BMJ Open

Antibiotic prescription among outpatients in a prefecture of Japan, 2012–2013: A retrospective claims database study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026251
Article Type:	Research
Date Submitted by the Author:	23-Aug-2018

Complete List of Authors:	Hashimoto, Hideki; Jichi Medical University Hospital, Division of General Internal Medicine Matsui, Hiroki; Jichi Medical University, Data Science Center; School of Public Health, University of Tokyo, Department of Clinical Epidemiology and Health Economics Sasabuchi, Yusuke; Jichi Medical University, Data Science Center Yasunaga, Hideo; Jichi Medical University, Data Science Center; School of Public Health, The University of Tokyo, Department of Clinical Epidemiology and Health Economics Kotani, Kazuhiko; Jichi Medical University, Division of Community and Family Medicine Nagai, Ryozo; Jichi Medical University, President Hatakeyama, Shuji; Jichi Medical University Hospital, Division of General Internal Medicine/Division of Infectious Diseases

Keywords:	Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, INFECTIOUS DISEASES

Antibiotic prescription among outpatients in a prefecture of Japan, 2012–2013: A retrospective claims database study

Hideki Hashimoto[1], Hiroki Matsui[2, 3], Yusuke Sasabuchi[2], Hideo Yasunaga[2, 3], Kazuhiko Kotani[4], Ryozo Nagai[5], Shuji Hatakeyama[1, 6*]

[1]Division of General Internal Medicine, Jichi Medical University Hospital, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

[2]Data Science Center, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

[3]Department of Clinical Epidemiology and Health Economics, School of Public Health, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

[4]Division of Community and Family Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

[5]President, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

[6]Division of Infectious Diseases, Jichi Medical University Hospital, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

***Corresponding author:**

Shuji Hatakeyama, M.D., Ph.D.

Division of General Internal Medicine/Division of Infectious Diseases, Jichi Medical University Hospital, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

Phone: +81-285-58-7498

Fax: +81-285-40-5160

E-mail: shatake-tky@umin.ac.jp

Key words: antibiotic, antimicrobial stewardship, antimicrobial-resistance, big data, inappropriate prescribing

Running title: Antibiotic prescriptions in Japan

Word count for the main text: 2,511 words

Abstract

Objectives: To investigate antibiotic prescribing patterns and identify factors associated with antibiotic prescriptions, with the aim of reducing inappropriate use.

Design: Retrospective cohort study.

Setting: Database of public health insurance claims in Kumamoto prefecture (Japan).

Participants: Individuals who joined the national or late elders' health insurance system between April 2012 and March 2013.

Main outcome measures: Of 7,770,481 patients, 682,822 had a code for antibiotics. Third-generation cephalosporins (35%), macrolides (32%), and quinolones (21%) were most frequently prescribed. Acute respiratory tract infections (ARTIs), including viral upper respiratory infections (URI) (22%), pharyngitis (18%), bronchitis (11%), and sinusitis (10%) were most frequently diagnosed for antibiotic prescribing; then, gastrointestinal infections (9%), urinary tract infections (8%); and skin, cutaneous, and mucosal infections (5%). Antibiotic prescribing rates for viral URI, pharyngitis, bronchitis, sinusitis, and gastrointestinal infections were 35%, 54%, 53%, 57%, and 30%, respectively. In multivariable analysis for ARTIs and gastrointestinal infections, patient age (10–19 years especially), gender (male), and facility scale (clinic or small-sized hospital visits) were associated with increased antibiotic prescribing.

Conclusions: Broad-spectrum antibiotics constituted 88% of oral antibiotic prescriptions. Approximately 70% of antibiotics were prescribed for ARTIs and gastroenteritis with modest benefit from antibiotic treatment. The quality of antibiotic prescribing needs to be improved. Antimicrobial stewardship interventions should target ARTIs and gastroenteritis, as well as young patients and small-sized institution groups.

Strength and limitations of this study

- This is the first Japanese study to describe antibiotic prescription patterns linked to individual diagnoses data, comprehensively, by use of the public health insurance claims database.
- This study included patients older than 65 years of age, who were hardly included in previous Japanese studies.
- The accuracy of the diagnosis has not been validated due to the nature of the administrative claims database.
- There are some unmeasured potential confounding factors such as out-of-hour visits and physician specialty.

Introduction

There is a growing concern about infections by antimicrobial-resistant bacteria. Antimicrobial resistance results in increased health care costs, prolonged hospitalization, and death.[1-3] The World Health Organization launched the global action plan to combat the antimicrobial-resistant bacteria in 2015[4] and requested Member States to endorse national action plans within two years. The government of Japan launched a national action plan in 2016 in response to the request.[5]

Since antimicrobial use is one of the important factors in the emergence of antimicrobial resistance,[6] it is essential to reduce the inappropriate use of antibiotics. In Japan, a previous study, based on sales data, revealed that oral antibiotics accounts for more than 90% of the total antibiotic consumption and that broad-spectrum antibiotics (third-generation cephalosporins, macrolides, and fluoroquinolones) accounts for 77% of oral antibiotic consumption (daily doses defined per 1,000 inhabitants per day).[7] The Japanese national action plan aims to reduce the total antimicrobial use to two-thirds, and the use of oral cephalosporins, quinolones, and macrolides to one-half, by 2020. To accomplish the reduction of inappropriate antimicrobial use, it is important to determine the antimicrobial prescribing patterns and factors associated with antibiotic prescription. However, such information is limited in Japan to date. Although a few recent studies[8,9] described the prescription patterns for upper respiratory tract infections and bronchitis, the prescription patterns of infections other than acute respiratory tract infections (ARTIs) have not been clarified. In addition, patients older than 65 years of age were hardly included in these studies; because these studies relied on data from employee-based insurance claims database. With the high rate in aging population in Japan, it is important to describe the prescription patterns in the elderly.

In this study, we described oral antibiotic prescribing patterns for all infections and in all ages, using Japanese administrative claims database. Also, we aimed to identify factors associated with antibiotic prescriptions for ARTIs and gastrointestinal infections, the targets of the antimicrobial stewardship guideline formulated by the government of Japan.[10]

Methods

Data sources

We conducted a retrospective analysis using the administrative health insurance claims database of Kumamoto prefecture, situated in the southwestern region of Japan, with a population of about 1.7 million. This database covers approximately 780,000 residents of Kumamoto prefecture who joined the national health insurance system (for those younger than 75 years of age),[11] or the late elders' health insurance system (for those aged 75 years and older).[12]

The database is composed of medical (inpatient and outpatient) and pharmacy claims. It provides monthly information about patient demographics (year and month of birth and gender), diagnoses, date of diagnoses, medical procedures, medications, scale (number of beds) of the medical facility, as well as the identification numbers assigned to each individual, medical facility, and dispensing pharmacy. The diagnoses were coded according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).

Data preparation

We linked the medical and pharmacy claims, on the database, using an identification number unique to each patient, medical facility, and dispensing pharmacy. We identified all newly diagnosed outpatients, with any infectious diseases, between April 2012 and March 2013. Infectious diseases diagnoses are categorized according to the indication for antibiotic use (Table S1, available as supplementary data). This categorization is based on the study by Fleming-Dutra KE *et al*.[13] Bronchitis and bronchiolitis were divided into two categories based on whether the patients had chronic obstructive pulmonary disease (COPD) as comorbidity or not, because of differing need of treatment with antibiotics. If a patient had multiple infectious diagnoses in one month, a single infectious diagnosis, selected in order from Group 1 (antibiotics are usually indicated) to Group 3 (antibiotics are rarely indicated), and the first-listed diagnosis in alphabetical order of ICD-10 codes in the selected group; was included in the analyses (Table S1).

We also identified all outpatients with any antibiotic prescriptions. Topical, intramuscular, and intravenous antibiotics were excluded. Antibiotics were categorized according to the Anatomical Therapeutic Chemical (ATC) classification system (http://www.whocc.no/atcddd/) into: tetracyclines (J01A), penicillins (J01C), first- and second-generation cephalosporins (J01DB and J01DC), third-generation cephalosporins (J01DD), sulphonamides and trimethoprim (J01E), macrolides (J01FA), quinolones (J01M), and others (J01B, J01DH, J01DI, J01FF, J01G, and J01X). We assumed that third-generation cephalosporins accounted for most of cephalosporins used in Japan; hence, we divided cephalosporins into two groups: first/second- and third-generation cephalosporins.

Data Analysis

We calculated the frequency of antibiotic prescription for all visits with infections (according to diagnosis and antibiotic class). For ARTIs (including pharyngitis, sinusitis, bronchitis/bronchiolitis, and viral upper respiratory infections [URI]) and gastrointestinal infections separately, we performed multivariable logistic regression analyses to identify the factors associated with antibiotic prescriptions. The variables were as follows: age and gender of patients and scale (number of beds) of the medical facilities. Generalized estimating equations with exchangeable correlation structure were used to account for the clustering of the medical facilities. P-values < 0.05 were considered statistically significant. All statistical analyses were performed with the statistical package R, v.3.5.0 (http://cran.r-project.org).

Patient involvement

No patients were involved in the development of the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the study results to the relevant patient community.

Results

In total, there were 7,770,481 patients between April 2012 and March 2013. Antibiotics were prescribed in 682,822 patients. Among these, third-generation cephalosporins were most frequently prescribed (237,372 patients, 35%), followed by macrolides (215,656 patients, 32%) and quinolones (145,135 patients, 21%). This trend was observed regardless of age group (Table 1) and scale of the medical facility (Table 2), except with those less than 9 years of age in whom the systemic use of quinolones is not recommended. Information about facility scale was available from 669,086 out of 682,822 patients. Of these, antibiotics were prescribed most frequently at clinics (530,916 patients, 79%), followed by small-sized (< 200 beds; 78,546 patients, 12%), medium-sized (200–499 beds; 45,271 patients, 7%), and large-sized (500 beds or more; 14,353 patients, 2%) hospitals (Table 2).

We could link the individual diagnoses to the antibiotic prescription in 447,232 patients (Table 3). Of these patients, approximately 60% of antibiotics were prescribed for ARTIs; viral URI (96,989 patients, 22%), followed by pharyngitis (78,469 patients, 18%), bronchitis without COPD (47,248 patients, 11%), and sinusitis (45,456 patients, 10%). Other than ARTIs, there were frequent antibiotic prescriptions for gastrointestinal infections (41,309 patients, 9%), urinary tract infections (37,674 patients, 8%), and skin, cutaneous, and mucosal infections (23,572 patients, 5%). The antibiotic prescription rates for viral URI, pharyngitis, bronchitis (without underlying COPD), sinusitis, and gastrointestinal infections were 35% (96,989 out of 274,441 patients), 54% (78,469 out of 146,508 patients), 53% (47,248 out of 89,479 patients), 57% (45,456 out of 80,078 patients), and 30% (41,309 out of 137,661 patients), respectively (Table 3).

Table 4 shows the results of the logistic regression analysis about antibiotic prescription for ARTIs. Male gender was associated with more antibiotic prescription (adjusted odds ratio [OR], 1.10; 95% confidence interval [CI], 1.08 to 1.11). With patients aged 65 years or older as reference, patients aged 10 to 19 years were more likely to be prescribed antibiotics (adjusted OR, 2.75; 95% CI, 2.69 to 2.82), followed by patients aged 20 to 64 years (adjusted OR, 1.92; 95% CI, 1.89 to 1.94), and patients younger than 10 years (adjusted OR, 1.48; 95% CI, 1.46 to 1.50). With facility scale, with large-sized (500 beds or more) hospitals as reference, clinic (adjusted OR, 4.24; 95% CI, 4.03 to 4.45), small-sized (< 200 beds) hospitals (adjusted OR, 2.07; 95% CI, 1.97 to 2.18), and medium-sized (200–499 beds) hospitals (adjusted OR, 1.71; 95% CI, 1.62 to 1.80) were significantly associated with more antibiotic prescription.

Similar results were shown with the logistic regression analysis for gastrointestinal infections (Table 5). Male gender was associated with slightly more antibiotic prescription (adjusted OR, 1.04; 95% CI, 1.01 to 1.06) than female gender. Patients aged 10 to 19 years (adjusted OR, 1.92; 95% CI, 1.83 to 2.00), 20 to 64 years (adjusted OR, 1.55; 95% CI, 1.51 to 1.60), and younger than 10 years (adjusted OR, 1.76; 95% CI, 1.71 to 1.82) received more antibiotic prescriptions compared with patients aged 65 years or older. With reference to large-sized (≥ 500 beds) hospital, clinic (adjusted OR, 1.88; 95% CI, 1.68 to 2.10) and small-sized (< 200 beds) hospital (adjusted OR, 1.17; 95% CI, 1.04 to 1.32) were associated with frequent antibiotic prescription for gastrointestinal infections.

Discussion

We described oral antibiotic prescription patterns in outpatient care setting, in Japan. To the best of our knowledge, this is the first Japanese study to comprehensively describe antibiotic prescription patterns linked to individual diagnoses data, by use of the claims database. Broad-spectrum antibiotics consisting of third-generation cephalosporins, macrolides, and quinolones accounted for nearly 90% of antibiotic prescriptions in the primary care settings. Prescription of penicillin, a representative narrow-spectrum antibiotic, was only 5%. This prescription pattern is consistent with the results of an analysis of antibiotic sales data in Japan in which 77% of oral antibiotics shipped, were broad-spectrum.[7] In contrast, the use of cephalosporins, macrolides, and quinolones in the United States of America (USA) and Europe were much lower than Japan. Hicks *et al*.[14] analyzed the sales data of oral antibiotics in the USA and showed that cephalosporins, macrolides, and quinolones accounted for 48% of the total oral antibiotics. In their study, penicillin had the largest share of the antibiotics (23%). Data from the European Surveillance of Antimicrobial Consumption project[15] also showed that cephalosporins, macrolides, and quinolones accounted for about one third of the total oral antibiotic consumptions, in Europe. This study demonstrated a rather high ratio of broad-spectrum to narrow-spectrum oral antibiotics, in Japan; therefore, the quality of antibiotic prescribing needs to be improved.

Among antibiotics linked with individual diagnosis data, over 60% of antibiotics were prescribed for ARTIs, followed by gastrointestinal infections (9%), urinary tract infections (8%); and skin, cutaneous, and mucosal infections (5%). Surprisingly, viral URI (common cold) was the most frequent infection associated with antibiotic prescription. In the ambulatory care setting in the USA, antibiotics were prescribed most frequently for acute respiratory conditions (41–44%), followed by skin and mucosal conditions (15–19%), urinary tract infections (7–8%), and gastrointestinal conditions (5–6%).[13,16] Another study using primary care data in the United Kingdom (UK)[17] demonstrated that 46% of antibiotics were prescribed for respiratory tract conditions, followed by urogenital tract (23%), and skin conditions (10%). Only 1% was prescribed for gastrointestinal conditions. Our study demonstrated a higher proportion of antibiotic prescription for ARTIs (approximately 15% higher than those in USA or UK) and gastrointestinal infections (approximately 5% higher), in Japan.

Antibiotics were prescribed for 35% of viral URI and approximately 50–60% of pharyngitis, bronchitis, and sinusitis in our study. These prescription rates were approximately similar to the USA study results;[13] showing a rate of 30% for viral URI, 62% for pharyngitis, 65% for bronchitis, and 72% for sinusitis. Medically, antibiotics are rarely indicated for ARTIs.[18] Antibiotics have no role in the treatment of both viral URI (common cold) and the majority of acute bronchitis, which are caused by viral infection. Only a minority of patients with bronchitis (< 10%), for example patients who have underlying COPD or whooping cough, may derive any benefit from antibiotic treatment. With pharyngitis, antibiotics are mainly indicated only for streptococcal pharyngitis, which account for 5%–15% of pharyngitis in adults and 20%–30% in children.[19,20]

The antibiotic prescription rate for gastrointestinal infections was 3 times higher than the rate reported in the USA (30% vs 10%).[13] As most acute gastroenteritis are self-limiting, Japanese national guideline recommended the non-usage of antibiotics for gastroenteritis unless symptoms are severe.[10] Based on our study, approximately 70% of oral antibiotics are prescribed for ARTIs or acute gastroenteritis; however, most (>

80%), did not require antibiotics. Therefore, there is need for suitable targets for the reduction of unnecessary antibiotic use in accordance with antimicrobial stewardship program.

