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Changes in antibiotic consumption patterns after the implementation of the National Action Plan according to the Access, Watch, Reserve (AWaRe) classification system

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ABSTRACT

Objective: The Korean government published the first National Action Plan (NAP) on antimicrobial resistance (AMR) in August 2016, followed by a second plan in November 2021. The objective of this study was to analyze changes in antibiotic use patterns after the implementation of the NAP in South Korea.
Methods: We analyzed National Health Insurance claims data for hospitals and clinics from January 2011 to December 2020. Consumption was measured using a defined daily dose per 1000 inhabitants per day (DID). We analyzed data for each year, dimension, and category of the Access, Watch, Reserve classification system by the World Health Organization. Monthly inpatient and outpatient antibiotic use were calculated, and an interrupted time-series (ITS) analysis to assess the trend in antibiotic use was conducted.
Results: The consumption of antibiotics increased from 25.78 DID in 2011 to 29.06 DID in 2016, then decreased in 2017 after the implementation of the NAP on AMR. The watch group showed a temporal decrease after the implementation of the NAP; however, these figures increased until 2019, and the reserve group showed a downward trend beginning in 2017. According to the ITS analysis, the level (β_2) and the slope of the trend (β_3) of total antibiotic use decreased by 0.17 and 0.001, respectively. After implementation of the NAP, antibiotic use was reduced from 7.18 DID in 2016 to 4.84 DID in 2017 for amoxicillin and beta-lactamase inhibitors, 0.86 DID to 0.70 DID for ciprofloxacin, and 0.66 DID to ***0.66*** DID for levofloxacin.
Conclusion: After the implementation of the NAP in South Korea, antibiotic use in terms of total antibiotics and fluoroquinolone in the watch and reserve groups decreased. Further policies to improve the use of antibiotics in the watch and reserve groups are needed.

1. Introduction

Antimicrobial resistance (AMR) occurs when microorganisms evolve after exposure to antimicrobial drugs, thereby rendering antibacterials ineffective and increasing the risk of the spread of germs to others (Harbarth and Samore, 2005; Marston et al., 2016). However, novel antibiotics are limited, and AMR constitutes a major worldwide public health concern (Health Insurance Review & Assessment Service, 2021; Laxminarayan et al., 2013; Laxminarayan et al., 2020). The spread of AMR not only worsens the prognoses of patients but also leads to various problems, such as long periods of hospitalization and higher medical costs (Laxminarayan et al., 2013). The increase in AMR has been driven by excessive exposure to antibiotics in healthcare practice and the use of antibiotics outside of healthcare settings, and the main drivers of AMR in healthcare include the inappropriate use of antimicrobials (Marshall and Levy, 2011; Morel et al., 2020; Holmes et al., 2016; Marston et al., 2016).

As AMR has been a high-priority issue worldwide, the 68th World Health Assembly in 2015 adopted the Global Action Plan on Antimicrobial Resistance, which included five strategic objectives. The World Health Organization (WHO) recommended that each member country should establish a National Action Plan (NAP)

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to tackle AMR-related issues by 2019 (World Health Organization, 2016). As a result, the number of countries to have implemented a NAP has increased, with a total of 88.2% of countries reporting that they had implemented a NAP on AMR (World Health Organization, 2021).

In response to this collaborative global initiative, in June 2016, the South Korean government established the first NAP on AMR (2016-2020), which was implemented by eight ministries under the supervision of the Office for Government Policy Coordination. Ongoing efforts to address AMR in the NAP were designed to strengthen multisector coordination and collaboration, promote targeted AMR education and campaigns to raise awareness, and improve surveillance related to AMR, including data monitoring and reporting. With the NAP, the Korea Disease Control and Prevention Agency (KDCA) with Medical Society published guidelines for antibiotic use such as acute upper respiratory tract infection (URTI), lower respiratory tract infection, skin & soft tissue infection, community-acquired pneumonia, and urinary tract infection during 2016 and 2018. In addition, the NAP pushed the eight ministries to submit the execution report of the action plan by each trimester, and the Ministry of Health and Welfare (MoHW) strengthened antibiotic use monitoring and feedback according to Quality Assessment (QA) program by increasing the amount of incentive according to the QA results.

This study examined changes in the use of antibiotics after the implementation of Korea's NAP on AMR.

