J Infect Chemother 26 (2020) 367–371

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

National trend of blood-stream infection attributable deaths caused by *Staphylococcus aureus* and *Escherichia coli* in Japan

Shinya Tsuzuki [a, b, *], Nobuaki Matsunaga [a], Koji Yahara [c], Yoshiaki Gu [a], Kayoko Hayakawa [a], Aki Hirabayashi [c], Toshiki Kajihara [c], Motoyuki Sugai [c], Keigo Shibayama [c, d], Norio Ohmagari [a, e]

[a] *AMR Clinical Reference Center, National Center for Global Health and Medicine, Tokyo, Japan*
[b] *Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium*
[c] *Antimicrobial Resistance Research Center, National Institute of Infectious Diseases, Tokyo, Japan*
[d] *Department of Bacteriology II, National Institute of Infectious Diseases, Tokyo, Japan*
[e] *Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan*

ARTICLE INFO

Article history:
Received 12 September 2019
Received in revised form
21 October 2019
Accepted 29 October 2019
Available online 1 December 2019

Keywords:
Blood-stream infection
MRSA
Fluoroquinolone-resistant *E. coli*
Mortality
Surveillance

ABSTRACT

There has been scarce evidence about deaths due to blood stream infection (BSI) in Japan so far. The main objective of this study is to understand the epidemiological trend of deaths caused by BSIs due to *Staphylococcus aureus* and *Escherichia coli* including Methicillin-resistant *S. aureus* (MRSA) and fluoroquinolone-resistant *E. coli* (FQREC) at national level. We annually estimated the number of BSI caused by *S. aureus* and *E. coli* between 2011 and 2017 across Japan using comprehensive data of bacterial culturing and drug susceptibilities collected in Japan Nosocomial Infection Surveillance (JANIS). The number of death was estimated by using BSI mortality obtained from previous studies in Japan. The number of BSI death attributable to *S. aureus* was estimated to 17,412 in 2011 and 17,157 in 2017, respectively, out of the whole population (126.8 million) in Japan. Among them, cases attributed to MRSA accounted for 5924 (34.0%) in 2011, and decreased to 4224 (24.6%) cases in 2017. On the other hand, the number of BSI death attributable to *E. coli* was estimated to 9044 in 2011 and increased to 14,016 in 2017. Among them, cases attributed to FQREC accounted for 2045 (22.6%) in 2011 and increased to 3915 (27.9%) cases in 2017. The number of BSI death attributable to MRSA has been decreasing and that attributable to FQREC has been increasing. This study provides the first annual estimate of disease burden of BSI caused by antimicrobial resistant (AMR) bacteria in Japan, and basis for formulating health policy to deal with AMR.

1. Introduction

Blood stream infection (BSI) is the main cause of deaths attributable to infectious diseases [1–3]. Especially, *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*) are important causative organisms of BSIs, both in view of healthcare-associated infection (HAI) surveillance and antimicrobial resistance (AMR) in modern global health.

As for the disease burden of Methicillin-resistant *S. aureus* (MRSA) as a proportion of all *S. aureus*, it peaked a decade ago and has declined [4] since it was first reported in 1960s [5,6]. Not only a continuous decline of invasive MRSA disease were observed, these decreases were also greater when the analysis was limited to BSIs in the United States and European countries [7,8].

On the other hand, *E. coli*, which is another the most important causative organism of BSIs, has demonstrated quite the opposite trend. The number and proportion of BSIs caused by *E. coli* has been increasing globally [9–11]. Furthermore, the proportion of antimicrobial resistant *E. coli* has increased in this century [12–15]. We can observe this increasing trend of antimicrobial resistance in *E. coli* for various class of antimicrobials like carbapenem, third-generation cephalosporins, and fluoroquinolones.

