Infect Dis Ther (2023) 12:1823–1834
https://doi.org/10.1007/s40121-023-00829-7

ORIGINAL RESEARCH

Decline in Antimicrobial Consumption and Stagnation in Reducing Disease Burden due to Antimicrobial Resistance in Japan

Shinya Tsuzuki · Ryuji Koizumi · Nobuaki Matsunaga · Norio Ohmagari

Received: April 26, 2023 / Accepted: May 23, 2023 / Published online: June 15, 2023

ABSTRACT

Introduction: Antimicrobial resistance (AMR) is a major global health threat. While antimicrobial consumption (AMC) in Japan substantially decreased after implementation of the AMR National Action Plan, the disease burden due to AMR seems to be unchanged. The main objective of this study is to examine the relationship between AMC and the disease burden due to AMR in Japan.

Methods: We estimated the annual population-standardized AMC from 2015 to 2021 using defined daily doses (DDDs) per 1000 inhabitants per day (DIDs) and the disease burden due to bloodstream infections caused by nine major antimicrobial-resistant bacteria (AMR-BSIs) from 2015 to 2021 using disability-adjusted life years (DALYs). We then examined the correlation between AMC and DALYs using Spearman's rank correlation coefficient and cross-correlation function. Spearman's $\rho > 0.7$ was considered to indicate a strong correlation.

Results: The sales amounts of third-generation cephalosporins, fluoroquinolones, and macrolides were 3.82 DIDs, 2.71 DIDs, and 4.59 DIDs, respectively, in 2015, but 2.11, 1.48, and 2.72 in 2021. This corresponded to reductions of 44.8%, 45.4%, and 40.7% during the study period. DALYs due to AMR-BSIs were 164.7 per 100,000 population in 2015 but 195.2 per 100,000 in 2021. Spearman's rank correlation coefficients between AMC and DALYs were − 0.37 (total antibiotics), − 0.50 (oral antibiotics), − 0.43 (third-generation cephalosporins), − 0.5 (fluoroquin,olones) and − 0.5 (macrolides). No obvious cross-correlations were found.

Conclusions: Our results reveal that changes in AMC are not associated with DALYs caused by AMR-BSIs. AMR countermeasures besides efforts to reduce inappropriate AMC might be necessary to mitigate the disease burden due to AMR.

Keywords: Antimicrobial resistance; Antimicrobial consumption; Disease burden

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40121-023-00829-7.

S. Tsuzuki (✉) · R. Koizumi · N. Matsunaga · N. Ohmagari
AMR Clinical Reference Center, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-Ku, Tokyo 162-8655, Japan
e-mail: stsuzuki@hosp.ncgm.go.jp

S. Tsuzuki · N. Ohmagari
Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan

S. Tsuzuki
Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

Key Summary Points

Why carried out this study?

Antimicrobial consumption (AMC) has declined in Japan in recent years.

However, we do not know whether or not the disease burden due to antimicrobial resistance (AMR) has been mitigated.

What was learned from this study?

Disease burden due to AMR in Japan did not decrease during the study period (2015–2020).

A decrease in AMC might not be a sufficient AMR countermeasure.

INTRODUCTION

Antimicrobial resistance (AMR) is a persistent and major global health issue [1–4]. In 2015, the World Health Organization published the Global Action Plan on Antimicrobial Resistance, which advocated for improved awareness and understanding of antimicrobial resistance and strengthening of knowledge through surveillance and research [1].

Nonetheless, despite continuous effort to combat AMR by each country, AMR is still a substantial cause of disease burden in society. In the European Union and European Economic Area, Cassini et al. reported that the total disease burden of AMR in 2018 in terms of disability-adjusted life years (DALYs) and the calculated 115 DALYs per 100,000 population in 2015 were caused by infections with four major antibiotic-resistant bacteria [third-generation cephalosporin-resistant *Escherichia coli*, methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Pseudomonas aeruginosa*, and third-generation cephalosporin-resistant *Klebsiella pneumoniae*] [5]. According to a more recent report by Murray et al., 64.0 deaths and 2448.1 DALYs per 100,000 population were associated with bacterial AMR globally in 2019 [4].

The Ministry of Health, Labour and Welfare of Japan established a national action plan against AMR in 2016 and implemented several surveillance systems and interventions at the population level [6]. We previously estimated the number of deaths and DALYs due to bloodstream infections caused by major antimicrobial-resistant organisms (AMR-BSIs), which were the targets of a comprehensive national surveillance program [7, 8]. Our results showed that BSIs due to MRSA and fluoroquinolone-resistant *E. coli* (FQREC) caused 4244 and 3915 deaths in 2017, respectively [7]. In addition, BSIs caused by nine major antimicrobial-resistant bacteria [MRSA, FQREC, third-generation cephalosporin-resistant *E. coli* (3GREC), third-generation cephalosporin-resistant *K. pneumoniae* (3GRKP), carbapenem-resistant *P. aeruginosa* (CRPA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), carbapenem-resistant *Enterobacterales* (CRE), vancomycin-resistant *Enterococci* (VRE) and multidrug-resistant *Acinetobacter spp.* (MDRA)] led to 137.9 DALYs per 100,000 population in 2018 [8].