2. Methods

2.1. Data source and study population

We conducted a retrospective population-based study using data from the Korean National Health Insurance (NHI) claims database from January 2011 to December 2020. South Korea has a single-payer NHI system, which provides coverage for all citizens (population: 51.8 million) and reimburses healthcare providers through a fee-for-service system. This database covers all in-hospital and outpatient visits and, as such, includes demographic characteristics, diagnosis, healthcare use (test, procedure, length of treatment, and spending), and medicine use (product name, ingredient name, dose, length of treatment, and drug cost) (Park et al., 2021). All claims are electronically submitted to the Health Insurance Review & Assessment Service (HIRA), and all medicines are recorded using international nonproprietary names and codes for individual products. In South Korea, antibiotics can only be obtained through prescriptions, which are recorded in the NHI claims database.

The subjects of the analysis were patients eligible for NHI, including Medical Aid and Veterans Health Services, and who received one or more prescriptions for medications from a medical institution, including tertiary, secondary, general, and nursing hospitals, clinics, or public health centers.

2.2. Study antibiotics and therapeutic class

Therapeutic subgroups were classified according to the Anatomic Therapeutic Chemical (ATC) classification system of the WHO Collaborating Center (World Health Organization Collaborating Center, 2021). In this study, antibiotics were defined as medications with an ATC classification of J01 (antibacterials for systemic use). Each drug was registered in the NHI reimbursement list scheme, which included information on the manufacturer, the individual product number, active ingredient codes, dose, and formulation. We mapped ATC classifications using the main active ingredient name and method of administration and classified antibiotics according to the ATC-3 level, which refers to the pharmacological subgroup.

In 2019, the WHO published the Access, Watch, Reserve (AWaRe) classification system to reduce AMR on the regional, national, and global levels. The "Access" category includes antibiotics that are active against various common infectious pathogens. "Watch" includes antibiotics with a higher potential for AMR than those included in the access group and should be monitored. "Reserve" refers to last-resort antibiotics for the treatment of confirmed infections caused by multidrug-resistant organisms and should only be used for specific patients under specific circumstances (World Health Organization, 2019).

2.3. Measures and calculations

The outcome measure was consumption, presented as the number of defined daily doses (DDDs) per 1,000 inhabitants per day (DID), which was calculated as the number of DDDs $\times$ 1,000 $\div$ total population $\div$ 365. DID provides a rough estimate of the proportion of the population within a defined area that is treated with certain drugs on a daily basis. The WHO defines the DDD of a single formulation based on the typical daily dose of an adult (70 kg). Because biological efficacy is different for each formulation, DDDs of the same drug differ according to the formulation. DDDs provide a fixed unit of measurement independent of price, package size, and strength, enabling trends in drug consumption to be assessed (Organization for Economic Co-operation and Development, 2020).

We analyzed changes in the use of antibiotics each year across multiple dimensions. The analytical dimensions were inpatient/outpatient status, the patients' characteristics (gender and age), drug formulation (oral administration/injection), and drug classification (ATC-3 level and AWaRe group). The age group was divided into <6 years, 7-19 years, 20-64 years, and ≥65 years old. Children were defined as <6 years of age because school -ages are 7-18 years. We used the total population by year, age, and gender using the estimated population from Statistics Korea.

2.4. Statistical analysis

Segmented regression analysis of an interrupted time-series (ITS) was conducted to identify the effects of the NAP on the consumption of antibiotics. The equation is shown in the following paragraph, and we analyzed the change in level and change in trend after the NAP. SAS Enterprise version 7.1 (SAS Institute Inc., Cary, North Carolina, USA) was used for the statistical analysis.

$$Y_t = \beta_0 + \beta_1 \, \mathrm{TIME}_t + \beta_2 \, \mathrm{INTERVENTION}_t + \beta_3 \, \mathrm{TREND}_t + \varepsilon_t \quad (1)$$

Where Y referred to antibiotic use and t referred to the month. TIME was a continuous variable and had a value of 1 for January 2010 and increased by 1 monthly. INTERVENTION was a dummy indicator for the NAP in August 2016 and had a value of 0 during and before August 2016 and a value of 1 during and after September 2016. Therefore, the coefficient β_1 represented the baseline monthly trend before the implementation of the NAP, β_2 represented immediate changes in the level of antibiotic use after the NAP, and β_3 represented the change in the slope of the monthly trend after the NAP.