These contrasting trends can be observed ubiquitously [4,9,10,12,13]. However, whether these trends can also be observed

DOI of original article: https://doi.org/10.1016/S1341-321X(20)30116-1.
* Corresponding author. 1-21-1, Toyama, Shinjuku-ku, Tokyo, 162-8655, Japan.
E-mail address: stsuzuki@hosp.ncgm.go.jp (S. Tsuzuki).

https://doi.org/10.1016/j.jiac.2019.10.017

in Japan remains unknown. In the first place, there is no estimate in Japan about the number of deaths attributed to these BSIs. BSI attributable deaths could account for the most part of AMR disease burden as Cassini and colleagues suggested [16]. Therefore, the number of deaths attributed to BSIs is an important indicator of AMR disease burden, and its estimation provides a basis in the process of health policy planning to understand how much disease burden has been imposed by antimicrobial resistant organisms on our society, For that purpose, we utilize data collected by one of the largest AMR surveillance systems in the world, Japan Nosocomial Infections Surveillance (JANIS), which is organized by Ministry of Health, Labour and Welfare [17,18]. JANIS Clinical Laboratory module comprehensively collects all routine microbiological test results including blood culture-positive and -negative diagnostic from approximately 2000 hospitals that voluntarily participated in the surveillance, which account for a quarter of the total of approximately 8000 hospitals across Japan. Although the data in JANIS don't include patient outcome, we combine the data with BSI mortality obtained from previous studies in Japan in order to for the first time estimate the quantitative disease burden of BSI.

The main objective of this report is to assess the actual number and the epidemiological trend of deaths attributed to BSIs caused by the two major bacterial species that account for majority of disease burden of AMR: *S. aureus* and *E. coli* including Methicillin-resistant *S. aureus* (MRSA) and fluoroquinolone-resistant *E. coli* (FQREC) at national level by extrapolating from the JANIS data.

2. Materials and methods

2.1. Dataset

We extracted the data fields of *S. aureus* and *E. coli* isolates of blood specimen between 2011 and 2017 from the database of JANIS Clinical Laboratory module. Patient identifiers are de-identified by each hospital before data submission to JANIS. Approval for extraction and use of the data was granted by Ministry of Health, Labour and Welfare (0424–1).

2.2. Definition of cases

Each *S. aureus* and *E. coli* isolate detected from blood specimen was counted as one case of BSIs. To avoid duplication from the same patient, we included only one specimen from the same patient within one month.

The judgment criteria about antimicrobial susceptibility of each bacteria is in accordance with the regulation of JANIS, which follows the criteria defined by Clinical Laboratory Standards Institute (CLSI) [19]. MRSA is defined as *S. aureus* resistant to Oxacillin (MPIPC) and/or Cefoxitin (CFX). FQREC is defined as *E. coli* resistant to Ciprofloxacin (CPFX) and/or Levofloxacin (LVFX).

2.3. Statistical analysis

Since participating facilities of JANIS has increased year by year, the coverage of the number of beds varies by year and prefecture. The annual number of facilities that participated in JANIS and analysed in the present study from 2011 to 2017 is shown in Table 1, after excluding hospitals that submitted dubious or incomplete data, We adjusted the total number of reported BSIs by year and prefecture according to the proportion of the number of beds participating in JANIS. Each prefecture's number of beds participating in JANIS was calculated as the sum of each participating facility's number of beds. Information about total number of beds was obtained from the website of e-Stat, a portal site for Japanese Government Statistics [20]. We included only beds for acute care and infectious diseases and excluded psychiatric beds and long-term care beds.

Table 1
The number of facilities that participated in JANIS and analysed in the present study.

	2011	2012	2013	2014	2015	2016	2017
Number of facilities	594	659	742	881	1421	1629	1737

JANIS; Japan Nosocomial Infections Surveillance.

The number of death (30-day mortality) attributable to these BSIs was estimated by using BSI mortality obtained from previous studies [21–24]. We also followed the annual trend of the number of BSI death attributable to MRSA and FQREC. The details of parameters about mortality of BSIs are shown in Table 2.

As our estimation was constructed by three components (bed coverage, reported number of BSIs, and mortality), we calculated 95% confidence intervals (CIs) for both bed coverage and mortality.

In addition, JANIS increased its participants year by year, and small facilities below 200 beds greatly increased since 2014. It is expected that large facilities report larger numbers of resistant organisms and BSIs then therefore underestimation might occur when we include all facilities in our analyses. Considering this, we also estimated the same indicators (BSI deaths attributable to *S. aureus*, MRSA, *E. coli*, and FQREC) with data in which we exclude small health facilities which has below 200 beds in order to reflect different characteristics of each health facility due to its scale.

We use a JAVA toolkit to extract aggregated data of *S. aureus* and *E. coli* from raw data extracted from JANIS database. All statistical analyses were performed with R, version 3.5.3 [25].