On the other hand, because inappropriate antimicrobial consumption (AMC) is said to exacerbate AMR [9, 10], the need to reduce AMC as a measure against AMR has been advocated in recent years. Indeed, AMC has decreased in Japan since the introduction of the National Action Plan [11]. Furthermore, the emergence of COVID-19 promoted this decreasing trend in AMC. After the occurrence of the COVID-19 pandemic, a considerable drop in AMC was seen worldwide, and Japan was no exception [12, 13].

The decline in AMC is itself a pleasing phenomenon. However, the original, primary objective of AMR countermeasures should be to reduce the disease burden, including deaths due to AMR, and a reduction in AMC should only be a secondary goal that may contribute to the primary one. Nevertheless, research has focused on the reduction in AMC as a result of AMR countermeasures, and has not sufficiently examined whether the disease burden due to AMR has actually been reduced.

A previous study of the relationship between the AMC reduction and AMR from the UK reported that implementation of the Quality Premium in England did not improve the fluoroquinolone susceptibility of *E. coli*, despite a substantial reduction in ciprofloxacin consumption [14]. Considering this, AMR countermeasures implemented in Japan might not have decreased the disease burden, even if they reduced AMC. Accordingly, the main objective of this study was to examine the relationship between AMC and the disease burden due to AMR in Japan.

METHODS

Data Sources

For AMC, we used sales data from IQVIA Japan, a multinational company that collects sales data at the national level and encompasses more than 99% of all drug distributions among wholesalers in Japan. Our dataset includes only sales data and does not include claims data, data for research use, or sales data for animals. The annual population-standardized AMC from 2015 to 2021 was estimated using the defined daily doses (DDDs) per 1000 inhabitants per day (DIDs). The DDD for each drug was obtained from data published in January 2022 [15]. Population data were based on estimates published every year on 1 October by the Statistics Bureau of the Japanese Government [16].

With regard to the estimation of annual DALYs due to AMR-BSIs, we limited the objective of the study to BSIs, following the method of our previous study, in order to enable easier comparison of the results [8]. We used data collected by the Japan Nosocomial Infections Surveillance (JANIS) program organized by the Ministry of Health, Labour and Welfare [17–19]. We extracted data on MRSA, FQREC, 3GREC, 3GRKP, CRPA, PRSP, CRE, VRE, and MDRA isolates from blood specimens collected between 2015 and 2021 in the JANIS Clinical Laboratory database. Patient identifiers were removed by each hospital before the data were submitted to JANIS. Approval for the extraction and use of the data was granted by the Ministry of Health, Labour and Welfare (approval number 0424e1).

Each isolate detected in a blood specimen was counted as one case of BSI. To avoid duplication from the same patient, we included only one specimen from each patient within one year, following the protocol of the European Antimicrobial Resistance Surveillance Network [5]. The judgement criteria for assessing the antimicrobial susceptibility of each bacterium were in accordance with the regulations of JANIS, which follows the criteria defined by the Clinical Laboratory Standards Institute [20].

Statistical Analysis

We conducted three separate statistical analyses. First, we described the annual AMC and DALYs due to AMR-BSIs in Japan in recent years. Next, we analyzed the impact of the National Action Plan and the emergence of COVID-19 on AMC based on our monthly time series data. Lastly, we examined the correlation between annual AMC and DALYs due to AMR-BSIs.

DIDs of three antibiotic classes (third-generation cephalosporins, macrolides, and fluoroquinolones) from 2015 to 2021 are presented descriptively. For the estimation of DALYs, we adjusted the total number of reported BSIs by year and prefecture according to the proportion of the number of beds in hospitals participating in JANIS, similar to our previous work [7]. The number of beds in each prefecture was calculated as the sum of the number of beds in each participating facility. Information on the total number of beds was obtained from the e-Stat website, a portal site for Japanese Government Statistics [21]. We excluded psychiatric beds and long-term care beds to specifically include beds for acute care and infectious diseases.

Because DALYs are a composite health measure estimating both years lived with disabilities (YLDs) and years of life lost (YLLs) due to premature mortality [22], we estimated the number of deaths attributable to the nine aforementioned BSIs according to the method we used in our previous study to calculate YLLs [8]. Fatality data were obtained from a review of the

literature [5, 23–25], as shown in Table S1 in the Supplementary Material. As for YLDs, there is scarce information on the incidence of morbidity caused by BSIs in Japan, and we thus used disease model trees and parameters from previous studies conducted in Europe [26, 27], similar to our previous study [8].

We used the Abridged Life Tables for Japan from 2015 to 2021 [28] to calculate the expected lifespan at the time of death in each BSI case, and adopted the BSI outcome tree derived from the BCoDE project [29]. An outline of the outcome tree is shown in Figure S1 and Table S2 in the Supplementary Material. We excluded the burden of uncomplicated cases from the total disease burden.

We drew 2000 random samples for each of bed coverage, case fatality, probability, and utility of each health status according to their distribution (details are shown in Table S2 in the Supplementary Material) and calculated the DALYs 2000 times to reflect inherent uncertainties.

