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# BMJ Open

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

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Manuscripts

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9 2 **retrospective claims database study**  
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37 28 **Key words:** antibiotic, antimicrobial stewardship, antimicrobial-resistance, big data,  
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39 29 inappropriate prescribing  
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42 30 **Running title:** Antibiotic prescriptions in Japan  
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6 33 **Abstract**

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9 34 **Objectives:** To investigate antibiotic prescribing patterns and identify factors associated  
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12 35 with antibiotic prescriptions, with the aim of reducing inappropriate use.

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15 36 **Design:** Retrospective cohort study.

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18 37 **Setting:** Database of public health insurance claims in Kumamoto prefecture (Japan).

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21 38 **Participants:** Individuals who joined the national or late elders' health insurance  
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24 39 system between April 2012 and March 2013.

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27 40 **Main outcome measures:** Of 7,770,481 patients, 682,822 had a code for antibiotics.

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30 41 Third-generation cephalosporins (35%), macrolides (32%), and quinolones (21%) were

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33 42 most frequently prescribed. Acute respiratory tract infections (ARTIs), including viral

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36 43 upper respiratory infections (URI) (22%), pharyngitis (18%), bronchitis (11%), and

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39 44 sinusitis (10%) were most frequently diagnosed for antibiotic prescribing; then,

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42 45 gastrointestinal infections (9%), urinary tract infections (8%); and skin, cutaneous, and

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45 46 mucosal infections (5%). Antibiotic prescribing rates for viral URI, pharyngitis,

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48 47 bronchitis, sinusitis, and gastrointestinal infections were 35%, 54%, 53%, 57%, and

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51 48 30%, respectively. In multivariable analysis for ARTIs and gastrointestinal infections,

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6 49 patient age (10–19 years especially), gender (male), and facility scale (clinic or  
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9 50 small-sized hospital visits) were associated with increased antibiotic prescribing.

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12 51 **Conclusions:** Broad-spectrum antibiotics constituted 88% of oral antibiotic  
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15 52 prescriptions. Approximately 70% of antibiotics were prescribed for ARTIs and  
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18 53 gastroenteritis with modest benefit from antibiotic treatment. The quality of antibiotic  
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21 54 prescribing needs to be improved. Antimicrobial stewardship interventions should target  
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24 55 ARTIs and gastroenteritis, as well as young patients and small-sized institution groups.  
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6 **57 Strength and limitations of this study**  
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9 • 58 This is the first Japanese study to describe antibiotic prescription patterns linked to  
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12 59 individual diagnoses data, comprehensively, by use of the public health insurance  
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15 60 claims database.  
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18 • 61 This study included patients older than 65 years of age, who were hardly included  
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21 62 in previous Japanese studies.  
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24 • 63 The accuracy of the diagnosis has not been validated due to the nature of the  
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27 64 administrative claims database.  
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31 • 65 There are some unmeasured potential confounding factors such as out-of-hour  
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34 66 visits and physician specialty.  
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6 **68 Introduction**  
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9 **69** There is a growing concern about infections by antimicrobial-resistant bacteria.  
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12 **70** Antimicrobial resistance results in increased health care costs, prolonged hospitalization,  
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15 **71** and death.<sup>1-3</sup> The World Health Organization launched the global action plan to combat  
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18 **72** the antimicrobial-resistant bacteria in 2015<sup>4</sup> and requested Member States to endorse  
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21 **73** national action plans within two years. The government of Japan launched a national  
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24 **74** action plan in 2016 in response to the request.<sup>5</sup>  
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28 **75** Since antimicrobial use is one of the important factors in the emergence of  
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31 **76** antimicrobial resistance,<sup>6</sup> it is essential to reduce the inappropriate use of antibiotics. In  
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34 **77** Japan, a previous study, based on sales data, revealed that oral antibiotics accounts for  
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37 **78** more than 90% of the total antibiotic consumption and that broad-spectrum antibiotics  
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40 **79** (third-generation cephalosporins, macrolides, and fluoroquinolones) accounts for 77%  
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43 **80** of oral antibiotic consumption (daily doses defined per 1,000 inhabitants per day).<sup>7</sup> The  
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46 **81** Japanese national action plan aims to reduce the total antimicrobial use to two-thirds,  
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49 **82** and the use of oral cephalosporins, quinolones, and macrolides to one-half, by 2020. To  
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52 **83** accomplish the reduction of inappropriate antimicrobial use, it is important to determine  
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6 84 the antimicrobial prescribing patterns and factors associated with antibiotic prescription.  
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9 85 However, such information is limited in Japan to date. Although a few recent studies<sup>8,9</sup>  
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12 86 described the prescription patterns for upper respiratory tract infections and bronchitis,  
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15 87 the prescription patterns of infections other than acute respiratory tract infections  
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18 88 (ARTIs) have not been clarified. In addition, patients older than 65 years of age were  
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21 89 hardly included in these studies; because these studies relied on data from  
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24 90 employee-based insurance claims database. With the high rate in aging population in  
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27 91 Japan, it is important to describe the prescription patterns in the elderly.

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31 92 In this study, we described oral antibiotic prescribing patterns for all infections and in  
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34 93 all ages, using Japanese administrative claims database. Also, we aimed to identify  
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37 94 factors associated with antibiotic prescriptions for ARTIs and gastrointestinal infections,  
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40 95 the targets of the antimicrobial stewardship guideline formulated by the government of  
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43 96 Japan.<sup>10</sup>

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6 98 **Methods**

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9 99 *Data sources*

10 We conducted a retrospective analysis using the administrative health insurance  
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15 101 claims database of Kumamoto prefecture, situated in the southwestern region of Japan,  
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18 102 with a population of about 1.7 million. This database covers approximately 780,000  
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21 103 residents of Kumamoto prefecture who joined the national health insurance system (for  
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24 104 those younger than 75 years of age),<sup>11</sup> or the late elders' health insurance system (for  
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27 105 those aged 75 years and older).<sup>12</sup>

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31 106 The database is composed of medical (inpatient and outpatient) and pharmacy claims.  
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34 107 It provides monthly information about patient demographics (year and month of birth  
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37 108 and gender), diagnoses, date of diagnoses, medical procedures, medications, scale  
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40 109 (number of beds) of the medical facility, as well as the identification numbers assigned  
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43 110 to each individual, medical facility, and dispensing pharmacy. The diagnoses were  
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46 111 coded according to the International Classification of Diseases and Related Health  
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49 112 Problems, 10th Revision (ICD-10).