The logistic regression analyses revealed several factors associated with antibiotic prescriptions for ARTIs and gastrointestinal infections. The smaller the facility scale, the higher the odds of antibiotic prescribing observed. Recent studies from Japan[8] and Taiwan[21] have found similar results. As family practitioners, pediatricians, and internists usually prescribe a high number of antibiotic courses,[14] greater adherence to treatment guidelines among physicians in these specialties is particularly important. It has also been reported that mid- or late-career stage physicians (because the effect of training received during medical education might have reduced, after this long time) were more likely to prescribe antibiotics for nonbacterial acute URI.[22]

Patient age was another factor associated with antibiotic prescription. In this study, antibiotic prescription rates for ARTIs and gastrointestinal infections were highest in patients aged 10–19 years, followed by patients aged 20–64 years (ARTIs) or 0–9 years (gastrointestinal infections). A previous study in Dutch primary care showed similar results of antibiotic over-prescribing for ARTIs in patients aged 31–65 years (i.e., not in children or the elderly).[23] As adolescents and young adults generally pose a much lower risk of disease complications than young children or elderly, antimicrobial stewardship should be focused on these age groups of patients. In this study, male sex was also associated with increased antibiotic prescribing. Although sex difference was observed in another study, the results differed; females were more likely to have high prescribing in the USA.[14]

Our study has several limitations. First, our results do not represent the entire antibiotic prescription patterns in Japan because the claims database used in this study was composed of claims in only one prefecture. Geographical diversity may be present, as observed in the previous study from the USA.[14] Second, since we used an administrative claims database; the accuracy of the diagnosis was not validated. In addition, we could not link diagnosis and antibiotic prescriptions on a one-to-one level when patients had multiple infectious diagnoses. Third, there may be other potential confounding factors that were not included in this study. For example, information on out-of-hour visits,[8] non-physician practitioners or non-specialty physician,[8, 21, 24] and patient's low-per capita income, black race, or low-education,[14] which have been reported as potential factors associated with inappropriate antibiotics prescribing, could not be extracted from the claims database in this study. Fourth, we found no follow-up visit when patients had multiple visits for a single infection. Consequently, inappropriate antibiotic prescription might be underestimated rather than overestimated.

In conclusion, this Japanese study demonstrated that third-generation cephalosporins, macrolides, and quinolones accounted for 88% of oral antibiotic prescription. Approximately 60% of antibiotic prescription was provided for ARTIs, with viral URI and pharyngitis being the two ARTI diagnoses with the largest antibiotic prescriptions. Gastrointestinal infections were the second most common diagnosis for antibiotic prescribing. The scale of the facilities (clinic or small-sized hospital) and patient age (adolescents and young adults) were factors associated with antibiotic over-prescription. Antimicrobial stewardship interventions should focus on targeting antibiotic prescribing for these infectious diagnoses, and patients and institution groups. Further nationwide studies are needed to support our data, and longitudinal studies using medical-claims data are needed to evaluate the effectiveness of antimicrobial stewardship.

Authors' contributions

HH and SH conceived the study, interpreted the data and results, and drafted the manuscript. HH, HM, YS, and HY collected, organized, and analyzed the data, and performed statistical analyses. KK and RN conceived the study and collected and interpreted the data. All authors critically revised the manuscript for intellectual content. All authors read and approved the final manuscript.

Funding

This work was funded by ImPACT Program of Council for Science, Technology, and Innovation (Cabinet Office, Government of Japan) and by MEXT KAKENHI, Grant Number 16K09254.

Competing interests

None declared.

Data sharing

No additional data available.

Transparency declarations

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethical approval

This study was approved by the Ethics Committee of the Jichi Medical University (Number 17-002).

Table 1. Frequency of oral antibiotic prescriptions by age and antibiotic groups

Antibiotic groups coded by ATC* classification**	Number of visits with antibiotic prescription				
	Age Group, y				
	0–9	10–19	20–64	≥ 65	All ages
Penicillins	7,495	1,724	8,574	14,924	32,717
First/second-generation cephalosporins	964	411	2,987	5,719	10,081
Third-generation cephalosporins	52,082	16,367	60,621	108,302	237,372
Macrolides	28,597	14,691	56,719	115,649	215,656
Quinolones	7,286	4,158	48,843	84,848	145,135
Sulphonamides and trimethoprim	32	53	1,389	4,520	5,994
Tetracyclines	915	1,366	4,366	5,147	11,794
Other antibiotics	6,901	2,021	7,186	7,965	24,073
All antibiotics	104,272	40,791	190,685	347,074	682,822

*ATC: Anatomical Therapeutic Chemical

**Penicillins, J01C; First-generation cephalosporins, J01DB; Second-generation cephalosporins, J01DC; Third-generation cephalosporins, J01DD; Macrolides, J01FA; Quinolones, J01M; Sulphonamides and trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH, J01DI, J01FF, J01G, and J01X

Table 2. Frequency of oral antibiotic prescriptions by facility scale and antibiotic group*

Antibiotic groups coded by ATC** classification***	Number of visits with antibiotic prescription				
	Facility scale (clinic and hospitals)				
	Clinic	Small-sized (< 200 beds)	Medium-sized (200–499 beds)	Large-sized (≥ 500 beds)	All facilities
Penicillins	25,225	3,453	2,968	565	32,211
First/second-generation cephalosporins	6,755	1,789	1,245	158	9947
Third-generation cephalosporins	187,928	25,463	15,252	4,139	232,782
Macrolides	169,980	26,307	11,319	3,833	211,439
Quinolones	110,770	17,877	9,992	3,402	142,041
Sulphonamides and trimethoprim	712	1,069	2,234	1,618	5,633
Tetracyclines	9,477	846	803	320	11,446
Other antibiotics	20,069	1,742	1,458	318	23,587
All antibiotics	530,916	78,546	45,271	14,353	669,086

*13,736 patients with antibiotic prescription were excluded due to missing data about facility scale.

**ATC: Anatomical Therapeutic Chemical

***Penicillins, J01C; First-generation cephalosporins, J01DB; Second-generation cephalosporins, J01DC; Third-generation cephalosporins, J01DD; Macrolides, J01FA; Quinolones, J01M; Sulphonamides and trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH, J01DI, J01FF, J01G, and J01X

Table 3. Frequency of oral antibiotic prescriptions by antibiotic groups and diagnoses

Diagnoses	All visits	Visits with any antibiotic prescription and prescription rate (%)	Number of visits with antibiotic prescriptions by antibiotic groups*							
			Penicillins	1st/2nd cephem	3rd cephem	Macrolides	Quinolones	ST	Tetracyclines	Other antibiotics
Miscellaneous bacterial infections	45,061	20,429 (45.3)	2,969	468	7,404	7,868	5,731	181	444	728
STD	14,051	3,931 (28.0)	86	76	836	1515	496	14	147	1,260
Bacterial Pneumonia	47,035	21,473 (45.7)	916	121	5,044	8,568	11,236	191	238	316
Abdominal infection	9,208	2,077 (22.6)	69	29	680	142	1,086	≤ 10	≤ 10	177
Orthopedic infection	1,749	380 (21.7)	36	22	225	21	93	≤ 10	19	22
Urinary tract infections	97,948	37,674 (38.5)	1,195	567	14,735	1,998	20,229	429	521	1,232
PID	11,621	1,763 (15.2)	84	26	1127	164	167	≤ 10	≤ 10	273
GI infections	137,661	41,309 (30.0)	2,121	264	12,060	8603	13206	196	232	9,680
Skin, cutaneous and mucosal infections	62,202	23,572 (37.9)	1,167	1,337	15,311	1,975	2,848	25	997	1,615
Suppurative otitis media	16,059	9,958 (62.0)	1,566	18	5,213	1,972	3,654	≤ 10	92	812

Pharyngitis	146,508	78,469 (53.6)	4,372	450	35,958	27,454	16,387	121	301	976
Sinusitis	80,078	45,456 (56.8)	3,654	481	15,282	20,677	11,441	≤ 10	779	766
Bronchitis with COPD	6,832	4,313 (63.1)	208	14	912	2,178	1,762	28	11	17
Acne	6,939	2,030 (29.3)	≤ 10	32	174	739	41	≤ 10	1,050	62
Nonbacterial GI infections	1,215	116 (9.5)	≤ 10	≤ 10	42	38	33	≤ 10	≤ 10	14
Nonsuppurative otitis media	2,807	888 (31.6)	63	≤ 10	384	481	128	≤ 10	≤ 10	26
Viral URI	274,441	96,989 (35.3)	4,839	825	44,475	37,001	16,941	160	790	601
Influenza	22,868	8,665 (37.9)	296	74	3,030	3,934	2,040	≤ 10	47	69
Viral pneumonia	15	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10
Bronchitis without COPD	89,479	47,248 (52.8)	1,509	332	14,521	22,779	11,078	58	250	346
Noninfectious diarrhea	1,597	50 (3.1)	≤ 10	≤ 10	≤ 10	19	15	≤ 10	≤ 10	≤ 10
Fever	2,908	438 (15.1)	20	≤ 10	190	103	156	≤ 10	≤ 10	≤ 10

341 1st/2nd cephem, first/second-generation cephalosporins; 3rd cephem, third-generation cephalosporins; ST, Sulphonamides and trimethoprim; STD, sexual transmitted diseases; PID, pelvic inflammatory diseases; GI infections, gastrointestinal infections; COPD, chronic obstructive pulmonary disease; URI, upper respiratory infections

344 *Antibiotics were coded according to Anatomical Therapeutic Chemical (ATC) codes: Penicillins, J01C; First-generation cephalosporins, J01DB; Second-generation cephalosporins, J01DC; Third-generation cephalosporins, J01DD; Macrolides, J01FA; Quinolones, J01M; Sulphonamides and

trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH, J01DI, J01FF, J01G, and J01X

Table 4. Factors associated with antibiotic prescription for acute upper respiratory infections*

Characteristics	Antibiotic prescription, n (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Patient age			
0–9	44,413 (50.4)	1.66 (1.64 to 1.69)	1.48 (1.46 to 1.50)
10–19	20,822 (65.1)	3.08 (3.00 to 3.15)	2.75 (2.69 to 2.82)
20–64	85,952 (54.6)	1.98 (1.95 to 2.00)	1.92 (1.89 to 1.94)
≥ 65	121,289 (37.9)	1	1
Patient sex			
Male	112,643 (47.4)	1.13 (1.12 to 1.14)	1.10 (1.08 to 1.11)
Female	155,038 (44.4)	1	1
Facility scale			
Clinic	233,078 (49.8)	4.48 (4.27 to 4.70)	4.24 (4.03 to 4.45)
Hospital (< 200 beds)	23,012 (30.8)	2.01 (1.91 to 2.11)	2.07 (1.97 to 2.18)
Hospital (200–499 beds)	9,327 (28.2)	1.77 (1.68 to 1.89)	1.71 (1.62 to 1.80)
Hospital (≥ 500 beds)	2,064 (18.2)	1	1

CI, confidence interval

*Acute upper respiratory infections include viral upper respiratory infections, pharyngitis, bronchitis, and sinusitis.

Table 5. Factors associated with antibiotic prescription for gastrointestinal infections.

Characteristics	Antibiotic prescription, n (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Patient age			
0–9	10,809 (37.0)	1.92 (1.86 to 1.98)	1.76 (1.71 to 1.82)
10–19	4,395 (38.7)	2.07 (1.98 to 2.16)	1.92 (1.83 to 2.00)
20–64	12,310 (32.4)	1.57 (1.53 to 1.61)	1.55 (1.51 to 1.60)
≥ 65	13,795 (23.4)	1	1
Patient sex			
Male	59,937 (30.9)	1.09 (1.06 to 1.12)	1.04 (1.01 to 1.06)
Female	74,902 (29.1)	1	1
Facility type			
Clinic	33,712 (32.9)	2.03 (1.82 to 2.27)	1.88 (1.68 to 2.10)
Hospital (< 200 beds)	4,056 (21.7)	1.15 (1.02 to 1.29)	1.17 (1.04 to 1.32)
Hospital (200–499 beds)	2,214 (18.9)	0.97 (0.86 to 1.09)	0.93 (0.82 to 1.05)
Hospital (≥ 500 beds)	396 (19.4)	1	1

CI, confidence interval

References

1. de Kraker ME, Wolkewitz M, Davey PG et al. Clinical impact of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay related to methicillin-resistant Staphylococcus aureus bloodstream infections. Antimicrob Agents Chemother 2011; 55: 1598-605.

2. Stewardson AJ, Allignol A, Beyersmann J et al. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and 2011: a multicentre retrospective cohort study. Euro Surveill 2016; 21: pii=30319.

3. Ammerlaan HS, Harbarth S, Buiting AG et al. Secular trends in nosocomial bloodstream infections: antibiotic-resistant bacteria increase the total burden of infection. Clin Infect Dis 2013; 56: 798-805.

4. World Health Organization. Global action plan on antimicrobial resistance. Available at: http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf?ua=1 (Accessed: August 3, 2018).

5. The Government of Japan. National Action Plan on Antimicrobial Resistance (AMR)

2016-2020. Available at: https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000138942.pdf. (Accessed: August 3, 2018).

6. Tacconelli E. Antimicrobial use: risk driver of multidrug resistant microorganisms in healthcare settings. Curr Opin Infect Dis 2009; 22: 352-8.

7. Muraki Y, Yagi T, Tsuji Y et al. Japanese antimicrobial consumption surveillance: First report on oral and parenteral antimicrobial consumption in Japan (2009-2013). J Glob Antimicrob Resist 2016; 7: 19-23.

8. Yoshida S, Takeuchi M, Kawakami K. Prescription of antibiotics to pre-school children from 2005 to 2014 in Japan: a retrospective claims database study. J Public Health (Oxf) 2018; 40: 397-403.

9. Higashi T, Fukuhara S. Antibiotic prescriptions for upper respiratory tract infection in Japan. Intern Med 2009; 48: 1369-75.

10. The Government of Japan, Ministry of Health, Labour and Welfare. Manual of Antimicrobial Stewardship (1st Edition). Available at: http://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000193504.pdf. (Accessed: August 3,

2018).

11. Kumamoto prefectural government. 2012 Kumamoto National Health Insurance business situation report. Available at: http://www.pref.kumamoto.jp.e.qp.hp.transer.com/kiji_2735.html (Accessed: August 3, 2018).

12. Kumamoto prefectural government. The situation such as Kumamoto elderly aged 75 or over medical expenses. Available at: http://www.pref.kumamoto.jp.e.qp.hp.transer.com/kiji_13777.html (Accessed: August 3, 2018).

13. Fleming-Dutra KE, Hersh AL, Shapiro DJ et al. Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. JAMA 2016; 315: 1864-73.

14. Hicks LA, Bartoces MG, Roberts RM et al. US outpatient antibiotic prescribing variation according to geography, patient population, and provider specialty in 2011. Clin Infect Dis 2015; 60: 1308-16.

15. ESAC-Net surveillance data. Surveillance of antimicrobial consumption in Europe. Available at: http://ecdc.europa.eu/en/publications/Publications/antimicrobial-consumption-europe-es

ac-net-2012.pdf (Accessed: August 3, 2018).

16. Shapiro DJ, Hicks LA, Pavia AT et al. Antibiotic prescribing for adults in ambulatory care in the USA, 2007-09. J Antimicrob Chemother 2014; 69: 234-40.

17. Dolk FCK, Pouwels KB, Smith DRM et al. Antibiotics in primary care in England: which antibiotics are prescribed and for which conditions? J Antimicrob Chemother 2018; 73: ii2-ii10.

18. Harris AM, Hicks LA, Qaseem A. Appropriate Antibiotic Use for Acute Respiratory Tract Infection in Adults: Advice for High-Value Care From the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med 2016; 164: 425-434.