To evaluate the impact of the National Action Plan and the emergence of COVID-19, we used a generalized least squares model that included time (month), introduction of the National Action Plan, the emergence of COVID-19, and seasonality as explanatory variables. Dependent variables were total AMC, oral AMC, and each of the three classes of AMC (third-generation cephalosporins, fluoroquinolones, and macrolides).

Next, we examined the correlation between AMC and DALYs by using Spearman's rank correlation coefficient and cross-correlation function because both are time series data. A Spearman's $\rho > 0.7$ was considered to indicate a strong correlation. Two-sided p values of < 0.05 were considered statistically significant. All statistical analyses were performed using *R* 4.1.3 [30].

Ethics Approval

Patient identifiers were removed by each hospital before the data were submitted to the surveillance system. Therefore, no ethics approval was required to conduct the present study. However, we needed to request approval for data extraction and use from the Ministry of Health, Labour and Welfare Japan because the data were provided by the national surveillance system. The approval number for the data extraction is 0424e1.

RESULTS

Figure 1 shows the annual AMC of three major classes of oral antibiotics in Japan. The sales amounts of third-generation cephalosporins, fluoroquinolones, and macrolides were 3.82 DIDs, 2.71 DIDs, and 4.59 DIDs, respectively, in 2015, but just 2.11, 1.48, and 2.72 in 2021. This corresponded to reductions of 44.8%, 45.4%, and 40.7% during the study period.

Figure 2 shows the annual total AMC in Japan from 2015 to 2021. Total sales of oral and parenteral antibiotics were 13.68 DIDs and 1.00 DIDs, respectively, in 2015 and 9.25 and 0.96 in 2021. Thus, the proportion of oral antibiotics among the total AMC decreased from 93.2% to 90.6% during the study period.

Generalized least squares models suggested that the sales amount of the total and three major classes decreased gradually over time ($p < 0.001$) and that the COVID-19 pandemic had a substantial negative impact on AMC ($p < 0.001$). The results of multivariable analyses are detailed in Table 1.

Figures 3 and 4 show the estimated numbers of deaths due to BSIs caused by MRSA and FQREC, respectively. The number of deaths due to MRSA BSIs did not change substantially and remained at around 4000 per year (medians of 3863 in 2015 and 3916 in 2021). The number of deaths due to FQREC BSIs increased during the study period from 3070 to 4169.

Figure 5 shows DALYs due to BSIs caused by nine major antimicrobial-resistant bacteria from 2015 to 2021. DALYs due to AMR-BSIs were 164.7 per 100,000 population in 2013 but 195.2 per 100,000 in 2021. The proportion of YLLs was 90.0% in both 2013 and 2021.

Spearman's rank correlation coefficients between AMC and DALYs were − 0.37 (total antibiotics), − 0.50 (oral antibiotics), − 0.43 (third-generation cephalosporins), − 0.50

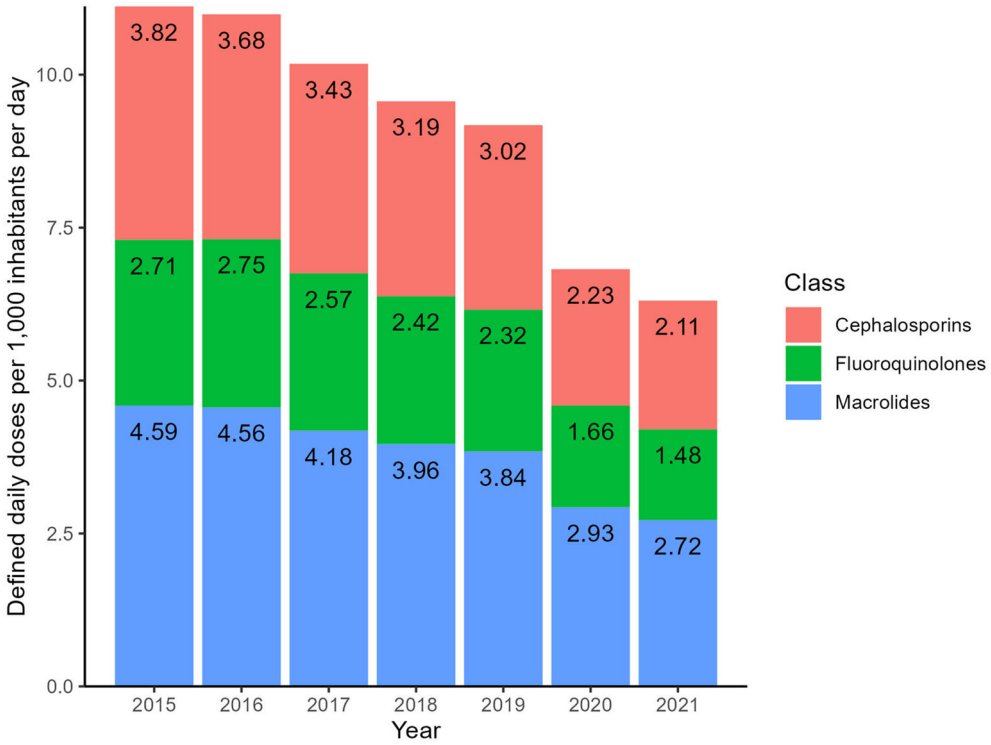

Fig. 1 Annual sales amounts of third-generation cephalosporins, fluoroquinolones, and macrolides from 2015 to 2021; *red bars* represent the sales amounts of third-generation cephalosporins, *green bars* those of fluoroquinolones, and *blue bars* those of macrolides

