 (29.9–119.3)
All	1719 (1252–2140)	981 (654.2–1406)	617.3 (354.1–885.3)
No. of patients with bacteria/100 beds (median, IQR)			
Staphylococcus aureus	64 (50.5–80.9)	52.6 (36.4–73.3)	43.7 (31.6–69)
Enterococcus faecalis	26.2 (18.2–36.1)	18.4 (11.9–26.4)	12.2 (6–22.2)
Enterococcus faecium	9.1 (6.3–13.8)	6.4 (3–10.5)	3.4 (1–7.3)
Escherichia coli	56.1 (43.4–74.9)	53.0 (38.2–75.1)	47.8 (31–69.7)
Klebsiella pneumoniae	27.6 (19.8–36.2)	24.5 (16.4–35.1)	20.8 (14.6–30)
Enterobacter spp.	19.1 (13.5–27.5)	13.8 (8.5–20.9)	8.8 (5.5–14.4)
Serratia marcescens	5.3 (3.8–7.6)	3.9 (2.3–6.2)	4.4 (2.4–7.5)
Pseudomonas aeruginosa	28.5 (20.5–37.2)	24.0 (16.6–35.9)	24.0 (14.1–36.8)
Acinetobacter spp.	5.1 (3.3–8)	3.5 (1.7–6.4)	2.5 (1.4–5)

IQR, interquartile range; CSF, cerebrospinal fluid.
Large, ≥500 beds; mid-sized, 200–499 beds; small, <200 beds.

Table II
Patients per cluster detected with WHONET-SaTScan in the 1031 hospitals in 2016

	No. of patients/cluster					
	Large hospitals ($N = 190$)		Mid-sized hospitals ($N = 418$)		Small hospitals ($N = 86$)	
	≤5	>5	≤5	>5	≤5	>5
Staphylococcus aureus	213	37 (15%)	299	44 (13%)	53	10 (16%)
Enterococcus faecalis	20	0	26	2 (7%)	1	0
Enterococcus faecium	5	4 (44%)	10	5 (33%)	0	0
Escherichia coli	119	18 (13%)	256	26 (9%)	47	5 (10%)
Klebsiella pneumoniae	46	5 (29%)	101	25 (20%)	19	4 (17%)
Enterobacter cloacae	17	2 (11%)	16	1 (6%)	0	0
Enterobacter aerogenes	9	0	7	2 (22%)	0	0
Serratia marcescens	9	0	11	0	3	1 (25%)
Pseudomonas aeruginosa	25	4 (14%)	50	1 (2%)	10	1 (9%)
Acinetobacter spp.	7	1 (13%)	10	0	0	1 (100%)

Large, ≥500 beds; mid-sized, 200–499 beds; small, <200 beds.

Table III
Duration of clusters detected with WHONET-SaTScan in the 1031 hospitals in 2016

	Duration of cluster					
	Large hospitals ($N = 190$)		Mid-sized hospitals ($N = 418$)		Small hospitals ($N = 86$)	
	≤30	>30	≤30	>30	≤30	>30
Staphylococcus aureus	211	39 (16%)	247	96 (28%)	37	26 (41%)
Enterococcus faecalis	15	5 (25%)	15	13 (46%)	1	0
Enterococcus faecium	5	4 (44%)	12	3 (20%)	0	0
Escherichia coli	118	19 (14%)	227	55 (20%)	31	21 (40%)
Klebsiella pneumoniae	43	8 (16%)	68	58 (46%)	10	13 (57%)
Enterobacter cloacae	12	7 (37%)	9	8 (47%)	0	0
Enterobacter aerogenes	4	5 (56%)	1	8 (89%)	0	0
Serratia marcescens	4	5 (56%)	7	4 (36%)	3	1 (25%)
Pseudomonas aeruginosa	20	9 (31%)	37	14 (27%)	7	4 (36%)
Acinetobacter spp.	2	6 (75%)	3	7 (70%)	1	0

Large, ≥500 beds; mid-sized, 200–499 beds; small, <200 beds.

pathogens, clusters >30 days were detected more in small hospitals than in mid-sized and large hospitals (*S. aureus* 41% vs 23% and *E. coli* 40% vs 18%, both with $P < 0.005$ by χ^2-test).