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6 114 *Data preparation*  
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9 115 We linked the medical and pharmacy claims, on the database, using an identification  
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12 116 number unique to each patient, medical facility, and dispensing pharmacy. We identified  
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15 117 all newly diagnosed outpatients, with any infectious diseases, between April 2012 and  
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18 118 March 2013. Infectious diseases diagnoses are categorized according to the indication  
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21 119 for antibiotic use (Table S1, available as supplementary data). This categorization is  
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24 120 based on the study by Fleming-Dutra KE *et al.*<sup>13</sup> Bronchitis and bronchiolitis were  
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27 121 divided into two categories based on whether the patients had chronic obstructive  
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30 122 pulmonary disease (COPD) as comorbidity or not, because of differing need of  
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33 123 treatment with antibiotics. If a patient had multiple infectious diagnoses in one month, a  
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36 124 single infectious diagnosis, selected in order from Group 1 (antibiotics are usually  
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39 125 indicated) to Group 3 (antibiotics are rarely indicated), and the first-listed diagnosis in  
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42 126 alphabetical order of ICD-10 codes in the selected group; was included in the analyses  
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45 127 (Table S1).

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49 128 We also identified all outpatients with any antibiotic prescriptions. Topical,  
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52 129 intramuscular, and intravenous antibiotics were excluded. Antibiotics were categorized  
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6 130 according to the Anatomical Therapeutic Chemical (ATC) classification system  
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9 131 (<http://www.whooc.no/atcddd/>) into: tetracyclines (J01A), penicillins (J01C), first- and  
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12 132 second-generation cephalosporins (J01DB and J01DC), third-generation cephalosporins  
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15 133 (J01DD), sulphonamides and trimethoprim (J01E), macrolides (J01FA), quinolones  
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18 134 (J01M), and others (J01B, J01DH, J01DI, J01FF, J01G, and J01X). We assumed that  
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21 135 third-generation cephalosporins accounted for most of cephalosporins used in Japan;  
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24 136 hence, we divided cephalosporins into two groups: first/second- and third-generation  
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28 137 cephalosporins.  
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### 34 139 *Data Analysis*

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37 140 We calculated the frequency of antibiotic prescription for all visits with infections  
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40 141 (according to diagnosis and antibiotic class). For ARTIs (including pharyngitis, sinusitis,  
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43 142 bronchitis/bronchiolitis, and viral upper respiratory infections [URI]) and  
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46 143 gastrointestinal infections separately, we performed multivariable logistic regression  
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50 144 analyses to identify the factors associated with antibiotic prescriptions. The variables  
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53 145 were as follows: age and gender of patients and scale (number of beds) of the medical  
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6 146 facilities. Generalized estimating equations with exchangeable correlation structure  
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9 147 were used to account for the clustering of the medical facilities. *P*-values < 0.05 were  
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12 148 considered statistically significant. All statistical analyses were performed with the  
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15 149 statistical package R, v.3.5.0 (<http://cran.r-project.org>).  
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22 151 *Patient involvement*  
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24 152 No patients were involved in the development of the research question or the outcome  
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28 153 measures, nor were they involved in developing plans for design or implementation of  
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31 154 the study. No patients were asked to advise on interpretation or writing up of results.  
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34 155 There are no plans to disseminate the study results to the relevant patient community.  
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6 157 **Results**  
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9 158 In total, there were 7,770,481 patients between April 2012 and March 2013.  
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12 159 Antibiotics were prescribed in 682,822 patients. Among these, third-generation  
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15 160 cephalosporins were most frequently prescribed (237,372 patients, 35%), followed by  
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18 161 macrolides (215,656 patients, 32%) and quinolones (145,135 patients, 21%). This trend  
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21 162 was observed regardless of age group (Table 1) and scale of the medical facility (Table  
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24 163 2), except with those less than 9 years of age in whom the systemic use of quinolones is  
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27 164 not recommended. Information about facility scale was available from 669,086 out of  
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30 165 682,822 patients. Of these, antibiotics were prescribed most frequently at clinics  
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33 166 (530,916 patients, 79%), followed by small-sized (< 200 beds; 78,546 patients, 12%),  
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36 167 medium-sized (200–499 beds; 45,271 patients, 7%), and large-sized (500 beds or more;  
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39 168 14,353 patients, 2%) hospitals (Table 2).  
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43 169 We could link the individual diagnoses to the antibiotic prescription in 447,232  
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46 170 patients (Table 3). Of these patients, approximately 60% of antibiotics were prescribed  
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49 171 for ARTIs; viral URI (96,989 patients, 22%), followed by pharyngitis (78,469 patients,  
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52 172 18%), bronchitis without COPD (47,248 patients, 11%), and sinusitis (45,456 patients,  
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6 173 10%). Other than ARTIs, there were frequent antibiotic prescriptions for gastrointestinal  
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9 174 infections (41,309 patients, 9%), urinary tract infections (37,674 patients, 8%), and skin,  
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12 175 cutaneous, and mucosal infections (23,572 patients, 5%). The antibiotic prescription  
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15 176 rates for viral URI, pharyngitis, bronchitis (without underlying COPD), sinusitis, and  
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18 177 gastrointestinal infections were 35% (96,989 out of 274,441 patients), 54% (78,469 out  
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21 178 of 146,508 patients), 53% (47,248 out of 89,479 patients), 57% (45,456 out of 80,078  
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24 179 patients), and 30% (41,309 out of 137,661 patients), respectively (Table 3).