3. Results

3.1. Overall trend and use according to the AWaRe classification

As shown in Figure 1, antibiotic use declined after the implementation of the NAP for AMR in 2016. The consumption of antibiotics increased from 25.78 DID in 2011 to 29.06 DID in 2016, then decreased beginning in 2017. Antibiotic use in inpatient care

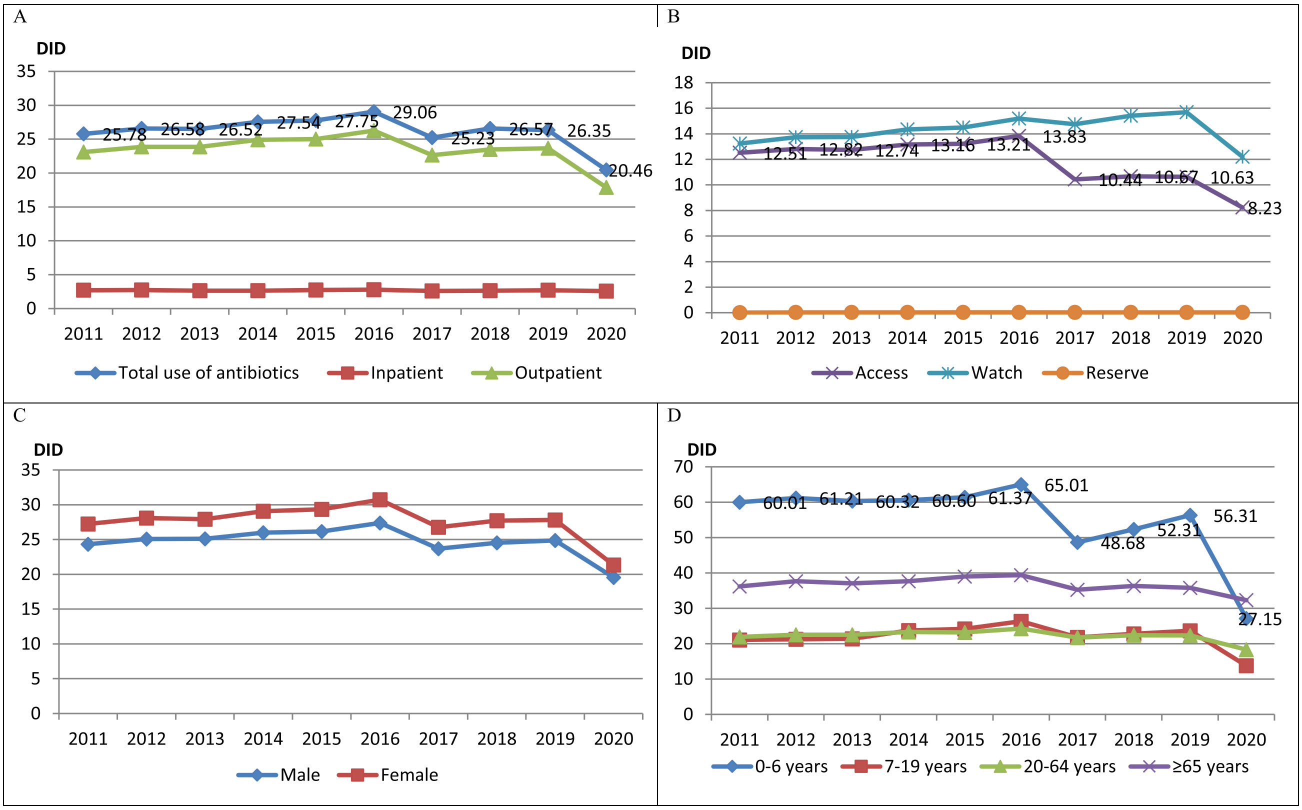


Figure 1. The consumption of antibiotics by year and dimension.
DID = defined daily dosage per 1,000 inhabitants per day.

averaged 2.71 DID, whereas, in outpatient care, it averaged 23.64 DID, accounting for 89.7% of total antibiotic use in 2019. In 2020, there was a sharp decline because of the COVID-19 pandemic.