In-depth analysis and assessments of the 10 representative hospitals

Table IV shows the characteristics of the 10 hospitals under focused study. The number of specimens per 100 beds varied between the hospitals; there was a 15.9-fold difference between the largest and the smallest, hospitals G and J, respectively. Hospital G did not conduct active screening testing for inpatients; however, the number of specimens per 100 beds was prominent because the number of emergency patients accepted was high and several samples were obtained from patients on admission.

The 10 hospitals used similar, though not identical, criteria for monitoring and defining outbreaks of AMR bacteria; all used the official notice issued by the MHLW as a basis. A suspected outbreak in the MHLW notice is defined as at least three cases of AMR bacteria within four weeks in the same unit, or a single case of either carbapenem-resistant Enterobacteriaceae (CRE), vancomycin-resistant *S. aureus* (VRSA), VRE, multidrug-resistant *Pseudomonas aeruginosa* (MDRP), or multidrug-resistant *Acinetobacter* spp. (MDRA). Nine out of 10 of the hospitals had a fixed list of priority AMR bacteria for routine surveillance, based in part on the MHLW notice and in part on local pathogen priorities and decisions, such as MRSA and extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL). The core set of antimicrobials was mostly tested in the 10 hospitals except for a few drugs which were not always tested, especially in small hospitals.

The cluster detection period varied among the hospitals; there were four, two, two, and two hospitals that had a five-, three-, two-, and one-year period, respectively. Clusters detected by SaTScan and responses to the clusters in the 10 hospitals are summarized in Table V. The clusters detected by SaTScan were categorized into three groups (left, middle, and right in Table V): (i) previously recognized as clusters requiring intervention by infection control staff ('high interest'), (ii) not

Table IV
Characteristics of 10 hospitals in 2016

Hospital	Location	No. of specimens per 100 beds in 2016	Active screening testing for MRSA among inpatients	Definition of AMR outbreak	AMR bacteria under surveillance[a]
Large hospitals					
A	Tokyo	1948	NICU, ICU	MHLW notice[b], >2 SD[c]	MRSA, PRSP, BLNAR, ESBL, CPE, 2DRP, 2DRA
B	Tottori	2074	NICU, GCU	Modified MHLW notice[b]	MRSA, ESBL, AmpC, MBL, 2DRP
C	Aichi	2472	NICU, GCU, preoperative (cardiac, and any surgeries with implant)	Modified MHLW notice[b]	MRSA, ESBL, AmpC, CPE, 2DRP
Mid-sized hospitals					
D	Tottori	1232	None	MHLW notice[b]	MRSA, MRSE, PRSP, BLNAR, ESBL, 2DRP
E	Miyagi	1740	NICU, ICU, HCU	MHLW notice[b]	Not specified (difference in MIC pattern)
F	Hokkaido	1509	Premature room	MHLW notice[b]	MRSA, ESBL, MBL, NDM-1, KPC, 1DRP
G	Osaka	4302	None	MHLW notice[b]	MRSA, ESBL
Small hospitals					
H	Tokushima	1047	Emergency ward, preoperative	MHLW notice[b]	MRSA, ESBL, 2DRP
I	Niigata	475	Orthopaedic preoperative	MHLW notice[b]	MRSA, ESBL, CRP, CRSerratia
J	Fukuoka	270	High-risk patients in general practice	MHLW notice[b], >2 SD[c]	MRSA, ESBL, CRP, QRE

