Interhospital Transmission of Vancomycin-resistant *Enterococcus Faecium* in Aomori, Japan

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Research

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Abstract

A series of vancomycin-resistant *Enterococcus faecium* (VREf) outbreaks caused by clonal propagation due to inter-hospital transmission occurred in six general hospitals in Aomori prefecture, Japan. This was the first multi-jurisdictional outbreak of VREf sequence type 1421 in Japan. It took almost three years for VREf prevalence to return to pre-outbreak levels. The duration and size of outbreaks differed between hospitals according to the countermeasures available at each hospital. Prompt and strong countermeasures including patient isolation and repetitive screening of all inpatients were required to control the outbreaks. In addition to strict infection control measures, continuous monitoring of VREf prevalence in local medical regions and smooth and immediate communication among hospitals are required to prevent VREf outbreaks.

Introduction

Vancomycin (VCM)-resistant enterococci (VRE) are listed by the Centers for Disease Control and Prevention (CDC) of the United States of America (USA) as antibiotic-resistant bacteria that present “serious threats” to human health ¹⁾. Spread of VRE is a global concern as a significant cause of healthcare-associated infections ²⁾. Among patients tested for bacteriological cultures in Japan in 2019, the prevalence of VRE-positive patients was 0.04% ³⁾, which is much lower than in countries such as the USA, Germany, Italy, France, China and South Korea ⁴⁾. Healthcare-associated VRE infections have been reported in many Japanese hospitals since the beginning of this century ⁵⁾. A series of *vanA*-positive *E. faecium* outbreaks occurred in Aomori prefecture, at the northern end of Honshu, Japan, between January 2018 and January 2021 that took almost three years to eliminate. We report a series of VRE outbreaks that were spread by interhospital transmission in Aomori prefecture by *vanA* type vancomycin-resistant *Enterococcus faecium* (VREf) sequence type 1421.

Materials And Methods

Identification of VRE

VRE was identified by the clinical laboratory at each affected hospital. Prepared fecal samples were inoculated onto VRE selective agar (Becton Dickinson and Company, Franklin Lakes, NJ, USA). Identification of the isolates and drug susceptibility tests were performed by MicroScan WalkAway using Combo panel PC1J (Dade MicroScan, Sacramento, CA, USA). The Biotyper matrix-assisted laser desorption/ionization system (Bruker Daltonics GmbH and Co., Bremen, Germany) in combination with MicroScan WalkAway and PM1J panel was utilized. Several samples isolated in the early phase of outbreaks at each hospital were sent to the Aomori Prefectural Public Health and Environment Center for detection of *vanA* and *vanB* genes using multiplex PCR.

Data collection

The number of patients sampled for bacteriological tests and the number of patients with multidrug-resistant organisms (MDRO) in hospitals participating in the Aomori Infection Control Network (AICON) were obtained through the Microbiological Information Network Aomori (MINA). AICON is a local infection control network managed by the Infection Control Center at Hirosaki University Hospital. AICON covers all general hospitals and approximately 50% of all hospitals in Aomori prefecture. Participating hospitals can share information about infection control through the network. MINA is a bacteriological database run by AICON. The microbiological test results obtained at each hospital were uploaded via an information network and stored in web servers located and managed at the Infection Control Center of Hirosaki University Hospital. The information processing systems for the database was supplied by KD-ICONS (Tokyo, Japan). Data regarding the prevalence rate of VRE and the number of bacteriological samples in the 47 prefectures of Japan were obtained from Japan Nosocomial Infection Surveillance (JANIS). JANIS is a national surveillance program organized by the Ministry of Health, Labor and Welfare (MHLW) of Japan. Its clinical laboratory division collects information regarding the prevalence of nosocomial infections and antimicrobial-resistant bacteria in Japanese hospitals. As of January 2020, JANIS covered 2,418 hospitals, including > 80% of hospitals with 500 beds or more ^{6, 7)}. JANIS member hospitals are required to submit surveillance data on a regular basis. National data of the prevalence of drug-resistant bacteria in Japan are publicly available on the JANIS website ⁸⁾. VRE was defined following the standard provided by the infectious diseases control law (Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases ⁹⁾) as *Enterococcus* spp. resistant to VCM with MIC of ≥ 16 $\mu\text{g/mL}$ in the microdilution method, which is the definition used by JANIS since 2007. Pulsed-field gel electrophoresis (PFGE) was applied to differentiate the VRE strains isolated from five general hospitals during the outbreak, together with the VRE strains isolated from patients referred to Hirosaki University Hospital during the series of VRE outbreaks in Aomori prefecture.