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28 180 Table 4 shows the results of the logistic regression analysis about antibiotic  
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31 181 prescription for ARTIs. Male gender was associated with more antibiotic prescription  
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34 182 (adjusted odds ratio [OR], 1.10; 95% confidence interval [CI], 1.08 to 1.11). With  
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37 183 patients aged 65 years or older as reference, patients aged 10 to 19 years were more  
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40 184 likely to be prescribed antibiotics (adjusted OR, 2.75; 95% CI, 2.69 to 2.82), followed  
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43 185 by patients aged 20 to 64 years (adjusted OR, 1.92; 95% CI, 1.89 to 1.94), and patients  
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46 186 younger than 10 years (adjusted OR, 1.48; 95% CI, 1.46 to 1.50). With facility scale,  
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49 187 with large-sized (500 beds or more) hospitals as reference, clinic (adjusted OR, 4.24;  
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52 188 95% CI, 4.03 to 4.45), small-sized (< 200 beds) hospitals (adjusted OR, 2.07; 95% CI,  
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6 189 1.97 to 2.18), and medium-sized (200–499 beds) hospitals (adjusted OR, 1.71; 95% CI,  
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9 190 1.62 to 1.80) were significantly associated with more antibiotic prescription.

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12 191 Similar results were shown with the logistic regression analysis for gastrointestinal  
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15 192 infections (Table 5). Male gender was associated with slightly more antibiotic  
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18 193 prescription (adjusted OR, 1.04; 95% CI, 1.01 to 1.06) than female gender. Patients  
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21 194 aged 10 to 19 years (adjusted OR, 1.92; 95% CI, 1.83 to 2.00), 20 to 64 years (adjusted  
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24 195 OR, 1.55; 95% CI, 1.51 to 1.60), and younger than 10 years (adjusted OR, 1.76; 95% CI,  
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27 196 1.71 to 1.82) received more antibiotic prescriptions compared with patients aged 65  
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30 197 years or older. With reference to large-sized ( $\geq 500$  beds) hospital, clinic (adjusted OR,  
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33 198 1.88; 95% CI, 1.68 to 2.10) and small-sized ( $< 200$  beds) hospital (adjusted OR, 1.17;  
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36 199 95% CI, 1.04 to 1.32) were associated with frequent antibiotic prescription for  
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39 200 gastrointestinal infections.

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6       202    **Discussion**

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9       203    We described oral antibiotic prescription patterns in outpatient care setting, in Japan.  
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12       204    To the best of our knowledge, this is the first Japanese study to comprehensively  
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15       205    describe antibiotic prescription patterns linked to individual diagnoses data, by use of  
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18       206    the claims database. Broad-spectrum antibiotics consisting of third-generation  
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21       207    cephalosporins, macrolides, and quinolones accounted for nearly 90% of antibiotic  
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24       208    prescriptions in the primary care settings. Prescription of penicillin, a representative  
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27       209    narrow-spectrum antibiotic, was only 5%. This prescription pattern is consistent with  
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30       210    the results of an analysis of antibiotic sales data in Japan in which 77% of oral  
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33       211    antibiotics shipped, were broad-spectrum.<sup>7</sup> In contrast, the use of cephalosporins,  
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36       212    macrolides, and quinolones in the United States of America (USA) and Europe were  
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39       213    much lower than Japan. Hicks *et al.*<sup>14</sup> analyzed the sales data of oral antibiotics in the  
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42       214    USA and showed that cephalosporins, macrolides, and quinolones accounted for 48% of  
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45       215    the total oral antibiotics. In their study, penicillin had the largest share of the antibiotics  
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48       216    (23%). Data from the European Surveillance of Antimicrobial Consumption project<sup>15</sup>  
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51       217    also showed that cephalosporins, macrolides, and quinolones accounted for about one  
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6 218 third of the total oral antibiotic consumptions, in Europe. This study demonstrated a  
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9 219 rather high ratio of broad-spectrum to narrow-spectrum oral antibiotics, in Japan;  
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12 220 therefore, the quality of antibiotic prescribing needs to be improved.  
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15 221 Among antibiotics linked with individual diagnosis data, over 60% of antibiotics were  
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18 222 prescribed for ARTIs, followed by gastrointestinal infections (9%), urinary tract  
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21 223 infections (8%); and skin, cutaneous, and mucosal infections (5%). Surprisingly, viral  
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24 224 URI (common cold) was the most frequent infection associated with antibiotic  
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28 225 prescription. In the ambulatory care setting in the USA, antibiotics were prescribed  
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31 226 most frequently for acute respiratory conditions (41–44%), followed by skin and  
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34 227 mucosal conditions (15–19%), urinary tract infections (7–8%), and gastrointestinal  
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37 228 conditions (5–6%).<sup>13,16</sup> Another study using primary care data in the United Kingdom  
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40 229 (UK)<sup>17</sup> demonstrated that 46% of antibiotics were prescribed for respiratory tract  
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43 230 conditions, followed by urogenital tract (23%), and skin conditions (10%). Only 1%  
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46 231 was prescribed for gastrointestinal conditions. Our study demonstrated a higher  
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50 232 proportion of antibiotic prescription for ARTIs (approximately 15% higher than those in  
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53 233 USA or UK) and gastrointestinal infections (approximately 5% higher), in Japan.  
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6 234 Antibiotics were prescribed for 35% of viral URI and approximately 50–60% of  
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9 235 pharyngitis, bronchitis, and sinusitis in our study. These prescription rates were  
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12 236 approximately similar to the USA study results;<sup>13</sup> showing a rate of 30% for viral URI,  
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15 237 62% for pharyngitis, 65% for bronchitis, and 72% for sinusitis. Medically, antibiotics  
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18 238 are rarely indicated for ARTIs.<sup>18</sup> Antibiotics have no role in the treatment of both viral  
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21 239 URI (common cold) and the majority of acute bronchitis, which are caused by viral  
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24 240 infection. Only a minority of patients with bronchitis (< 10%), for example patients who  
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28 241 have underlying COPD or whooping cough, may derive any benefit from antibiotic  
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31 242 treatment. With pharyngitis, antibiotics are mainly indicated only for streptococcal  
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34 243 pharyngitis, which account for 5%–15% of pharyngitis in adults and 20%–30% in  
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37 244 children.<sup>19,20</sup>

40 245 The antibiotic prescription rate for gastrointestinal infections was 3 times higher than  
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43 246 the rate reported in the USA (30% vs 10%).<sup>13</sup> As most acute gastroenteritis are  
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47 247 self-limiting, Japanese national guideline recommended the non-usage of antibiotics for  
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50 248 gastroenteritis unless symptoms are severe.<sup>10</sup> Based on our study, approximately 70% of  
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53 249 oral antibiotics are prescribed for ARTIs or acute gastroenteritis; however, most (>

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6 250 80%), did not require antibiotics. Therefore, there is need for suitable targets for the  
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9 251 reduction of unnecessary antibiotic use in accordance with antimicrobial stewardship  
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12 252 program.