AMR, antimicrobial resistance; NICU, neonatal intensive care unit; ICU, intensive care unit; GCU, growing care unit; HCU, high-care unit; MRSA, meticillin-resistant *Staphylococcus aureus*; PRSP, penicillin-resistant *Streptococcus pneumoniae*; BLNAR, β-lactamase-non-producing ampicillin-resistant *Haemophilus influenzae*; ESBL, extended-spectrum β-lactamase-producing Enterobacteriaceae; CPE, carbapenemase-producing Enterobacteriaceae; 2DRP, two-drug-resistant *Pseudomonas aeruginosa*; 2DRA, two-drug-resistant *Acinetobacter* spp.; AmpC, AmpC β-lactamase-producing Enterobacteriaceae; MBL, metallo-β-lactamase-producing Enterobacteriaceae and non-fermenters; MRSE, meticillin-resistant *Staphylococcus epidermidis*; NDM-1, New Delhi metallo-β-lactamase-1 (NDM-1)-producing Enterobacteriaceae; KPC, *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacteriaceae; 1DRP, one-drug-resistant *Pseudomonas aeruginosa*; CRSerratia, carbapenem-resistant *Serratia marcescens*; CRP, carbapenem-resistant *Pseudomonas aeruginosa*; QRE, fluoroquinolone-resistant *Escherichia coli*; MIC, minimum inhibitory concentration.
Large, ≥500 beds; mid-sized, 200–499 beds; small, <200 beds.
[a] Basic set of antimicrobial-resistant bacteria: carbapenem-resistant Enterobacteriaceae (CRE), vancomycin-resistant *S. aureus* (VRSA), vancomycin-resistant enterococci (VRE), multidrug-resistant *Pseudomonas aeruginosa* (MDRP), and multidrug-resistant *Acinetobacter* spp. (MDRA).
[b] Ministry of Health, Labour and Welfare (MHLW) notice: Three cases of identical AMR bacteria in the same ward within four weeks, and the first case for CRE, VRSA, VRE, MDRP, MDRA is defined as suspected outbreak by the MHLW.
[c] >2 standard deviations from the baseline.

Table V
Response in the 10 hospitals to clusters detected by SaTScan

Cluster detection period	Recognized as cluster requiring intervention		Not recognized as cluster but meriting intervention		Not recognized as cluster and not meriting intervention	
	Organism (resistance profile)	Reason for intervention	Organism (resistance profile)	Reason for intervention	Organism (resistance profile)	Reason for no intervention
Hospital A 2012—2016	*S. aureus* (MRSA)	Same doctors in NICU and paediatrics, same wards	*S. aureus* (MSSA)	Later MRSA outbreaks in NICU and paediatrics, respectively		
	E. coli (ESBL)	Same ward				
			K. pneumoniae (PIP)	All bronchial, ICU	*K. pneumoniae* (PIP)	PIP, different specimen
	E. aerogenes (AmpC)	NICU	*E. aerogenes* (AmpC)	All bronchial, ICU		
			P. aeruginosa (LVX)	All bronchial, ICU		
Hospital B 2012—2016	*S. aureus* (MRSA)	Same ward				
					E. coli (PIP)	Community origin
					K. pneumoniae (PIP)	More than four weeks interval
	P. aeruginosa (MEM)	ICU	*P. aeruginosa* (MEM)	Later outbreak in ICU		
Hospital C 2012—2016			*S. aureus* (MSSA)	Blood/bile		
					K. pneumoniae (PIP)	PIP
	S. marcescens (CMZ)	SICU				
Hospital D 2016					*S. aureus* (MRSA)	Community origin
					E. coli (ESBL)	Urine/stool
Hospital E 2012—2016			*S. aureus* (MSSA)	Intubated patients in HCU	*S. aureus* (MRSA, MSSA)	Community origin, different resistance
					E. coli (PIP and/or LVX)	Community origin, different resistance, different specimen, Urine/stool
Hospital F 2014—2016			*S. aureus* (MRSA)	Same ward		
					E. coli (ESBL, PIP and/or LVX)	Community origin
					K. pneumoniae (PIP)	PIP, community origin
Hospital G 2016					*S. aureus* (MRSA)	Community origin
					K. oxytoca (PIP)	Community origin
Hospital H 2014—2016					*S. aureus* (MRSA)	Community origin
			E. coli (PIP + LVX)	Same ward		
Hospital I 2015—2016					*S. aureus* (MRSA)	Community origin, different specimen
	E. coli (ESBL)	Same ward (internal medicine)	*E. coli* (PIP + LVX)	Later ESBL outbreak in internal medicine		
					K. pneumoniae (PIP)	Community origin, different specimen
Hospital J 2015—2016	*S. aureus* (MRSA)	Same ward				