Whole genome sequencing

Genomic DNA was extracted with QIAamp DNA purification kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. DNA libraries were prepared for sequencing with Enzymatics 5X WGS reagents (BioStream Co., Ltd, Tokyo, Japan) and then pooled. For Illumina sequencing, paired-end sequencing (2 · 300 bp) was performed using the MiSeq reagent kit v3 on the MiSeq platform. Raw reads were assembled using Shovill v1.0.9 ¹⁰⁾ with the default settings. Multilocus sequence typing (MLST) determination was performed using staramr v0.7.2 ¹¹⁾. For single nucleotide polymorphism (SNP) phylogenetic tree analysis, sequences of each strain were aligned using the Snippy pipeline (v4.4.5) ¹²⁾. Reads were mapped to EF_DMG1500501 (a closed annotated Australian genome, Accession No. LT603678). Phylogenetic trees were displayed, annotated, and decorated with FigTree v1.4.4 ¹³⁾. All sequence data have been deposited in the DDBJ/EMBL/GenBank databases Sequence Read Archive (DRA) under accession number DRA012428.

Ethical approval

The study protocol was approved by the Ethics Committee of Hirosaki University Graduate School of Medicine (approval number 2019-1012). Patient consent was not required because of the retrospective nature of the study, which was based entirely on anonymized data.

Outbreak Report

Setting

Aomori prefecture has six major medical regions: Shimokita, Kamitosa, Hachinohe, Aomori city, Seihokugo, and Tsugaru. The Hachinohe, Aomori city, and Tsugaru regions each have a tertiary general hospital with more than 500 beds. There are several medium-sized general hospitals in these six medical regions. The prevalence rates of VRE-positive patients among patients tested for bacteriological cultures in 2017 in Aomori prefecture and in Japan were 0.003% and 0.024%, respectively ³⁾. During the period from January 2018 to January 2021, interhospital transmission of VRE occurred in 14 hospitals in Aomori prefecture, indicated as A–N in chronological order according to the date of the first VRE-positive case identified at each hospital (Fig. 1), and included two tertiary general hospitals. Six hospitals had insidious intra-institutional spread of VRE, and required long-lasting strict countermeasures to end the outbreak.

Index case

Hospital A is a small-sized hospital with < 100 beds in the Hachinohe area. The first VRE-positive patient was detected there on January 26, 2018, followed by a second case three weeks later. The *vanA* gene was detected by PCR in the VRE isolates. Bacteriological screening of hospitalized patients, as instructed by the health center of Hachinohe city, revealed four additional cases in February. The health center shared information with AICON about the VRE outbreak at hospital A, which is not a member of AICON. On March 16, 2018, an emergent external inspection was carried out at hospital A by the health center of Hachinohe city. Genetic analysis and PFGE analysis suggested healthcare-associated transmission of *vanA* type VREf. A total of 15 cases were identified at this hospital during the eight-month period of the outbreak (Fig. 2).

Hospital B

Following the outbreak at hospital A, VRE outbreaks occurred in five general hospitals (B, C, D, E and G) from 2018 to 2020 (Fig. 2). Hospitals B, C, D and G belonged to AICON at the onset of the outbreaks. In hospital B, a general hospital with > 400 beds, five VRE-positive patients were identified in a medical ward in May 2018 following the identification of one patient in April 2018. VRE spread to five other wards in the next few months despite countermeasures that included patient cohorting, active surveillance, and education of medical staff. A second outbreak then occurred in December 2018, during which all inpatients were screened monthly and VRE-positive patients were cared for in a newly prepared isolation ward. Four external inspections were carried out during this long-standing outbreak (June 2018, January 2019, February 2019, and March 2019) by different teams of specialists sent from among the Japan Red

Cross Society, Iwate University Hospital, and the National Institute of Infectious Diseases. Active surveillance of all patients at admission detected very few VRE-positive patients, indicating that there was no spread of VRE within the community. It took 33 months for hospital B to end the outbreak.