19. Bisno AL. Acute pharyngitis: etiology and diagnosis. Pediatrics 1996; 97: 949-54.

20. Ebell MH, Smith MA, Barry HC et al. The rational clinical examination. Does this patient have strep throat? JAMA 2000; 284: 2912-8.

21. Lee ML, Cho CY, Hsu CL, et al. Recent trends in antibiotic prescriptions for acute respiratory tract infections in pediatric ambulatory care in Taiwan, 2000-2009: A nationwide population-based study. J Microbiol Immunol Infect 2016; 49: 554-560.

418 22. Silverman M, Povitz M, Sontrop JM, et al. Antibiotic Prescribing for Nonbacterial Acute Upper Respiratory Infections in Elderly Persons. Ann Intern Med 2017; 166: 765-774.

421 23. Akkerman AE, van der Wouden JC, Kuyvenhoven MM et al. Antibiotic prescribing for respiratory tract infections in Dutch primary care in relation to patient age and clinical entities. J Antimicrob Chemother 2004; 54: 1116-1121.

424 24. Schmidt ML, Spencer MD, Davidson LE. Patient, Provider, and Practice Characteristics Associated with Inappropriate Antimicrobial Prescribing in Ambulatory Practices. Infect Control Hosp Epidemiol. 2018; 39:307-315.

Table S1. Classification of infections by groups with corresponding ICD-10 codes

	Diagnosis	ICD-10 codes
Group 1: Infections for which antibiotics are usually indicated		
1	Miscellaneous bacterial infections	Tuberculosis (A15–A19); Certain zoonotic bacterial diseases (A20–A28); Other bacterial diseases including listeriosis, diphtheria, bartonellosis, erysipelas, and rickettsioses (A30–A37, A39–A49, A75–A79); Bacterial meningitis, encephalitis, and intracranial abscess (G00, G042, G049, G06); Mastoiditis (H70); Infective endocarditis (I33, T826); Acute epiglottitis (J051); Deep neck space infections (J36, J390, J391); Abscess of lung and mediastinum; Pyothorax (J85, J86); Infections of the jaws and mouth (K102, K122); Infections due to cardiac and vascular devices (T827); Infection due to internal prosthetic devices, implants and grafts (T857)
2	Sexually transmitted infections	Infections with a predominantly sexual mode of transmission (A50–A64); Other spirochetal diseases (A65–A69); Other diseases caused by chlamydia (A70–A74)
3	Pneumonia	Bacterial pneumonia (J13–J18)
4	Abdominal infections	Acute appendicitis (K35); Abscess of anal and rectal regions, intestine, and liver (K61, K630, K750); Peritonitis (K65); Cholecystitis and cholangitis (K800, K801, K803, K804, K810, K819, K830)
5	Orthopedic infections	Pyogenic arthritis and prosthetic joint infection (M00, T845); necrotizing fasciitis (M726); Infective myositis, synovitis and bursitis (M600, M650–M651, M710–M711); Osteomyelitis (M462–M465, M86)
6	Urinary tract infections	Acute pyelonephritis/pyonephrosis ((N10, N12, N136); Renal abscess (N151); Kidney infection, unspecified (N159); Acute cystitis (N300); Cystitis, unspecified (N308, N309); Urethritis and urethral abscess (N34); Urinary tract infections, unspecified (N390); Prostatitis and abscess of prostate (N41); Orchitis and epididymitis (N45); Catheter associated urinary tract infections (T835)

7	Pelvic inflammatory diseases	Pelvic inflammatory diseases (N70–N73, N751, N760–N764); Infections of genitourinary tract in pregnancy (O23)
Group 2：Infections for which antibiotics are potentially indicated		
1	Gastrointestinal infections	Intestinal infectious diseases (A00–A07, A09); Diverticulitis of intestine (K57)
2	Skin, cutaneous and mucosal infections	Infections of other skin and subcutaneous tissue including cellulitis, cutaneous abscess, furuncle, carbuncle, impetigo, acute lymphadenitis, folliculitis, mastitis (H050, J340, L00–L08, N61, T814); Infections of the eye and adnexa (H00, H440); Infective otitis externa (H600–H603)
3	Suppurative otitis media	Suppurative and unspecified otitis media (H66)
4	Pharyngitis	Streptococcal pharyngitis/tonsillitis (J020, J030); Acute pharyngitis/tonsillitis, unspecified (J029, J039); Scarlet fever (A38)
5	Sinusitis	Acute sinusitis (J01); Chronic sinusitis (J32)
6	Bronchitis and bronchiolitis with COPD	Acute bronchitis (J20) *; Acute bronchiolitis (J21) *; Unspecified acute lower respiratory infection (J22) *
7	Acne	Acne (L70)
Group 3: Infections for which antibiotics are rarely indicated		
1	Nonbacterial gastrointestinal infections	Viral and other specified intestinal infections (A08)
2	Nonsuppurative otitis media	Nonsuppurative otitis media (H65)
3	Viral upper respiratory infection	Acute nasopharyngitis [common cold] (J00); Acute pharyngitis/tonsillitis due to other specified organisms (J028, J038); Acute laryngitis and tracheitis (J04); Acute obstructive laryngitis [croup] (J050); Acute upper respiratory infections of multiple and unspecified sites (J06); Cough (R05)
4	Influenza	Influenza (J10, J11)
5	Viral pneumonia	Viral pneumonia (J12)
6	Bronchitis and bronchiolitis without COPD	Acute bronchitis (J20) **; Acute bronchiolitis (J21) **; Unspecified acute lower respiratory infection (J22) **
7	Noninfectious diarrhea	Noninfective gastroenteritis and colitis, unspecified (K529)

8	Fever	Fever of unknown origin (R50)

3 *includes visits in which ICD-10 code for COPD (J41–J44) are present

4 **includes visits in which ICD-10 code for COPD (J41–J44) are not present

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7–8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8–9
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9–10
		(*b*) Describe any methods used to examine subgroups and interactions	9–10
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12–13
		(*b*) Report category boundaries when continuous variables were categorized	11–13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	14–18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18–19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19–20
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Antibiotic prescription among outpatients in a prefecture of Japan, 2012–2013: A retrospective claims database study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026251.R1
Article Type:	Research
Date Submitted by the Author:	12-Dec-2018
Complete List of Authors:	Hashimoto, Hideki; Jichi Medical University Hospital, Division of General Internal Medicine Matsui, Hiroki; Jichi Medical University, Data Science Center; School of Public Health, University of Tokyo, Department of Clinical Epidemiology and Health Economics Sasabuchi, Yusuke; Jichi Medical University, Data Science Center Yasunaga, Hideo; Jichi Medical University, Data Science Center; School of Public Health, The University of Tokyo, Department of Clinical Epidemiology and Health Economics Kotani, Kazuhiko; Jichi Medical University, Division of Community and Family Medicine Nagai, Ryozo; Jichi Medical University, President Hatakeyama, Shuji; Jichi Medical University Hospital, Division of General Internal Medicine/Division of Infectious Diseases
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, INFECTIOUS DISEASES

Antibiotic prescription among outpatients in a prefecture of Japan, 2012–2013: A retrospective claims database study

Hideki Hashimoto[1], Hiroki Matsui[2, 3], Yusuke Sasabuchi[2], Hideo Yasunaga[2, 3], Kazuhiko Kotani[4], Ryozo Nagai[5], Shuji Hatakeyama[1, 6*]

[1]Division of General Internal Medicine, Jichi Medical University Hospital, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

[2]Data Science Center, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

[3]Department of Clinical Epidemiology and Health Economics, School of Public Health, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

[4]Division of Community and Family Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

[5]President, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

[6]Division of Infectious Diseases, Jichi Medical University Hospital, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

***Corresponding author:**

Shuji Hatakeyama, M.D., Ph.D.

Division of General Internal Medicine/Division of Infectious Diseases, Jichi Medical University Hospital, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

Phone: +81-285-58-7498

Fax: +81-285-40-5160

E-mail: shatake-tky@umin.ac.jp

Key words: antibiotic, antimicrobial stewardship, antimicrobial-resistance, big data, inappropriate prescribing

Running title: Antibiotic prescriptions in Japan

Word count for the main text: 3,069 words

Abstract

Objectives: To investigate oral antibiotic prescribing patterns and identify factors associated with antibiotic prescriptions, with the aim of guiding future interventions to reduce inappropriate prescribing.

Design: Retrospective cohort study.

Setting: Database of public health insurance claims in Kumamoto prefecture (Japan).

Participants: Beneficiaries of the national or late elders' health insurance system between April 2012 and March 2013.

Main outcome measures: Of 7,770,481 outpatient visits, 682,822 had a code for antibiotics (860 antibiotic prescriptions per 1000 population). Third-generation cephalosporins (35%), macrolides (32%), and quinolones (21%) were most frequently prescribed. Acute respiratory tract infections (ARTIs), including viral upper respiratory infections (URI) (22%), pharyngitis (18%), bronchitis (11%), and sinusitis (10%) were most frequently diagnosed for antibiotic prescribing, followed by gastrointestinal (9%), urinary tract (8%), and skin, cutaneous, and mucosal infections (5%). Antibiotic prescribing rates for viral URI, pharyngitis, bronchitis, sinusitis, and gastrointestinal

49 infections were 35%, 54%, 53%, 57%, and 30%, respectively. In multivariable analysis
50 for ARTIs and gastrointestinal infections, patient age (10–19 years especially), patient
51 sex (male), and facility scale (free-standing clinics or small-scale hospital-based clinics)
52 were associated with increased antibiotic prescribing.

53 **Conclusions:** Broad-spectrum antibiotics constituted 88% of oral outpatient antibiotic
54 prescriptions. Approximately 70% of antibiotics were prescribed for ARTIs and
55 gastroenteritis with modest benefit from antibiotic treatment. The quality of antibiotic
56 prescribing needs to be improved. Antimicrobial stewardship interventions should target
57 ARTIs and gastroenteritis, as well as young patients and small-scale institutions.

Strength and limitations of this study

- This is the first Japanese study to describe outpatient antibiotic prescription patterns linked to individual diagnosis data, comprehensively, by use of the public health insurance claims database.
- This study included patients older than 65 years of age, who have not typically been included in previous Japanese studies.
- The accuracy of the diagnosis has not been validated due to the nature of the administrative claims database.
- There are some unmeasured potential confounding factors such as out-of-hours visits and physician specialty.

Introduction

There is a growing concern about antimicrobial-resistant bacterial infections. Antimicrobial resistance results in increased health care costs, prolonged hospitalization, and death.[1-3] The World Health Organization launched the global action plan to combat the antimicrobial-resistant bacteria in 2015[4] and requested Member States to endorse national action plans within two years. The government of Japan launched a national action plan in 2016 in response to the request.[5]

Since antimicrobial use is one of the important factors in the emergence of antimicrobial resistance,[6] it is essential to reduce the inappropriate use of antibiotics. In Japan, a previous sales data-based study revealed that oral antibiotics account for more than 90% of total antibiotic consumption and that broad-spectrum antibiotics (third-generation cephalosporins, macrolides, and fluoroquinolones) account for 77% of oral antibiotic consumption (daily doses defined per 1000 inhabitants per day).[7] The Japanese national action plan aims to reduce the total antimicrobial use to two-thirds of current use, and the use of oral cephalosporins, quinolones, and macrolides to one-half, by 2020. To reduce inappropriate antimicrobial use, it is important to determine the antimicrobial prescribing patterns and factors associated with antibiotic prescription. However, such information has been limited in Japan to date. Although a few recent studies[8,9] described the prescription patterns for upper respiratory tract infections and bronchitis, the prescription patterns of infections other than acute respiratory tract infections (ARTIs) have not been clarified. In addition, patients older than 65 years of age have not been commonly included in these studies, because these studies relied on data from an employee-based insurance claims database. With the high rate in aging population in Japan, it is important to describe the prescription patterns in elderly patients.

In this study, we described outpatient oral antibiotic prescribing patterns for all infections and in all ages, using the Japanese administrative claims database. Furthermore, we aimed to identify factors associated with antibiotic prescriptions for ARTIs and gastrointestinal infections, the targets of the antimicrobial stewardship guideline formulated by the government of Japan in 2017.[10]

Methods

Data sources

The current population of Japan is approximately 127 million. All citizens are enrolled in a universal health coverage insurance program provided by the social insurance system (for employees younger than 75 years of age), national health insurance system (for self-employed or unemployed people younger than 75 years of age), and the late elders' health insurance system (for those aged 75 years and older). In Japan, patients can visit any clinic of their choice. All physicians working at any free-standing or hospital-based clinics can provide primary care and prescribe antibiotics.

We conducted a retrospective analysis using the administrative health insurance claims database of Kumamoto prefecture, situated in the southwestern region of Japan, with a population of about 1.7 million. This database covers approximately 780,000 residents of Kumamoto prefecture (44% of the population) who were beneficiaries of the national health insurance system,[11] or the late elders' health insurance system. [12] The participants in this study may be older than the general population of Japan.

The database is composed of medical and pharmacy claims. It provides monthly information about patient demographics (year and month of birth and sex), diagnoses, date of diagnoses, medical procedures, medications, scale (number of beds) of the medical facility, as well as the identification numbers assigned to each individual, medical facility, and dispensing pharmacy. At the end of each month, claims are registered from each medical facility. The diagnoses were recorded by physicians of each medical facility and coded according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).

Data preparation

We linked the medical and pharmacy claims on the database using an identification number unique to each patient, medical facility, and dispensing pharmacy. We identified all newly diagnosed outpatients, with any infectious diseases, between April 2012 and March 2013. Infectious diseases diagnoses were categorized according to the indication for antibiotic use (Table S1, available as supplementary data). This categorization was based on the study by Fleming-Dutra KE *et al*.[13] Bronchitis and bronchiolitis were divided into two categories based on whether the patients had chronic obstructive pulmonary disease (COPD) as comorbidity or not, because of differing need of treatment with antibiotics. If a patient had multiple infectious diagnoses in one month, a single infectious diagnosis, selected in order from Group 1 (antibiotics are usually indicated) to Group 3 (antibiotics are rarely indicated), and the first-listed diagnosis in alphabetical order of ICD-10 codes in the selected group was included in the analyses (Table S1).

We also identified all outpatients with any antibiotic prescriptions. Topical, intramuscular, and intravenous antibiotics were excluded. Antibiotics were categorized according to the Anatomical Therapeutic Chemical (ATC) classification system (http://www.whocc.no/atcddd/) as follows: tetracyclines (J01A), penicillins (J01C), first- and second-generation cephalosporins (J01DB and J01DC), third-generation cephalosporins (J01DD), sulfonamides and trimethoprim (J01E), macrolides (J01FA), quinolones (J01M), and others (J01B, J01DH, J01DI, J01FF, J01G, and J01X). We assumed that third-generation cephalosporins accounted for most of cephalosporins used in Japan; hence, we divided cephalosporins into two groups: first/second- and third-generation cephalosporins. Antibiotics were linked to the infectious diagnoses in each patient's claims when both the code of antibiotics and the code of diagnoses were recorded in the same month.

Data Analysis

We calculated the frequency of antibiotic prescription for all visits with infections (according to diagnosis and antibiotic class). For ARTIs (including pharyngitis, sinusitis, bronchitis/bronchiolitis, and viral upper respiratory infections [URI]) and gastrointestinal infections, we performed separate multivariable logistic regression analyses to identify the factors associated with antibiotic prescriptions. The variables were as follows: age and sex of patients and scale (number of beds) of the medical facilities. Generalized estimating equations with exchangeable correlation structure were used to account for the clustering of the medical facilities. *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed with the statistical package R, v.3.5.0 (http://cran.r-project.org).

Patient involvement

No patients were involved in the development of the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked for advice regarding the interpretation or writing of results. There are no plans to disseminate the study results to the relevant patient community.

