Disease burden of bloodstream infections caused by antimicrobial-resistant bacteria: A population-level study, Japan, 2015–2018

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ABSTRACT

Background: Antimicrobial resistance (AMR) is a global health problem. However, quantitative evaluation of its disease burden is challenging. This study aimed to estimate the disease burden of bloodstream infections (BSIs) caused by major antimicrobial-resistant bacteria in Japan between 2015 and 2018 in terms of disability-adjusted life-years (DALYs).

Methods: DALYs of BSIs caused by nine major antimicrobial-resistant bacteria in Japan were estimated using comprehensive national surveillance data of all routine bacteriological test results from more than 1400 hospitals between 2015 and 2018. The methodology of Cassini et al. was modified to enable comparison of the present results with those in other countries.

Results: It was estimated that 137.9 [95% uncertainty interval (UI) 130.7–145.2] DALYs per 100,000 population were attributable to BSIs caused by nine antimicrobial-resistant bacteria in 2018. Methicillin-resistant *Staphylococcus aureus* (MRSA), fluoroquinolone-resistant *Escherichia coli* (FQREC) and third-generation cephalosporin-resistant *E. coli* (3GREC) accounted for 87.2% overall. The burden did not decrease during the study period and was highest in people aged ≥ 65 years.

Conclusion: The results revealed, for the first time, the disease burden of BSIs caused by nine major antimicrobial-resistant bacteria in Japan. The estimated disease burden associated with AMR in Japan is substantial and has not begun to decrease. Notably, the burden from FQREC and 3GREC has increased steadily, and that from MRSA is larger in Japan than in the European Union/European Economic Area, whereas the burden from other bacteria is comparatively small. These results are expected to provide useful information for healthcare policy makers for prioritizing interventions for AMR.

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Introduction

Antimicrobial resistance (AMR) is a major global health threat (World Health Organization, 2015; European Commission, 2017; Centers for Disease Control and Prevention, 2019). The World Health Organization published the Global Action Plan on Antimicrobial Resistance in 2015, the strategic objectives of which include improving awareness and understanding of AMR, and

strengthening knowledge through surveillance and research (World Health Organization, 2015). The following year, the Japanese Ministry of Health, Labour and Welfare published the National Action Plan, which aimed to grasp the state of AMR emergence and its prevalence in Japan (Government of Japan, 2016).

When considering the implementation of health policies and interventions against AMR, it is necessary to assess its disease burden quantitatively. However, the evidence to date is scarce, especially in the Western Pacific region. Although Tsuzuki et al. estimated the number of deaths associated with bloodstream infections (BSIs) caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and fluoroquinolone-resistant *Escherichia coli*

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(FQREC) in Japan (Tsuzuki et al., 2020), these two organisms represent only a fraction of all antimicrobial-resistant organisms, and ‘death’ is only one aspect of disease burden. Therefore, a more extensive evaluation is desirable in order to improve understanding of the threat of AMR.

Several indicators are used to evaluate disease burden and/or health status, including quality-adjusted life years (EuroQol Group, 1990) and disability-adjusted life years (DALYs; Murray and Lopez, 1997). These might be useful indicators for understanding the burden of AMR on a society because they are measurable and comparable.

In the European Union and European Economic Area (EU/EEA), Cassini et al. (2019) reported the total disease burden of AMR in 2018 in terms of DALYs. To the present authors’ knowledge, their study is the only extensive evaluation of the disease burden of AMR to date. Therefore, the present authors aimed to evaluate the disease burden of AMR in terms of DALYs in the Western Pacific region, and compare the results with those of Cassini et al. (2019).

This study focused on BSIs caused by nine major antimicrobial-resistant organisms which were the targets of a comprehensive national surveillance of all routine bacteriological tests performed at more than 1400 hospitals between 2015 and 2018: MRSA, FQREC, third-generation cephalosporin-resistant *E. coli* (3GREC), third-generation cephalosporin-resistant *Klebsiella pneumoniae* (3GRKP), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), carbapenem-resistant Enterobacteriaceae (CRE), vancomycin-resistant enterococcus (VRE) and multi-drug-resistant *Acinetobacter* spp. (MDRA). The presence of bacteria in a blood specimen almost always means that the patient has bacteraemia; accordingly, disease burden can be estimated from blood culture surveillance data. Additionally, BSIs usually account for the largest part of the burden of infectious diseases due to their high fatality rate (Pittet et al., 1997; Anderson et al., 2014). Therefore, assessing the disease burden of BSIs would provide a useful indicator for healthcare policy makers.