Hospital C

The first VRE-positive case appeared in August 2018 in the emergency department of hospital C, a tertiary general hospital in the same medical region as hospitals A and B. Despite countermeasures such as isolation and strict hand washing, active screening in the emergency department of hospital C revealed an abrupt increase in positive cases between December 2018 and January 2019, and a patient with severe burns was infected with VRE during this period. It was thought that meticulous wound care and handling of wet wound coverings contaminated with VRE would minimize the risk of spread; however, screening of all patients revealed additional VRE-positive cases in other wards. Scheduled hospitalizations and surgeries were postponed and the hospital accepted only emergent cases. External inspection was carried out by team of specialists sent by Hirosaki University Hospital, a member of AICON. An isolation ward was prepared as soon as the spread of VRE within the hospital was confirmed. Monthly screening of all inpatients was repeated between February 2019 and December 2019. The spread of VRE was brought under control after February 2019, and the number of VRE-positive patients decreased gradually thereafter.

Hospital D

One VRE-positive patient was found in September 2018, followed in November 2018 by two more patients in hospital D, a tertiary general hospital in Aomori city in the Tosei medical area. An additional six cases were found in screening of patients hospitalized on the same floor in December 2018. The first wave of the VRE outbreak was controlled by regular countermeasures such as strict hand washing, patient isolation, and active VRE screening of patients at hospitalization and at every month after hospitalization in the ward. After the curve of the epidemic showed a nadir in February 2018, a second outbreak occurred in May 2019, during which countermeasures for VRE-outbreak in the hospital were evaluated by specialists from the local government, Aomori City Health Center, AMR Clinical Reference Center in National Center for Global Health and Medicine, and AICON at an external inspection in December 2018. Monthly screening of all inpatients was repeated from May 2019. Active screening for VRE during the period from September 2019 to July 2020 revealed that 12/49 (24.5%) VRE-positive cases were already infected with VRE at the time of admission. VRE-positive patients at admission suggested the spread of VRE within the medical region. The number of VRE-positive patients gradually decreased after August 2019, and returned to zero in December 2019.

Hospital E

Hospital E is a medium-sized general hospital in the Hachinohe medical region. Patients are referred between hospitals B and E. Because of the VRE outbreak at hospital B, active VRE screening began at hospital E in May 2019. Six VRE-positive inpatients were found at the first screening. Monthly screening

of all inpatients was introduced after the first external inspection by infection control specialists arranged through AICON. Follow-up external inspection was carried out in late November 2019. Infection control activities such as hand washing, zoning, environmental hygiene, and education were evaluated and encouraged. The number of VRE-positive patients returned to zero in January 2020.

Hospital G

Hospital G is a medium-sized general hospital in the Kamitosan medical region. VRE-positive patients were found sporadically at this hospital during periods of VRE outbreaks at other hospitals. The local health center of Kamitosan detected sporadic cases of VRE-positive patients in hospitals in their area of responsibility. Following the recommendation of the local health center, the first screening for VRE was carried out for hospitalized patients in December 2019, and found five VRE-positive patients. In addition to the reinforcement of routine infection control activities, VRE screening of patients at hospitalization was started immediately after the first screening. The outbreak ended within six months.

Other hospitals

From 2019, AICON recommended that participating hospitals should screen for VRE at hospitalization, which was conducted at 12 general hospitals and 1 special hospital. A small number of VRE-positive patients was detected by this screening and there was minimal intra-hospital transmission. No new VRE-positive cases were detected after May 2020 (Fig. 3).

Changes in VRE prevalence in 47 Japanese prefectures in 2015–2020

Figure 4 shows the VRE prevalence rate in the 47 prefectures of Japan, obtained from the JANIS surveillance data. VRE outbreaks at multiple hospitals in the same period caused a sharp peak in VRE prevalence. The remarkable size of the area under the curve representing Aomori prefecture suggests the epidemiological importance of the series of VRE outbreaks in this prefecture.