(fluoroquinolones), and − 0.50 (macrolides). The cross-correlation function revealed no strong correlation between any class of AMC (total antibiotics, oral antibiotics, third-generation cephalosporins, fluoroquinolones, and macrolides) and DALYs. Cross-correlation function plots are presented in Table 2.

DISCUSSION

Our results demonstrated that AMC in Japan fell substantially after the introduction of the National Action Plan. Nevertheless, there was no obvious change in the disease burden due to BSIs caused by nine major antimicrobial-resistant bacteria. In addition, we could not find any obvious correlation between AMC and DALYs due to these BSIs. These findings suggest that AMC reduction is not always key to improving the disease burden due to AMR and that interventions other than antimicrobial stewardship might be necessary to improve the situation.

We usually expect that a reduction in AMC will lead to decreases in the disease burden due to AMR, as a result of a lower resistance rate related to the AMC reduction because inappropriate AMC is regarded as one of the major causes of AMR [9, 10]. Notably, the resistance rate of major bacteria in Japan did not decrease during the study period. MRSA as a proportion of *S. aureus* was 48.2% in 2016 (data for 2015 were not available) and 48.5% in 2020. The FQREC as a proportion of *E. coli* was 30.5% in 2016 (data for 2015 were not available) and 35.0% in 2020 [18]. However, several previous studies had already reported results similar to ours, namely that AMC reduction did not reduce resistance. As mentioned above, Aliabadi et al. showed that the decrease in ciprofloxacin consumption was paradoxically associated with an increased rate of ciprofloxacin resistance in

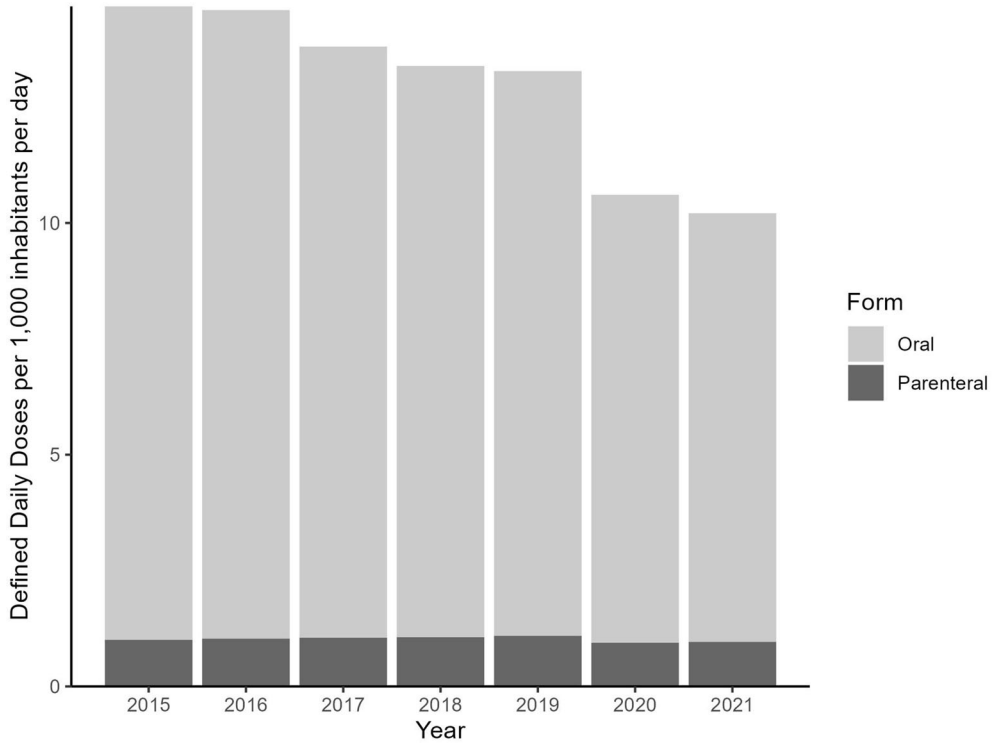

Fig. 2 Annual sales amounts of oral and parenteral antibiotics from 2015 to 2021; *light gray bars* represent the sales amounts of oral antibiotics and *dark gray bars* the sales amounts of parenteral antibiotics

E. coli in the UK [14]. Hernandez-Santiago et al. also reported that the prescription of fluoroquinolones, cephalosporins, and co-amoxiclav decreased after introduction of a primary care antimicrobial stewardship intervention in 2009, but that the resistance rate of coliform (*E. coli*, *Proteus* spp., or *Klebsiella* spp.) bacteraemia among adult patients did not decrease significantly [31]. According to Enne et al. and Sundqvist et al., the prevalence of sulfonamide resistance in *E. coli* did not decrease despite a huge decrease in sulfonamide prescriptions [32, 33]. Considering our method to calculate DALYs due to AMR-BSIs, the disease burden due to AMR in these countries might also not decrease with a reduction in AMR.