Methods

Data sources

Data collected by the Japan Nosocomial Infections Surveillance (JANIS) programme, organized by the Ministry of Health, Labour and Welfare, were used in this study (Tsutsui and Suzuki, 2018; Ministry of Health, Labour and Welfare, 2020; Kajihara et al., 2021). The JANIS Clinical Laboratory module collects all routine microbiological test results, including culture-positive and -negative results, from hospitals participating voluntarily in the surveillance, which account for one-quarter of the hospitals in Japan.

Data on MRSA, FQREC, 3GREC, 3GRKP, CRPA, PRSP, CRE, VRE and MDRA isolates from blood specimens collected between 2015 and 2018 were extracted from the JANIS Clinical Laboratory database. Patient identifiers were de-identified by each hospital before the data were submitted to JANIS. Approval for extraction and use of the data was granted by the Ministry of Health, Labour and Welfare (0424e1).

Each isolate detected from a blood specimen was counted as one case of BSI. To avoid duplication from the same patient, only one specimen from each patient within 1 year was included, following the protocol of the European Antimicrobial Resistance Surveillance Network (Cassini et al., 2019). The judgement criteria for assessing the antimicrobial susceptibility of each bacterium were in accordance with the regulations of JANIS, which follow the criteria defined by the Clinical Laboratory Standards Institute (Clinical and Laboratory Standards Institute, 2015). MRSA is defined as *S. aureus* resistant to oxacillin and/or cefoxitin. FQREC is defined as *E. coli* resistant to ciprofloxacin and/or levofloxacin.

3GREC is defined as *E. coli* resistant to ceftazidime and/or cefotaxime. 3GRKP is defined as *Klebsiella pneumoniae* resistant to ceftazidime and/or cefotaxime. CRPA is defined as *P. aeruginosa* resistant to imipenem and/or meropenem. PRSP is defined as *S. pneumoniae* resistant to penicillin G. CRE is defined as *Enterococcus* spp. resistant to meropenem and/or imipenem and cefmetazole. VRE is defined as *Enterococcus* spp. resistant to vancomycin. MDRA is defined as *Acinetobacter* spp. resistant to carbapenems, aminoglycosides and fluoroquinolones.

Statistical analysis

The number of beds covered by JANIS varies by year and prefecture because the number of participating facilities has increased each year. Therefore, the total number of reported BSIs was adjusted by year and prefecture according to the proportion of the number of beds in participating hospitals, similar to the authors’ previous work (Tsuzuki et al., 2020). The number of beds in each prefecture was calculated as the sum of the number of beds in each participating facility. Information about the total number of beds was obtained from the e-Stat website, a portal site for Japanese Government Statistics (Ministry of Internal Affairs and Communications, 2020). Psychiatric beds and long-term care beds were excluded. Thus, only beds for acute care and infectious diseases were included.

DALYs is a composite health measure estimating both years lived with disabilities (YLDs) following the onset of sequelae, and years of life lost (YLLs) due to premature mortality compared with standard life expectancy (Lier et al., 2007). The number of deaths attributable to the nine aforementioned BSIs was estimated by using fatality data obtained from a review of the literature (Nagao, 2013; Gallagher et al., 2014; Takeshita et al., 2017; Cassini et al., 2019), as shown in Table S1 (see online supplementary material). The estimated number of deaths due to BSIs by age group and life expectancy in Japan were used to calculate YLLs. As for YLDs, there is scarce evidence about the incidence of morbidity caused by BSIs in Japan, and thus disease model trees and parameters from previous studies conducted in Europe (Kretzschmar et al., 2012; Colzani et al., 2017) were used.