Change in the number of patients tested for bacteriological cultures in 2017–2020

The number of patients tested for bacteriological cultures in hospitals participating in AICON showed a remarkable increase during the VRE outbreak period. The total number in 2019 was 41.7% greater than that in 2017 (Figure 5).

Decrease in MRSA prevalence by countermeasures against VRE

Although the MRSA prevalence rate in hospitals B, C, and D had been consistently much lower than the average in Japanese hospitals participating in JANIS before the VRE outbreak, reinforced countermeasures against nosocomial infections resulted in a further decrease in the prevalence of MRSA during VRE outbreaks. In comparison between the data from MINA and JANIS, which represent Aomori prefecture and Japan, respectively, the MRSA prevalence rate decreased in MINA but not in JANIS (Figure 6).

Analysis of VRE strains using PFGE

Table 1 lists six source hospitals and sampling year for 20 isolates that were tested by PFGE analysis. VRE strains showed identical or very close patterns in PFGE analysis (Fig. 7). Lanes 1, 3, 6, 10, 11, 12, 15, 16, and 18 were judged as identical strains. Lanes 2, 4, and 19 were also identical. The former and the latter were judged as closely related with more than 85% similarity, which indicates interhospital clonal spread of VRE in this series of outbreaks.

SNPs phylogenetic tree analysis

Figure 8 shows the phylogenetic tree based on the core genome SNPs of the same 20 isolates. Whole genome sequencing analysis indicated *vanA*-type VREf ST1421 for most samples except samples 7 and 8 from hospital D. These were identified as other *vanB*-type strains, although sample 6, also from hospital D, was identified as *vanA*-type VREf ST1421.

Discussion

VRE had spread worldwide by the year 2000 ⁴⁾; however, the VRE prevalence rate was still low in Japan as of 2019 ³⁾. It is not easy to prevent VRE spread without active screening because patients infected by VRE are usually asymptomatic. By the time that the first symptomatic patient infected by VRE is found, several asymptomatic patients can be found by spot surveillance, as was the case in hospitals in the present series. It takes months for colonized patients to be free from VRE ¹⁴⁾. Furthermore, colonized patients show no obvious signs of infection but can spread VRE through person-to-person contact during hospitalization. Screening for VRE at hospitalization is strongly recommended if VRE is prevalent in the medical region. Common understanding of the need for screening, patient selection, and evaluation of the clinical and economic benefits based on VRE prevalence should be shared by cooperating hospitals within medical regions. Inter-hospital patient transfer is commonly required to improve patient management; however, transferring patients can promote inter-hospital transfer of MDROs. Interhospital VRE transmissions have been reported in Australia ¹⁵⁾, Taiwan ¹⁶⁾, and Kyoto (Japan) ¹⁷⁾. If VRE is detected in a hospital, the information should be shared by other hospitals in the medical region to prevent interhospital transmission. In their systemic review, Ulrich et al (2017) ¹⁸⁾ reported that the duration of VRE outbreak in hematology and oncology departments ranged from 1 to 36 months, with a mean value of 11 months. Strong countermeasures, including active VRE screening, are necessary to shorten the duration of VRE outbreaks ¹⁹⁻²¹⁾.

PFGE and whole genome sequencing analysis clearly indicated that the multi-jurisdictional outbreaks were caused by *vanA*-type VREf ST1421, whereas 2 of 20 isolates showed different patterns of PFGE and were identified as other *vanB*-type strains by whole genome sequencing. The *vanA* and *vanB* types could generally be distinguished by susceptibility, but confirmation by genetic analysis was useful. The ST1421 clone lacks the *pstS* housekeeping gene of the MLST allele ²²⁾. *pstS*-null VREf clones have recently emerged worldwide and regional spread has been reported in numerous countries, including the Australia

²²⁾, UK ²³⁾, Scotland ²⁴⁾, Denmark ²⁵⁾ and Korea ²⁶⁾. To the best of our knowledge, this is the first report of a VRE outbreak by *pstS*-null VREf ST1421 in Japan.