We can consider several hypotheses concerning these undesirable findings. If we think optimistically, more time will simply be required for the influence of AMR reduction on the disease burden to be reflected. However, because AMR is a multifactorial phenomenon associated with various elements, it would therefore not be a good idea for us to maintain the status quo. If we think pessimistically, the AMR situation has already reached a point of no return. For instance, Enne et al. attributed the cause of the sustained resistance rate to the genetic linkage of the index resistance to other resistance determinants [33]. Aliabadi et al. agreed with the suggestion of Collignon et al. that one of the most likely reasons for this was the accumulation of mutations conferring resistance within bacterial populations [14, 34]. Our findings support their suggestion that focusing on AMC reduction might be insufficient to counter resistance that has already become established in the bacterial population.

Furthermore, we should take note that, although efforts to reduce oral AMC were a resounding success, parenteral AMC did not decrease during the study period. This means that room for improvement remains in our antimicrobial stewardship programme, especially at inpatient care. A previous study reported improved antibiotic susceptibility after a

Table 1 Results of multivariable linear regression analysis

Dependent variable	Independent variable	Coefficient	95% CI	*P* value
Total antibiotics	Time	− 0.04	− 0.06, − 0.02	< 0.001
	National Action Plan	0.22	− 0.67, 1.11	0.626
	COVID-19 pandemic	− 1.84	− 2.73, − 0.95	< 0.001
Oral antibiotics	Time	− 0.04	− 0.06, − 0.02	< 0.001
	National Action Plan	0.24	− 0.57, 1.05	0.560
	COVID-19 pandemic	− 1.67	− 2.48, − 0.86	< 0.001
Third-generation cephalosporins	Time	− 0.02	− 0.02, − 0.01	< 0.001
	National Action Plan	0.08	− 0.13, 0.28	0.456
	COVID-19 pandemic	− 0.51	− 0.72, − 0.31	< 0.001
Fluoroquinolones	Time	− 0.01	− 0.02, − 0.01	< 0.001
	National Action Plan	0.18	− 0.04, 0.39	0.103
	COVID-19 pandemic	− 0.46	− 0.68, − 0.25	< 0.001
Macrolides	Time	− 0.02	− 0.03, − 0.01	< 0.001
	National Action Plan	0.15	− 0.14, 0.45	0.291
	COVID-19 pandemic	− 0.56	− 0.85, − 0.27	< 0.001

Dependent variables were monthly antibiotic sales (unit = defined daily doses per 1000 inhabitants per day)
CI confidence interval

reduction in AMC in healthcare settings [35], which may support this hypothesis. It is worth investigating if we can lower the resistance rate by reducing the inappropriate use of parenteral antibiotics, because a lower resistance rate will result in smaller disease burden, as discussed above. The National Action Plan against AMR in Japan is now due for revision, and our findings should be taken into consideration.

With regard to the results of multivariable linear regression analysis, COVID-19 was associated with lower AMC in all classes of antibiotics included in the analysis, while the National Action Plan was not. Nevertheless, we should interpret these results with caution, given that our previous studies found a significant AMC reduction after the introduction of the National Action Plan [11] and a substantial decline of AMC after the emergence of COVID-19 [13]. However, the impact of COVID-19 seemed larger than that of the National Action Plan. That is one of the reasons why the National Action Plan did not show a statistically significant association with AMC.

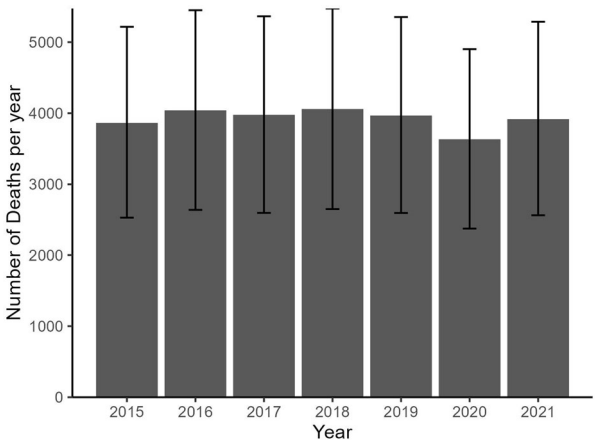

Fig. 3 Estimated numbers of deaths due to bloodstream infections caused by methicillin-resistant *S. aureus* from 2015 to 2021; *whiskers* represent 95% uncertainty intervals