Results

In total, there were 7,770,481 outpatient visits between April 2012 and March 2013. Antibiotics were prescribed in 682,822 visits (860 antibiotic prescriptions per 1000 population). Among these, third-generation cephalosporins were most frequently prescribed (237,372 visits, 35%), followed by macrolides (215,656 visits, 32%) and quinolones (145,135 visits, 21%). This trend was observed regardless of age group (Table 1) and scale of the medical facility (Table 2), except for those less than 9 years of age in whom the systemic use of quinolones is not recommended. Information about facility scale was available from 669,086 out of 682,822 visits. Of these, antibiotics were prescribed most frequently at free-standing clinics (530,916 visits, 79%), followed by small-scale (< 200 beds; 78,546 visits, 12%), medium-scale (200–499 beds; 45,271 visits, 7%), and large-scale (500 beds or more; 14,353 visits, 2%) hospital-based clinics (Table 2).

We were able to link the individual diagnoses to the antibiotic prescription in 447,232 visits (Table 3). Of these patients, approximately 60% of antibiotics were prescribed for ARTIs, including viral URI (96,989 visits, 22%), pharyngitis (78,469 visits, 18%), bronchitis without COPD (47,248 visits, 11%), and sinusitis (45,456 visits, 10%). Other than ARTIs, there were frequent antibiotic prescriptions for gastrointestinal infections (41,309 visits, 9%), urinary tract infections (37,674 visits, 8%), and skin, cutaneous, and mucosal infections (23,572 visits, 5%). The antibiotic prescription rates for viral URI, pharyngitis, bronchitis (without underlying COPD), sinusitis, and gastrointestinal infections were 35% (96,989 out of 274,441 visits), 54% (78,469 out of 146,508 visits), 53% (47,248 out of 89,479 visits), 57% (45,456 out of 80,078 visits), and 30% (41,309 out of 137,661 visits), respectively (Table 3).

Table 4 shows the results of the logistic regression analysis of antibiotic prescription for ARTIs. Patient sex of male was associated with more antibiotic prescription (adjusted odds ratio [OR], 1.10; 95% confidence interval [CI], 1.08 to 1.11). With patients aged 65 years or older as reference, patients aged 10 to 19 years were more likely to be prescribed antibiotics (adjusted OR, 2.75; 95% CI, 2.69 to 2.82), followed by patients aged 20 to 64 years (adjusted OR, 1.92; 95% CI, 1.89 to 1.94), and patients younger than 10 years (adjusted OR, 1.48; 95% CI, 1.46 to 1.50). Regarding facility scale, with large-scale (500 beds or more) hospital-based clinics as reference, free-standing clinics (adjusted OR, 4.24; 95% CI, 4.03 to 4.45), small-scale (< 200 beds) hospital-based clinics (adjusted OR, 2.07; 95% CI, 1.97 to 2.18), and medium-scale (200–499 beds) hospital-based clinics (adjusted OR, 1.71; 95% CI, 1.62 to 1.80) were significantly associated with more frequent antibiotic prescription.

Similar results were shown with the logistic regression analysis for gastrointestinal infections (Table 5). Patient sex of male was associated with slightly more antibiotic prescription (adjusted OR, 1.04; 95% CI, 1.01 to 1.06) than was patient sex of female. Patients aged 10 to 19 years (adjusted OR, 1.92; 95% CI, 1.83 to 2.00), 20 to 64 years (adjusted OR, 1.55; 95% CI, 1.51 to 1.60), and younger than 10 years (adjusted OR, 1.76; 95% CI, 1.71 to 1.82) received more antibiotic prescriptions compared with patients aged 65 years or older. With reference to large-scale (≥ 500 beds) hospital-based clinics, free-standing clinics (adjusted OR, 1.88; 95% CI, 1.68 to 2.10) and small-scale (< 200 beds) hospital-based clinics (adjusted OR, 1.17; 95% CI, 1.04 to 1.32) were associated with frequent antibiotic prescription for gastrointestinal infections.

Discussion

We described oral antibiotic prescription patterns in the outpatient care setting in Japan. To the best of our knowledge, this is the first Japanese study to comprehensively describe antibiotic prescription patterns linked to individual diagnoses data, using the claims database. Broad-spectrum antibiotics consisting of third-generation cephalosporins, macrolides, and quinolones accounted for nearly 90% of antibiotic prescriptions in the primary care settings. Prescription of penicillin was only 5%. This prescription pattern is consistent with the results of an analysis of antibiotic sales data in Japan, in which 77% of oral antibiotics shipped were broad-spectrum.[7] In contrast, the use of cephalosporins, macrolides, and quinolones in the United States of America (USA) and Europe were much lower than in Japan. Hicks *et al*.[14] analyzed the sales data of oral antibiotics in the USA and showed that cephalosporins, macrolides, and quinolones accounted for 48% of the total oral antibiotics. In their study, penicillin had the largest share of the antibiotics (23%). Data from the European Surveillance of Antimicrobial Consumption project[15] also showed that cephalosporins, macrolides, and quinolones accounted for about one third of the total oral antibiotic consumptions, in Europe. This study demonstrated a rather high ratio of broad-spectrum to narrow-spectrum oral antibiotics, in Japan; therefore, the quality of antibiotic prescribing needs to be improved.

Although quinolones are not recommended for children, quinolones were prescribed as much as penicillins in children aged 0–9 years in our study. This may be because oral fluoroquinolones such as tosufloxacin are approved for children to treat otitis media and pneumonia in Japan. Since the approval of quinolones in 2010, despite the recommendation to prescribe quinolones carefully for children, many physicians prescribed tosufloxacin to children in expectation of clinical effectiveness.

Among antibiotics linked with individual diagnosis data, over 60% of antibiotics were prescribed for ARTIs, followed by gastrointestinal infections (9%), urinary tract infections (8%), and skin, cutaneous, and mucosal infections (5%). Surprisingly, viral URI (common cold) was the most frequent infection associated with antibiotic prescription. In the ambulatory care setting in the USA, antibiotics were prescribed most frequently for acute respiratory conditions (41–44%), followed by skin and mucosal conditions (15–19%), urinary tract infections (7–8%), and gastrointestinal conditions (5–6%).[13,16] Another study using primary care data in the United Kingdom (UK)[17] demonstrated that 46% of antibiotics were prescribed for respiratory tract conditions, followed by urogenital tract (23%), and skin conditions (10%). Only 1% was prescribed for gastrointestinal conditions. Our study demonstrated a higher proportion of antibiotic prescription for ARTIs (approximately 15% higher than those in USA or UK) and gastrointestinal infections (approximately 5% higher) in Japan.

Antibiotics were prescribed for 35% of viral URI cases and approximately 50–60% of pharyngitis, bronchitis, and sinusitis cases in our study. These prescription rates were approximately similar to those of a USA study,[13] which showed a rate of 30% for viral URI, 62% for pharyngitis, 65% for bronchitis, and 72% for sinusitis. Medically, antibiotics are rarely indicated for ARTIs.[18] Antibiotics have no role in the treatment of either viral URI (common cold) or the majority of acute bronchitis cases, which are generally caused by viral infection. Only a minority of patients with bronchitis (< 10%), for example patients who have underlying COPD or whooping cough, may derive any benefit from antibiotic treatment. With pharyngitis, antibiotics are mainly indicated only for streptococcal pharyngitis, which accounts for 5–15% of pharyngitis in adults and 20–30% in children.[19, 20]

263 The antibiotic prescription rate for gastrointestinal infections was three times higher than
264 the rate reported in the USA (30% vs. 10%).[13] As most acute gastroenteritis is self-
265 limiting, the Japanese national guideline recommends the non-usage of antibiotics for
266 gastroenteritis unless symptoms are severe.[10] Based on our study, approximately 70% of
267 oral antibiotics are prescribed for ARTIs or acute gastroenteritis; however, most (> 80%),
268 did not require antibiotics. Therefore, there is a need for suitable targets to reduce
269 unnecessary antibiotic use in accordance with antimicrobial stewardship program.
270 Previous studies from the UK[21, 22] analyzed reasons for antibiotic prescribing for sore
271 throats and assessed that patient demand for antibiotics and physician pressure to meet
272 patient demand are associated with antibiotic prescription. In addition, we suppose that
273 physicians frequently prescribe antibiotics for URI as prophylaxis for complicating
274 secondary bacterial infections.

275 As for antibiotic prescription for ARTIs and gastrointestinal infections, most
276 antibiotics prescribed were broad-spectrum. For example, quinolones accounted for 15–
277 35% of the antibiotics prescribed for ARTIs in this study, although the proportion of
278 quinolones to whole antibiotics prescribed for ARTIs should be <5% according to the

ESAC disease-specific quality indicators[23]. Accordingly, the quality of antibiotic prescribing should be improved.

The logistic regression analyses revealed several factors associated with antibiotic prescriptions for ARTIs and gastrointestinal infections. The smaller the facility scale, the higher the odds of antibiotic prescribing. Recent studies from Japan[8] and Taiwan[24] have found similar results. As family practitioners, pediatricians, and internists usually prescribe a high number of antibiotic courses,[14] greater adherence to treatment guidelines among physicians in these specialties is particularly important. It has also been reported that mid- or late-career stage physicians (because the effect of training received during medical education might have reduced, after this long time) were more likely to prescribe antibiotics for nonbacterial acute URI.[25]

Patient age was another factor associated with antibiotic prescription. In this study, antibiotic prescription rates for ARTIs and gastrointestinal infections were highest in patients aged 10–19 years, followed by patients aged 20–64 years (ARTIs) or 0–9 years (gastrointestinal infections). A previous study concerning Dutch primary care showed similar results of antibiotic over-prescribing for ARTIs in patients aged 31–65 years (i.e., not in children or the elderly).[26] As adolescents and young adults generally pose a much lower risk of disease complications than young children or elderly individuals, antimicrobial stewardship should focus on these age groups of patients. In this study, patient sex of male was also associated with increased antibiotic prescribing. Although a patient sex difference was observed in another study, the results differed; female patients were more likely to have high prescribing in the USA.[14] The reason for patient age and sex difference in antibiotic prescribing remains to be clarified. Patient sex and age-standardized antibiotic prescription rates need to be assessed in Japan for effective intervention.

Our study has several limitations. First, our results do not represent the entire antibiotic prescription pattern in Japan because the claims database used in this study was composed of claims in only one prefecture. Geographical diversity in antibiotic prescribing may be present, as observed in the previous study from the USA.[14] Second, since we used an administrative claims database; the accuracy of the diagnosis was not validated. In addition, we could not link diagnosis and antibiotic prescriptions on a one-to-one level when patients had multiple infectious diagnoses. Third, there may be other potential confounding factors that were not included in this study. For example, information on out-of-hours visits,[8] non-specialty physicians,[8, 24, 27] and patient's low-per capita income or low-education,[14] which have been reported as potential factors associated with inappropriate antibiotics prescribing, could not be extracted from the claims database in this study. Fourth, only 65% of antibiotic prescriptions were linked to infectious disease visits. This may be partly because we could not capture the information concerning follow-up visits when patients had multiple visits for a single infection (antibiotics were linked to the infectious diagnoses only when they were prescribed at the first visit of an illness episode). In addition, approximately 3–5% of medical claims that included diagnostic codes and 0.1% of pharmacy claims that included prescription (medication) codes were registered in non-digital format. As non-digital insurance claims were not included in our database, 3–5% of antibiotic prescriptions were not linked to diagnoses. Therefore, inappropriate antibiotic prescription might be underestimated rather than overestimated.

In conclusion, this Japanese study demonstrated that third-generation cephalosporins, macrolides, and quinolones accounted for 88% of oral antibiotic prescription.

327 Approximately 60% of antibiotic prescription was provided for ARTIs, with viral URI
328 and pharyngitis being the two ARTI diagnoses with the largest antibiotic prescriptions.
329 Gastrointestinal infections were the second most common diagnosis for antibiotic
330 prescribing. The scale of the facilities (clinic or small-scale hospital) and patient age
331 (adolescents and young adults) were factors associated with antibiotic over-prescription.
332 Antimicrobial stewardship interventions should focus on targeting antibiotic prescribing
333 for these infectious diagnoses, patients, and institutions. Further nationwide studies are
334 needed to support our data, and longitudinal studies using medical claims data are needed
335 to evaluate the effectiveness of antimicrobial stewardship.

Authors' contributions

HH and SH conceived the study, interpreted the data and results, and drafted the manuscript. HH, HM, YS, and HY collected, organized, analyzed the data, and performed statistical analyses. KK and RN conceived the study and collected and interpreted the data. All authors critically revised the manuscript for intellectual content. All authors read and approved the final manuscript.

Funding

This work was funded by ImPACT Program of Council for Science, Technology, and Innovation (Cabinet Office, Government of Japan) and by MEXT KAKENHI, Grant Number 16K09254.

Competing interests

None declared.

Data sharing

No additional data available.

Transparency declarations

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethical approval

This study was approved by the Ethics Committee of the Jichi Medical University (Number 17-002).

Table 1. Frequency of oral antibiotic prescriptions by age and antibiotic groups

Antibiotic groups coded by ATC* classification**	Number (%) of visits with antibiotic prescription				
	Age Group, y				
	0–9	10–19	20–64	≥ 65	All ages
Penicillins	7,495 (7.2)	1,724 (4.2)	8,574 (4.5)	14,924 (4.3)	32,717 (4.8)
First/second-generation cephalosporins	964 (0.9)	411 (1.0)	2,987 (1.6)	5,719 (1.6)	10,081 (1.5)
Third-generation cephalosporins	52,082 (49.9)	16,367 (40.1)	60,621 (31.8)	108,302 (31.2)	237,372 (34.8)
Macrolides	28,597 (27.4)	14,691 (36.0)	56,719 (29.7)	115,649 (33.3)	215,656 (31.6)
Quinolones	7,286 (7.0)	4,158 (10.2)	48,843 (25.6)	84,848 (24.4)	145,135 (21.3)
Sulfonamides and trimethoprim	32 (0.0)	53 (0.1)	1,389 (0.7)	4,520 (1.3)	5,994 (0.9)
Tetracyclines	915 (0.9)	1,366 (3.3)	4,366 (2.3)	5,147 (1.5)	11,794 (1.7)
Other antibiotics	6,901 (6.6)	2,021 (5.0)	7,186 (3.8)	7,965 (2.3)	24,073 (3.5)
All antibiotics	104,272	40,791	190,685	347,074	682,822

*ATC: Anatomical Therapeutic Chemical

**Penicillins, J01C; First-generation cephalosporins, J01DB; Second-generation cephalosporins, J01DC; Third-generation cephalosporins, J01DD; Macrolides, J01FA; Quinolones, J01M; Sulfonamides and trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH, J01DI, J01FF, J01G, and J01X

Table 2. Frequency of oral antibiotic prescriptions by facility scale and antibiotic group*

Antibiotic groups coded by ATC** classification***	Number (%) of visits with antibiotic prescription				
	Free-standing clinic	Small-scale hospital (< 200 beds)-based clinic	Medium-scale hospital (200–499 beds)-based clinic	Large-scale hospital (≥ 500 beds)-based clinic	All facilities
Penicillins	25,225 (4.8)	3,453 (4.4)	2,968 (6.6)	565 (3.9)	32,211 (4.8)
First/second-generation cephalosporins	6,755 (1.3)	1,789 (2.3)	1,245 (2.8)	158 (1.1)	9947 (1.5)
Third-generation cephalosporins	187,928 (35.4)	25,463 (32.4)	15,252 (33.7)	4,139 (28.8)	232,782 (34.8)
Macrolides	169,980 (32.0)	26,307 (33.5)	11,319 (25.0)	3,833 (26.7)	211,439 (31.6)
Quinolones	110,770 (20.9)	17,877 (22.8)	9,992 (22.1)	3,402 (23.7)	142,041 (21.2)
Sulfonamides and trimethoprim	712 (0.1)	1,069 (1.4)	2,234 (4.9)	1,618 (11.3)	5,633 (0.8)
Tetracyclines	9,477 (1.8)	846 (1.1)	803 (1.8)	320 (2.2)	11,446 (1.7)
Other antibiotics	20,069 (3.8)	1,742 (2.2)	1,458 (3.2)	318 (2.2)	23,587 (3.5)
All antibiotics	530,916	78,546	45,271	14,353	669,086

*13,736 patients with antibiotic prescription were excluded due to missing data about facility scale.