Increases in medical costs due to spread of VRE is a matter of concern in countries such as the United States ²⁷⁾, Germany ²⁸⁾, France ²⁹⁾, China ³⁰⁾ and Canada ³¹⁾. The cost-saving effect has been shown in a detailed analysis of the costs associated with implementation of a strict policy for controlling spread during outbreaks, including active screening for highly resistant microorganisms ³²⁾. Hospital administrators and infection control specialists need to discuss the costs and benefits of VRE screening to achieve efficient and effective countermeasures based on the medical conditions in each area ³³⁾. Once a VRE outbreak has occurred at one hospital, VRE can spread to other healthcare facilities via transmission by patients and healthcare workers in the same medical area.

Conclusion

Interhospital transmission of VREf ST1421 occurred in Aomori prefecture despite a prefecture-wide infection control network that provides data of microbiological test results uploaded from 40 hospitals in the prefecture. In addition to strict infection control measures and a system of continuous monitoring of MDRO prevalence, sustained interest in the rate of VRE prevalence in local medical regions and smooth and immediate communication among hospitals are required to prevent VRE outbreaks.

Study Limitation

Data analyzed in the present study were provided by hospitals connected through AICON; therefore, data from hospitals not connected to AICON were not included.

Declarations

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Conflict of interest:

None of the authors has any conflicts of interest to declare.

Authorship:

Saito N analyzed the data and wrote the manuscript. Minakawa S and Kimura M prepared VRE samples for PFGE analysis. Inoue F and Hisatsune J collected and conducted detailed analysis of data from the hospitals that participated in this study. Itoga M analyzed the data with Saito N. Kitazawa J, Yamamoto T, Horiuchi H and Matsui M improved the study by screening the bacteriological samples, preserving and providing VRE strains, and discussing the results. Tsuchiya J collected and analyzed the data and created the graphics presented in this manuscript. Gu Y, Suzuki S and Sugai M devised countermeasures to contain outbreaks and participated in study design and data analysis. Kayaba H designed the study and checked the first draft and the final version of the manuscript.

References

1. Centers for Disease Control and Prevention. Biggest threats and data.
[https://www.cdc.gov/drugresistance/biggest-threats.html?](https://www.cdc.gov/drugresistance/biggest-threats.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fdrugresistance%2Fbiggest_threats.html)
[CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fdrugresistance%2Fbiggest_threats.html](https://www.cdc.gov/drugresistance/biggest_threats.html)
(accessed March 24 2021)
2. Cetinkaya Y, Falk P, Mayhall CG. Vancomycin-resistant enterococci. Clin Microbiol Rev. 2000; 13: 686-707. <https://doi.org/10.1128/CMR.13.4.686>
3. Japan nosocomial infections surveillance (CLSI2012 version), Clinical laboratory division. Annual open report 2019, https://janis.mhlw.go.jp/english/report/open_report/2019/3/1/ken_Open_Report_Eng_201900_clsi2012.pdf (accessed March 24, 2021)
4. Vancomycin-resistant enterococci rates by country, CDDEP, https://cddep.org/tool/vancomycin_resistant_enterococci_rates_country/ (Accessed on March 26, 2021)
5. Hoshuyama T, Moriguchi H, Muratani T, et al. Vancomycin-resistant enterococci outbreak at a university hospital in Kitakyushu, Japan: Case-control studies. J Infect Chemother. 2008; 14: 354-360. <https://doi.org/10.1007/s10156-008-0628-x>
6. Japan nosocomial infections surveillance Sankairyousisetu Ichiran (in Japanese). <https://janis.mhlw.go.jp/hospitallist/index.html> (Accessed March 26 2021)
7. Tsutsui A, Suzuki S. Japan nosocomial infections surveillance (JANIS): a model of sustainable national antimicrobial resistance surveillance based on hospital diagnostic microbiology laboratories. BMC Health Serv Res. 2018; 18: 799. <https://doi.org/10.1186/s12913-018-3604-x>.
8. Japan Nosocomial Infection Surveillance (JANIS) website. <https://janis.mhlw.go.jp/>
9. Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases. Act No. 114 of October 2, 1998. http://www.japaneselawtranslation.go.jp/law/detail_main?re=&vm=02&id=2830
10. Shovill v1.0.9 . <https://github.com/tseemann/shovill>
11. The staramr v0.7.2. <https://github.com/phac-nml/staramr>
12. The pipeline Snippy v4.4.5. <https://github.com/tseemann/snippy>
13. FigTree v1.4.4. <http://tree.bio.ed.ac.uk/software/figtree/>