Antibiotic consumption in the access group increased from 12.51 DID in 2011 to 13.83 DID in 2016 and decreased beginning in 2017. However, in the watch group, antibiotic use continuously increased from 13.24 DID in 2011 to 15.69 DID in 2019. Antibiotic consumption in the reserve group was low at 0.01-0.02 DID and showed a downward trend from 0.03 DID in 2016 to 0.02 DID in 2017 and beyond.

We also analyzed the use of antibiotics according to inpatient/outpatient status and age in the access and watch group. For the access group, the antibiotic use in the access group showed a considerable decline since 2017 in the inpatient setting and a slight decrease in the outpatient setting. In contrast, the antibiotic use of the watch group showed a continuous increase in inpatient and outpatient settings. All age groups, except children in the watch group, showed an increase (Figure 2).

3.2. Antibiotic use according to age and sex

As listed in Table 1, all sex and age groups showed an increase in the use of antibiotics until 2016, after which a temporary decrease was observed in 2017, followed by yearly increases since 2018. The use of antibiotics in the access group was higher among women (10.95 DID) than men (10.31 DID) in 2019. In terms of age, their use was the highest among children (≤6 years old) at 33.08 DID in 2019, followed by senior adults (≥65 years old) at 11.29 DID, adolescents (aged 7-19 years) at 9.96 DID, and adults (aged 20-64 years) at 8.83 DID.

The use of antibiotics in the watch group was also higher among women (16.85 DID) than men (14.54 DID) in 2019. In terms of age, their use was the highest among senior adults at 24.40 DID in 2019, followed by children (23.23 DID), adolescents (13.71 DID), and adults (13.50 DID). The use of antibiotics in the reserve group was higher among men than among women in 2019. In terms of age, their use was the highest among senior adults (0.06 DID), followed by children (0.01 DID).

3.3. The most frequently used drugs

As listed in Table 2, in the access group, the most-used drugs had ATC classifications of J01CR02 (amoxicillin and beta-lactamase inhibitor), J01AA02 (doxycycline), and J01CA04 (amoxicillin). In the watch group, the most-used drugs had ATC classifications of J01DC04 (cefaclor), J01FA09 (clarithromycin), and J01FA06 (roxithromycin). In the reserve group, the most-used antibiotics had ATC classifications of J01XB01 (colistin) and J01XX08 (linezolid). After the NAP, antibiotic use decreased from 7.18 DID in 2016 to 4.84 DID in 2017 for amoxicillin and beta-lactamase inhibitors, 0.86 DID and 0.70 DID for ciprofloxacin, and 0.66 DID and ***0.66*** DID for levofloxacin.

Most antibiotics prescribed on an inpatient basis had ATC classifications of J01D (cephalosporin), J01C (beta-lactam antibacterials), J01M (quinolone antibacterials), J01F (macrolides), and J01X (other antibacterials), accounting for 94.8% of antibiotics as of 2019. In addition, the use of antibiotics with ATC classifications of J01M (quinolone antibacterials) and J01X (other antibacterials) has increased each year. Among the outpatient antibiotics taken, approximately 90% had ATC classifications of J01D (cephalosporin), J01C (beta-lactam antibacterials), J01M (quinolone antibacterials), and J01F (macrolides). Approximately 15.8% and 6.3% of antibiotics for inpatient care had an ATC classification of J01M (quinolone antibacterials) or J01X (other antibacterials), respectively, whereas they comprised 7% and 0.1% of antibiotics, respectively, for outpatient care. The use of antibiotics classified as J01M (quinolone

Figure 2. The consumption of antibiotics by year and AwaRe.
A, B: Access group, C, D: Watch group.
AwaRe = Access, Watch, Reserve; DID = defined daily dosage per 1,000 inhabitants per day.

Table 1
The consumption of antibiotics by the AWaRe classification (DID).