DALYs were calculated using the following equations:

$$DALY = YLL + YLD$$

$$YLL = \sum_{i=1}^d e_i$$

$$YLD = \sum_{i=1}^n \sum_{l=1}^L t_{il} w_l$$

YLLs due to a specific disease in a given population are calculated by summation of all fatal cases (d). Each case (i) is multiplied by the expected individual lifespan at the age of death (e). YLD is calculated by the product of duration (t) and the severity weight (w) of a specific health outcome, accumulated over all cases (n) and all health outcomes ($L = 8$; complicated cases are defined in Figure S1, see online supplementary material). In the present study, all sequelae (i.e. health outcomes except for death derived from complicated BSIs) are assumed to persist throughout life. A time discount rate of 0.02 per year was assumed in accordance with the Japanese guidelines (Shiomiwa et al., 2017).

The abridged life table for Japan from 2015 to 2018 (National Institute of Population and Social Security Research, 2020) was used to calculate the expected lifespan at the time of death in each

BSI case, and the BSI outcome tree derived from the BCoDE project (European Centre for Disease Prevention and Control, 2019) was adopted because there is scarce evidence about the incidence of complications from BSIs. An outline of the outcome tree is shown in Figure S1 (see online supplementary material). The probability of each condition resulting from a complicated BSI and the respective disability weights are shown in Table S2 (see online supplementary material). As for uncomplicated cases, their acute phase burden was not taken into consideration when calculating DALYs. Although it is known that the length of stay in Japanese hospitals is generally much longer than that in other developed countries (Tiessen et al., 2013), no precise data are available about the length of stay due to bacteraemia in Japan. In addition, the burden of fatal cases and sequelae account for most of the DALYs due to bacteraemia. After considering these conditions, the burden of uncomplicated cases was excluded from the total disease burden.

The uncertainties inherent in this analysis were taken into consideration by estimating uncertainty intervals (UIs). Two thousand random samples were drawn for each of bed coverage, case fatality, probability and utility of each health status according to their distribution (details are shown in Table S1, see online supplementary material), and DALYs were calculated 2000 times.

Nine age groups were set: <1 year, 1–14 years, 15–24 years, 25–34 years, 35–44 years, 45–54 years, 55–64 years, 65–74 years and ≥75 years. Both bed coverage and fatality/morbidity were taken into consideration to estimate 95% UIs. All statistical analyses were performed using R Version 4.0.3 (R Core Team, 2018).

Results

Table 1 shows the actual number of isolates reported to JANIS between 2015 and 2018. In 2018, the proportion of MRSA among *S. aureus* was 39.0%, the proportion of fluoroquinolone-resistant strains among *E. coli* was 27.7%, the proportion of third-generation cephalosporin-resistant strains among *Klebsiella pneumoniae* was 6.4%, the proportion of carbapenem-resistant strains among *P. aeruginosa* was 8.7%, the proportion of penicillin-resistant strains among *S. pneumoniae* was 27.0%, the proportion of CRE among Enterobacteriaceae was 0.9%, the proportion of VRE among

Table 1
Number of isolated bacteria reported to the Japan Nosocomial Infections Surveillance.

	2015	2016	2017	2018
<i>Staphylococcus aureus</i>	5419	5904	6246	6281
MRSA	2287	2427	2444	2448
<i>Escherichia coli</i>	8149	8911	9622	9837
FQREC	2005	2307	2497	2722
3GREC	1554	1606	1802	1993
<i>Klebsiella pneumoniae</i>	3273	3600	3740	3956
3GRKP	230	217	217	252
<i>Pseudomonas aeruginosa</i>	1515	1613	1631	1675
CRPA	161	155	146	146
<i>Streptococcus pneumoniae</i>	423	412	452	430
PRSP	115	113	103	116
Enterobacteriaceae	14,866	16,294	17,291	17,832
CRE	128	154	142	161
<i>Enterococcus faecalis</i>	1840	1814	1886	1835
<i>Enterococcus faecium</i>	1208	1373	1440	1389
VRE	2	2	5	7
<i>Acinetobacter</i> spp.	501	499	441	398
MDRA	0	3	0	0

MRSA, methicillin-resistant *Staphylococcus aureus*; FQREC, fluoroquinolone-resistant *Escherichia coli*; 3GREC, third-generation cephalosporin-resistant *E. coli*; 3GRKP, third-generation cephalosporin-resistant *Klebsiella pneumoniae*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; PRSP, penicillin-resistant *Streptococcus pneumoniae*; CRE, carbapenem-resistant Enterobacteriaceae; VRE, vancomycin-resistant enterococcus; MDRA, multi-drug-resistant *Acinetobacter* spp.