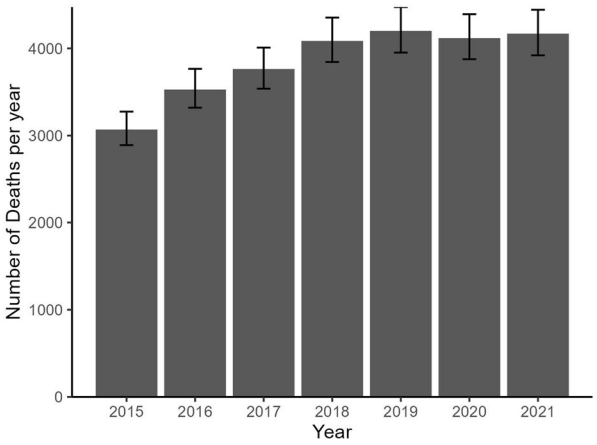

Fig. 4 Estimated numbers of deaths due to bloodstream infections caused by fluoroquinolone-resistant *E. coli* from 2015 to 2021; *whiskers* represent 95% uncertainty intervals

This study has some limitations. First, we could not examine AMC outside the human sector (e.g., the animal and environmental sectors) due to a scarcity of data. AMC in the animal sector may influence AMR in human society. Nevertheless, that would support our conclusion that we should take more comprehensive countermeasures that are not just limited to AMC reduction at the primary care level. Second, this was an ecological study without genetic information on bacteria. Accordingly, we could not appropriately assess the influence of accumulated gene mutations. This is one of the outstanding challenges requiring attention. Third, we did not consider the burden of minor bacteria and infectious diseases other than BSIs. There is no doubt that other major infectious diseases, such as pneumonia and urinary tract infections, are other causes of disease burden. Because we can diagnose BSIs easily and definitively, they are a good choice for understanding the chronological trend in the disease burden due to AMR. In addition, the nine major bacteria chosen in this study account for almost

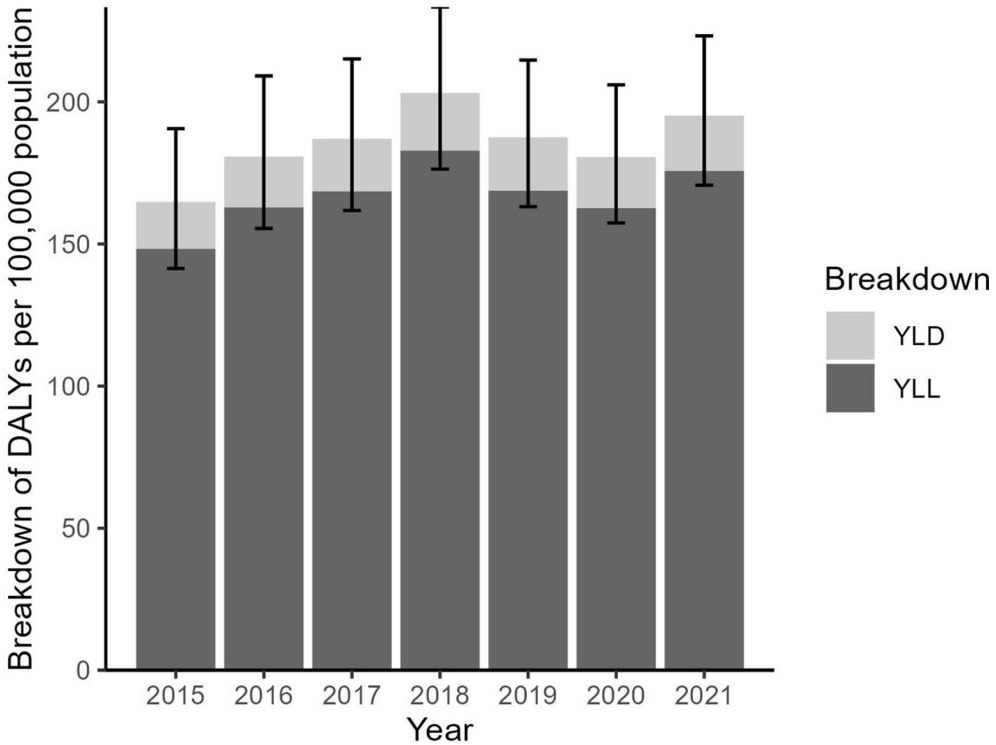

Fig. 5 DALYs due to bloodstream infections caused by nine major antimicrobial-resistant organisms from 2015 to 2021; *light gray bars* represent the burden of YLDs , *dark gray bars* the burden of YLL, and *whiskers* uncertainty intervals. *DALYs* disability-adjusted life years, *YLLs* years of life lost, *YLDs* years lived with disability

Table 2 Results of cross-correlation function between antimicrobial consumption and DALYs

Lag/class	− 3	− 2	− 1	0	1	2	3
Total antibiotics	0.20	0.16	0.12	− 0.51	− 0.12	− 0.33	− 0.53
Oral antibiotics	0.32	0.06	0.02	− 0.32	− 0.26	− 0.58	− 0.49
Third-generation cephalosporins	0.27	0.14	0.03	− 0.38	− 0.25	− 0.56	− 0.48
Fluoroquinolones	0.31	0.18	− 0.06	− 0.34	− 0.29	− 0.45	− 0.54
Macrolides	0.36	0.04	− 0.02	− 0.38	− 0.20	− 0.53	− 0.49