**ATC: Anatomical Therapeutic Chemical

***Penicillins, J01C; First-generation cephalosporins, J01DB; Second-generation cephalosporins, J01DC; Third-generation cephalosporins, J01DD; Macrolides, J01FA; Quinolones, J01M; Sulfonamides and trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH, J01DI, J01FF, J01G, and J01X

Table 3. Frequency of oral antibiotic prescriptions by antibiotic groups and diagnoses

Diagnoses	All visits	Visits with any antibiotic prescription and prescription rate (%)	Number (%) of visits with antibiotic prescriptions by antibiotic groups*							
			Penicillins	$1^{st}/2^{nd}$ cephem	3^{rd} cephem	Macrolides	Quinolones	ST	Tetracyclines	Other antibiotics
Miscellaneous bacterial infections	45,061	20,429 (45.3)	2,969 (11.5)	468 (1.8)	7,404 (28.7)	7,868 (30.5)	5,731 (22.2)	181 (0.7)	444 (1.7)	728 (2.8)
STD	14,051	3,931 (28.0)	86 (1.9)	76 (1.7)	836 (18.9)	1515 (34.2)	496 (11.2)	14 (0.3)	147 (3.3)	1,260 (28.4)
Bacterial Pneumonia	47,035	21,473 (45.7)	916 (3.4)	121 (0.5)	5,044 (18.9)	8,568 (32.2)	11,236 (42.2)	191 (0.7)	238 (0.9)	316 (1.2)
Abdominal infection	9,208	2,077 (22.6)	69 (3.2)	29 (1.3)	680 (31.1)	142 (6.5)	1,086 (49.7)	≤ 10	≤ 10	177 (8.1)
Orthopedic infection	1,749	380 (21.7)	36 (8.2)	22 (5.0)	225 (51.4)	21 (4.8)	93 (21.2)	≤ 10	19 (4.3)	22 (5.0)
Urinary tract infections	97,948	37,674 (38.5)	1,195 (2.9)	567 (1.4)	14,735 (36.0)	1,998 (4.9)	20,229 (49.5)	429 (1.0)	521 (1.3)	1,232 (3.0)
PID	11,621	1,763 (15.2)	84 (4.6)	26 (1.4)	1127 (61.	164 (8.9)	167 (9.1)	≤ 10	≤ 10	273 (14.8)

28

					2)					
GI infections	137,661	41,309 (30.0)	2,121 (4.6)	264 (0.6)	12,060 (26.0)	8603 (18.6)	13206 (28.5)	196 (0.4)	232 (0.5)	9,680 (20.9)
Skin infections	62,202	23,572 (37.9)	1,167 (4.6)	1,337 (5.3)	15,311 (60.6)	1,975 (7.8)	2,848 (11.3)	25 (0.1)	997 (3.9)	1,615 (6.4)
Suppurative otitis media	16,059	9,958 (62.0)	1,566 (11.8)	18 (0.1)	5,213 (39.1)	1,972 (14.8)	3,654 (27.4)	≤ 10	92 (0.7)	812 (6.1)
Pharyngitis	146,508	78,469 (53.6)	4,372 (5.1)	450 (0.5)	35,958 (41.8)	27,454 (31.9)	16,387 (19.1)	121 (0.1)	301 (0.3)	976 (1.1)
Sinusitis	80,078	45,456 (56.8)	3,654 (6.9)	481 (0.9)	15,282 (28.8)	20,677 (39.0)	11,441 (21.6)	≤ 10	779 (1.5)	766 (1.4)
Bronchitis with COPD	6,832	4,313 (63.1)	208 (4.1)	14 (0.3)	912 (17.8)	2,178 (42.5)	1,762 (34.3)	28 (0.5)	11 (0.2)	17 (0.3)
Acne	6,939	2,030 (29.3)	≤ 10	32 (1.5)	174 (8.3)	739 (35.2)	41 (2.0)	≤ 10	1,050 (50.0)	62 (3.0)
Nonbacterial GI infections	1,215	116 (9.5)	≤ 10	≤ 10	42 (33.1)	38 (29.9)	33 (26.0)	≤ 10	≤ 10	14 (11.0)
Nonsuppurative otitis media	2,807	888 (31.6)	63 (5.8)	≤ 10	384 (35.5)	481 (44.5)	128 (11.8)	≤ 10	≤ 10	26 (2.4)
Viral URI	274,441	96,989 (35.3)	4,839 (4.6)	825 (0.8)	44,475 (4	37,001 (3	16,941 (1	160 (0.2)	790 (0.7)	601 (0.6)

					2.1)	5.0)	6.0)			
Influenza	22,868	8,665 (37.9)	296 (3.1)	74 (0.8)	3,030 (31.9)	3,934 (41.5)	2,040 (21.5)	≤ 10	47 (0.5)	69 (0.7)
Viral pneumonia	15	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10
Bronchitis without COPD	89,479	47,248 (52.8)	1,509 (3.0)	332 (0.7)	14,521 (28.5)	22,779 (44.8)	11,078 (21.8)	58 (0.1)	250 (0.5)	346 (0.7)
Noninfectious diarrhea	1,597	50 (3.1)	≤ 10	≤ 10	≤ 10	19 (55.9)	15 (44.1)	≤ 10	≤ 10	≤ 10
Fever	2,908	438 (15.1)	20 (4.3)	≤ 10	190 (40.5)	103 (22.0)	156 (33.3)	≤ 10	≤ 10	≤ 10

1st/2nd cephem, first/second-generation cephalosporins; 3rd cephem, third-generation cephalosporins; ST, Sulfonamides and trimethoprim; STD, sexual transmitted diseases; PID, pelvic inflammatory diseases; GI infections, gastrointestinal infections; Skin infections, Skin, cutaneous and mucosal infections; COPD, chronic obstructive pulmonary disease; URI, upper respiratory infections

*Antibiotics were coded according to Anatomical Therapeutic Chemical (ATC) codes: Penicillins, J01C; First-generation cephalosporins, J01DB; Second-generation cephalosporins, J01DC; Third-generation cephalosporins, J01DD; Macrolides, J01FA; Quinolones, J01M; Sulfonamides and trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH, J01DI, J01FF, J01G, and J01X

Table 4. Factors associated with antibiotic prescription for acute upper respiratory infections*

Characteristics	Antibiotic prescription, n (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Patient age			
0–9	44,413 (50.4)	1.66 (1.64 to 1.69)	1.48 (1.46 to 1.50)
10–19	20,822 (65.1)	3.08 (3.00 to 3.15)	2.75 (2.69 to 2.82)
20–64	85,952 (54.6)	1.98 (1.95 to 2.00)	1.92 (1.89 to 1.94)
≥ 65	121,289 (37.9)	1	1
Patient sex			
Male	112,643 (47.4)	1.13 (1.12 to 1.14)	1.10 (1.08 to 1.11)
Female	155,038 (44.4)	1	1
Facility scale			
Free-standing clinic	233,078 (49.8)	4.48 (4.27 to 4.70)	4.24 (4.03 to 4.45)
Hospital (< 200 beds)-based clinic	23,012 (30.8)	2.01 (1.91 to 2.11)	2.07 (1.97 to 2.18)
Hospital (200–499 beds)-based clinic	9,327 (28.2)	1.77 (1.68 to 1.89)	1.71 (1.62 to 1.80)
Hospital (≥ 500 beds)-based clinic	2,064 (18.2)	1	1

CI, confidence interval

*Acute upper respiratory infections include viral upper respiratory infections, pharyngitis, bronchitis, and sinusitis.

Table 5. Factors associated with antibiotic prescription for gastrointestinal infections

Characteristics	Antibiotic prescription, n (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Patient age			
0–9	10,809 (37.0)	1.92 (1.86 to 1.98)	1.76 (1.71 to 1.82)
10–19	4,395 (38.7)	2.07 (1.98 to 2.16)	1.92 (1.83 to 2.00)
20–64	12,310 (32.4)	1.57 (1.53 to 1.61)	1.55 (1.51 to 1.60)
≥ 65	13,795 (23.4)	1	1
Patient sex			
Male	18,547 (30.9)	1.09 (1.06 to 1.12)	1.04 (1.01 to 1.06)
Female	21,831 (29.1)	1	1
Facility type			
Free-standing clinic	33,712 (32.9)	2.03 (1.82 to 2.27)	1.88 (1.68 to 2.10)
Hospital (< 200 beds)-based clinic	4,056 (21.7)	1.15 (1.02 to 1.29)	1.17 (1.04 to 1.32)
Hospital (200–499 beds)-based clinic	2,214 (18.9)	0.97 (0.86 to 1.09)	0.93 (0.82 to 1.05)
Hospital (≥ 500 beds)-based clinic	396 (19.4)	1	1

CI, confidence interval

References

392 References

393 1. de Kraker ME, Wolkewitz M, Davey PG et al. Clinical impact of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay related to methicillin-resistant Staphylococcus aureus bloodstream infections. Antimicrob Agents Chemother 2011; 55: 1598-605.

397 2. Stewardson AJ, Allignol A, Beyersmann J et al. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and 2011: a multicentre retrospective cohort study. Euro Surveill 2016; 21: pii=30319.

401 3. Ammerlaan HS, Harbarth S, Buiting AG et al. Secular trends in nosocomial bloodstream infections: antibiotic-resistant bacteria increase the total burden of infection. Clin Infect Dis 2013; 56: 798-805.

404 4. World Health Organization. Global action plan on antimicrobial resistance. Available at: http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf?ua=1 (Accessed: August 3, 2018).

407 5. The Government of Japan. National Action Plan on Antimicrobial Resistance (AMR)

2016-2020. Available at: https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000138942.pdf. (Accessed: August 3, 2018).

6. Tacconelli E. Antimicrobial use: risk driver of multidrug resistant microorganisms in healthcare settings. Curr Opin Infect Dis 2009; 22: 352-8.

7. Muraki Y, Yagi T, Tsuji Y et al. Japanese antimicrobial consumption surveillance: First report on oral and parenteral antimicrobial consumption in Japan (2009-2013). J Glob Antimicrob Resist 2016; 7: 19-23.

8. Yoshida S, Takeuchi M, Kawakami K. Prescription of antibiotics to pre-school children from 2005 to 2014 in Japan: a retrospective claims database study. J Public Health (Oxf) 2018; 40: 397-403.

9. Higashi T, Fukuhara S. Antibiotic prescriptions for upper respiratory tract infection in Japan. Intern Med 2009; 48: 1369-75.

10. The Government of Japan, Ministry of Health, Labour and Welfare. Manual of Antimicrobial Stewardship (1st Edition). Available at: http://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000193504.pdf. (Accessed: August 3, 2018).

11. Kumamoto prefectural government. 2012 Kumamoto National Health Insurance business situation report. Available at: http://www.pref.kumamoto.jp.e.qp.hp.transer.com/kiji_2735.html (Accessed: August 3, 2018).

12. Kumamoto prefectural government. The situation such as Kumamoto elderly aged 75 or over medical expenses. Available at: http://www.pref.kumamoto.jp.e.qp.hp.transer.com/kiji_13777.html (Accessed: August 3, 2018).

13. Fleming-Dutra KE, Hersh AL, Shapiro DJ et al. Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. JAMA 2016; 315: 1864-73.

14. Hicks LA, Bartoces MG, Roberts RM et al. US outpatient antibiotic prescribing variation according to geography, patient population, and provider specialty in 2011. Clin Infect Dis 2015; 60: 1308-16.

15. ESAC-Net surveillance data. Surveillance of antimicrobial consumption in Europe. Available at: http://ecdc.europa.eu/en/publications/Publications/antimicrobial-consumption-europe-esac-net-2012.pdf (Accessed: August 3, 2018).

16. Shapiro DJ, Hicks LA, Pavia AT et al. Antibiotic prescribing for adults in ambulatory

care in the USA, 2007-09. J Antimicrob Chemother 2014; 69: 234-40.

17. Dolk FCK, Pouwels KB, Smith DRM et al. Antibiotics in primary care in England: which antibiotics are prescribed and for which conditions? J Antimicrob Chemother 2018; 73: ii2-ii10.

18. Harris AM, Hicks LA, Qaseem A. Appropriate Antibiotic Use for Acute Respiratory Tract Infection in Adults: Advice for High-Value Care From the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med 2016; 164: 425-434.

19. Bisno AL. Acute pharyngitis: etiology and diagnosis. Pediatrics 1996; 97: 949-54.

20. Ebell MH, Smith MA, Barry HC et al. The rational clinical examination. Does this patient have strep throat? JAMA 2000; 284: 2912-8.

21. Butler CC, Rollnick S, Pill R et al. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. BMJ 1998; 317: 637-42.

22. Kumar S, Little P, Britten N. Why do general practitioners prescribe antibiotics for sore throat? Grounded theory interview study. BMJ 2003; 326: 138.

456 23. Adriaenssens N, Coenen S, Tonkin-Crine S, et al. European Surveillance of Antimicrobial Consumption (ESAC): disease-specific quality indicators for outpatient antibiotic prescribing. BMJ Qual Saf 2011; 20: 764-72.

459 24. Lee ML, Cho CY, Hsu CL, et al. Recent trends in antibiotic prescriptions for acute respiratory tract infections in pediatric ambulatory care in Taiwan, 2000-2009: A nationwide population-based study. J Microbiol Immunol Infect 2016; 49: 554-560.

462 25. Silverman M, Povitz M, Sontrop JM, et al. Antibiotic Prescribing for Nonbacterial Acute Upper Respiratory Infections in Elderly Persons. Ann Intern Med 2017; 166: 765-774.

465 26. Akkerman AE, van der Wouden JC, Kuyvenhoven MM et al. Antibiotic prescribing for respiratory tract infections in Dutch primary care in relation to patient age and clinical entities. J Antimicrob Chemother 2004; 54: 1116-1121.

468 27. Schmidt ML, Spencer MD, Davidson LE. Patient, Provider, and Practice Characteristics Associated with Inappropriate Antimicrobial Prescribing in Ambulatory Practices. Infect Control Hosp Epidemiol. 2018; 39:307-315.