Enterococcus faecalis and *E. faecium* was 0.2%, and the proportion of multi-drug-resistant strains among *Acinetobacter* spp. was 0%.

Figure 1 shows the estimated DALYs due to BSIs caused by the nine major antimicrobial-resistant organisms examined in this study.

BSIs caused by MRSA, FQREC and 3GREC account for most of the DALYs due to BSIs in Japan. Although the burden from MRSA decreased during the study period, the burden of FQREC increased.

Figure 2 shows a breakdown of DALYs according to causative organism and age group. Elderly people (aged ≥65 years) accounted for 62.4% of the total DALYs per 100,000 population (86.0/137.9) in 2018.

Table 2 shows the estimated number of deaths due to BSIs caused by each of the nine major antimicrobial-resistant organisms from 2015 to 2018. MRSA, FQREC and 3GREC accounted for 88.0% (8435/9587) of deaths due to BSIs caused by the nine organisms in 2018. Figure 3 shows the proportions of YLLs and YLDs in total DALYs; YLLs accounted for 88.6% of DALYs (122.2/137.9) in 2018.

Figure 4 is a choropleth map of DALYs in each prefecture in 2018. The median DALY value by prefecture is 145.7 (interquartile range 108.4–172.4) per 100,000 population. Fukuoka Prefecture had the largest DALY value (253.3/100,000 population), and Iwate Prefecture had the smallest DALY value (57.0/100,000 population).

Discussion

To the authors' knowledge, this is one of the first studies to quantitatively estimate the disease burden of BSIs due to antimicrobial-resistant organisms in the Western Pacific region. By comparing the present results with those of an earlier study conducted in the EU/EEA (Cassini et al., 2019), a more precise understanding of the disease burden caused by AMR can be

Figure 1. Disability-adjusted life-years (DALYs) due to bloodstream infections (BSIs) caused by nine major antimicrobial-resistant organisms from 2015 to 2018. MRSA, methicillin-resistant *Staphylococcus aureus*; FQREC, fluoroquinolone-resistant *Escherichia coli*; 3GREC, third-generation cephalosporin-resistant *Escherichia coli*; 3GRKP, third-generation cephalosporin-resistant *Klebsiella pneumoniae*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; PRSP, penicillin-resistant *Streptococcus pneumoniae*; CRE, carbapenem-resistant Enterobacteriaceae; VRE, vancomycin-resistant enterococcus; MDRA, multi-drug-resistant *Acinetobacter* spp. Orange line represents DALYs due to BSIs caused by MRSA. Brown line represents DALYs due to BSIs caused by FQREC. Dark green line represents DALYs due to BSIs caused by 3GREC. Green line represents DALYs due to BSIs caused by 3GRKP. Light green line represents DALYs due to BSIs caused by CRPA. Light blue line represents DALYs due to BSIs caused by PRSP. Blue line represents DALYs due to BSIs caused by CRE. Purple line represents DALYs due to BSIs caused by VRE. Pink line represents DALYs due to BSIs caused by MDRA. Circles represent medians, and whiskers represent 95% uncertainty intervals.

Figure 2. Breakdown of disability-adjusted life-years (DALYs) by age group in 2018. BSIs, bloodstream infections; MRSA, methicillin-resistant *Staphylococcus aureus*; FQREC, fluoroquinolone-resistant *Escherichia coli*; 3GREC, third-generation cephalosporin-resistant *Escherichia coli*; 3GRKP, third-generation cephalosporin-resistant *Klebsiella pneumoniae*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; PRSP, penicillin-resistant *Streptococcus pneumoniae*; CRE, carbapenem-resistant Enterobacteriaceae; VRE, vancomycin-resistant enterococcus; MDRA, multi-drug-resistant *Acinetobacter* spp. Lighter colours represent younger age groups. Whiskers represent 95% uncertainty intervals.