Year	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
AWaRe										
Access group	12.51	12.82	12.74	13.16	13.21	13.83	10.44	10.67	10.63	8.23
Total use in the watch group	13.24	13.73	13.75	14.35	14.50	15.19	14.76	15.42	15.69	12.20
Reserve group	0.01	0.02	0.02	0.02	0.03	0.03	0.02	0.02	0.02	0.02
Total use in the access group										
Gender										
Male	11.97	12.32	12.31	12.70	12.77	13.40	10.06	10.30	10.31	8.02
Female	13.05	13.32	13.17	13.61	13.65	14.26	10.81	11.04	10.95	8.45
Age										
0-6 years	36.32	39.02	39.84	40.25	40.50	43.24	29.30	31.36	33.08	16.65
7-19 years	10.95	11.10	11.20	12.26	12.32	13.37	9.48	9.79	9.96	5.96
20-64 years	10.39	10.46	10.28	10.66	10.63	11.06	8.77	8.93	8.83	7.50
≥65 years	13.88	14.11	13.83	13.97	14.54	14.71	11.34	11.46	11.29	10.36
Total use in the watch group										
Gender										
Male	12.33	12.73	12.77	13.24	13.34	13.95	13.60	14.21	14.54	11.51
Female	14.16	14.74	14.73	15.45	15.68	16.44	15.93	16.64	16.85	12.88
Age										
0-6 years	23.68	22.19	20.47	20.34	20.86	21.77	19.38	20.94	23.23	10.50
7-19 years	10.13	10.16	10.19	11.43	11.88	12.97	12.32	13.01	13.71	7.79
20-64 years	11.49	12.04	12.18	12.66	12.57	13.18	12.94	13.41	13.50	10.80
≥65 years	22.15	23.42	23.10	23.54	24.30	24.50	23.83	24.71	24.40	21.83
Total use in the reserve group										
Gender										
Male	0.017	0.022	0.025	0.030	0.034	0.037	0.021	0.025	0.022	0.026
Female	0.009	0.011	0.013	0.015	0.017	0.020	0.012	0.014	0.012	0.015
Age										
20-64 years	0.009	0.011	0.012	0.014	0.015	0.016	0.010	0.012	0.011	0.013
≥65 years	0.060	0.079	0.085	0.098	0.115	0.127	0.068	0.078	0.064	0.073

AwaRe = Access, Watch, Reserve; DID = defined daily dosage per 1,000 inhabitants per day.

Table 2
The most common ingredient names in the access and watch groups (DID).

ATC code Access		Name	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
1	J01CR02	amoxicillin and beta-lactamase inhibitor	6.02	6.22	6.28	6.67	6.72	7.18	4.84	5.01	5.01	3.11
2	J01AA02	doxycycline	1.23	1.25	1.22	1.27	1.44	1.65	1.84	1.93	2.00	2.02
3	J01CA04	amoxicillin	3.33	3.43	3.42	3.45	3.30	3.27	2.08	2.08	2.00	1.64
4	J01XD01	metronidazole	0.07	0.07	0.07	0.07	0.08	0.08	0.09	0.09	0.09	0.09
5	J01DB09	cefradine	0.60	0.56	0.50	0.48	0.46	0.45	0.42	0.40	0.38	0.33
6	J01DB01	cefalexin	0.18	0.20	0.22	0.25	0.26	0.31	0.23	0.24	0.24	0.21
7	J01DB05	cefadroxil	0.37	0.36	0.33	0.31	0.29	0.29	0.27	0.26	0.25	0.21
8	J01DB06	cefazedone	0.16	0.18	0.18	0.17	0.17	0.17	0.18	0.19	0.20	0.19
9	J01AA07	tetracycline	0.05	0.05	0.05	0.05	0.05	0.05	0.06	0.06	0.07	0.09
10	J01GB06	amikacin	0.08	0.08	0.08	0.07	0.07	0.07	0.07	0.07	0.07	0.08
Watch												
1	J01DC04	cefaclor	3.47	3.66	3.80	3.98	3.97	4.12	4.12	4.24	4.14	3.56
2	J01FA09	clarithromycin	2.09	2.07	2.10	2.37	2.53	2.75	2.63	2.80	2.98	1.76
3	J01FA06	roxithromycin	1.35	1.43	1.40	1.48	1.47	1.55	1.48	1.52	1.51	1.19
4	J01DC02	cefuroxime	0.75	0.82	0.85	0.95	0.97	1.04	1.07	1.15	1.19	0.86
5	J01MA02	ciprofloxacin	0.71	0.74	0.73	0.72	0.72	0.86	0.70	0.69	0.69	0.66
6	J01MA12	levofloxacin	1.00	1.11	1.07	0.93	0.81	0.66	0.66	0.70	0.73	0.66
7	J01DD13	cefpodoxime	0.31	0.39	0.41	0.45	0.48	0.53	0.54	0.62	0.68	0.44
8	J01MA01	ofloxacin	0.70	0.66	0.62	0.64	0.64	0.64	0.55	0.55	0.52	0.42
9	J01DD04	ceftriaxone	0.22	0.24	0.24	0.26	0.29	0.30	0.31	0.33	0.35	0.31
10	J01DD16	cefditoren	0.19	0.20	0.21	0.23	0.25	0.29	0.30	0.37	0.43	0.30
Reserve												
	J01XB01	colistin	0.008	0.011	0.012	0.015	0.018	0.020	0.007	0.008	0.008	0.008
	J01XX08	linezolid	0.002	0.002	0.002	0.002	0.002	0.003	0.003	0.005	0.005	0.006
	J01AA12	tigecycline	0.002	0.002	0.002	0.003	0.003	0.003	0.003	0.003	0.004	0.004
	J01DF01	aztreonam	0.002	0.002	0.002	0.002	0.003	0.003	0.003	0.003	0.000	0.003