Table S1. Classification of infections by groups with corresponding ICD-10 codes

	Diagnosis	ICD-10 codes
Group 1: Infections for which antibiotics are usually indicated		
1	Miscellaneous bacterial infections	Tuberculosis (A15–A19); Certain zoonotic bacterial diseases (A20–A28); Other bacterial diseases including listeriosis, diphtheria, bartonellosis, erysipelas, and rickettsioses (A30–A37, A39–A49, A75–A79); Bacterial meningitis, encephalitis, and intracranial abscess (G00, G042, G049, G06); Mastoiditis (H70); Infective endocarditis (I33, T826); Acute epiglottitis (J051); Deep neck space infections (J36, J390, J391); Abscess of lung and mediastinum; Pyothorax (J85, J86); Infections of the jaws and mouth (K102, K122); Infections due to cardiac and vascular devices (T827); Infection due to internal prosthetic devices, implants and grafts (T857)
2	Sexually transmitted infections	Infections with a predominantly sexual mode of transmission (A50–A64); Other spirochetal diseases (A65–A69); Other diseases caused by chlamydia (A70–A74)
3	Pneumonia	Bacterial pneumonia (J13–J18)
4	Abdominal infections	Acute appendicitis (K35); Abscess of anal and rectal regions, intestine, and liver (K61, K630, K750); Peritonitis (K65); Cholecystitis and cholangitis (K800, K801, K803, K804, K810, K819, K830)
5	Orthopedic infections	Pyogenic arthritis and prosthetic joint infection (M00, T845); necrotizing fasciitis (M726); Infective myositis, synovitis and bursitis (M600, M650–M651, M710–M711); Osteomyelitis (M462–M465, M86)
6	Urinary tract infections	Acute pyelonephritis/pyonephrosis ((N10, N12, N136); Renal abscess (N151); Kidney infection, unspecified (N159); Acute cystitis (N300); Cystitis, unspecified (N308, N309); Urethritis and urethral abscess (N34); Urinary tract infections, unspecified (N390); Prostatitis and abscess of prostate (N41); Orchitis and epididymitis (N45); Catheter associated urinary tract infections (T835)

7	Pelvic inflammatory diseases	Pelvic inflammatory diseases (N70–N73, N751, N760–N764); Infections of genitourinary tract in pregnancy (O23)
Group 2：Infections for which antibiotics are potentially indicated		
1	Gastrointestinal infections	Intestinal infectious diseases (A00–A07, A09); Diverticulitis of intestine (K57)
2	Skin, cutaneous and mucosal infections	Infections of other skin and subcutaneous tissue including cellulitis, cutaneous abscess, furuncle, carbuncle, impetigo, acute lymphadenitis, folliculitis, mastitis (H050, J340, L00–L08, N61, T814); Infections of the eye and adnexa (H00, H440); Infective otitis externa (H600–H603)
3	Suppurative otitis media	Suppurative and unspecified otitis media (H66)
4	Pharyngitis	Streptococcal pharyngitis/tonsillitis (J020, J030); Acute pharyngitis/tonsillitis, unspecified (J029, J039); Scarlet fever (A38)
5	Sinusitis	Acute sinusitis (J01); Chronic sinusitis (J32)
6	Bronchitis and bronchiolitis with COPD	Acute bronchitis (J20) *; Acute bronchiolitis (J21) *; Unspecified acute lower respiratory infection (J22) *
7	Acne	Acne (L70)
Group 3: Infections for which antibiotics are rarely indicated		
1	Nonbacterial gastrointestinal infections	Viral and other specified intestinal infections (A08)
2	Nonsuppurative otitis media	Nonsuppurative otitis media (H65)
3	Viral upper respiratory infection	Acute nasopharyngitis [common cold] (J00); Acute pharyngitis/tonsillitis due to other specified organisms (J028, J038); Acute laryngitis and tracheitis (J04); Acute obstructive laryngitis [croup] (J050); Acute upper respiratory infections of multiple and unspecified sites (J06); Cough (R05)
4	Influenza	Influenza (J10, J11)
5	Viral pneumonia	Viral pneumonia (J12)
6	Bronchitis and bronchiolitis without COPD	Acute bronchitis (J20) **; Acute bronchiolitis (J21) **; Unspecified acute lower respiratory infection (J22) **
7	Noninfectious diarrhea	Noninfective gastroenteritis and colitis, unspecified (K529)

8	Fever	Fever of unknown origin (R50)

3 *includes visits in which ICD-10 code for COPD (J41–J44) are present

4 **includes visits in which ICD-10 code for COPD (J41–J44) are not present

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7–8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8–9
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9–10
		(*b*) Describe any methods used to examine subgroups and interactions	9–10
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12–13
		(*b*) Report category boundaries when continuous variables were categorized	11–13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	14–18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18–19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19–20
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Antibiotic prescription among outpatients in a prefecture of Japan, 2012–2013: A retrospective claims database study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026251.R2
Article Type:	Research
Date Submitted by the Author:	21-Feb-2019
Complete List of Authors:	Hashimoto, Hideki; Jichi Medical University Hospital, Division of General Internal Medicine Matsui, Hiroki; Jichi Medical University, Data Science Center; School of Public Health, University of Tokyo, Department of Clinical Epidemiology and Health Economics Sasabuchi, Yusuke; Jichi Medical University, Data Science Center Yasunaga, Hideo; Jichi Medical University, Data Science Center; School of Public Health, The University of Tokyo, Department of Clinical Epidemiology and Health Economics Kotani, Kazuhiko; Jichi Medical University, Division of Community and Family Medicine Nagai, Ryozo; Jichi Medical University, President Hatakeyama, Shuji; Jichi Medical University Hospital, Division of General Internal Medicine/Division of Infectious Diseases
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, INFECTIOUS DISEASES

Antibiotic prescription among outpatients in a prefecture of Japan, 2012–2013: A retrospective claims database study

Hideki Hashimoto[1], Hiroki Matsui[2, 3], Yusuke Sasabuchi[2], Hideo Yasunaga[2, 3], Kazuhiko Kotani[4], Ryozo Nagai[5], Shuji Hatakeyama[1, 6*]

[1]Division of General Internal Medicine, Jichi Medical University Hospital, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

[2]Data Science Center, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

[3]Department of Clinical Epidemiology and Health Economics, School of Public Health, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

[4]Division of Community and Family Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

[5]President, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

[6]Division of Infectious Diseases, Jichi Medical University Hospital, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

***Corresponding author:**

Shuji Hatakeyama, M.D., Ph.D.

Division of General Internal Medicine/Division of Infectious Diseases, Jichi Medical University Hospital, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan.

Phone: +81-285-58-7498

Fax: +81-285-40-5160

E-mail: shatake-tky@umin.ac.jp

Key words: antibiotic, antimicrobial stewardship, antimicrobial-resistance, big data, inappropriate prescribing

Running title: Antibiotic prescriptions in Japan

Word count for the main text: 3,002 words

Abstract

Objectives: To investigate oral antibiotic prescribing patterns and identify factors associated with antibiotic prescriptions, with the aim of guiding future interventions to reduce inappropriate prescribing.

Design: Retrospective cohort study.

Setting: Database of public health insurance claims in Kumamoto prefecture (Japan).

Participants: Beneficiaries of the national or late elders' health insurance system between April 2012 and March 2013.

Main outcome measures: Of 7,770,481 outpatient visits, 682,822 had a code for antibiotics (860 antibiotic prescriptions per 1000 population). Third-generation cephalosporins (35%), macrolides (32%), and quinolones (21%) were most frequently prescribed. Acute respiratory tract infections (ARTIs), including viral upper respiratory infections (URI) (22%), pharyngitis (18%), bronchitis (11%), and sinusitis (10%) were most frequently diagnosed for antibiotic prescribing, followed by gastrointestinal (9%), urinary tract (8%), and skin, cutaneous, and mucosal infections (5%). Antibiotic prescribing rates for viral URI, pharyngitis, bronchitis, sinusitis, and gastrointestinal infections were 35%, 54%, 53%, 57%, and 30%, respectively. In multivariable analysis for ARTIs and gastrointestinal infections, patient age (10–19 years especially), patient sex (male), and facility scale (free-standing clinics or small-scale hospital-based clinics) were associated with increased antibiotic prescribing.

Conclusions: Broad-spectrum antibiotics constituted 88% of oral outpatient antibiotic prescriptions. Approximately 70% of antibiotics were prescribed for ARTIs and gastroenteritis with modest benefit from antibiotic treatment. The quality of antibiotic prescribing needs to be improved. Antimicrobial stewardship interventions should target ARTIs and gastroenteritis, as well as young patients and small-scale institutions.

Strength and limitations of this study

- This is the first Japanese study to describe outpatient antibiotic prescription patterns linked to individual diagnosis data, comprehensively, by use of the public health insurance claims database.
- This study included patients older than 65 years of age, who have not typically been included in previous Japanese studies.
- The accuracy of the diagnosis has not been validated due to the nature of the administrative claims database.
- There are some unmeasured potential confounding factors such as out-of-hours visits and physician specialty.

Introduction

There is a growing concern about antimicrobial-resistant bacterial infections. Antimicrobial resistance results in increased health care costs, prolonged hospitalization, and death.[1-3] The World Health Organization launched the global action plan to combat the antimicrobial-resistant bacteria in 2015[4] and requested Member States to endorse national action plans within two years. The government of Japan launched a national action plan in 2016 in response to the request.[5]

Since antimicrobial use is one of the important factors in the emergence of antimicrobial resistance,[6] it is essential to reduce the inappropriate use of antibiotics. In Japan, a previous sales data-based study revealed that oral antibiotics account for more than 90% of total antibiotic consumption and that broad-spectrum antibiotics (third-generation cephalosporins, macrolides, and fluoroquinolones) account for 77% of oral antibiotic consumption (daily doses defined per 1000 inhabitants per day).[7] The Japanese national action plan aims to reduce the total antimicrobial use to two-thirds of current use, and the use of oral cephalosporins, quinolones, and macrolides to one-half, by 2020. To reduce inappropriate antimicrobial use, it is important to determine the antimicrobial prescribing patterns and factors associated with antibiotic prescription. However, such information has been limited in Japan to date. Although a few recent studies[8,9] described the prescription patterns for upper respiratory tract infections and bronchitis, the prescription patterns of infections other than acute respiratory tract infections (ARTIs) have not been clarified. In addition, patients older than 65 years of age have not been commonly included in these studies, because these studies relied on data from an employee-based insurance claims database. With the high rate in aging population in Japan, it is important to describe the prescription patterns in elderly patients.

In this study, we described outpatient oral antibiotic prescribing patterns for all infections and in all ages, using the Japanese administrative claims database. Furthermore, we aimed to identify factors associated with antibiotic prescriptions for ARTIs and gastrointestinal infections, the targets of the antimicrobial stewardship guideline formulated by the government of Japan in 2017.[10]

99 **Methods**

100 *Data sources*

101 The current population of Japan is approximately 127 million. All citizens are enrolled in a universal health coverage insurance program provided by the social insurance system (for employees younger than 75 years of age), national health insurance system (for self-employed or unemployed people younger than 75 years of age), and the late elders' health insurance system (for those aged 75 years and older). In Japan, patients can visit any clinic of their choice. All physicians working at any free-standing or hospital-based clinics can provide primary care and prescribe antibiotics.

108 We conducted a retrospective analysis using the administrative health insurance claims database of Kumamoto prefecture, situated in the southwestern region of Japan, with a population of about 1.7 million. This database covers approximately 780,000 residents of Kumamoto prefecture (44% of the population) who were beneficiaries of the national health insurance system,[11] or the late elders' health insurance system. [12] The participants in this study may be older than the general population of Japan.

114 The database is composed of medical and pharmacy claims. It provides monthly

information about patient demographics (year and month of birth and sex), diagnoses, date of diagnoses, medical procedures, medications, scale (number of beds) of the medical facility, as well as the identification numbers assigned to each individual, medical facility, and dispensing pharmacy. At the end of each month, claims are registered from each medical facility. The diagnoses were recorded by physicians of each medical facility and coded according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).

Data preparation

We linked the medical and pharmacy claims on the database using an identification number unique to each patient, medical facility, and dispensing pharmacy. We identified all newly diagnosed outpatients, with any infectious diseases, between April 2012 and March 2013. Infectious diseases diagnoses were categorized according to the indication for antibiotic use (Table S1, available as supplementary data). This categorization was based on the study by Fleming-Dutra KE *et al*.[13] Bronchitis and bronchiolitis were divided into two categories based on whether the patients had chronic obstructive pulmonary disease (COPD) as comorbidity or not, because of differing need of treatment with antibiotics. If a patient had multiple infectious diagnoses in one month, a single infectious diagnosis, selected in order from Group 1 (antibiotics are usually indicated) to Group 3 (antibiotics are rarely indicated), and the first-listed diagnosis in alphabetical order of ICD-10 codes in the selected group was included in the analyses (Table S1).

We also identified all outpatients with any antibiotic prescriptions. Topical, intramuscular, and intravenous antibiotics were excluded. Antibiotics were categorized according to the Anatomical Therapeutic Chemical (ATC) classification system (http://www.whocc.no/atcddd/) as follows: tetracyclines (J01A), penicillins (J01C), first- and second-generation cephalosporins (J01DB and J01DC), third-generation cephalosporins (J01DD), sulfonamides and trimethoprim (J01E), macrolides (J01FA), quinolones (J01M), and others (J01B, J01DH, J01DI, J01FF, J01G, and J01X). We assumed that third-generation cephalosporins accounted for most of cephalosporins used in Japan; hence, we divided cephalosporins into two groups: first/second- and third-generation cephalosporins. Antibiotics were linked to the infectious diagnoses in each patient's claims when both the code of antibiotics and the code of diagnoses were recorded in the same month.

Data Analysis

We calculated the frequency of antibiotic prescription for all visits with infections (according to diagnosis and antibiotic class). For ARTIs (including pharyngitis, sinusitis, bronchitis/bronchiolitis, and viral upper respiratory infections [URI]) and gastrointestinal infections, we performed separate multivariable logistic regression analyses to identify the factors associated with antibiotic prescriptions. The variables were as follows: age and sex of patients and scale (number of beds) of the medical facilities. Generalized estimating equations with exchangeable correlation structure were used to account for the clustering of the medical facilities. *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed with the statistical package R, v.3.5.0 (http://cran.r-project.org).

Patient involvement

No patients were involved in the development of the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked for advice regarding the interpretation or writing of results. There are no plans to disseminate the study results to the relevant patient community.

Results

In total, there were 7,770,481 outpatient visits between April 2012 and March 2013. Antibiotics were prescribed in 682,822 visits (860 antibiotic prescriptions per 1000 population). Among these, third-generation cephalosporins were most frequently prescribed (237,372 visits, 35%), followed by macrolides (215,656 visits, 32%) and quinolones (145,135 visits, 21%). This trend was observed regardless of age group (Table 1) and scale of the medical facility (Table 2), except for those less than 9 years of age in whom the systemic use of quinolones is not recommended. Information about facility scale was available from 669,086 out of 682,822 visits. Of these, antibiotics were prescribed most frequently at free-standing clinics (530,916 visits, 79%), followed by small-scale (< 200 beds; 78,546 visits, 12%), medium-scale (200–499 beds; 45,271 visits, 7%), and large-scale (500 beds or more; 14,353 visits, 2%) hospital-based clinics (Table 2).

We were able to link the individual diagnoses to the antibiotic prescription in 447,232 visits (Table 3). Of these patients, approximately 60% of antibiotics were prescribed for ARTIs, including viral URI (96,989 visits, 22%), pharyngitis (78,469 visits, 18%), bronchitis without COPD (47,248 visits, 11%), and sinusitis (45,456 visits, 10%). Other than ARTIs, there were frequent antibiotic prescriptions for gastrointestinal infections (41,309 visits, 9%), urinary tract infections (37,674 visits, 8%), and skin, cutaneous, and mucosal infections (23,572 visits, 5%). The antibiotic prescription rates for viral URI, pharyngitis, bronchitis (without underlying COPD), sinusitis, and gastrointestinal infections were 35% (96,989 out of 274,441 visits), 54% (78,469 out of 146,508 visits), 53% (47,248 out of 89,479 visits), 57% (45,456 out of 80,078 visits), and 30% (41,309 out of 137,661 visits), respectively (Table 3).

Table 4 shows the results of the logistic regression analysis of antibiotic prescription for ARTIs. Male sex was associated with more antibiotic prescription (adjusted odds ratio [OR], 1.10; 95% confidence interval [CI], 1.08 to 1.11). With patients aged 65 years or older as reference, patients aged 10 to 19 years were more likely to be prescribed antibiotics (adjusted OR, 2.75; 95% CI, 2.69 to 2.82), followed by patients aged 20 to 64 years (adjusted OR, 1.92; 95% CI, 1.89 to 1.94), and patients younger than 10 years (adjusted OR, 1.48; 95% CI, 1.46 to 1.50). Regarding facility scale, with large-scale (500 beds or more) hospital-based clinics as reference, free-standing clinics (adjusted OR,

200 4.24; 95% CI, 4.03 to 4.45), small-scale (< 200 beds) hospital-based clinics (adjusted OR,
201 2.07; 95% CI, 1.97 to 2.18), and medium-scale (200–499 beds) hospital-based clinics
202 (adjusted OR, 1.71; 95% CI, 1.62 to 1.80) were significantly associated with more
203 frequent antibiotic prescription.

204 Similar results were shown with the logistic regression analysis for gastrointestinal
205 infections (Table 5). Male sex was associated with slightly more antibiotic prescription
206 (adjusted OR, 1.04; 95% CI, 1.01 to 1.06) than the female sex. Patients aged 10 to 19
207 years (adjusted OR, 1.92; 95% CI, 1.83 to 2.00), 20 to 64 years (adjusted OR, 1.55; 95%
208 CI, 1.51 to 1.60), and younger than 10 years (adjusted OR, 1.76; 95% CI, 1.71 to 1.82)
209 received more antibiotic prescriptions compared with patients aged 65 years or older.
210 With reference to large-scale (≥ 500 beds) hospital-based clinics, free-standing clinics
211 (adjusted OR, 1.88; 95% CI, 1.68 to 2.10) and small-scale (< 200 beds) hospital-based
212 clinics (adjusted OR, 1.17; 95% CI, 1.04 to 1.32) were associated with frequent antibiotic
213 prescription for gastrointestinal infections.