DALYs disability-adjusted life years

all of the burden of BSIs, as demonstrated in our previous study [8]. For *E. coli*, it is difficult to assess the disease burden due to AMR because there are various types of epidemiologically important resistance in *E. coli*. Although we used FQREC as representative of *E. coli* resistance, resistance to third-generation cephalosporins should be noted as another major resistance. However, DALYs due to FQREC BSIs were 71.4 per 100,000 population in 2020, while those due to third-generation cephalosporin resistant EC (3GCREC) BSIs were 49.0 per 100,000 population. DALYs due to BSIs caused by EC resistant to both FQ and third-generation cephalosporin were 39.1 in the same year. The most prevalent and important *E. coli* resistance in Japan can be regarded as fluoroquinolone resistance, which is why we have used FQREC as one of the indicators of the disease burden due to AMR. Fourth, our data on AMC were derived from sales data and there should thus be little discrepancy between these data and the actual consumption at the individual level. However, a previous study reported that similar trends were observed when AMC in sales data were compared with that in claims data [36], indicating that our findings would not change substantially even if we used claims data.

CONCLUSIONS

Our findings showed that AMC in Japan fell substantially after the introduction of the National Action Plan. However, disease burden due to AMR did not decrease, and there was no correlation between AMC and the disease burden due to BSIs caused by major AMR bacteria. These results suggest that AMC reduction might be insufficient as an appropriate countermeasure against AMR, and that a more comprehensive approach is required to improve the situation.

ACKNOWLEDGEMENTS

Funding. This research was supported by research grants from the Ministry of Health, Labour and Welfare (23HA2002 and 23HA1004). The journal's fee was waived.

Medical writing and/or Editorial assistance. Editing was provided by ThinkSCIENCE, Inc. The cost of the editing service was supported by research grants from the Ministry of Health, Labour and Welfare (23HA2002 and 23HA1004).

Author Contributions. Shinya Tsuzuki conceived the study. Ryuji Koizumi aggregated and managed part of the raw data. Shinya Tsuzuki constructed the model, ran simulations and drafted the first manuscript. Shinya Tsuzuki and Ryuji Koizumi created the tables and figures. Ryuji Koizumi, Nobuaki Matsunaga and Norio Ohmagari critically reviewed the manuscript. Norio Ohmagari supervised the project. All authors approved the final version of the manuscript.

Disclosures. Shinya Tsuzuki, Ryuji Koizumi, Nobuaki Matsunaga, Norio Ohmagari declare no competing interests.

Compliance with Ethics Guidelines. Patient identifiers were removed by each hospital before the data were submitted to the surveillance system. Therefore, no ethics approval was required to conduct the present study. However, we needed to request approval for data extraction and use from the Ministry of Health, Labour and Welfare Japan because the data were provided by the national surveillance system. The approval number for the data extraction is 0424e1.

Data Availability. The data used in this study will be made available by the corresponding author upon reasonable request.

REFERENCES

1. World Health Organization. Global Action Plan on Antimicrobial Resistance [Internet]. Geneva; 2015. https://apps.who.int/iris/bitstream/handle/10665/254352/sea-cd-308.pdf?sequence=1&isAllowed=y

2. European Commission. A European one health action plan against antimicrobial resitance (AMR). [Internet]. 2017 [cited 2019 Mar 13]. https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf

3. CDC. The biggest antibiotic-resistant threats in the U.S. [Internet]. Cent. Dis. Control Prev. 2019 [cited 2019 Jun 30]. https://www.cdc.gov/drugresistance/biggest_threats.html

4. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet. 2022;399:629–55.

5. 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;

6. The Government of Japan. National Action Plan on Antimicrobial Resistance (AMR) 2016–2020 [Internet]. 2016. https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000138942.pdf

7. Tsuzuki S, Matsunaga N, Yahara K, Gu Y, Hayakawa K, Hirabayashi A, et al. National trend of bloodstream infection attributable deaths caused by Staphylococcus aureus and Escherichia coli in Japan. J Infect Chemother Off J Jpn Soc Chemother. Netherlands; 2020;26:367–71.

8. Tsuzuki S, Matsunaga N, Yahara K, Shibayama K, Sugai M, Ohmagari N. Disease burden of bloodstream infections caused by antimicrobial-resistant bacteria: A population-level study, Japan, 2015–2018. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. Canada; 2021;108:119–24.

9. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ. 2010;340:c2096–c2096.

10. Pouwels KB, Freeman R, Muller-Pebody B, Rooney G, Henderson KL, Robotham JV, et al. Association between use of different antibiotics and trimethoprim resistance: going beyond the obvious crude association. J Antimicrob Chemother. 2018;73:1700–7.

11. Kusama Y, Tsuzuki S, Muraki Y, Koizumi R, Ishikane M, Ohmagari N. The effects of Japan's national action plan on antimicrobial resistance on antimicrobial use. Int J Infect Dis Elsevier BV. 2021;103:154–6.

12. Khouja T, Mitsantisuk K, Tadrous M, Suda KJ. Global consumption of antimicrobials: impact of the WHO Global Action Plan on Antimicrobial Resistance and 2019 coronavirus pandemic (COVID-19). J Antimicrob Chemother Oxford University Press (OUP). 2022;77:1491–9.