14. Sohn KM, Peck KR, Joo EJ, et al. Duration of colonization and risk factors for prolonged carriage of vancomycin-resistant enterococci after discharge from the hospital. *Int J Infect Dis.* 2013; 17: e240-246. <https://doi.org/10.1016/j.ijid.2012.09.019>
15. Mahony AA, Buultjens AH, Ballard SA, et al. Vancomycin-resistant *Enterococcus faecium* sequence type 796 - rapid international dissemination of a new epidemic clone. *Antimicrob Resist Infect Control.* 2018; 7: 44. <https://doi.org/10.1186/s13756-018-0335-z>
16. Lee SC, Wu MS, Shih HJ, et al. Identification of vancomycin-resistant enterococci clones and inter-hospital spread during an outbreak in Taiwan. *BMC Infect Dis.* 2013; 13: 163. <https://doi.org/10.1186/1471-2334-13-163>
17. Matsushima A, Takakura S, Yamamoto M, et al. Regional spread and control of vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* in Kyoto, Japan. *Eur J Clin Microbiol Infect Dis.* 2012; 31: 1095-1100. <https://doi.org/10.1007/s10096-011-1412-x>
18. Ulrich N, Vonberg RP, Gastmeier P. Outbreaks caused by vancomycin-resistant *Enterococcus faecium* in hematology and oncology departments: A systematic review. *Heliyon.* 2017; 3: e00473. <https://doi.org/10.1016/j.heliyon.2017>.
19. Yoon YK, Sim HS, Kim JY, et al. Epidemiology and control of an outbreak of vancomycin-resistant enterococci in the intensive care units. *Yonsei Med J.* 2009; 50: 637-643. <https://doi.org/10.3349/ymj.2009.50.5.637>
20. Lai CKC, Wong SYN, Lee SS, et al. A hospital-wide screening programme to control an outbreak of vancomycin-resistant enterococci in a large tertiary hospital in Hong Kong. *Hong Kong Med J.* 2017; 23: 140-149. <https://doi.org/10.12809/hkmj164939>
21. Frakking FN. Recommendations for the successful control of a large outbreak of vancomycin-resistant *Enterococcus faecium* in a non-endemic hospital setting. *J Hosp Infect.* 2018; 100: e216-225. <https://doi.org/10.1016/j.jhin.2018.02.016>
22. Carter GP, Buultjens AH, Ballard SA, et al. Emergence of endemic MLST non-typeable vancomycin-resistant *Enterococcus faecium*. *J Antimicrob Chemother.* 2016; 71: 3367-3371. doi: 10.1093/jac/dkw314
23. Raven KE, Reuter S, Reynolds S, et al. A decade of genomic history for healthcare-associated *Enterococcus faecium* in the United Kingdom and Ireland. *Genome Res.* 2016; 26: 1388-1396. doi: 10.1101/gr.204024.116.
24. Lemonidis K, Salih TS, Dancer SJ, et al. Emergence of an Australian-like pstS-null vancomycin resistant *Enterococcus faecium* clone in Scotland. *PLoS One.* 2019; 14: doi: 10.1371/journal.pone.0218185.
25. Hansen TA, Pedersen MS, Nielsen LG, et al. Emergence of a vancomycin-variable *Enterococcus faecium* ST1421 strain containing a deletion in vanX. *J Antimicrob Chemother.* 2018; 73: 2936-40. doi: 10.1093/jac/dky308.

