Short Communication

Regional Variation of Antimicrobial Use in Japan from 2013–2016, as Estimated by the Sales Data

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SUMMARY: The National Action Plan on Antimicrobial Resistance in Japan aims to achieve a 50% reduction in the use of broad-spectrum oral antimicrobials (cephalosporins, macrolides, and quinolones) from 2013 to 2020. Based on the national sales data for antimicrobials, we estimated the regional antimicrobial use (AMU) from 2013–2016 and evaluated the differences in the use of broad-spectrum oral antimicrobials among three regions in which differences had been identified previously. The AMU was standardized based on the defined daily dose (DDD) and described as the DDDs/1,000 inhabitants/day (DID). Annual combined total oral and parenteral AMU during 2013–2016 was 14.9, 14.5, 14.7, and 14.6 DID, respectively. The change in mean $\pm$ standard deviation in the total AMU at the prefectural level was -0.2 ± 0.8 DID. Among the 47 prefectures, decreasing trends were observed in 34, while in the remaining 13 prefectures increasing trends were recorded. In 2016, no significant differences in the mean usage of oral cephalosporins among the three regions were observed. The mean usage of oral macrolides in the eastern (4.1 DID) was significantly lower than that in the central region (4.7 DID) ($p = 0.009$) and the western (4.8 DID) ($p = 0.002$). The mean usage of oral quinolones in the western (3.2 DID) was significantly higher than that in the eastern (2.3 DID) ($p < 0.001$) and central (2.7 DID) ($p = 0.001$) regions. To determine appropriate targets for the implementation of antimicrobial stewardship for reducing the use of broad-spectrum oral antimicrobials, further studies are required to identify the reasons underlying these differences.

In Japan, the National Action Plan on Antimicrobial Resistance (AMR) 2016–2020 was developed in 2016 (1). Between 2013 and 2020, this plan aims to achieve a 50% reduction in the use of broad-spectrum oral antimicrobials (cephalosporins, macrolides and quinolones), which are used more frequently in Japan than in the countries of the European Union (2). Antimicrobial stewardship (AMS) is the key approach to reduce antimicrobial use (AMU) and a national surveillance of AMU is necessary for the appropriate implementation of AMS. The National Action Plan focuses on regional AMS (1). Some studies conducted in the US and European countries have already reported differences in AMUs at the regional level (3–6). Although some studies have documented AMU at the national level in Japan using antimicrobial sales data (2,7), very few studies have been conducted at the regional level. Tanabe et al. reported differences in the

total AMU between the three regions (eastern, central, and western) in Japan (8) but did not evaluate them from the standpoint of the use of broad-spectrum oral antimicrobials. Therefore, we estimated the regional AMU in Japan from 2013–2016 using sales data of antimicrobials and evaluated the regional differences, focusing particularly on oral cephalosporins, macrolides, and quinolones.

The national sales data (from 2013–2016) of systemic antimicrobials, administered usually via the oral and parenteral routes, were obtained at the prefectural level from IQVIA Services Japan K.K. (Tokyo, Japan) (2). These data were of systemic antimicrobials that were mostly administered via oral and parenteral routes. The antimicrobials were classified according to the anatomical therapeutic chemical classification system developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology (9). We defined the antimicrobials as J01 (anti-infectives for systemic use). AMU was standardized based on the defined daily dose (DDD) (version 2018) and described as DDDs/1,000 inhabitants/day (DID). Data pertaining to the population of Japan were obtained from the results of a population survey report published by the Ministry of Health, Labour and Welfare of Japan (10). The AMU among 47 prefectures was analyzed and differences from 2013 to 2016 among the eastern, central, and

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Regional Variation of Antimicrobial Use in Japan

Fig. 1. Trend in national antimicrobial use in Japan from 2013 to 2016. Bars represent the defined daily dose per 1,000 inhabitants per day (DID); black indicates oral macrolides, dark gray oral cephalosporins, light gray oral quinolones, and white other antimicrobials.

Fig. 2. Distribution of antimicrobial use in Japan in 2016, stratified by total antimicrobials, and oral macrolides, cephalosporins, and quinolones. Maps express the values of defined daily dose per 1,000 inhabitants per day (DID): total antimicrobials (A), oral macrolides (B), oral cephalosporins (C), and oral quinolones (D).

western regions of Japan were compared by an analysis of variance. Multiple comparisons were conducted by the Tukey-Kramer method. All statistical analyses were conducted using the SPSS version 25 software (IBM Corp., Armonk, NY, USA). The present study did not require any approval by an ethics committee because all personal information was anonymized by IQVIA Japan.