Discussion

We described oral antibiotic prescription patterns in the outpatient care setting in Japan. To the best of our knowledge, this is the first Japanese study to comprehensively describe antibiotic prescription patterns linked to individual diagnoses data, using the claims database. Broad-spectrum antibiotics consisting of third-generation cephalosporins, macrolides, and quinolones accounted for nearly 90% of antibiotic prescriptions in the primary care settings. Prescription of penicillin was only 5%. This prescription pattern is consistent with the results of an analysis of antibiotic sales data in Japan, in which 77% of oral antibiotics shipped were broad-spectrum.[7] In contrast, the use of cephalosporins, macrolides, and quinolones in the United States of America (USA) and Europe were much lower than in Japan. Hicks *et al*.[14] analyzed the sales data of oral antibiotics in the USA and showed that cephalosporins, macrolides, and quinolones accounted for 48% of the total oral antibiotics. In their study, penicillin had the largest share of the antibiotics (23%). Data from the European Surveillance of Antimicrobial Consumption project[15] also showed that cephalosporins, macrolides, and quinolones accounted for about one third of the total oral antibiotic consumptions, in Europe. This study demonstrated a rather high ratio of broad-spectrum to narrow-spectrum oral antibiotics, in Japan; therefore, the quality of antibiotic prescribing needs to be improved.

Although quinolones are not recommended for children, quinolones were prescribed as much as penicillins in children aged 0–9 years in our study. This may be because oral fluoroquinolones such as tosufloxacin are approved for children to treat otitis media and pneumonia in Japan. Since the approval of quinolones in 2010, despite the recommendation to prescribe quinolones carefully for children, many physicians prescribed tosufloxacin to children in expectation of clinical effectiveness.

Among antibiotics linked with individual diagnosis data, over 60% of antibiotics were prescribed for ARTIs, followed by gastrointestinal infections (9%), urinary tract infections (8%), and skin, cutaneous, and mucosal infections (5%). Surprisingly, viral URI (common cold) was the most frequent infection associated with antibiotic prescription. In the ambulatory care setting in the USA, antibiotics were prescribed most frequently for acute respiratory conditions (41–44%), followed by skin and mucosal conditions (15–19%), urinary tract infections (7–8%), and gastrointestinal conditions (5–6%).[13,16] Another study using primary care data in the United Kingdom (UK)[17] demonstrated that 46% of antibiotics were prescribed for respiratory tract conditions, followed by urogenital tract (23%), and skin conditions (10%). Only 1% was prescribed for gastrointestinal conditions. Our study demonstrated a higher proportion of antibiotic prescription for ARTIs (approximately 15% higher than those in USA or UK) and gastrointestinal infections (approximately 5% higher) in Japan.

Antibiotics were prescribed for 35% of viral URI cases and approximately 50–60% of pharyngitis, bronchitis, and sinusitis cases in our study. These prescription rates were approximately similar to those of a USA study,[13] which showed a rate of 30% for viral URI, 62% for pharyngitis, 65% for bronchitis, and 72% for sinusitis. Medically, antibiotics are rarely indicated for ARTIs.[18] Antibiotics have no role in the treatment of either viral URI (common cold) or the majority of acute bronchitis cases, which are generally caused by viral infection. Only a minority of patients with bronchitis (< 10%), for example patients who have underlying COPD or whooping cough, may derive any benefit from antibiotic treatment. With pharyngitis, antibiotics are mainly indicated only for streptococcal pharyngitis, which accounts for 5–15% of pharyngitis in adults and 20–30% in children.[19, 20]

The antibiotic prescription rate for gastrointestinal infections was three times higher than the rate reported in the USA (30% vs. 10%).[13] As most acute gastroenteritis is self-limiting, the Japanese national guideline recommends the non-usage of antibiotics for gastroenteritis unless symptoms are severe.[10] Based on our study, approximately 70% of oral antibiotics are prescribed for ARTIs or acute gastroenteritis; however, most (> 80%), did not require antibiotics. Therefore, there is a need for suitable targets to reduce unnecessary antibiotic use in accordance with antimicrobial stewardship program. Previous studies from the UK[21, 22] analyzed reasons for antibiotic prescribing for sore throats and assessed that patient demand for antibiotics and physician pressure to meet patient demand are associated with antibiotic prescription. In addition, we suppose that physicians frequently prescribe antibiotics for URI as prophylaxis for complicating secondary bacterial infections. Previous qualitative studies identified that additional factors associated with antibiotic prescription included diagnostic uncertainty, unawareness of guidelines, time pressure at work, and patient expectations regarding antibiotics.[23-25]

As for antibiotic prescription for ARTIs and gastrointestinal infections, most antibiotics prescribed were broad-spectrum. For example, quinolones accounted for 15–35% of the antibiotics prescribed for ARTIs in this study, although the proportion of quinolones to whole antibiotics prescribed for ARTIs should be <5% according to the ESAC disease-specific quality indicators.[26] Accordingly, the quality of antibiotic prescribing should be improved.

The logistic regression analyses revealed several factors associated with antibiotic prescriptions for ARTIs and gastrointestinal infections. The smaller the facility scale, the higher the odds of antibiotic prescribing. Recent studies from Japan[8] and Taiwan[27] have found similar results. As family practitioners, pediatricians, and internists usually prescribe a high number of antibiotic courses,[14] greater adherence to treatment guidelines among physicians in these specialties is particularly important. It has also been reported that mid- or late-career stage physicians (because the effect of training received during medical education might have reduced, after this long time) were more likely to prescribe antibiotics for nonbacterial acute URI.[28]

Patient age was another factor associated with antibiotic prescription. In this study, antibiotic prescription rates for ARTIs and gastrointestinal infections were highest in patients aged 10–19 years, followed by patients aged 20–64 years (ARTIs) or 0–9 years (gastrointestinal infections). A previous study concerning Dutch primary care showed similar results of antibiotic over-prescribing for ARTIs in patients aged 31–65 years (i.e., not in children or the elderly).[29] As adolescents and young adults generally pose a much lower risk of disease complications than young children or elderly individuals, antimicrobial stewardship should focus on these age groups of patients. In this study, male sex was also associated with increased antibiotic prescribing. Although a patient sex difference was observed in another study, the results differed; female patients were more likely to have high prescribing in the USA.[14] The reason for patient age and sex difference in antibiotic prescribing remains to be clarified. Patient sex and age-standardized antibiotic prescription rates need to be assessed in Japan for effective intervention.

Our study has several limitations. First, our results do not represent the entire antibiotic prescription pattern in Japan because the claims database used in this study was composed of claims in only one prefecture. Geographical diversity in antibiotic prescribing may be present, as observed in the previous study from the USA.[14] Second, since we used an administrative claims database; the accuracy of the diagnosis was not validated. In addition, we could not link diagnosis and antibiotic prescriptions on a one-to-one level when patients had multiple infectious diagnoses. Third, there may be other potential confounding factors that were not included in this study. For example, information on out-of-hours visits,[8] non-specialty physicians,[8, 27, 30] and patient's low-per capita income or low-education,[14] which have been reported as potential factors associated with inappropriate antibiotics prescribing, could not be extracted from the claims database in this study. Fourth, only 65% of antibiotic prescriptions were linked to infectious disease visits. This may be partly because we could not capture the information concerning follow-up visits when patients had multiple visits for a single infection (antibiotics were linked to the infectious diagnoses only when they were prescribed at the first visit of an illness episode). In addition, approximately 3–5% of medical claims that included diagnostic codes and 0.1% of pharmacy claims that included prescription (medication) codes were registered in non-digital format. As non-digital insurance claims were not included in our database, 3–5% of antibiotic prescriptions were not linked to diagnoses. Therefore, inappropriate antibiotic prescription might be underestimated rather than overestimated.

In conclusion, this Japanese study demonstrated that third-generation cephalosporins, macrolides, and quinolones accounted for 88% of oral antibiotic prescription. Approximately 60% of antibiotic prescription was provided for ARTIs, with viral URI and pharyngitis being the two ARTI diagnoses with the largest antibiotic prescriptions. Gastrointestinal infections were the second most common diagnosis for antibiotic prescribing. The scale of the facilities (clinic or small-scale hospital) and patient age (adolescents and young adults) were factors associated with antibiotic over-prescription. Antimicrobial stewardship interventions should focus on targeting antibiotic prescribing for these infectious diagnoses, patients, and institutions. Further nationwide studies are needed to support our data, and longitudinal studies using medical claims data are needed to evaluate the effectiveness of antimicrobial stewardship.

Authors' contributions

HH and SH conceived the study, interpreted the data and results, and drafted the manuscript. HH, HM, YS, and HY collected, organized, analyzed the data, and performed statistical analyses. KK and RN conceived the study and collected and interpreted the data. All authors critically revised the manuscript for intellectual content. All authors read and approved the final manuscript.

Funding

This work was funded by ImPACT Program of Council for Science, Technology, and Innovation (Cabinet Office, Government of Japan) and by MEXT KAKENHI, Grant Number 16K09254.

Competing interests

None declared.

Data sharing

No additional data available.

Transparency declarations

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethical approval

This study was approved by the Ethics Committee of the Jichi Medical University (Number 17-002).

Table 1. Frequency of oral antibiotic prescriptions by age and antibiotic groups

Antibiotic groups coded by ATC* classification**	Number (%) of visits with antibiotic prescription				
	Age Group, y				
	0–9	10–19	20–64	≥ 65	All ages
Penicillins	7,495 (7.2)	1,724 (4.2)	8,574 (4.5)	14,924 (4.3)	32,717 (4.8)
First/second-generation cephalosporins	964 (0.9)	411 (1.0)	2,987 (1.6)	5,719 (1.6)	10,081 (1.5)
Third-generation cephalosporins	52,082 (49.9)	16,367 (40.1)	60,621 (31.8)	108,302 (31.2)	237,372 (34.8)
Macrolides	28,597 (27.4)	14,691 (36.0)	56,719 (29.7)	115,649 (33.3)	215,656 (31.6)
Quinolones	7,286 (7.0)	4,158 (10.2)	48,843 (25.6)	84,848 (24.4)	145,135 (21.3)
Sulfonamides and trimethoprim	32 (0.0)	53 (0.1)	1,389 (0.7)	4,520 (1.3)	5,994 (0.9)
Tetracyclines	915 (0.9)	1,366 (3.3)	4,366 (2.3)	5,147 (1.5)	11,794 (1.7)
Other antibiotics	6,901 (6.6)	2,021 (5.0)	7,186 (3.8)	7,965 (2.3)	24,073 (3.5)
All antibiotics	104,272	40,791	190,685	347,074	682,822

*ATC: Anatomical Therapeutic Chemical

**Penicillins, J01C; First-generation cephalosporins, J01DB; Second-generation cephalosporins, J01DC; Third-generation cephalosporins, J01DD; Macrolides, J01FA; Quinolones, J01M; Sulfonamides and trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH, J01DI, J01FF, J01G, and J01X

Table 2. Frequency of oral antibiotic prescriptions by facility scale and antibiotic group*

Antibiotic groups coded by ATC** classification***	Number (%) of visits with antibiotic prescription				
	Free-standing clinic	Small-scale hospital (< 200 beds)-based clinic	Medium-scale hospital (200–499 beds)-based clinic	Large-scale hospital (≥ 500 beds)-based clinic	All facilities
Penicillins	25,225 (4.8)	3,453 (4.4)	2,968 (6.6)	565 (3.9)	32,211 (4.8)
First/second-generation cephalosporins	6,755 (1.3)	1,789 (2.3)	1,245 (2.8)	158 (1.1)	9947 (1.5)
Third-generation cephalosporins	187,928 (35.4)	25,463 (32.4)	15,252 (33.7)	4,139 (28.8)	232,782 (34.8)
Macrolides	169,980 (32.0)	26,307 (33.5)	11,319 (25.0)	3,833 (26.7)	211,439 (31.6)
Quinolones	110,770 (20.9)	17,877 (22.8)	9,992 (22.1)	3,402 (23.7)	142,041 (21.2)
Sulfonamides and trimethoprim	712 (0.1)	1,069 (1.4)	2,234 (4.9)	1,618 (11.3)	5,633 (0.8)
Tetracyclines	9,477 (1.8)	846 (1.1)	803 (1.8)	320 (2.2)	11,446 (1.7)
Other antibiotics	20,069 (3.8)	1,742 (2.2)	1,458 (3.2)	318 (2.2)	23,587 (3.5)
All antibiotics	530,916	78,546	45,271	14,353	669,086

*13,736 patients with antibiotic prescription were excluded due to missing data about facility scale.

**ATC: Anatomical Therapeutic Chemical

***Penicillins, J01C; First-generation cephalosporins, J01DB; Second-generation cephalosporins, J01DC; Third-generation cephalosporins, J01DD; Macrolides, J01FA; Quinolones, J01M; Sulfonamides and trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH, J01DI, J01FF, J01G, and J01X

Table 3. Frequency of oral antibiotic prescriptions by antibiotic groups and diagnoses

Diagnoses	All visits	Visits with any antibiotic prescription and prescription rate (%)	Number (%) of visits with antibiotic prescriptions by antibiotic groups*							
			Penicillins	1st/2nd cephem	3rd cephem	Macrolides	Quinolones	ST	Tetracyclines	Other antibiotics
Miscellaneous bacterial infections	45,061	20,429 (45.3)	2,969 (11.5)	468 (1.8)	7,404 (28.7)	7,868 (30.5)	5,731 (22.2)	181 (0.7)	444 (1.7)	728 (2.8)
STD	14,051	3,931 (28.0)	86 (1.9)	76 (1.7)	836 (18.9)	1515 (34.2)	496 (11.2)	14 (0.3)	147 (3.3)	1,260 (28.4)
Bacterial Pneumonia	47,035	21,473 (45.7)	916 (3.4)	121 (0.5)	5,044 (18.9)	8,568 (32.2)	11,236 (42.2)	191 (0.7)	238 (0.9)	316 (1.2)
Abdominal infection	9,208	2,077 (22.6)	69 (3.2)	29 (1.3)	680 (31.1)	142 (6.5)	1,086 (49.7)	≤ 10	≤ 10	177 (8.1)
Orthopedic infection	1,749	380 (21.7)	36 (8.2)	22 (5.0)	225 (51.4)	21 (4.8)	93 (21.2)	≤ 10	19 (4.3)	22 (5.0)
Urinary tract infections	97,948	37,674 (38.5)	1,195 (2.9)	567 (1.4)	14,735 (36.0)	1,998 (4.9)	20,229 (49.5)	429 (1.0)	521 (1.3)	1,232 (3.0)
PID	11,621	1,763 (15.2)	84 (4.6)	26 (1.4)	1127 (61.	164 (8.9)	167 (9.1)	≤ 10	≤ 10	273 (14.8)