3. Results

The number of BSI death attributable to *S. aureus* was estimated to 17,412 (95% CI: 13,388–22,119) in 2011 and 17,157 (95% CI: 13,347–21,533) in 2017, respectively. The number of BSI death attributable to MRSA was estimated to 5924 (95% CI: 3837–8513) in 2011 and 4224 (95% CI: 2769–5994) in 2017, respectively. Table 3 shows the details of these results.

The number of BSI death attributable to *E. coli* was estimated to 9044 (95% CI: 7101–11,335) in 2011 and 14,016 (95% CI: 11,140–17,344) in 2017, respectively. The number of BSI death attributable to FQRECwas estimated to 2045 (1869–2220) in 2011 and 3915 (3629–4189) in 2017, respectively. Table 4 shows the details of these results.

Fig. 1 shows the comparison of the annual trend of BSI deaths caused by MRSA and FQREC. Fig. 2 shows the comparison of proportion of resistant organisms among BSIs caused by *S. aureus* and *E. coli*. The absolute number of BSI deaths caused by MRSA has decreased and that caused by FQREC has gradually increased. On the other hand, the proportion of MRSA among BSIs caused by *S. aureus* has decreased (28.7% in 2011 and 20.8% in 2017, respectively. p-value < 0.001) and that of FQREC among BSIs caused by *E. coli* has slightly increased (14.0% in 2011 and 17.3% in 2017, respectively. p-value < 0.001). Statistical comparison of these results between 2011 and 2017 is available in Table 5.

Table 2
Assumed mortality of blood stream infections.

	All strains	Resistant strain
S. aureus	0.21 [23]	0.25 [23]
E. coli	0.14 [23]	0.22 [22]

Table 3
Number of BSI attributable deaths caused by *S. aureus* and MRSA.

	2011	2012	2013	2014	2015	2016	2017
S. aureus (95% CI)	17,412 (13,388–22,119)	16,951 (13,058–21,491)	16,789 (12,962–21,233)	16,517 (12,773–20,856)	16,443 (12,777–20,660)	16,565 (12,883–20,796)	17,157 (13,347–21,533)
MRSA (95% CI)	5924 (3837–8513)	5365 (3478–7702)	4755 (3092–6802)	4380 (2853–6256)	4357 (2852–6190)	4298 (2817–6100)	4224 (2769–5994)

BSI; blood stream infection, MRSA; methicillin resistant *S. aureus*, CI; confidence interval.

Table 4
Number of BSI attributable deaths caused by *E. coli* and FQREC.

	2011	2012	2013	2014	2015	2016	2017
E. coli (95% CI)	9044 (7101–11,335)	9650 (7585–12,080)	10,896 (8594–13,589)	11,621 (9178–14,471)	12,587 (9991–15,595)	13,356 (10,612–16,532)	14,016 (11,140–17,344)
FQREC (95% CI)	2045 (1869–2220)	2317 (2120–2513)	2753 (2532–2970)	3012 (2774–3243)	3377 (3126–3619)	3678 (3408–3937)	3915 (3629–4189)

BSI; blood stream infection, FQREC; fluoroquinolone resistant *E. Coli*, CI; confidence interval.

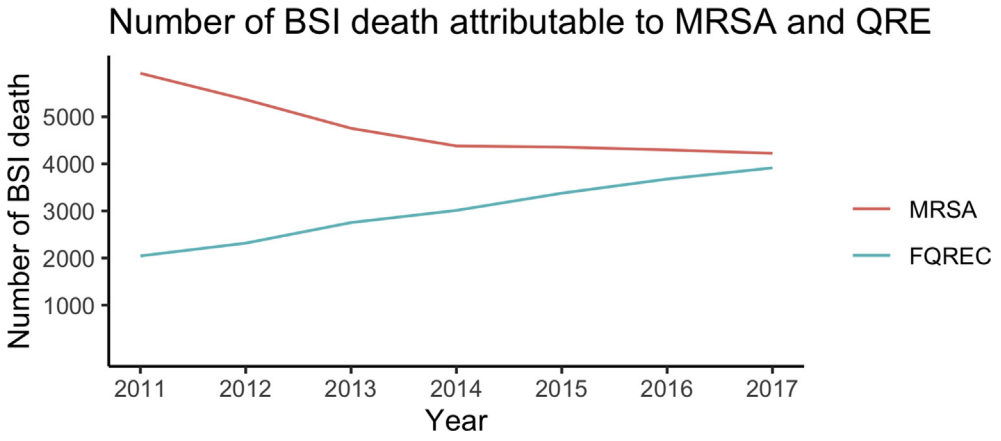

Fig. 1. The annual trend of BSI deaths caused by MRSA and FQREC.