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15 253 The logistic regression analyses revealed several factors associated with antibiotic  
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18 254 prescriptions for ARTIs and gastrointestinal infections. The smaller the facility scale,  
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21 255 the higher the odds of antibiotic prescribing observed. Recent studies from Japan<sup>8</sup> and  
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24 256 Taiwan<sup>21</sup> have found similar results. As family practitioners, pediatricians, and internists  
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28 257 usually prescribe a high number of antibiotic courses,<sup>14</sup> greater adherence to treatment  
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31 258 guidelines among physicians in these specialties is particularly important. It has also  
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34 259 been reported that mid- or late-career stage physicians (because the effect of training  
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37 260 received during medical education might have reduced, after this long time) were more  
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40 261 likely to prescribe antibiotics for nonbacterial acute URI.<sup>22</sup>

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43 262 Patient age was another factor associated with antibiotic prescription. In this study,  
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46 263 antibiotic prescription rates for ARTIs and gastrointestinal infections were highest in  
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49 264 patients aged 10–19 years, followed by patients aged 20–64 years (ARTIs) or 0–9 years  
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53 265 (gastrointestinal infections). A previous study in Dutch primary care showed similar  
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6 266 results of antibiotic over-prescribing for ARTIs in patients aged 31–65 years (i.e., not in  
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9 267 children or the elderly).<sup>23</sup> As adolescents and young adults generally pose a much lower  
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12 268 risk of disease complications than young children or elderly, antimicrobial stewardship  
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15 269 should be focused on these age groups of patients. In this study, male sex was also  
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18 270 associated with increased antibiotic prescribing. Although sex difference was observed  
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21 271 in another study, the results differed; females were more likely to have high prescribing  
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24 272 in the USA.<sup>14</sup>

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28 273 Our study has several limitations. First, our results do not represent the entire  
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31 274 antibiotic prescription patterns in Japan because the claims database used in this study  
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34 275 was composed of claims in only one prefecture. Geographical diversity may be present,  
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37 276 as observed in the previous study from the USA.<sup>14</sup> Second, since we used an  
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40 277 administrative claims database; the accuracy of the diagnosis was not validated. In  
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43 278 addition, we could not link diagnosis and antibiotic prescriptions on a one-to-one level  
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46 279 when patients had multiple infectious diagnoses. Third, there may be other potential  
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50 280 confounding factors that were not included in this study. For example, information on  
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53 281 out-of-hour visits,<sup>8</sup> non-physician practitioners or non-specialty physician,<sup>8, 21, 24</sup> and  
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6 282 patient's low-per capita income, black race, or low-education,<sup>14</sup> which have been  
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9 283 reported as potential factors associated with inappropriate antibiotics prescribing, could  
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12 284 not be extracted from the claims database in this study. Fourth, we found no follow-up  
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15 285 visit when patients had multiple visits for a single infection. Consequently,  
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18 286 inappropriate antibiotic prescription might be underestimated rather than overestimated.

21 287 In conclusion, this Japanese study demonstrated that third-generation cephalosporins,  
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24 288 macrolides, and quinolones accounted for 88% of oral antibiotic prescription.  
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28 289 Approximately 60% of antibiotic prescription was provided for ARTIs, with viral URI  
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31 290 and pharyngitis being the two ARTI diagnoses with the largest antibiotic prescriptions.  
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34 291 Gastrointestinal infections were the second most common diagnosis for antibiotic  
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37 292 prescribing. The scale of the facilities (clinic or small-sized hospital) and patient age  
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40 293 (adolescents and young adults) were factors associated with antibiotic over-prescription.  
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43 294 Antimicrobial stewardship interventions should focus on targeting antibiotic prescribing  
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46 295 for these infectious diagnoses, and patients and institution groups. Further nationwide  
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49 296 studies are needed to support our data, and longitudinal studies using medical-claims  
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52 297 data are needed to evaluate the effectiveness of antimicrobial stewardship.  
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6 298 **Authors' contributions**

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9 299 HH and SH conceived the study, interpreted the data and results, and drafted the  
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12 300 manuscript. HH, HM, YS, and HY collected, organized, and analyzed the data, and  
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15 301 performed statistical analyses. KK and RN conceived the study and collected and  
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18 302 interpreted the data. All authors critically revised the manuscript for intellectual content.  
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21 303 All authors read and approved the final manuscript.  
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37 308 Number 16K09254.  
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43 310 **Competing interests**

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46 311 None declared.  
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53 313 **Data sharing**

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6 314 No additional data available.  
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12 316 **Transparency declarations**  
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15 317 The lead author (the manuscript's guarantor) affirms that the manuscript is an honest,  
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18 318 accurate, and transparent account of the study reported; that no important aspects of the  
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21 319 study have been omitted; and that any discrepancies from the study as planned have  
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25 320 been explained.  
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31 322 **Ethical approval**  
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34 323 This study was approved by the Ethics Committee of the Jichi Medical University  
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37 324 (Number 17-002).  
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325 **Table 1.** Frequency of oral antibiotic prescriptions by age and antibiotic groups

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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

327 \*ATC: Anatomical Therapeutic Chemical

328 \*\*Penicillins, J01C; First-generation cephalosporins, J01DB; Second-generation cephalosporins,

329 J01DC; Third-generation cephalosporins, J01DD; Macrolides, J01FA; Quinolones, J01M;

330 Sulphonamides and trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH,

331 J01DI, J01FF, J01G, and J01X

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

333

Antibiotic groups coded by ATC** classification***	Number of visits with antibiotic prescription				
	Facility scale (clinic and hospitals)				All facilities
	Clinic	Small-sized (< 200 beds)	Medium-sized (200–499 beds)	Large-sized (≥ 500 beds)	
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

334 \*13,736 patients with antibiotic prescription were excluded due to missing data about facility scale.