The total national AMU in Japan from 2013 to 2016 was 14.9 DID, 14.5 DID, 14.7 DID, and 14.6 DID, respectively (Fig. 1). The proportion of AMU of the broad-spectrum oral antimicrobials combined (cephalosporins, macrolides, and quinolones) during these years was 77.7%, 76.8%, 75.8%, and 75.2%, respectively. During the study period, the proportion of AMU for oral macrolides, cephalosporins, and quinolones ranged from 31.1%–32.4%, 25.2%–26.3%, and 18.5%–19.6%, respectively. The mean $\pm$ standard deviation of change in the total AMU at the prefecture level was -0.2 ± 0.8 DID from 2013 (14.8 ± 1.5

DID) to 2016 (14.5 ± 1.6 DID). While 34 prefectures (72.3%) showed a decreasing trend, 13 (27.7%) showed an increasing trend in AMU (Table 1). Fig. 2 indicates the distribution of AMU in Japan in 2016 stratified by total antimicrobials such as oral cephalosporins, macrolides, and quinolones. The mean of total AMU in the eastern (13.2 DID) was significantly lower than that in the western (15.5 DID) ($p < 0.001$) and the central region (14.7 DID) ($p = 0.012$). The mean usage of oral cephalosporins in the eastern (3.3 DID), central region (3.9 DID) and western (3.6 DID) was not found to differ significantly. However, the mean usage of oral macrolides was significantly lower in the eastern (4.1 DID) than that of the central region (4.7 DID) ($p = 0.009$) and the western (4.8 DID) ($p = 0.002$). The mean usage of oral quinolones was significantly higher in the western (3.2 DID) than that of the eastern (2.3 DID) ($p < 0.001$) and central region (2.7 DID) ($p = 0.001$) (Fig. 2).