MRSA, meticillin-resistant *Staphylococcus aureus*; MSSA, meticillin-susceptible *Staphylococcus aureus*; ESBL, extended-spectrum β-lactamase-producing Enterobacteriaceae; AmpC, AmpC β-lactamase-producing Enterobacteriaceae; NICU, neonatal intensive care unit; ICU, intensive care unit; SICU, surgical intensive care unit; PIP, piperacillin-resistant; LVX, levofloxacin-resistant; MEM, meropenem-resistant; CMZ, cefmetazole-resistant.

previously recognized as clusters but judged upon review during this study as meriting intervention, and (iii) not previously recognized as clusters and judged upon review during this study as not meriting intervention ('low interest'). There were: (i) 12 clusters recognized as clusters requiring intervention, (ii) 12 clusters not recognized as clusters meriting intervention, and (iii) 31 clusters not recognized as clusters and not meriting intervention (further details on each cluster are shown in Supplementary Table S1).

A further category denoted (iv) the previously known clusters for which intervention was required that were not detected in this study by SaTScan. Approximately 80% of the detected clusters were unrecognized by infection control staff because they were not included in the list of priority pathogens under routine surveillance. Compared to the clusters previously recognized by the hospitals, the WHONET-SaTScan detected clusters not previously known by the infection control staff but needing intervention, which were generally of more susceptible isolates; clusters of MSSA were detected in three hospitals, and clusters of *E. coli* resistant to piperacillin and levofloxacin in two hospitals. Moreover, clusters of more susceptible isolates were detected before outbreaks of more resistant pathogens occurred (Supplementary Figure S1); hospital A had clusters of MSSA before MRSA outbreaks, whereas hospital I had a cluster of *E. coli* resistant to piperacillin and levofloxacin before an ESBL outbreak. If the unrecognized clusters had been detected in real-time, the infection control staff would consider that intervention was merited if the isolates had been obtained from the same ward and specimen type, and that intervention would not be merited if the isolates were piperacillin-resistant *K. pneumoniae*, obtained from different specimen types, or considered to have been acquired in the community setting. WHONET-SaTScan did not detect five out of 17 known clusters which required interventions. The reason for failure to detect the known clusters was the lack of resistance profile, except for two MRSA clusters in hospital A ('Clusters which required intervention but were not detected by SaTScan' column on the right in Supplementary Table S1). Two of the three clusters lacking resistance profile were MRSA outbreaks detected by screening media; the remaining cluster consisted of three patients with *Pseudomonas aeruginosa* whose resistance profile was accidentally not submitted to the JANIS system.

Discussion

This is the first publication on WHONET-SaTScan applied to an Asian country and to the largest number of facilities to date. Even though we used historical data, many of the clusters detected by the simulated prospective analysis of WHONET-SaTScan were closely related to findings from real-time practice in the 10 representative hospitals.

The AMR bacteria under routine surveillance varied among the 10 hospitals, indicating differences in patient characteristics, capacity of hospital staff, and the local epidemiology of the resistance strains. Given that all these factors can change, a comprehensive approach with flexibility in the target AMR bacteria is essential. One thing in common among the 10 hospitals was that WHONET-SaTScan detected clusters of bacteria beyond their list of pre-defined specific AMR bacteria, and those with less resistance, such as erythromycin-resistant MSSAs, were overlooked by infection control staff even though the cluster was detected as statistically significant by WHONET-SaTScan. Generally, clusters of organisms with unusual resistance profiles are more easily recognized, whereas clusters of organisms with an unremarkable resistance profile are less likely to be recognized as significant [16,17]. One benefit of detecting clusters of more susceptible isolates is that detection may improve infection control practices before the outbreak of more resistant isolates occurs.