26. Kim KM, Chung DR, Choet SY, et al. Emergence of vancomycin-resistant *Enterococcus faecium* ST1421 lacking the *pstS* gene in Korea. *Eur J Clin Microbiol Infect Dis*. 2020; 39: 1349-56. doi: 10.1007/s10096-020-03853-4.
27. Carmeli Y, Eliopoulos G, Mozaffari E, et al. Health and economic outcomes of vancomycin-resistant enterococci. *Arch Intern Med*. 2002; 162: 2223-2228. doi: 10.1001/archinte.162.19.2223.
28. Escaut L, Bouam S, Frank-Soltysiak M, et al. Eradication of an outbreak of vancomycin-resistant *Enterococcus* (VRE): the cost of a failure in the systematic screening. *Antimicrob Resist Infect Control*. 2013; 2: 18. <https://doi.org/10.1186/2047-2994-2-18>
29. Puchter L, Chaberny IF, Schwab F, et al. Economic burden of nosocomial infections caused by vancomycin-resistant enterococci. *Antimicrob Resist Infect Control*. 2018; 7: 1. <https://doi.org/10.1186/s13756-017-0291-z>
30. Jia H, Li W, Hou T, et al. The attributable direct medical cost of healthcare associated infection caused by multidrug resistance organisms in 68 hospitals of China. *Biomed Res Int*. 2019; 5: 7634528. doi: 10.1155/2019/7634528.
31. Lloyd-Smith P, Younger J, Lloyd-Smith E, et al. Economic analysis of vancomycin-resistant enterococci at a Canadian hospital: assessing attributable cost and length of stay. *J Hosp Infect*. 2013; 85: 54-59. <https://doi.org/10.1016/j.jhin.2013.06.016>
32. Birgand G, Leroy C, Nerome S, et al. Costs associated with implementation of a strict policy for controlling spread of highly resistant microorganisms in France. *BMJ Open*. 2016; 6: e009029. <https://doi.org/10.1136/bmjopen-2015-009029>
33. Humphreys H. Controlling the spread of vancomycin-resistant enterococci. Is active screening worthwhile? *J Hosp Infect*. 2014; 88: 191-198. <https://doi.org/10.1016/j.jhin.2014.09.002>

Table

Due to technical limitations, table 1 pptx is only available as a download in the Supplemental Files section.

Figures

Figure 1

The six medical regions in Aomori prefecture. The map shows the locations of the fourteen hospitals in which interhospital VRE transmissions occurred within the six medical regions in Aomori. Hospitals indicated by the solid black circles had insidious intra-institutional spread of VRE, and required long-lasting strict countermeasures to end the outbreak.

Figure 2

Number of VRE-positive patients per month in all affected hospitals. The monthly number of VRE-positive patients is shown for hospitals A–N. The numbers include new patients and those who repeatedly tested positive for VRE. Hospitals B and C are major tertiary general hospitals in adjacent medical regions.

Figure 3

New VRE-positive cases and positivity rate detected by active screening at time of hospitalization in 13 hospitals. No new VRE-positive cases were detected after May 2020.

Figure 4

Prevalence of VRE in the 47 prefectures of Japan between 2015 and 2020. Trends of the prevalence rate of VRE-positive patients in the 47 prefectures of Japan are shown. The peak value of 1344.68 was recorded during the outbreak in Aomori. The prevalence rate was calculated as (number of VRE-positive patients / total number of patients tested for bacterial cultures) x 105. Recent high prevalence rates in several other prefectures are also evident.

Figure 5

Number of patients sampled for bacteriological tests in hospitals participating in AICON. The remarkable increase in bacteriological samples obtained during the period of VRE outbreaks is largely due to active screening for VRE in major hospitals participating in AICON.

Figure 6

Trends in MRSA prevalence rates in hospitals B, C, and D, and JANIS hospitals during VRE outbreaks. The prevalence rate was calculated as (number of MRSA-positive patients / total number of patients with bacteriological cultures) x 100. Solid arrows indicate detection of the first VRE-positive patient at each hospital. Open arrows indicate the start of strengthening countermeasures, including extensive screening against VRE transmission.

Figure 7

PFGE results of 20 VRE strains isolated from five general hospitals and Hirosaki University Hospital during the VRE outbreaks. The sample numbers are the same as those shown in Table 1. kbp: kilobase pairs, M: DNA size marker (lambda ladder).

Figure 8

Core genome SNP phylogenetic tree of 20 isolates. The sample numbers are the same as those shown in Table 1. Reference genome: Ef_DMG1500501.

Supplementary Files

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