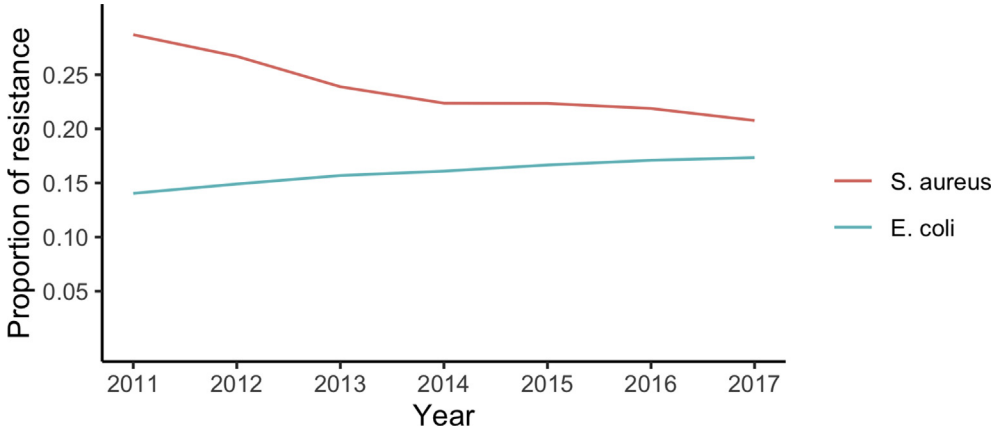

Fig. 2. The annual trend of proportion of resistant organisms among BSIs caused by *S. aureus* and *E. coli*.

The estimated number of BSI deaths derived from the dataset which exclude small health facilities below 200 beds are as follows; The number of BSI death attributable to *S. aureus* was estimated to 17,529 in 2011 and 17,714 in 2017, respectively. Among them, 5,972 cases in 2011 and 4,285 cases in 2017 were attributed to MRSA. The number of BSI death attributable to *E. coli* was estimated to 9,094 in 2011 and 14,283 in 2017, respectively. Among them, 2,055 cases in 2011 and 3,954 cases in 2017 were attributed to FQREC. Details are available at the supplementary file (see Appendix).

4. Discussion

To our knowledge, there are only few previous studies which explored the actual number of deaths attributable to antimicrobial

Table 5
Comparison of results between 2011 and 2017.

	2011	2017	*p*-value[a]
Number of BSI attributable deaths caused by *S. aureus* per 100,000 population	13.7	13.5	0.735
Number of BSI attributable deaths caused by MRSA per 100,000 population	4.7	3.3	<0.001
Number of BSI attributable deaths caused by *E. coli* per 100,000 population	7.1	11.1	<0.001
Number of BSI attributable deaths caused by FQREC per 100,000 population	1.6	3.1	<0.001
Proportion of resistant strain among BSI deaths caused by *S. aureus*	34.0%	24.6%	<0.001
Proportion of resistant strain among BSI deaths caused by *E. coli*	22.6%	27.9%	<0.001

BSI; blood stream infection, MRSA; methicillin resistant *S. aureus*, FQREC; fluoroquinolone resistant *E. Coli*.
[a] Results of chi-square test between numbers in 2011 and 2017.

resistant organisms in Japan. JANIS has also not estimated the quantitative disease burden of the antimicrobial resistance, because JANIS program is originally designed to focus on the antimicrobial resistance rates of organisms. The present study extrapolates the disease burden of MRSA and FQREC in Japan, in view of number of deaths caused by BSIs. Furthermore, our findings were compatible with the global trend of antimicrobial resistance (AMR) that *S. aureus* and *E. coli* are the most important organisms in view of disease burden at population level [12,16], and prevalence of MRSA demonstrated obvious decrease, whereas that of FQREC demonstrated gradual increase [4,7,10,12,26].