335 \*\*ATC: Anatomical Therapeutic Chemical

336 \*\*\*Penicillins, J01C; First-generation cephalosporins, J01DB; Second-generation cephalosporins, J01DC; Third-generation cephalosporins, J01DD;

337 Macrolides, J01FA; Quinolones, J01M; Sulphonamides and trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH, J01DI, J01FF,

338 J01G, and J01X

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

340

Diagnoses	All visits	Visits with any antibiotic prescription and prescription rate (%)	Number of visits with antibiotic prescriptions by antibiotic groups*							
			Penicillins	1 <sup>st</sup> /2 <sup>nd</sup> cephem	3 <sup>rd</sup> cephem	Macrolide s	Quinolone s	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 1<sup>st</sup>/2<sup>nd</sup> cephem, first/second-generation cephalosporins; 3<sup>rd</sup> cephem, third-generation cephalosporins; ST, Sulphonamides and trimethoprim; STD, sexual  
 342 transmitted diseases; PID, pelvic inflammatory diseases; GI infections, gastrointestinal infections; COPD, chronic obstructive pulmonary disease; URI,  
 343 upper respiratory infections

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

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

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

348

Characteristics	Antibiotic prescription, n (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
<b>Patient age</b>			
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
<b>Patient sex</b>			
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
<b>Facility scale</b>			
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

349 CI, confidence interval

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

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

352

Characteristics	Antibiotic prescription, n (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
<b>Patient age</b>			
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
<b>Patient sex</b>			
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
<b>Facility type</b>			
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

353 CI, confidence interval

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27 425 Characteristics Associated with Inappropriate Antimicrobial Prescribing in Ambulatory  
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1 **Table S1.** Classification of infections by groups with corresponding ICD-10 codes  
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	Diagnosis	ICD-10 codes
<b>Group 1: Infections for which antibiotics are usually indicated</b>		
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)
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### 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)

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8	Fever	Fever of unknown origin (R50)
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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

For peer review only

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

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	9
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

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<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	11
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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	
		(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	
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026251.R1
Article Type:	Research
Date Submitted by the Author:	12-Dec-2018
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<b>Primary Subject Heading</b>:	Infectious diseases
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Manuscripts

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10 **2 retrospective claims database study**

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17 4 Hideki Hashimoto<sup>1</sup>, Hiroki Matsui<sup>2,3</sup>, Yusuke Sasabuchi<sup>2</sup>, Hideo Yasunaga<sup>2,3</sup>, Kazuhiko  
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39 28 **Key words:** antibiotic, antimicrobial stewardship, antimicrobial-resistance, big data,

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45 30 **Running title:** Antibiotic prescriptions in Japan

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48 31 **Word count for the main text:** 3,069 words

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7 **33 Abstract**  
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10 **34 Objectives:** To investigate oral antibiotic prescribing patterns and identify factors  
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13 **35** associated with antibiotic prescriptions, with the aim of guiding future interventions to  
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16 **36** reduce inappropriate prescribing.  
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20 **37 Design:** Retrospective cohort study.  
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23 **38 Setting:** Database of public health insurance claims in Kumamoto prefecture (Japan).  
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26 **39 Participants:** Beneficiaries of the national or late elders' health insurance system  
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30 between April 2012 and March 2013.  
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33 **41 Main outcome measures:** Of 7,770,481 outpatient visits, 682,822 had a code for  
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36 **42** antibiotics (860 antibiotic prescriptions per 1000 population). Third-generation  
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40 **43** cephalosporins (35%), macrolides (32%), and quinolones (21%) were most frequently  
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43 **44** prescribed. Acute respiratory tract infections (ARTIs), including viral upper respiratory  
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46 **45** infections (URI) (22%), pharyngitis (18%), bronchitis (11%), and sinusitis (10%) were  
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50 **46** most frequently diagnosed for antibiotic prescribing, followed by gastrointestinal (9%),  
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53 **47** urinary tract (8%), and skin, cutaneous, and mucosal infections (5%). Antibiotic  
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56 **48** prescribing rates for viral URI, pharyngitis, bronchitis, sinusitis, and gastrointestinal  
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7 49 infections were 35%, 54%, 53%, 57%, and 30%, respectively. In multivariable analysis  
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10 50 for ARTIs and gastrointestinal infections, patient age (10–19 years especially), patient  
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13 51 sex (male), and facility scale (free-standing clinics or small-scale hospital-based clinics)  
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16 52 were associated with increased antibiotic prescribing.  
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20 53 **Conclusions:** Broad-spectrum antibiotics constituted 88% of oral outpatient antibiotic  
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23 54 prescriptions. Approximately 70% of antibiotics were prescribed for ARTIs and  
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26 55 gastroenteritis with modest benefit from antibiotic treatment. The quality of antibiotic  
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29 56 prescribing needs to be improved. Antimicrobial stewardship interventions should target  
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33 57 ARTIs and gastroenteritis, as well as young patients and small-scale institutions.  
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7 **58 Strength and limitations of this study**  
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- 10 • This is the first Japanese study to describe outpatient antibiotic prescription patterns  
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13 60 linked to individual diagnosis data, comprehensively, by use of the public health  
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16 61 insurance claims database.  
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20 62 • This study included patients older than 65 years of age, who have not typically been  
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23 63 included in previous Japanese studies.  
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26 64 • The accuracy of the diagnosis has not been validated due to the nature of the  
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30 65 administrative claims database.  
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33 66 • There are some unmeasured potential confounding factors such as out-of-hours  
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36 67 visits and physician specialty.  
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## 69 Introduction

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

76 Since antimicrobial use is one of the important factors in the emergence of antimicrobial  
77 resistance,<sup>6</sup> it is essential to reduce the inappropriate use of antibiotics. In Japan, a  
78 previous sales data-based study revealed that oral antibiotics account for more than 90%  
79 of total antibiotic consumption and that broad-spectrum antibiotics (third-generation  
80 cephalosporins, macrolides, and fluoroquinolones) account for 77% of oral antibiotic  
81 consumption (daily doses defined per 1000 inhabitants per day).<sup>7</sup> The Japanese national  
82 action plan aims to reduce the total antimicrobial use to two-thirds of current use, and the  
83 use of oral cephalosporins, quinolones, and macrolides to one-half, by 2020. To reduce  
84 inappropriate antimicrobial use, it is important to determine the antimicrobial prescribing



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7 85 patterns and factors associated with antibiotic prescription. However, such information  
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13 87 prescription patterns for upper respiratory tract infections and bronchitis, the prescription  
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16 88 patterns of infections other than acute respiratory tract infections (ARTIs) have not been  
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20 89 clarified. In addition, patients older than 65 years of age have not been commonly  
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23 90 included in these studies, because these studies relied on data from an employee-based  
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26 91 insurance claims database. With the high rate in aging population in Japan, it is important  
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30 92 to describe the prescription patterns in elderly patients.