Table 1. Trends of the total antimicrobial sales by prefecture from 2013 to 2016

		2013				2016				Difference between 2013 and 2016*			
		Total	Cephalo sporins	Macro lides	Quino lones	Total	Cephalo sporins	Macro lides	Quino lones	Total (%)	Cephalo sporins (%)	Macro lides (%)	Quino lones (%)
Easteru	Hokkaido	14.1	3.6	4.6	2.6	13.6	3.5	4.1	2.5	-0.5 (-3.5)	-0.1 (-3.3)	-0.5 (-11.1)	-0.2 (-5.9)
	Aomori	12.7	2.9	4.4	2.4	12.0	2.6	4.1	2.1	-0.7 (-5.5)	-0.3 (-11.5)	-0.3 (-6.2)	-0.3 (-11.4)
	Iwate	11.9	2.8	4.1	2.2	11.2	2.5	3.6	1.9	-0.7 (-5.9)	-0.3 (-10.2)	-0.4 (-10.6)	-0.2 (-10.2)
	Miyagi	14.1	3.5	4.7	2.5	13.6	3.1	4.5	2.4	-0.5 (-3.5)	-0.4 (-11)	-0.2 (-4.3)	-0.2 (-7.5)
	Akita	14.9	3.7	5.4	2.9	13.9	3.4	4.5	2.8	-1.0 (-6.7)	-0.3 (-7.9)	-0.8 (-15.1)	-0.1 (-4.9)
	Yamagata	11.9	3.0	4.1	2.2	11.2	2.8	3.7	1.9	-0.7 (-5.9)	-0.2 (-7.4)	-0.4 (-9.7)	-0.3 (-14.7)
	Fukushima	13.9	3.8	4.4	2.7	12.8	3.3	3.8	2.4	-1.1 (-7.9)	-0.5 (-12.3)	-0.6 (-13)	-0.3 (-10.9)
	Ibaraki	13.4	3.4	4.6	2.3	12.9	3.0	4.2	2.2	-0.5 (-3.7)	-0.4 (-12.4)	-0.3 (-7.3)	-0.1 (-3.5)
	Tochigi	14.9	4.4	4.7	2.6	14.7	4.2	4.5	2.4	-0.2 (-1.3)	-0.2 (-4.2)	-0.1 (-3.1)	-0.2 (-7.3)
	Gunma	13.2	3.9	3.7	2.4	12.5	3.6	3.2	2.2	-0.7 (-5.3)	-0.3 (-6.5)	-0.5 (-14.1)	-0.2 (-8.3)
Central	Saitama	12.6	3.5	4.0	2.3	13.3	4.0	3.9	2.2	0.7 (5.6)	0.5 (13.7)	0.0 (-1)	-0.1 (-4.5)
	Chiba	12.9	3.3	4.1	2.3	12.3	2.9	3.8	2.1	-0.6 (-4.7)	-0.4 (-11)	-0.3 (-7.8)	-0.2 (-6.7)
	Tokyo	17.8	4.9	5.7	3.3	16.7	4.2	5.2	3.2	-1.1 (-6.2)	-0.6 (-12.5)	-0.5 (-8.5)	-0.1 (-3.7)
	Kanagawa	14.3	3.9	4.7	2.6	13.7	3.4	4.4	2.5	-0.6 (-4.2)	-0.6 (-14.6)	-0.2 (-4.7)	-0.1 (-2.1)
	Niigata	15.3	3.9	5.4	2.8	14.5	3.5	4.9	2.6	-0.8 (-5.2)	-0.4 (-9.5)	-0.5 (-9.2)	-0.1 (-4.9)
	Toyama	14.2	4.2	4.2	2.8	13.8	3.9	4.0	2.7	-0.4 (-2.8)	-0.3 (-6.8)	-0.2 (-5.9)	-0.1 (-3.7)
	Ishikawa	15.8	3.9	5.5	3.1	18.6	6.9	5.4	2.9	2.8 (17.7)	3.0 (75.7)	-0.1 (-2.6)	-0.2 (-6.3)
	Fukui	14.3	3.4	4.8	2.2	14.0	3.2	4.5	2.1	-0.3 (-2.1)	-0.2 (-5.2)	-0.3 (-7)	-0.1 (-3.9)
	Yamanashi	13.9	3.8	5.1	2.2	13.4	3.7	4.5	2.1	-0.5 (-3.6)	-0.1 (-3.8)	-0.6 (-12.6)	-0.1 (-3.7)
	Nagano	12.7	3.2	4.5	2.3	13.1	3.6	4.6	2.4	0.4 (3.1)	0.5 (14.9)	0.1 (1.7)	0.1 (2.5)
Westeru	Gifu	16.0	4.3	5.5	3.1	15.8	4.1	5.3	3.0	-0.2 (-1.3)	-0.2 (-4.1)	-0.2 (-3.8)	-0.2 (-5.4)
	Shizuoka	14.8	3.6	5.3	2.8	15.0	3.5	5.1	2.8	0.2 (1.4)	-0.1 (-1.5)	-0.2 (-3.4)	0.0 (0.6)
	Aichi	14.5	3.9	4.8	2.7	14.4	3.7	4.6	2.8	-0.1 (-0.7)	-0.2 (-5.9)	-0.1 (-2.5)	0.1 (3.3)
	Mie	14.9	4.1	5.3	2.8	14.5	3.7	5.0	2.9	-0.4 (-2.7)	-0.4 (-9.1)	-0.3 (-6.4)	0.1 (3.2)
	Shiga	14.5	3.7	5.5	2.3	13.6	3.3	4.9	2.2	-0.9 (-6.2)	-0.4 (-11.7)	-0.5 (-9.7)	-0.1 (-3.2)
	Kyoto	15.1	4.0	4.9	2.8	14.2	3.5	4.5	2.6	-0.9 (-6)	-0.5 (-11.9)	-0.4 (-8.3)	-0.2 (-6.9)
	Osaka	16.4	4.6	5.1	3.1	16.0	4.4	4.8	3.0	-0.4 (-2.4)	-0.2 (-4.4)	-0.3 (-5)	-0.2 (-5.4)
	Hyogo	14.4	3.8	4.7	2.9	13.9	3.5	4.2	2.8	-0.5 (-3.5)	-0.3 (-8.4)	-0.5 (-9.8)	-0.1 (-3.2)
	Nara	14.8	4.3	4.8	2.6	14.4	4.2	4.4	2.5	-0.4 (-2.7)	-0.1 (-1.4)	-0.4 (-7.4)	-0.1 (-5)
	Wakayama	15.7	4.1	4.7	3.4	15.2	3.8	4.3	3.4	-0.5 (-3.2)	-0.3 (-7.6)	-0.4 (-8.1)	0.0 (0.7)
Westeru	Tottori	13.5	3.4	4.1	2.7	12.9	3.1	3.9	2.5	-0.6 (-4.4)	-0.4 (-10.3)	-0.2 (-5.2)	-0.2 (-7.8)
	Shimane	13.7	3.7	4.1	2.7	14.3	3.4	4.4	2.8	0.6 (4.4)	-0.3 (-8.4)	0.3 (7.2)	0.1 (4.4)
	Okayama	16.3	4.0	5.5	3.3	16.3	3.8	5.2	3.2	0.0 (0)	-0.1 (-3)	-0.3 (-4.7)	-0.1 (-1.7)
	Hiroshima	16.6	4.3	5.1	3.7	16.4	4.6	5.0	3.7	-0.2 (-1.2)	0.3 (6.9)	-0.1 (-1.9)	0.0 (-1.3)
	Yamaguchi	14.8	3.6	4.4	3.5	15.3	3.7	4.4	3.5	0.5 (3.4)	0.1 (2.7)	0.0 (-0.6)	0.0 (0.5)
	Tokushima	19.5	6.2	5.6	4.1	17.9	5.0	5.2	3.7	-1.6 (-8.2)	-1.1 (-18.4)	-0.4 (-7.3)	-0.4 (-9.5)
	Kagawa	16.5	4.0	5.2	3.7	15.0	3.5	4.2	3.4	-1.5 (-9.1)	-0.4 (-11.2)	-1.0 (-18.9)	-0.3 (-8.6)
	Ehime	16.1	4.2	5.0	3.4	16.3	4.2	4.7	3.6	0.2 (1.2)	0.0 (-0.2)	-0.3 (-6.4)	0.1 (4.3)
	Kochi	16.0	3.3	4.9	3.3	15.1	2.9	4.3	3.3	-0.9 (-5.6)	-0.4 (-11.4)	-0.6 (-12.7)	0.0 (0)
	Fukuoka	15.3	4.0	4.6	3.2	15.8	3.7	4.7	3.4	0.5 (3.3)	-0.3 (-6.9)	0.1 (2.7)	0.3 (8.3)
Westeru	Saga	15.6	3.2	5.6	3.0	15.9	3.2	5.2	3.0	0.3 (1.9)	-0.1 (-1.6)	-0.4 (-6.9)	0.1 (2.8)
	Nagasaki	15.5	3.5	5.3	3.1	14.7	3.2	4.7	3.0	-0.8 (-5.2)	-0.3 (-8.3)	-0.6 (-11.2)	-0.1 (-4.4)
	Kumamoto	15.4	3.9	5.0	3.2	15.9	3.8	5.1	3.4	0.5 (3.2)	0.0 (-1.2)	0.1 (2.6)	0.1 (4.2)
	Oita	16.6	3.6	6.2	3.3	17.5	3.7	6.3	3.6	0.9 (5.4)	0.1 (2.2)	0.0 (0.5)	0.2 (7.1)
	Miyazaki	15.7	3.8	5.2	3.4	15.9	3.8	4.9	3.3	0.2 (1.3)	0.1 (1.8)	-0.2 (-4.5)	-0.1 (-3.6)
	Kagoshima	14.4	3.4	4.7	3.0	14.3	3.3	4.3	2.9	-0.1 (-0.7)	-0.1 (-3.2)	-0.4 (-8.7)	-0.1 (-3.1)
	Okinawa	12.2	2.6	3.6	1.9	13.7	2.7	4.3	2.1	1.5 (12.3)	0.1 (5.7)	0.7 (18.5)	0.2 (8.6)