Our findings would help us to understand the approximate disease burden due to MRSA and FQREC because the number of deaths accounts for the largest part of disease burden caused by infectious diseases due to AMR bacterial species [16]. However, if we would like to assess disease burden of AMR and/or BSIs in more detailed manner, death is only one aspect because other complications and sequelae are also significant outcomes of diseases [27]. As the previous studies demonstrated [16,28], it would be more appropriate that disease burden be evaluated more extensively with indicators such as Disability-adjusted life years (DALYs) or Quality-adjusted life years (QALYs). We will have to evaluate various outcomes of infectious diseases in view of utility based on our own epidemiological and societal background, as EU/EEA countries had already evaluated [29,30]. The present study will be a subjacent evidence for our future challenges.

Since *S. aureus* is the most popular causative organism of BSIs in Gram positive coccus and *E. coli* is that in Gram negative rods, the present study suggests that we need to continue to take appropriate countermeasures against HAI, especially to Gram negative rods. Gradual decrease of BSI deaths caused by MRSA might be attributed to our appropriate intervention against AMR, but it cannot explain the reason why BSI deaths caused by FQREC has been increasing. The increase of BSIs caused by FQREC might have negative influence on mortality of whole BSIs, however, we have implemented an incentive for having antimicrobial stewardship team as a required condition for additional reimbursement for infection prevention. Further investigation would be required in order to speculate the reason of increase of *E. coli* and its resistant rate, and the effect of such incentives as one of countermeasures against AMR in HAI.

The present study has some limitations. The incidence of BSIs was estimated by extrapolation from the number of positive blood specimens weighted uniformly by coverage of the number of beds of JANIS hospitals in this study. The number of deaths was estimated by employing the mortality rates published by the two previous multicentre studies [22,23], in which the mortality was assessed by the analysis of mainly tertiary care hospitals. Since there is no published evidence about 30-day mortality of FQREC, we cited previous studies from England [22,24] for 30-day mortality of FQREC. After that, we referred crude mortality of multidrug resistant *E. coli* in Japan [21] and confirmed that there was no great difference between them. Therefore, our results might be difficult to be generalized as a finding wholly from domestic data. Additionally, their results were not stratified by age and other patients' backgrounds, it is possible that our results were biased to some extent. As the properties of hospitals are diverse, the incidence and the mortality rates of hospitals might be more complex. While small-scale hospitals with less than 200 beds are most common (68%; 5793/8442 in 2016) in Japan, their ratio in JANIS database is relatively small (26.9%; 483/1795 in 2017), so our results might be biased towards large-scale hospitals. Nevertheless, we consider that our results are robust and representative because our analyses with another dataset which exclude facilities below 200 beds demonstrated quite similar results.

Also, we should take note that our references about 30-day mortality are conducted in different period each other. Most of these values are derived from Takeshita et al. [23] which was conducted during 2012–2013, then there is a possibility of overestimation because the prognosis of BSIs might improve after 2013.

Next, the present study does not include any organisms other than *S. aureus* and *E. coli*. Since there are only two studies which investigated the mortality of BSIs caused by various organisms extensively [21,23], it should be an appropriate way to include only two major organisms in our analysis to avoid misunderstandings. In addition, we did not use third-generation cephalosporin resistance but fluoroquinolone resistance as the indicator of AMR of *E. coli*. It is due to change of minimum inhibitory concentration (MIC) breakpoint. As JANIS follows the CLSI criteria, MIC breakpoint of *E. coli* for third-generation cephalosporins changed in 2015. Consequently, the number of BSI caused by third-generation cephalosporin resistant *E. coli* must be underestimated between 2011 and 2014. Therefore, FQREC is appropriate target to follow chronological trend of AMR in *E. coli* in Japan.

In conclusion, similar to the previous findings from other countries, the number of BSI death attributable to MRSA has been decreasing recently. On the other hand, the number of BSI death attributable to FQREC has been increasing year by year. Whereas prevalence of BSIs caused by *S. aureus* had been stable, that of caused by *E. coli* had increased gradually. Although these results should be interpreted carefully due to several limitations, they suggest that continuous surveillance and countermeasures against HAI and AMR would be necessary and *E. coli* has increased its importance among total disease burden of BSIs. Further research would be desirable to understand more precise disease burden of BSIs in Japan.