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33 93 In this study, we described outpatient oral antibiotic prescribing patterns for all  
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36 94 infections and in all ages, using the Japanese administrative claims database. Furthermore,  
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40 95 we aimed to identify factors associated with antibiotic prescriptions for ARTIs and  
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43 96 gastrointestinal infections, the targets of the antimicrobial stewardship guideline  
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46 97 formulated by the government of Japan in 2017.<sup>10</sup>

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7 **99 Methods**  
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10 *Data sources*  
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13 101 The current population of Japan is approximately 127 million. All citizens are enrolled  
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19 103 (for employees younger than 75 years of age), national health insurance system (for self-  
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23 104 employed or unemployed people younger than 75 years of age), and the late elders' health  
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26 105 insurance system (for those aged 75 years and older). In Japan, patients can visit any  
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29 106 clinic of their choice. All physicians working at any free-standing or hospital-based  
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33 107 clinics can provide primary care and prescribe antibiotics.  
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36 108 We conducted a retrospective analysis using the administrative health insurance claims  
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39 109 database of Kumamoto prefecture, situated in the southwestern region of Japan, with a  
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43 110 population of about 1.7 million. This database covers approximately 780,000 residents of  
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46 111 Kumamoto prefecture (44% of the population) who were beneficiaries of the national  
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49 112 health insurance system,<sup>11</sup> or the late elders' health insurance system.<sup>12</sup> The participants  
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53 113 in this study may be older than the general population of Japan.  
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56 114 The database is composed of medical and pharmacy claims. It provides monthly  
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7 115 information about patient demographics (year and month of birth and sex), diagnoses,  
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10 116 date of diagnoses, medical procedures, medications, scale (number of beds) of the  
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13 117 medical facility, as well as the identification numbers assigned to each individual, medical  
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16 118 facility, and dispensing pharmacy. At the end of each month, claims are registered from  
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19 119 each medical facility. The diagnoses were recorded by physicians of each medical facility  
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23 120 and coded according to the International Classification of Diseases and Related Health  
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33 123 *Data preparation*  
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36 124 We linked the medical and pharmacy claims on the database using an identification  
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40 125 number unique to each patient, medical facility, and dispensing pharmacy. We identified  
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43 126 all newly diagnosed outpatients, with any infectious diseases, between April 2012 and  
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46 127 March 2013. Infectious diseases diagnoses were categorized according to the indication  
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50 128 for antibiotic use (Table S1, available as supplementary data). This categorization was  
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53 129 based on the study by Fleming-Dutra KE *et al.*<sup>13</sup> Bronchitis and bronchiolitis were divided  
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56 130 into two categories based on whether the patients had chronic obstructive pulmonary  
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7 131 disease (COPD) as comorbidity or not, because of differing need of treatment with  
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10 132 antibiotics. If a patient had multiple infectious diagnoses in one month, a single infectious  
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13 133 diagnosis, selected in order from Group 1 (antibiotics are usually indicated) to Group 3  
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16 134 (antibiotics are rarely indicated), and the first-listed diagnosis in alphabetical order of  
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20 135 ICD-10 codes in the selected group was included in the analyses (Table S1).  
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23 136 We also identified all outpatients with any antibiotic prescriptions. Topical,  
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26 137 intramuscular, and intravenous antibiotics were excluded. Antibiotics were categorized  
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30 138 according to the Anatomical Therapeutic Chemical (ATC) classification system  
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33 139 (<http://www.whooc.no/atcddd/>) as follows: tetracyclines (J01A), penicillins (J01C), first-  
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36 140 and second-generation cephalosporins (J01DB and J01DC), third-generation  
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40 141 cephalosporins (J01DD), sulfonamides and trimethoprim (J01E), macrolides (J01FA),  
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43 142 quinolones (J01M), and others (J01B, J01DH, J01DI, J01FF, J01G, and J01X). We  
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46 143 assumed that third-generation cephalosporins accounted for most of cephalosporins used  
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50 144 in Japan; hence, we divided cephalosporins into two groups: first/second- and third-  
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53 145 generation cephalosporins. Antibiotics were linked to the infectious diagnoses in each  
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56 146 patient's claims when both the code of antibiotics and the code of diagnoses were  
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7 147 recorded in the same month.  
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13 149 *Data Analysis*  
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16 150 We calculated the frequency of antibiotic prescription for all visits with infections  
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20 151 (according to diagnosis and antibiotic class). For ARTIs (including pharyngitis, sinusitis,  
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23 152 bronchitis/bronchiolitis, and viral upper respiratory infections [URI]) and gastrointestinal  
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26 153 infections, we performed separate multivariable logistic regression analyses to identify  
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30 154 the factors associated with antibiotic prescriptions. The variables were as follows: age  
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33 155 and sex of patients and scale (number of beds) of the medical facilities. Generalized  
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36 156 estimating equations with exchangeable correlation structure were used to account for the  
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40 157 clustering of the medical facilities.  $P$ -values  $< 0.05$  were considered statistically  
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43 158 significant. All statistical analyses were performed with the statistical package R, v.3.5.0  
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46 159 (<http://cran.r-project.org>).  
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53 161 *Patient involvement*  
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56 162 No patients were involved in the development of the research question or the outcome  
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7 163 measures, nor were they involved in developing plans for design or implementation of  
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10 164 the study. No patients were asked for advice regarding the interpretation or writing of  
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13 165 results. There are no plans to disseminate the study results to the relevant patient  
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For peer review only