Data show defined daily dose (version 2018) per 1,000 inhabitants per days, DID.

*: Data about difference between 2013 and 2016 are presented as DID (%).

As seen previously in the US and European countries (3–6), we showed regional differences in the AMU based on the antimicrobial sales data in Japan. Since Japan is an island country, our situation may be different from other countries. Socio-economic and cultural reasons have previously been considered to explain regional variation in the European countries (4–6), while a study in the US showed that a high proportion of obese, female, black individuals were the factors considered to explain the high frequency of antibiotic prescriptions

(3). Although these studies have evaluated the regional variation in the total AMU, in the present study we have demonstrated the regional variation in more detail (Fig. 2). Possible reasons for regional differences in AMU in Sweden were identified as variations in the distribution of hospitals and doctors, including infectious disease specialists, age of the population, and burden of the disease (11). However, further studies are needed to evaluate the reasons for regional differences in AMUs in Japan.

Our study showed differences in the trends of total AMU at the prefecture level between 2013 and 2016 (Table 1). Although no major changes were observed in the total AMU in Japan during this time period (-0.3 DID), the change was considerable at the prefectural level. Similar to the findings of a previous study (8), we demonstrated that among all the three regions, the total AMU was highest in the western region. Our study extended the results of Tanabe et al. by evaluating regional differences in AMU of major broad-spectrum oral antibiotics. During the study period, 13 prefectures (27.7%) showed increasing trends in their AMU. The issue of AMR could be improved using appropriate strategies based on the National Action Plan (1).

This study has the following limitations: first, we used the sales data to estimate AMU, but these might differ from the actual AMU. However, the data provided by IQVIA Services Japan K.K. cover 99% of the total sales in Japan and have been used by many research groups to estimate AMU (2,7,12,13). Moreover, a previous study from Japan demonstrated a correlation between the sales and claimed data of antibiotic consumption (14). Second, we analyzed only the regional differences in AMU and did not evaluate factors such as the potential quality of medical care associated with it. Although AMU is one of the indicators of AMS, to the best of our knowledge, this is the first study that demonstrates regional differences in AMU in Japan.

In conclusion, we showed regional differences in AMU of broad-spectrum oral antimicrobials (macrolides, cephalosporins, and quinolones) using the national sales data of antimicrobials from Japan. Since the National Action Plan requires a 50% reduction in AMU, additional studies should be conducted to identify the reasons underlying these differences and specify appropriate targets for AMS intervention.

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Conflict of interest None to declare.

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