obtained compared with evaluations based on single indicators, such as number of deaths. In the present study, DALYs due to BSIs caused by the nine major antimicrobial-resistant organisms was 137.9 per 100,000 population. This number is higher than that in the EU/EEA study (approximately 122 per 100,000 population), which included other minor organisms. A major factor contributing to the observed difference is the disease burden caused by MRSA, which is substantially higher in Japan than in EU/EEA countries (57.8 vs 20.9 per 100,000 population). Another factor may be the age distribution of the Japanese population, which has a higher old-age dependency ratio (47% in Japan and 31% in the EU/EEA in 2019) (Eurostat, 2020; National Institute of Population and Social Security Research, 2020). As suggested in Figure 2, the burden derived from elderly patients (aged ≥ 65 years) might be considerably larger in Japan than in EU/EEA countries. In contrast, the disease burden of 3GRKP in Japan is lower than that in the EU/EEA (7.8 vs 22.5 per 100,000 population). Furthermore, the burdens of other Gram-negative rods (CRE and MDRA) in Japan are also lower. The disease burden of VRE is 0.18 in Japan and 5.49 in EU/EEA countries, and that of MDRA is 0.0095 in Japan and 0.90 in EU/EEA countries (Cassini et al., 2019). The burden of CRE is 2.03

Figure 3. Breakdown of years of life lost (YLLs) and years lived with disability (YLDs) among disability-adjusted life years (DALYs) from 2015 to 2018. Light grey bars represent the burden of YLDs. Dark grey bars represent the burden of YLLs. Whiskers represent uncertainty intervals.

in Japan. Although not mentioned in the previous study, the burden of CRE is substantially lower in Japan than in EU/EEA countries, because the burden of carbapenem-resistant *K. pneumoniae* in EU/EEA countries (11.5) is higher than the burden of total CRE in Japan.

It is noteworthy that Cassini et al. did not discount their results, and thus the possibility of overestimation by their study should be considered (Cassini et al., 2019). For more precise comparison of the results of the present study with those of the study of Cassini et al. (2019), DALYs was calculated without discounting in this study, and the total DALYs caused by the nine major AMR-BSIs in Japan was 163.5 [95% confidence interval (CI) 154.3–172.6] per 100,000 population in 2015. As discussed above, a major factor contributing to this difference is the burden of MRSA, because DALYs due to MRSA BSIs in 2015 in Japan was 75.6 (95% CI 51.6–101.3) without adjustment, whereas that in EU/EEA countries was 20.9 (95% CI 19.0–22.7). During the study period, the burden of MRSA was higher in Japan, and thus MRSA will continue to be one of the most important organisms for AMR intervention in Japan. Although 3GREC also showed a higher DALY value in Japan (40.0, 95% UI 23.1–57.6) compared with EU/EEA countries (29.9, 95% UI 26.4–33.6), the difference between the two areas was smaller than that for MRSA. Cassini et al. (2019) used the life table developed by Murray et al. (2012), and thus the difference in life expectancy should be trivial; indeed, it did not have a substantial impact on

Table 2

Estimated number of deaths due to bloodstream infections caused by antimicrobial-resistant organisms.

	2015	2016	2017	2018
MRSA	3,834 (2,498–5,301)	3,914 (2,551–5,418)	3,990 (2,601–5,510)	3,902 (2,542–5,396)
FQREC	3,045 (2,868–3,234)	3,437 (3,239–3,649)	3,561 (3,358–3,777)	3,936 (3,706–4,176)
3GREC	2,225 (1,197–3,266)	2,321 (1,248–3,409)	2,494 (1,341–3,661)	2,784 (1,497–4,090)
3GRKP	483 (362–617)	511 (383–653)	484 (363–618)	421 (561–719)
CRPA	362 (313–413)	385 (333–440)	310 (268–353)	333 (288–380)
PRSP	126 (42–231)	108 (36–198)	94 (31–173)	115 (38–211)
CRE	117 (29–234)	131 (33–263)	124 (31–248)	130 (33–261)
VRE	4 (3–4)	3 (3–4)	7 (7–7)	11 (10–11)
MDRA	0 (0–0)	3 (1–5)	0 (0–0)	0 (0–0)
Total	8,629 (7,234–10,041)	9,042 (7,636–10,521)	9,162 (7,738–10,678)	9,587 (8,170–11,068)

MRSA, methicillin-resistant *Staphylococcus aureus*; FQREC, fluoroquinolone-resistant *Escherichia coli*; 3GREC, third-generation cephalosporin-resistant *E. coli*; 3GRKP, third-generation cephalosporin-resistant *Klebsiella pneumoniae*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; PRSP, penicillin-resistant *Streptococcus pneumoniae*; CRE, carbapenem-resistant Enterobacteriaceae; VRE, vancomycin-resistant enterococcus; MDRA, multi-drug-resistant *Acinetobacter* spp. Numbers in parentheses represent 95% uncertainty intervals.