ATC = Anatomic Therapeutic Chemical classification; DID = defined daily dosage per 1,000 inhabitants per day.

antibacterials) in particular decreased from 2.51 DIDs in 2011 to 2.09 DIDs in 2019, whereas the use of antibiotics classified as J01C (beta-lactam antibacterials) increased from ***9.55*** DIDs in 2011to 10.66 DIDs in 2016 and has subsequently decreased each year since 2017 (Supplementary Table).

3.4. Changes in antibiotic use after the NAP

Figure 3 shows the monthly trend of antibiotic use and the effects of the NAP on antibiotic consumption overall and the consumption of antibiotics in the access and watch groups. Total antibiotic use by month at the baseline level (β_0) was 2.158, and the baseline trend (β_1) was 0.003. After the NAP, total antibiotic use (β_2) decreased by 0.154; however, that is not statistically significant, and the slope of the trend (β_3) decreased by 0.003.

For antibiotics in the access group, the baseline level (β_0) and the baseline trend (β_1) of use were 1.038 and 0.002, respectively. Total antibiotic use (β_2) and the slope of the trend (β_3) in this group decreased by 0.139 and 0.004, respectively.

For antibiotics in the watch group, the baseline level (β_0) and the baseline trend (β_1) of use were 1.109 and 0.002, respectively. Total antibiotic use (β_2) in this group decreased by 0.023, and the slope of the trend (β_3) increased by 0.001.