13. Ono A, Koizumi R, Tsuzuki S, Asai Y, Ishikane M, Kusama Y, et al. Antimicrobial Use Fell Substantially in Japan in 2020—The COVID-19 Pandemic May Have Played a Role. Int J Infect Dis [Internet]. Elsevier BV; 2022; https://doi.org/10.1016/j.ijid.2022.03.019

14. Aliabadi N, Antoni S, Mwenda JM, Weldegebriel G, Biey JNM, Cheikh D, et al. Global impact of rotavirus vaccine introduction on rotavirus hospitalisations among children under 5 years of age, 2008–16: findings from the Global Rotavirus Surveillance Network. Lancet Glob Health. 2019;7:e893-903.

15. Norwegian Institute of Public Health. Guidelines for ATC classification and DDD assignment [Internet]. 2022 [cited 2022 Dec 12]. Available from: https://www.whocc.no/atc_ddd_index_and_guidelines/guidelines/

16. Statistics Bureau Japan. Portal Site of Official Statistics of Japan.

17. Kajihara T, Yahara K, Hirabayashi A, Shibayama K, Sugai M. current status, international collaboration, and future directions of a comprehensive antimicrobial resistance surveillance system. Jpn J Infect Dis [Internet]. 2020 [cited 2021 Feb 5]; Available from: https://www.jstage.jst.go.jp/article/yoken/advpub/0/advpub_JJID.2020.499/_article

18. Ministry of Health Labour and Welfare Japan. Japan Nosocomial Infections Surveillance (JANIS).

19. 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.

20. Clinical and Laboratory Standars Institute. Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria. 3rd ed. CLSI guideline M45. Wayne, PA; 2015.

21. Ministry of Internal Affairs and Communications. System of Social and Demographic Statistics I Health and Medical Care [Internet]. Portal Site Off. Stat. Jpn. [cited 2019 Jun 26]. Available from: https://www.e-stat.go.jp/en/stat-search/database?page=1&query=hospital%20bed&layout=dataset&statdisp_id=0000010109&metadata=1&data=1

22. Lier EA van, Havelaar AH, Nanda A. The burden of infectious diseases in Europe: a pilot study. Eurosurveillance. European Centre for Disease Prevention and Control; 2007;12:3–4.

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.

24. Nagao M. A multicentre analysis of epidemiology of the nosocomial bloodstream infections in Japanese university hospitals. Clin Microbiol Infect. 2013;19:852–8.

25. Gallagher JC, Kuriakose S, Haynes K, Axelrod P. Case-case-control study of patients with carbapenem-resistant and third-generation-cephalosporin-resistant Klebsiella pneumoniae bloodstream infections. Antimicrob Agents Chemother. 2014;58:5732–5.

26. 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.

27. Colzani E, Cassini A, Lewandowski D, Mangen M-JJ, Plass D, McDonald SA, et al. A Software Tool for Estimation of Burden of Infectious Diseases in Europe Using Incidence-Based Disability Adjusted Life Years. PloS One. 2017;12:e0170662.

28. National Institute of Population and Social Security Research. Population Statistics [Internet]. 2020 [cited 2020 Dec 20]. Available from: http://www.ipss.go.jp/syoushika/tohkei/Popular/Popular2014.asp?chap=5&title1=%87X%81D%8E%80%96S%81E%8E%F5%96%BD

29. European Centre for Disease Prevention and Control. Toolkit—Application to calculate DALYs [Internet]. 2019 [cited 2020 Dec 20]. Available from: https://www.ecdc.europa.eu/en/publications-data/toolkit-application-calculate-dalys

30. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2018.

31. Hernandez-Santiago V, Davey PG, Nathwani D, Marwick CA, Guthrie B. Changes in resistance among coliform bacteraemia associated with a primary care antimicrobial stewardship intervention: A population-based interrupted time series study. PLOS Med. Public Library of Science (PLoS); 2019;16:e1002825.

32. Sundqvist M, Geli P, Andersson DI, Sjölund-Karlsson M, Runehagen A, Cars H, et al. Little evidence

for reversibility of trimethoprim resistance after a drastic reduction in trimethoprim use. J Antimicrob Chemother. 2010;65:350–60.

33. Enne VI, Livermore DM, Stephens P, Hall LM. Persistence of sulphonamide resistance in Escherichia coli in the UK despite national prescribing restriction. The Lancet Elsevier. 2001;357:1325–8.

34. Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. Lancet Planet Health. 2018;2:e398-405.

35. Livermore DM, Hope R, Reynolds R, Blackburn R, Johnson AP, Woodford N. Declining cephalosporin and fluoroquinolone non-susceptibility among bloodstream Enterobacteriaceae from the UK: links to prescribing change? J Antimicrob Chemother. 2013;68:2667–74.

36. Kusama Y, Muraki Y, Tanaka C, Koizumi R, Ishikane M, Yamasaki D, et al. Characteristics and limitations of national antimicrobial surveillance according to sales and claims data. PLOS ONE. Public Library of Science (PLoS); 2021;16:e0251299.

Publisher's Note