DALYs due to AMR-BSIs in 2018

Figure 4. Choropleth map of disability-adjusted life years (DALYs) due to bloodstream infections caused by antimicrobial-resistant organisms (AMR-BSIs). Darker colours represent heavier burdens of AMR-BSIs. The red circle indicates the prefecture with the highest DALY value (Fukuoka), and the blue circle indicates the prefecture with the lowest DALY value (Iwate).

this comparison. Considering the results of these comparisons, the AMR disease burden in Japan might be higher than that in EU/EEA countries, and MRSA can be considered an important target organism for AMR countermeasures in Japan in addition to *E. coli*. One of the strengths of the present study is that the results are also useful for understanding chronological trends within the same country. As shown in [Figures 2 and 4](#), MRSA and drug-resistant *E. coli* were the largest causes of disease burden due to BSIs among antimicrobial-resistant bacteria in Japan during the study period. Interestingly, the MRSA burden has decreased gradually each year, whereas the burden of FQREC has increased. This trend is in line with the findings of the authors' previous study ([Tsuzuki et al., 2020](#)), as well as studies conducted in other countries ([Perencevich and Diekema, 2010](#); [Gagliotti et al., 2011](#); [Wilson et al., 2011](#); [Musicha et al., 2017](#)). These findings suggest that MRSA and FQREC would be appropriate target organisms for countermeasures against AMR. At the same time, the findings suggest that the importance of countermeasures against Gram-negative bacilli, especially *E. coli*, will continue to grow.

Additionally, the present findings may be useful for other countries in the Western Pacific region. Given that AMR has become a major public health concern in this part of the world ([Adamson et al., 2020](#); [Argimón et al., 2020](#); [Han and Zhang, 2020](#); [Opatowski et al., 2020](#)), the present findings may be useful for comparing the situation in each country, although direct comparisons may be difficult due to differences in healthcare systems and other aspects.

The present study has several limitations. First, many of the parameters required for estimating DALYs were borrowed from previous studies. For instance, the probability of having sequelae in each BSI case was derived from [Cassini et al. \(2019\)](#) and implemented using the BCoDE toolkit ([European Centre for Disease Prevention and Control, 2019](#)). Elaborate simulations were conducted to reflect uncertainties related to the data; however, fatality and morbidity values should differ according to the country. It is more desirable to conduct similar estimations based on epidemiological data specific to Japan; therefore, establishing systems that enable such information to be obtained will be a challenge for the future. Second, the burden of BSIs themselves was not included in the current analysis, mainly due to scarcity of data about length of stay in Japanese hospitals. Consequently, the burden of uncomplicated cases was excluded

in its entirety. Although BSI is basically an acute curable disease, YLLs and YLDs should explain almost all of its disease burden; however, this may lead to underestimation. Third, the same parameter values were used for fatality and morbidity in all years. In addition, a small number of patients whose ages were not known (because it is not a mandatory input item in the national surveillance) were excluded; therefore, this may be another cause of underestimation. It is possible that fatality was lower in 2018 than in 2015, which may be a cause of overestimation.

In conclusion, although the results should be interpreted with caution in consideration of their limitations, the present study provides a quantitative estimation of the AMR disease burden in Japan. The results should be useful for comparisons with studies conducted in other countries, as well as the past situation within the same country. Nevertheless, further efforts are needed to resolve the limitations and obtain more precise results.

Author contributions

ST and NO conceived the study. ST constructed the model, ran the simulations and drafted the first manuscript. KY and KS aggregated and managed the raw data. KY, NM, KS, MS and NO critically reviewed the manuscript. All authors approved the final version of the manuscript.

Conflict of interest

None declared.

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Ethical approval

Patient identifiers were de-identified by each hospital before the data were submitted to the surveillance system. Approval for extraction and use of the data was granted by the Ministry of Health, Labour and Welfare (0424e1).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ijid.2021.05.018>.

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