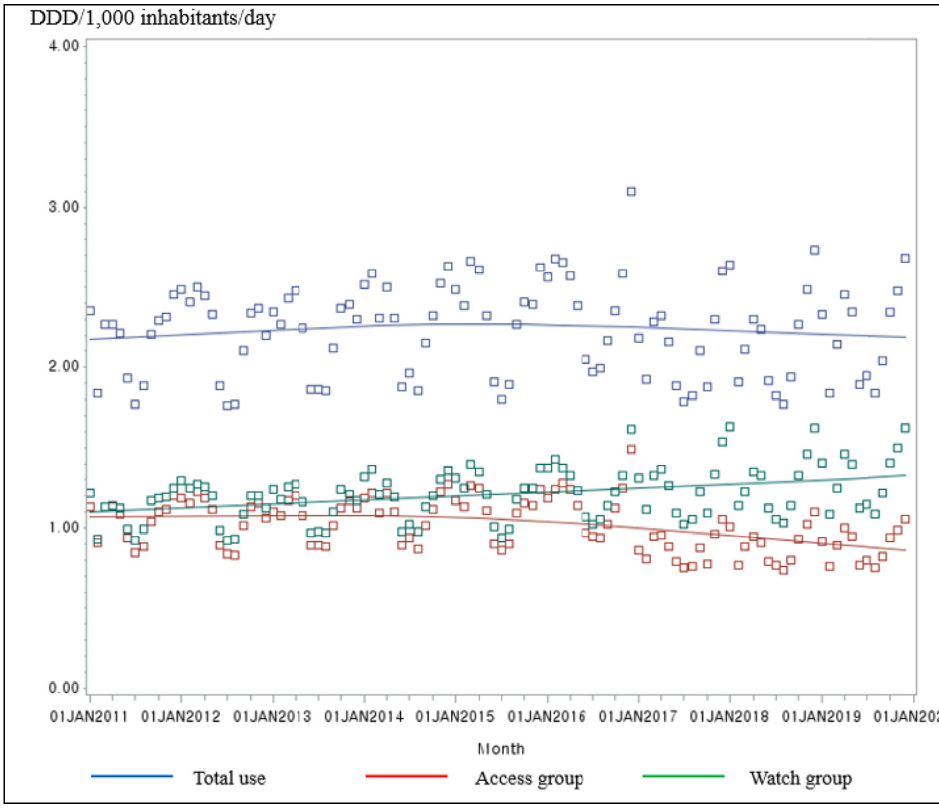
4. Discussion

To our knowledge, this is the first study to investigate changes in antibiotic use since the implementation of the NAP on AMR and examine the consumption of antibiotics according to the WHO's AWaRe classification system in South Korea. The Korean government implemented the NAP on AMR in August 2016. As a result, the consumption of antibiotics decreased overall after the NAP. However, the use of antibiotics in the watch group, in particular, has not decreased.

Our analyses yielded four main findings. First, it is notable that the use of antibiotics has decreased since 2017 after the NAP on AMR was first implemented. After the NAP, total antibiotic use (β2) and the slope of the trend (β3) decreased; however, the decline of the slope was only statistically significant. However, it is significant that it reduced the overall tendency to increase the use of antibiotics rather than a temporary decrease in the fragmentation. This result is consistent with previous studies conducted in Japan and Italy (Kusama et al., 2021; Gu et al., 2021; Cangini et al., 2021). The first NAP (2016-2020) on AMR set targets related to both the prescription rate of antibiotics for acute URTIs and total antibiotic use overall (22% and 25.4 DID in 2020, respectively). Although the target for the overall use of antibiotics was reached as a result of the decrease in outpatient visits because of the COVID-19 pandemic, several ministries, including the MoHW and KDCA, have actively worked on implementing the main goals from the first NAP. The NAP could further reduce AMR as a result of the following measures: improving awareness and understanding of AMR, strengthening surveillance and research related to AMR, and optimizing the use of antimicrobial medicines.

Second, after the implementation of the NAP, the reduction of antibiotic use is consistent with the trend of antibiotic prescription rate in the QA program. The prescription rate of antibiotics for URTIs decreased from 44.04% in 2015 to 36.06% in 2020 (Health Insurance Review & Assessment Service, 2020). However, there was an overall decrease in consumption of antibiotics in 2017, followed by an increase in 2018 with a plateau in 2019. This change in consumption is led by the decrease in use in outpatients, whereas inpatients have not changed their consumption of antibiotics. The key tasks of the NAP were reinforcing antibiotic use surveillance, such as the QA program on antibiotic use for acute URTI in the outpatient setting. MoHW and HIRA introduced the QA program in 2001 to decrease the prescription rate of antibiotics for acute URTIs. Through the QA program, government agencies evaluate and disclose the information on antibiotic use for acute URTI and lower RTI by medical institution.

In addition, in this study, outpatient care is responsible for most antibiotic use. Therefore, measures should be taken to optimize the use of antibiotics in the context of outpatient visits to emphasize patient-centered management.



	Total use			Access			Watch		
Variable	β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Intercept (β_0)	2.158	0.085	<.0001	1.038	0.034	<.0001	1.109	0.047	<.0001
Time (β_1)	0.003	0.002	0.1474	0.002	0.001	0.1438	0.002	0.001	0.1163
Intervention (β_2)	-0.154	0.132	0.2446	-0.139	0.054	0.0117	-0.023	0.072	0.7499
Trend (β_3)	-0.003	0.005	0.5228	-0.004	0.002	0.0264	0.001	0.003	0.6754
DW		2.0302			0.8405			2.0277	
Total R-square		0.4558			<.0001			0.5174	

Figure 3. Beta values of the interrupted time-series analysis in antibiotic use of access and watch group.
DID = defined daily dosage per 1,000 inhabitants per day; DW = Durbin-Watson Statistics; SE, standard error.