Authorship statement

ST, NM and NO conceived the study. KY, TK and KS aggregated and managed the raw data. ST analysed data and wrote the first draft of the manuscript. NM, KY, YG, KH and NO critically interpreted the results. All the authors other than ST reviewed the first draft critically and provided revisions. All the authors approved the final version of the manuscript. All authors meet the ICMJE authorship criteria.

Funding

This study was supported by a Ministry of Health, Labour and Welfare (MHLW) research grant of Japan (H29-shinkougyousei-shitei-005) and Research Program on Emerging and Re-emerging Infectious Diseases from the Japan Agency for Medical Research and Development (AMED) under grant number JP19fk0108061.

Declaration of Competing Interest

All authors declare no competing interests.

Acknowledgements

We would like to thank all facilities that participated in JANIS.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2019.10.017.

References

[1] Japanese Government. Vital Statistics vital statistics of Japan final data general mortality yearly. 2017. Portal Site of Official Statistics of Japan n.d, https://www.e-stat.go.jp/en/stat-search/files?page=1&layout=datalist&toukei=00450011&tstat=000001028897&cycle=7&year=20170&month=0&tclass1=000001053058&tclass2=000001053061&tclass3=000001053065&result_back=1&second2=1. [Accessed 6 June 2019].

[2] Pittet D, Li N, Woolson RF, Wenzel RP. Microbiological factors influencing the outcome of nosocomial bloodstream infections: a 6-year validated, population-based model. Clin Infect Dis 1997;24:1068–78. https://doi.org/10.1086/513640.

[3] Anderson DJ, Moehring RW, Sloane R, Schmader KE, Weber DJ, Fowler VG, et al. Bloodstream infections in community hospitals in the 21st century: a multicenter cohort study. PLoS One 2014;9:e91713. https://doi.org/10.1371/journal.pone.0091713.

[4] Diekema DJ, Pfaller MA, Shortridge D, Zervos M, Jones RN. Twenty-year trends in antimicrobial susceptibilities among Staphylococcus aureus from the SENTRY antimicrobial surveillance program. Open Forum Infect Dis 2019;6:S47–53. https://doi.org/10.1093/ofid/ofy270.

[5] Barber M. Methicillin-resistant staphylococci. J Clin Pathol 1961;14:385–93. https://doi.org/10.1136/jcp.14.4.385.

[6] Benner EJ, Kayser FH. Growing clinical significance of methicillin-resistant staphylococcus aureus. The Lancet 1968;292:741–4. https://doi.org/10.1016/S0140-6736(68)90947-1.

[7] Perencevich EN, Diekema DJ. Decline in invasive MRSA infection: where to go from here? J Am Med Assoc 2010;304:687–9. https://doi.org/10.1001/jama.2010.1125.

[8] Wilson J, Elgohari S, Livermore DM, Cookson B, Johnson A, Lamagni T, et al. Trends among pathogens reported as causing bacteraemia in England, 2004-2008. Clin Microbiol Infect 2011;17:451–8. https://doi.org/10.1111/j.1469-0691.2010.03262.x.

[9] Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309–17. https://doi.org/10.1086/421946.

[10] de Kraker MEA, Jarlier V, Monen JCM, Heuer OE, van de Sande N, Grundmann H. The changing epidemiology of bacteraemias in Europe: trends from the European antimicrobial resistance surveillance system. Clin Microbiol Infect 2013;19:860–8. https://doi.org/10.1111/1469-0691.12028.

[11] Goto M, McDanel JS, Jones MM, Livorsi DJ, Ohl ME, Beck BF, et al. Antimicrobial nonsusceptibility of gram-negative bloodstream isolates, veterans health administration system, United States, 2003–20131. Emerg Infect Dis 2017;23:1815–25. https://doi.org/10.3201/eid2311.161214.

[12] Gagliotti C, Balode A, Baquero F, Degener J, Grundmann H, Gür D, et al. Escherichia coli and Staphylococcus aureus: bad news and good news from the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS), 2002 to 2009. Euro Surveill 2011;16:19819. https://doi.org/10.2807/ese.16.11.19819-en.

[13] Musicha P, Cornick JE, Bar-Zeev N, French N, Masesa C, Denis B, et al. Trends in antimicrobial resistance in bloodstream infection isolates at a large urban hospital in Malawi (1998–2016): a surveillance study. Lancet Infect Dis 2017;17:1042–52. https://doi.org/10.1016/S1473-3099(17)30394-8.