We should keep in mind that the core set of antimicrobials was not fully tested among the 10 hospitals, especially in smaller facilities, and it is thus difficult to precisely compare the results between the hospitals. Comparison of findings between hospitals and the detection of regional and national outbreaks would be facilitated by routine testing of a standard set of antimicrobials.

Nationwide analysis of 1031 hospitals revealed that, among the large hospitals, more specimens per 100 beds were obtained and more clusters were proportionally detected. Specimen obtainment is crucial for identifying patients with AMR bacteria because there are no distinctive clinical flags such as symptoms. The severity of illness and underlying conditions of the admitted patients can be the reason for the variation in the number of specimens in each hospital.

An outbreak is a situation where the observed number of cases exceeds the expected number of cases in a limited area [18]. The traditional MHLW approach has its deficiencies as it does not consider the underlying endemic rate of isolates. For example, in Japan, carbapenem-resistant *Acinetobacter* spp. are rarely isolated, whereas MRSA and ESBLs are frequently identified in almost all facilities [2]. Thus, the same role of 'three cases of AMR bacteria within 4 weeks in the same unit' would not have consistent sensitivity, specificity, and positive predictive value for all organisms. In recognition of this, the MHLW criterion does not apply to areas where MRSA is known to be endemic [15], but this only partially addresses the limitation. Another limitation of the MLHW criterion is that it does not consider different resistance profiles among the AMR strains found.

Most of the clusters detected by WHONET-SaTScan in Japan were of five or fewer patients with a duration of $\leq$30 days; however, the proportion of detected clusters of *S. aureus* and *E. coli* lasting $>$30 days was significantly higher in small hospitals than in mid-sized and large hospitals, possibly related to the longer length of stay and multiple counting of patient isolates after 30 days. Therefore, the existing definition of 'outbreak' as four weeks established in the MHLW notice may be too short. The clusters most detected were of *S. aureus* for all hospital sizes, even though *E. coli* was the most isolated pathogen from the patients in small hospitals. One explanation is that *S. aureus* may cause more hospital outbreaks than *E. coli*.

We studied inpatient samples including those obtained within 48 h of admission, most commonly acquired in the community. Hospitals with in-house microbiology laboratories have a microbiology data management system, but these laboratory systems are not always linked with clinical information such as the date of admission. Since electronic medical records are increasingly adopted in Japanese hospitals, systems that integrate microbiology data with clinical information may become much more affordable and commonplace, permitting the incorporation of date of admission in the algorithms.

Several limitations of this study are worth taking into consideration in future studies. First, ward names in the JANIS data are voluntarily filled in, which may lack consistency. Second, the first isolate per patient per species per 30 days was included in the analysis, irrespective of resistance profile. Patients who acquired isolates of different resistance profile of the same species within 30 days were overlooked with this approach. Third, WHONET-SaTScan considered 'intermediate' and 'resistance' groups as resistant; however, the difference between 'susceptible' and 'intermediate' can be within the range of reproducibility error. A comparison of 'susceptible' and 'resistance' may provide more discrimination of the isolates. Fourth, the thresholds for each parameter of WHONET-SaTScan for detecting clusters were based on previous studies and used for all species. Further assessment and validation may demonstrate that other parameter sets may be advantageous for different species. A recurrence interval was set at 60 days for each ward, while other studies have used 365 days for the whole hospital. The lower threshold should improve sensitivity of cluster detection but at the cost of lower specificity and positive predictive value. Fifth, in hospital A, some of the outbreaks recognized by the hospital were undetectable by SaTScan. The frequency of MRSA cases was consistently high since 2014, both in the neonatal intensive care unit and the paediatric ward, which hindered the detection by SaTScan of MRSA outbreaks occurring in 2015 and 2016. To facilitate the detection of subsequent similar clusters, including outbreak recurrence, an adjustment feature within WHONET-SaTScan to eliminate prospectively confirmed clusters from the baseline could be useful.

In conclusion, rapid recognition of outbreaks is one of the major objectives of surveillance. WHONET-SaTScan can suggest epidemiological links based on resistance profiles beyond the list of AMR bacteria under surveillance in each hospital and those of more susceptible isolates for early intervention in infection control practices.