					2)					
GI infections	137,661	41,309 (30.0)	2,121 (4.6)	264 (0.6)	12,060 (26.0)	8603 (18.6)	13206 (28.5)	196 (0.4)	232 (0.5)	9,680 (20.9)
Skin infections	62,202	23,572 (37.9)	1,167 (4.6)	1,337 (5.3)	15,311 (60.6)	1,975 (7.8)	2,848 (11.3)	25 (0.1)	997 (3.9)	1,615 (6.4)
Suppurative otitis media	16,059	9,958 (62.0)	1,566 (11.8)	18 (0.1)	5,213 (39.1)	1,972 (14.8)	3,654 (27.4)	≤ 10	92 (0.7)	812 (6.1)
Pharyngitis	146,508	78,469 (53.6)	4,372 (5.1)	450 (0.5)	35,958 (41.8)	27,454 (31.9)	16,387 (19.1)	121 (0.1)	301 (0.3)	976 (1.1)
Sinusitis	80,078	45,456 (56.8)	3,654 (6.9)	481 (0.9)	15,282 (28.8)	20,677 (39.0)	11,441 (21.6)	≤ 10	779 (1.5)	766 (1.4)
Bronchitis with COPD	6,832	4,313 (63.1)	208 (4.1)	14 (0.3)	912 (17.8)	2,178 (42.5)	1,762 (34.3)	28 (0.5)	11 (0.2)	17 (0.3)
Acne	6,939	2,030 (29.3)	≤ 10	32 (1.5)	174 (8.3)	739 (35.2)	41 (2.0)	≤ 10	1,050 (50.0)	62 (3.0)
Nonbacterial GI infections	1,215	116 (9.5)	≤ 10	≤ 10	42 (33.1)	38 (29.9)	33 (26.0)	≤ 10	≤ 10	14 (11.0)
Nonsuppurative otitis media	2,807	888 (31.6)	63 (5.8)	≤ 10	384 (35.5)	481 (44.5)	128 (11.8)	≤ 10	≤ 10	26 (2.4)
Viral URI	274,441	96,989 (35.3)	4,839 (4.6)	825 (0.8)	44,475 (4	37,001 (3	16,941 (1	160 (0.2)	790 (0.7)	601 (0.6)

						2.1)	5.0)	6.0)			
Influenza	22,868	8,665 (37.9)	296 (3.1)	74 (0.8)	3,030 (31.9)	3,934 (41.5)	2,040 (21.5)	≤ 10	47 (0.5)	69 (0.7)
Viral pneumonia	15	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10
Bronchitis without COPD	89,479	47,248 (52.8)	1,509 (3.0)	332 (0.7)	14,521 (28.5)	22,779 (44.8)	11,078 (21.8)	58 (0.1)	250 (0.5)	346 (0.7)
Noninfectious diarrhea	1,597	50 (3.1)	≤ 10	≤ 10	≤ 10	19 (55.9)	15 (44.1)	≤ 10	≤ 10	≤ 10
Fever	2,908	438 (15.1)	20 (4.3)	≤ 10	190 (40.5)	103 (22.0)	156 (33.3)	≤ 10	≤ 10	≤ 10

1st/2nd cephem, first/second-generation cephalosporins; 3rd cephem, third-generation cephalosporins; ST, Sulfonamides and trimethoprim; STD, sexual transmitted diseases; PID, pelvic inflammatory diseases; GI infections, gastrointestinal infections; Skin infections, Skin, cutaneous and mucosal infections; COPD, chronic obstructive pulmonary disease; URI, upper respiratory infections

*Antibiotics were coded according to Anatomical Therapeutic Chemical (ATC) codes: Penicillins, J01C; First-generation cephalosporins, J01DB; Second-generation cephalosporins, J01DC; Third-generation cephalosporins, J01DD; Macrolides, J01FA; Quinolones, J01M; Sulfonamides and trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH, J01DI, J01FF, J01G, and J01X

Table 4. Factors associated with antibiotic prescription for acute upper respiratory infections*

Characteristics	Antibiotic prescription, n (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Patient age			
0–9	44,413 (50.4)	1.66 (1.64 to 1.69)	1.48 (1.46 to 1.50)
10–19	20,822 (65.1)	3.08 (3.00 to 3.15)	2.75 (2.69 to 2.82)
20–64	85,952 (54.6)	1.98 (1.95 to 2.00)	1.92 (1.89 to 1.94)
≥ 65	121,289 (37.9)	1	1
Patient sex			
Male	112,643 (47.4)	1.13 (1.12 to 1.14)	1.10 (1.08 to 1.11)
Female	155,038 (44.4)	1	1
Facility scale			
Free-standing clinic	233,078 (49.8)	4.48 (4.27 to 4.70)	4.24 (4.03 to 4.45)
Hospital (< 200 beds)-based clinic	23,012 (30.8)	2.01 (1.91 to 2.11)	2.07 (1.97 to 2.18)
Hospital (200–499 beds)-based clinic	9,327 (28.2)	1.77 (1.68 to 1.89)	1.71 (1.62 to 1.80)
Hospital (≥ 500 beds)-based clinic	2,064 (18.2)	1	1

CI, confidence interval

*Acute upper respiratory infections include viral upper respiratory infections, pharyngitis, bronchitis, and sinusitis.

Table 5. Factors associated with antibiotic prescription for gastrointestinal infections

Characteristics	Antibiotic prescription, n (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Patient age			
0–9	10,809 (37.0)	1.92 (1.86 to 1.98)	1.76 (1.71 to 1.82)
10–19	4,395 (38.7)	2.07 (1.98 to 2.16)	1.92 (1.83 to 2.00)
20–64	12,310 (32.4)	1.57 (1.53 to 1.61)	1.55 (1.51 to 1.60)
≥ 65	13,795 (23.4)	1	1
Patient sex			
Male	18,547 (30.9)	1.09 (1.06 to 1.12)	1.04 (1.01 to 1.06)
Female	21,831 (29.1)	1	1
Facility type			
Free-standing clinic	33,712 (32.9)	2.03 (1.82 to 2.27)	1.88 (1.68 to 2.10)
Hospital (< 200 beds)-based clinic	4,056 (21.7)	1.15 (1.02 to 1.29)	1.17 (1.04 to 1.32)
Hospital (200–499 beds)-based clinic	2,214 (18.9)	0.97 (0.86 to 1.09)	0.93 (0.82 to 1.05)
Hospital (≥ 500 beds)-based clinic	396 (19.4)	1	1

CI, confidence interval

References

1. de Kraker ME, Wolkewitz M, Davey PG et al. Clinical impact of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay related to methicillin-resistant Staphylococcus aureus bloodstream infections. Antimicrob Agents Chemother 2011; 55: 1598-605.

2. Stewardson AJ, Allignol A, Beyersmann J et al. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and 2011: a multicentre retrospective cohort study. Euro Surveill 2016; 21: pii=30319.

3. Ammerlaan HS, Harbarth S, Buiting AG et al. Secular trends in nosocomial bloodstream infections: antibiotic-resistant bacteria increase the total burden of infection. Clin Infect Dis 2013; 56: 798-805.

4. World Health Organization. Global action plan on antimicrobial resistance. Available at: http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf?ua=1 (Accessed: August 3, 2018).

5. The Government of Japan. National Action Plan on Antimicrobial Resistance (AMR)

2016-2020. Available at: https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000138942.pdf. (Accessed: August 3, 2018).

6. Tacconelli E. Antimicrobial use: risk driver of multidrug resistant microorganisms in healthcare settings. Curr Opin Infect Dis 2009; 22: 352-8.

7. Muraki Y, Yagi T, Tsuji Y et al. Japanese antimicrobial consumption surveillance: First report on oral and parenteral antimicrobial consumption in Japan (2009-2013). J Glob Antimicrob Resist 2016; 7: 19-23.

8. Yoshida S, Takeuchi M, Kawakami K. Prescription of antibiotics to pre-school children from 2005 to 2014 in Japan: a retrospective claims database study. J Public Health (Oxf) 2018; 40: 397-403.

9. Higashi T, Fukuhara S. Antibiotic prescriptions for upper respiratory tract infection in Japan. Intern Med 2009; 48: 1369-75.

10. The Government of Japan, Ministry of Health, Labour and Welfare. Manual of Antimicrobial Stewardship (1st Edition). Available at: http://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000193504.pdf. (Accessed: August 3, 2018).

11. Kumamoto prefectural government. 2012 Kumamoto National Health Insurance business situation report. Available at: http://www.pref.kumamoto.jp.e.qp.hp.transer.com/kiji_2735.html (Accessed: August 3, 2018).

12. Kumamoto prefectural government. The situation such as Kumamoto elderly aged 75 or over medical expenses. Available at: http://www.pref.kumamoto.jp.e.qp.hp.transer.com/kiji_13777.html (Accessed: August 3, 2018).

13. Fleming-Dutra KE, Hersh AL, Shapiro DJ et al. Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. JAMA 2016; 315: 1864-73.

14. Hicks LA, Bartoces MG, Roberts RM et al. US outpatient antibiotic prescribing variation according to geography, patient population, and provider specialty in 2011. Clin Infect Dis 2015; 60: 1308-16.

15. ESAC-Net surveillance data. Surveillance of antimicrobial consumption in Europe. Available at: http://ecdc.europa.eu/en/publications/Publications/antimicrobial-consumption-europe-esac-net-2012.pdf (Accessed: August 3, 2018).

16. Shapiro DJ, Hicks LA, Pavia AT et al. Antibiotic prescribing for adults in ambulatory

care in the USA, 2007-09. J Antimicrob Chemother 2014; 69: 234-40.

17. Dolk FCK, Pouwels KB, Smith DRM et al. Antibiotics in primary care in England: which antibiotics are prescribed and for which conditions? J Antimicrob Chemother 2018; 73: ii2-ii10.

18. Harris AM, Hicks LA, Qaseem A. Appropriate Antibiotic Use for Acute Respiratory Tract Infection in Adults: Advice for High-Value Care From the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med 2016; 164: 425-34.

19. Bisno AL. Acute pharyngitis: etiology and diagnosis. Pediatrics 1996; 97: 949-54.

20. Ebell MH, Smith MA, Barry HC et al. The rational clinical examination. Does this patient have strep throat? JAMA 2000; 284: 2912-8.

21. Butler CC, Rollnick S, Pill R et al. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. BMJ 1998; 317: 637-42.

22. Kumar S, Little P, Britten N. Why do general practitioners prescribe antibiotics for sore throat? Grounded theory interview study. BMJ 2003; 326: 138.

23. Brookes-Howell L, Hood K, Cooper L et al. Understanding variation in primary medical care: a nine-country qualitative study of clinicians' accounts of the non-clinical factors that shape antibiotic prescribing decisions for lower respiratory tract infection. BMJ Open. 2012; 2: e000796.

24. Tonkin-Crine S, Yardley L, Little P. Antibiotic prescribing for acute respiratory tract infections in primary care: a systematic review and meta-ethnography. J Antimicrob Chemother. 2011; 66: 2215-23.

25. O'Connor R, O'Doherty J, O'Regan A et al. Antibiotic use for acute respiratory tract infections (ARTI) in primary care; what factors affect prescribing and why is it important? A narrative review. Ir J Med Sci. 2018; 187: 969-86.

26. Adriaenssens N, Coenen S, Tonkin-Crine S, et al. European Surveillance of Antimicrobial Consumption (ESAC): disease-specific quality indicators for outpatient antibiotic prescribing. BMJ Qual Saf 2011; 20: 764-72.

27. Lee ML, Cho CY, Hsu CL, et al. Recent trends in antibiotic prescriptions for acute respiratory tract infections in pediatric ambulatory care in Taiwan, 2000-2009: A nationwide population-based study. J Microbiol Immunol Infect 2016; 49: 554-60.

28. Silverman M, Povitz M, Sontrop JM, et al. Antibiotic Prescribing for Nonbacterial Acute Upper Respiratory Infections in Elderly Persons. Ann Intern Med 2017; 166: 765-74.

29. Akkerman AE, van der Wouden JC, Kuyvenhoven MM et al. Antibiotic prescribing for respiratory tract infections in Dutch primary care in relation to patient age and clinical entities. J Antimicrob Chemother 2004; 54: 1116-21.

30. Schmidt ML, Spencer MD, Davidson LE. Patient, Provider, and Practice Characteristics Associated with Inappropriate Antimicrobial Prescribing in Ambulatory Practices. Infect Control Hosp Epidemiol. 2018; 39: 307-15.

Table S1. Classification of infections by groups with corresponding ICD-10 codes

	Diagnosis	ICD-10 codes
Group 1: Infections for which antibiotics are usually indicated		
1	Miscellaneous bacterial infections	Tuberculosis (A15–A19); Certain zoonotic bacterial diseases (A20–A28); Other bacterial diseases including listeriosis, diphtheria, bartonellosis, erysipelas, and rickettsioses (A30–A37, A39–A49, A75–A79); Bacterial meningitis, encephalitis, and intracranial abscess (G00, G042, G049, G06); Mastoiditis (H70); Infective endocarditis (I33, T826); Acute epiglottitis (J051); Deep neck space infections (J36, J390, J391); Abscess of lung and mediastinum; Pyothorax (J85, J86); Infections of the jaws and mouth (K102, K122); Infections due to cardiac and vascular devices (T827); Infection due to internal prosthetic devices, implants and grafts (T857)
2	Sexually transmitted infections	Infections with a predominantly sexual mode of transmission (A50–A64); Other spirochetal diseases (A65–A69); Other diseases caused by chlamydia (A70–A74)
3	Pneumonia	Bacterial pneumonia (J13–J18)
4	Abdominal infections	Acute appendicitis (K35); Abscess of anal and rectal regions, intestine, and liver (K61, K630, K750); Peritonitis (K65); Cholecystitis and cholangitis (K800, K801, K803, K804, K810, K819, K830)
5	Orthopedic infections	Pyogenic arthritis and prosthetic joint infection (M00, T845); necrotizing fasciitis (M726); Infective myositis, synovitis and bursitis (M600, M650–M651, M710–M711); Osteomyelitis (M462–M465, M86)
6	Urinary tract infections	Acute pyelonephritis/pyonephrosis ((N10, N12, N136); Renal abscess (N151); Kidney infection, unspecified (N159); Acute cystitis (N300); Cystitis, unspecified (N308, N309); Urethritis and urethral abscess (N34); Urinary tract infections, unspecified (N390); Prostatitis and abscess of prostate (N41); Orchitis and epididymitis (N45); Catheter

		associated urinary tract infections (T835)
7	Pelvic inflammatory diseases	Pelvic inflammatory diseases (N70–N73, N751, N760–N764); Infections of genitourinary tract in pregnancy (O23)
Group 2：Infections for which antibiotics are potentially indicated		
1	Gastrointestinal infections	Intestinal infectious diseases (A00–A07, A09); Diverticulitis of intestine (K57)
2	Skin, cutaneous and mucosal infections	Infections of other skin and subcutaneous tissue including cellulitis, cutaneous abscess, furuncle, carbuncle, impetigo, acute lymphadenitis, folliculitis, mastitis (H050, J340, L00–L08, N61, T814); Infections of the eye and adnexa (H00, H440); Infective otitis externa (H600–H603)
3	Suppurative otitis media	Suppurative and unspecified otitis media (H66)
4	Pharyngitis	Streptococcal pharyngitis/tonsillitis (J020, J030); Acute pharyngitis/tonsillitis, unspecified (J029, J039); Scarlet fever (A38)
5	Sinusitis	Acute sinusitis (J01); Chronic sinusitis (J32)
6	Bronchitis and bronchiolitis with COPD	Acute bronchitis (J20) *; Acute bronchiolitis (J21) *; Unspecified acute lower respiratory infection (J22) *
7	Acne	Acne (L70)
Group 3: Infections for which antibiotics are rarely indicated		
1	Nonbacterial gastrointestinal infections	Viral and other specified intestinal infections (A08)
2	Nonsuppurative otitis media	Nonsuppurative otitis media (H65)
3	Viral upper respiratory infection	Acute nasopharyngitis [common cold] (J00); Acute pharyngitis/tonsillitis due to other specified organisms (J028, J038); Acute laryngitis and tracheitis (J04); Acute obstructive laryngitis [croup] (J050); Acute upper respiratory infections of multiple and unspecified sites (J06); Cough (R05)
4	Influenza	Influenza (J10, J11)
5	Viral pneumonia	Viral pneumonia (J12)
6	Bronchitis and bronchiolitis without	Acute bronchitis (J20) **; Acute bronchiolitis (J21) **; Unspecified acute lower respiratory infection (J22) **

	COPD	
7	Noninfectious diarrhea	Noninfective gastroenteritis and colitis, unspecified (K529)
8	Fever	Fever of unknown origin (R50)

*includes visits in which ICD-10 code for COPD (J41–J44) are present

**includes visits in which ICD-10 code for COPD (J41–J44) are not present

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7–8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8–9
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9–10
		(*b*) Describe any methods used to examine subgroups and interactions	9–10
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12–13
		(*b*) Report category boundaries when continuous variables were categorized	11–13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	14–18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18–19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19–20
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.