[14] Mineau S, Kozak R, Kissoon M, Paterson A, Oppedisano A, Douri F, et al. Emerging antimicrobial resistance among Escherichia coli strains in bloodstream infections in Toronto, 2006–2016: a retrospective cohort study. CMAJ Open 2018;6:E580–6. https://doi.org/10.9778/cmajo.20180039.

[15] De Socio GV, Rubbioni P, Botta D, Cenci E, Belati A, Paggi R, et al. Measurement and prediction of antimicrobial resistance in bloodstream infections by ESKAPE and Escherichia coli pathogens. J Glob Antimicrob Resist 2019. https://doi.org/10.1016/j.jgar.2019.05.013.

[16] Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis 2018. https://doi.org/10.1016/s1473-3099(18)30605-4.

[17] 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.

[18] Tsutsui A, Yahara K, Clark A, Fujimoto K, Kawakami S, Chikumi H, et al. Automated detection of outbreaks of antimicrobial-resistant bacteria in Japan. J Hosp Infect 2019;102:226–33. https://doi.org/10.1016/j.jhin.2018.10.005.

[19] Clinical and Laboratory Standards Institute. Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria. third ed. CLSI guideline M45; 2015.

[20] Ministry of Internal Affairs and Communications. System of social and demographic statistics I health and medical care. Portal Site of Official Statistics of Japan n.d, https://www.e-stat.go.jp/en/stat-search/database?page=1&query=hospital%20bed&layout=dataset&statdisp_id=0000010109&metadata=1&data=1. [Accessed 26 June 2019].

[21] Nagao M. A multicentre analysis of epidemiology of the nosocomial bloodstream infections in Japanese university hospitals. Clin Microbiol Infect 2013;19:852–8. https://doi.org/10.1111/1469-0691.12083.

[22] Abernethy JK, Johnson AP, Guy R, Hinton N, Sheridan EA, Hope RJ. Thirty day all-cause mortality in patients with Escherichia coli bacteraemia in England. Clin Microbiol Infect 2015;21. https://doi.org/10.1016/j.cmi.2015.01.001.251.e1-e8.

[23] Takeshita N, Kawamura I, Kurai H, Araoka H, Yoneyama A, Fujita T, et al. Unique characteristics of community-onset healthcare- associated bloodstream infections: a multi-centre prospective surveillance study of bloodstream infections in Japan. J Hosp Infect 2017;96:29–34. https://doi.org/10.1016/j.jhin.2017.02.022.

[24] Blandy O, Honeyford K, Gharbi M, Thomas A, Ramzan F, Ellington MJ, et al. Factors that impact on the burden of Escherichia coli bacteraemia: multivariable regression analysis of 2011–2015 data from West London. J Hosp Infect 2019;101:120–8. https://doi.org/10.1016/j.jhin.2018.10.024.

[25] R Core Team. R. A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2018.

[26] Vos MC, Behrendt MD, Melles DC, Mollema FP, de Groot W, Parlevliet G, et al. 5 years of experience implementing a methicillin-resistant Staphylococcus aureus search and destroy policy at the largest university medical center in The Netherlands. Infect Control Hosp Epidemiol 2009;30:977–84. https://doi.org/10.1086/605921.

[27] Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 2012;380:2197–223. https://doi.org/10.1016/S0140-6736(12)61689-4.

[28] CDC. The biggest antibiotic-resistant threats in the U.S. Centers for Disease Control and Prevention. 2019. https://www.cdc.gov/drugresistance/biggest_threats.html. [Accessed 30 June 2019].

[29] Kretzschmar M, Mangen MJ, Pinheiro P, Jahn B, Fevre EM, Longhi S, et al. New methodology for estimating the burden of infectious diseases in Europe. PLoS Med 2012;9:e1001205. https://doi.org/10.1371/journal.pmed.1001205.

[30] Cassini A, Colzani E, Pini A, Mangen MJ, Plass D, McDonald SA, et al. Impact of infectious diseases on population health using incidence-based disability-adjusted life years (DALYs): results from the Burden of Communicable Diseases in Europe study, European Union and European Economic Area countries, 2009 to 2013. Euro Surveill: Bulletin Europeen Sur Les Maladies Transmissibles Eur Commun Dis Bull 2018;23. https://doi.org/10.2807/1560-7917.ES.2018.23.16.17-00454.