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7 **168 Results**  
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10 169 In total, there were 7,770,481 outpatient visits between April 2012 and March 2013.  
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13 170 Antibiotics were prescribed in 682,822 visits (860 antibiotic prescriptions per 1000  
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16 171 population). Among these, third-generation cephalosporins were most frequently  
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19 172 prescribed (237,372 visits, 35%), followed by macrolides (215,656 visits, 32%) and  
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23 173 quinolones (145,135 visits, 21%). This trend was observed regardless of age group (Table  
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26 174 1) and scale of the medical facility (Table 2), except for those less than 9 years of age in  
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29 175 whom the systemic use of quinolones is not recommended. Information about facility  
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33 176 scale was available from 669,086 out of 682,822 visits. Of these, antibiotics were  
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36 177 prescribed most frequently at free-standing clinics (530,916 visits, 79%), followed by  
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40 178 small-scale (< 200 beds; 78,546 visits, 12%), medium-scale (200–499 beds; 45,271 visits,  
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43 179 7%), and large-scale (500 beds or more; 14,353 visits, 2%) hospital-based clinics (Table  
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49 181 We were able to link the individual diagnoses to the antibiotic prescription in 447,232  
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53 182 visits (Table 3). Of these patients, approximately 60% of antibiotics were prescribed for  
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56 183 ARTIs, including viral URI (96,989 visits, 22%), pharyngitis (78,469 visits, 18%),  
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7 184 bronchitis without COPD (47,248 visits, 11%), and sinusitis (45,456 visits, 10%). Other  
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10 185 than ARTIs, there were frequent antibiotic prescriptions for gastrointestinal infections  
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13 186 (41,309 visits, 9%), urinary tract infections (37,674 visits, 8%), and skin, cutaneous, and  
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16 187 mucosal infections (23,572 visits, 5%). The antibiotic prescription rates for viral URI,  
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20 188 pharyngitis, bronchitis (without underlying COPD), sinusitis, and gastrointestinal  
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23 189 infections were 35% (96,989 out of 274,441 visits), 54% (78,469 out of 146,508 visits),  
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26 190 53% (47,248 out of 89,479 visits), 57% (45,456 out of 80,078 visits), and 30% (41,309  
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30 191 out of 137,661 visits), respectively (Table 3).

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33 192 Table 4 shows the results of the logistic regression analysis of antibiotic prescription for  
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36 193 ARTIs. Patient sex of male was associated with more antibiotic prescription (adjusted  
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40 194 odds ratio [OR], 1.10; 95% confidence interval [CI], 1.08 to 1.11). With patients aged 65  
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43 195 years or older as reference, patients aged 10 to 19 years were more likely to be prescribed  
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46 196 antibiotics (adjusted OR, 2.75; 95% CI, 2.69 to 2.82), followed by patients aged 20 to 64  
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50 197 years (adjusted OR, 1.92; 95% CI, 1.89 to 1.94), and patients younger than 10 years  
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53 198 (adjusted OR, 1.48; 95% CI, 1.46 to 1.50). Regarding facility scale, with large-scale (500  
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56 199 beds or more) hospital-based clinics as reference, free-standing clinics (adjusted OR,



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7 200 4.24; 95% CI, 4.03 to 4.45), small-scale (< 200 beds) hospital-based clinics (adjusted OR,  
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10 201 2.07; 95% CI, 1.97 to 2.18), and medium-scale (200–499 beds) hospital-based clinics  
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13 202 (adjusted OR, 1.71; 95% CI, 1.62 to 1.80) were significantly associated with more  
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16 203 frequent antibiotic prescription.  
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20 204 Similar results were shown with the logistic regression analysis for gastrointestinal  
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23 205 infections (Table 5). Patient sex of male was associated with slightly more antibiotic  
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26 206 prescription (adjusted OR, 1.04; 95% CI, 1.01 to 1.06) than was patient sex of female.  
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30 207 Patients aged 10 to 19 years (adjusted OR, 1.92; 95% CI, 1.83 to 2.00), 20 to 64 years  
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33 208 (adjusted OR, 1.55; 95% CI, 1.51 to 1.60), and younger than 10 years (adjusted OR, 1.76;  
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36 209 95% CI, 1.71 to 1.82) received more antibiotic prescriptions compared with patients aged  
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40 210 65 years or older. With reference to large-scale ( $\geq$  500 beds) hospital-based clinics, free-  
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43 211 standing clinics (adjusted OR, 1.88; 95% CI, 1.68 to 2.10) and small-scale (< 200 beds)  
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46 212 hospital-based clinics (adjusted OR, 1.17; 95% CI, 1.04 to 1.32) were associated with  
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50 213 frequent antibiotic prescription for gastrointestinal infections.  
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7 **215 Discussion**  
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10 216 We described oral antibiotic prescription patterns in the outpatient care setting in Japan.  
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13 217 To the best of our knowledge, this is the first Japanese study to comprehensively describe  
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16 218 antibiotic prescription patterns linked to individual diagnoses data, using the claims  
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19 219 database. Broad-spectrum antibiotics consisting of third-generation cephalosporins,  
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22 220 macrolides, and quinolones accounted for nearly 90% of antibiotic prescriptions in the  
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25 221 primary care settings. Prescription of penicillin was only 5%. This prescription pattern is  
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28 222 consistent with the results of an analysis of antibiotic sales data in Japan, in which 77%  
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31 223 of oral antibiotics shipped were broad-spectrum.<sup>7</sup> In contrast, the use of cephalosporins,  
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34 224 macrolides, and quinolones in the United States of America (USA) and Europe were  
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37 225 much lower than in Japan. Hicks *et al.*<sup>14</sup> analyzed the sales data of oral antibiotics in the  
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40 226 USA and showed that cephalosporins, macrolides, and quinolones accounted for 48% of  
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43 227 the total oral antibiotics. In their study, penicillin had the largest share of the antibiotics  
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46 228 (23%). Data from the European Surveillance of Antimicrobial Consumption project<sup>15</sup> also  
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49 229 showed that cephalosporins, macrolides, and quinolones accounted for about one third of  
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52 230 the total oral antibiotic consumptions, in Europe. This study demonstrated a rather high  
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7 231 ratio of broad-spectrum to narrow-spectrum oral antibiotics, in Japan; therefore, the  
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10 232 quality of antibiotic prescribing needs to be improved.  
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13 233 Although quinolones are not recommended for children, quinolones were prescribed as  
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16 234 much as penicillins in children aged 0–9 years in our study. This may be because oral  
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20 235 fluoroquinolones such as tosufloxacin are approved for children to treat otitis media and  
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23 236 pneumonia in Japan. Since the approval of quinolones in 2010, despite the  
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27 237 recommendation to prescribe quinolones carefully for children, many physicians  
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30 238 prescribed tosufloxacin to children in expectation of clinical effectiveness.  
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33 239 Among antibiotics linked with individual diagnosis data, over 60% of antibiotics were  
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36 240 prescribed for ARTIs, followed by gastrointestinal infections (9%), urinary tract  
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40 241 infections (8%), and skin, cutaneous, and mucosal infections (5%). Surprisingly, viral  
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43 242 URI (common cold) was the most frequent infection associated with antibiotic  
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47 243 prescription. In the ambulatory care setting in the USA, antibiotics were prescribed most  
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50 244 frequently for acute respiratory conditions (41–44%), followed by skin and mucosal  
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53 245 conditions (15–19%), urinary tract infections (7–8%), and gastrointestinal conditions (5–  
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56 246 6%).<sup>13,16</sup> Another study using primary care data in the United Kingdom (UK)<sup>17</sup>  
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7 247 demonstrated that 46% of antibiotics were prescribed for respiratory tract conditions,  
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10 248 followed by urogenital tract (23%), and skin conditions (10%). Only 1% was prescribed  
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13 249 for gastrointestinal conditions. Our study demonstrated a higher proportion of antibiotic  
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16 250 prescription for ARTIs (approximately 15% higher than those in USA or UK) and  
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20 251 gastrointestinal infections (approximately 5% higher) in Japan.