Third, because the excessive use of broad-spectrum antibiotics can affect other antibiotic-resistant bacteria, it is important to administer antibiotics only when necessary (Kim et al., 2016b). A notable point is that the watch group's antibiotic use has increased since 2017, whereas the access group's antibiotics use has decreased. According to time-series analysis, there was a slight decrease in the trend slope among total antibiotic use, the access group, and the reserve group, whereas there was an increase in the watch group. In the watch group antibiotics, the use of fluoroquinolone class decreased; however, the antibiotic use of J01DC04 increased by 0.65, which may be because of the Korean government policy emphasizing the use of quinolone, macrolide, and the third or fourth cephalosporin. In addition, although the WHO announced the AWaRe classification, the importance and appliance of this AWaRe class were not discussed in Korea. It will be necessary to strengthen monitoring and guide the use of antibiotics by member states to reduce antibiotic use in the watch group to the level of the WHO requirements.

Fourth, antibiotic use in children has decreased since 2017. This may be because of the publishing of the guideline for antibiotic use in children with acute URTI in November 2016. However, because the use of antibiotics in hospitalization does not decrease, it is necessary for the NAP to design its main strategies to reduce the use of antibiotics by thoroughly analyzing the overall trend of antibiotic use.

This is the first study to examine changes in the use of antibiotics after the implementation of the NAP. Because the NHI database covers both inpatient and outpatient care, we were able to examine nearly all antibiotic use across the total population. Another aim of this study was to provide basic data on the use of antibiotics according to the WHO's AWaRe classification system. This system was developed by the WHO in 2019 to support antibiotic management tools and reduce AMR at the regional, national, and global levels. As a result of our analysis, the use of antibiotics in the watch group was found to steadily increase until 2019 in South Korea.

Our study had the following limitations. First, we used an administrative dataset that may not have fully captured clinical factors associated with the selection of antibiotics, such as bacterial culture test results and the duration of patients' fevers. Because we could not distinguish patients' conditions, we only analyzed medical conditions based on the claims data. Second, although our dataset covered the entire national population, including non-Korean citizens living in Korea, trends in antibiotic use may differ by country in terms of the epidemiology of diseases, the healthcare system, and a drug-heavy medical culture. For example, access to healthcare tends to be very high, and the number of outpatient visits per person tends to be the highest in the Organi zation for Economic Co-operation and Development (OECD) member countries (Organization for Economic Co-operation and Development, 2021a). Third, because we only analyzed claims data, the analysis may have included some prescriptions that were not dispensed for any given reason. We did not analyze the use of antibiotics in terms of both the presence of infection and the selection of antibiotics according to the results of a culture test. In addition, antibiotic use in the healthcare market overall, including noncovered drugs, totaled 26.1 DID in 2019, which is still relatively high compared with the average of 17.4 DID among OECD member countries in 2019 (Organization for Economic Co-operation and Development, 2021b). We referred to OECD pharmaceutical consumption because OECD Health Statistics was generated 'timely' and according to the predefined method of statistics. Lastly, in addition to the NAP, other factors may have influenced changes in the patterns of antibiotic use. The antimicrobial stewardship program, conducted at the individual hospital level, was gradually implemented before the NAP; however, it was not considered in this study (Kim et al., 2016a). In addition, there is the possibility that the effect of intervention might occur later than August 2016. However, the NAP requires the eight ministries to submit the execution report of the action plan by each trimester, so we supposed that the change was implemented immediately.

In conclusion, our findings showed that the overall use of antibiotics decreased in South Korea after implementing the NAP. However, further policies to improve the use of antibiotics in the watch and reserve groups are needed. It will be necessary to strengthen monitoring and guide the use of antibiotics and promote the prescribing according to the treatment guideline. In ad dition, to implement a coordinated "One Health" approach to promote best practices, cooperative global efforts, such as the Tripartite Joint Secretariat on Antimicrobial Resistance by the Food and Agriculture Organization of the United Nations, World Organization for Animal Health, and the WHO, might be an important factor for reducing AMR in the future.:

CRediT authorship contribution statement

Jungmi Chae: Writing – original draft, Data curation, Formal analysis. **Bongyoung Kim:** Writing – review & editing. **Dong-Sook Kim:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Conflict of interest statements

The authors have no competing interests to declare.

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Ethics committee approval

This study was approved and got a waiver using the anonymous data by the Institutional Review Board of HIRA (IRB number: 2021-016-001).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.06.013.

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