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Conflict of interest statement
None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2018.10.005.

References

[1] World Health Organization. Global action plan on antimicrobial resistance. 2015. Available at: http://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/ [last accessed May 2018].
[2] Japan Nosocomial Infections Surveillance (JANIS). Ministry of health, Labour and Welfare. 2016. Available at: https://janis.mhlw.go.jp/english/about/index.html [last accessed May 2018].
[3] WHONET, Developed by the WHO collaborating Centre for surveillance of antimicrobial resistance at the Brigham and Women's hospital in Boston, USA. Available at: http://whonet.org/ [last accessed May 2018].
[4] SaTScan. Software of the spatial, temporal, and space—time scan statistics. Available at: https://www.satscan.org/ [last accessed May 2018].
[5] Huang SS, Yokoe DS, Stelling J, Placzek H, Kulldorff M, Kleinman K, et al. Automated detection of infectious disease outbreaks in hospitals: a retrospective cohort study. PLoS Med 2010;7:e1000238.
[6] Vlek AL, Cooper BS, Kypraios T, Cox A, Edgeworth JD, Auguet OT. Clustering of antimicrobial resistance outbreaks across bacterial species in the intensive care unit. Clin Infect Dis 2013;57:65—76.
[7] Natale A, Stelling J, Meledandri M, Messenger LA, D'Ancona F. Use of WHONET-SaTScan system for simulated real-time detection of antimicrobial resistance clusters in a hospital in Italy, 2012 to 2014. Euro Surveill 2017;22:30484.
[8] Park R, O'Brien TF, Huang SS, Baker MA, Yokoe DS, Kulldorff M, et al. Statistical detection of geographic clusters of resistant *Escherichia coli* in a regional network with WHONET and SaTScan. Expert Rev Anti Infect Ther 2016;14:1097—107.
[9] Vinas MR, Tuduri E, Galar A, Yih K, Pichel M, Stelling J, et al. Laboratory-based prospective surveillance for community outbreaks of *Shigella* spp. in Argentina. PLoS Negl Trop Dis 2013;7:e2521.
[10] Stelling J, Yih WK, Galas M, Kulldorff M, Pichel M, Terragno R, et al. Automated use of WHONET and SaTScan to detect outbreaks of *Shigella* spp. using antimicrobial resistance phenotypes. Epidemiol Infect 2010;138:873—83.
[11] Lefebvre A, Bertrand X, Vanhems P, Lucet JC, Chavanet P, Astruc K, et al. Detection of temporal clusters of healthcare-associated infections or colonizations with Pseudomonas aeruginosa in two hospitals: comparison of SaTScan and WHONET software packages. PloS One 2015;10:e0139920.
[12] Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. 27th ed. Wayne, PA: CLSI; 2017. Supplement M100.
[13] Sullivan PS, McKenna MT, Waller LA, Williamson D, Lee LM. Analyzing public health surveillance data. In: Lee LM, Teutsch SM, Thacker SB, Louis ME, editors. Principles and practice of public health surveillance. 3rd ed. New York: Oxford University Press; 2010. p. 88—145.
[14] Kulldorff M, Heffernan R, Hartman J, Assuncao R, Mostashari F. A space—time permutation scan statistic for disease outbreak detection. PLoS Med 2005;2:e59.
[15] Wenzel RP, Reagan DR, Bertino Jr JS, Baron EJ, Arias K. Methicillin-resistant *Staphylococcus aureus* outbreak: a consensus panel's definition and management guidelines. Am J Infect Control 1998;26:102—10.
[16] Archibald LK, Jarvis WR. Incidence and nature of endemic and epidemic healthcare-associated infections. In: Jarvis WR, editor. Hospital infections. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2014. p. 451—75. Ch. 30.
[17] Baker MA, Huang SS, Letourneau AR, Kaganov RE, Peeples JR, Drees M, et al. Lack of comprehensive outbreak detection in hospitals. Infect Control Hosp Epidemiol 2016;37:466—8.
[18] Porta M. A dictionary of epidemiology. 6th ed. New York: Oxford University Press; 2014.