23 252 Antibiotics were prescribed for 35% of viral URI cases and approximately 50–60% of  
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26 253 pharyngitis, bronchitis, and sinusitis cases in our study. These prescription rates were  
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30 254 approximately similar to those of a USA study,<sup>13</sup> which showed a rate of 30% for viral  
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33 255 URI, 62% for pharyngitis, 65% for bronchitis, and 72% for sinusitis. Medically,  
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36 256 antibiotics are rarely indicated for ARTIs.<sup>18</sup> Antibiotics have no role in the treatment of  
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40 257 either viral URI (common cold) or the majority of acute bronchitis cases, which are  
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43 258 generally caused by viral infection. Only a minority of patients with bronchitis (< 10%),  
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46 259 for example patients who have underlying COPD or whooping cough, may derive any  
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50 260 benefit from antibiotic treatment. With pharyngitis, antibiotics are mainly indicated only  
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53 261 for streptococcal pharyngitis, which accounts for 5–15% of pharyngitis in adults and 20–  
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56 262 30% in children.<sup>19,20</sup>

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7 263 The antibiotic prescription rate for gastrointestinal infections was three times higher than  
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10 264 the rate reported in the USA (30% vs. 10%).<sup>13</sup> As most acute gastroenteritis is self-  
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13 265 limiting, the Japanese national guideline recommends the non-usage of antibiotics for  
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16 266 gastroenteritis unless symptoms are severe.<sup>10</sup> Based on our study, approximately 70% of  
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20 267 oral antibiotics are prescribed for ARTIs or acute gastroenteritis; however, most (> 80%),  
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23 268 did not require antibiotics. Therefore, there is a need for suitable targets to reduce  
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26 269 unnecessary antibiotic use in accordance with antimicrobial stewardship program.  
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30 270 Previous studies from the UK<sup>21, 22</sup> analyzed reasons for antibiotic prescribing for sore  
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33 271 throats and assessed that patient demand for antibiotics and physician pressure to meet  
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36 272 patient demand are associated with antibiotic prescription. In addition, we suppose that  
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40 273 physicians frequently prescribe antibiotics for URI as prophylaxis for complicating  
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43 274 secondary bacterial infections.

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46 275 As for antibiotic prescription for ARTIs and gastrointestinal infections, most  
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50 276 antibiotics prescribed were broad-spectrum. For example, quinolones accounted for 15–  
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53 277 35% of the antibiotics prescribed for ARTIs in this study, although the proportion of  
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56 278 quinolones to whole antibiotics prescribed for ARTIs should be <5% according to the

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7 279 ESAC disease-specific quality indicators<sup>23</sup>. Accordingly, the quality of antibiotic  
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10 280 prescribing should be improved.

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13 281 The logistic regression analyses revealed several factors associated with antibiotic  
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16 282 prescriptions for ARTIs and gastrointestinal infections. The smaller the facility scale, the  
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19 283 higher the odds of antibiotic prescribing. Recent studies from Japan<sup>8</sup> and Taiwan<sup>24</sup> have  
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23 284 found similar results. As family practitioners, pediatricians, and internists usually  
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26 285 prescribe a high number of antibiotic courses,<sup>14</sup> greater adherence to treatment guidelines  
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29 286 among physicians in these specialties is particularly important. It has also been reported  
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33 287 that mid- or late-career stage physicians (because the effect of training received during  
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36 288 medical education might have reduced, after this long time) were more likely to prescribe  
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39 289 antibiotics for nonbacterial acute URI.<sup>25</sup>

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43 290 Patient age was another factor associated with antibiotic prescription. In this study,  
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46 291 antibiotic prescription rates for ARTIs and gastrointestinal infections were highest in  
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49 292 patients aged 10–19 years, followed by patients aged 20–64 years (ARTIs) or 0–9 years  
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53 293 (gastrointestinal infections). A previous study concerning Dutch primary care showed  
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56 294 similar results of antibiotic over-prescribing for ARTIs in patients aged 31–65 years (i.e.,  
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7 295 not in children or the elderly).<sup>26</sup> As adolescents and young adults generally pose a much  
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10 296 lower risk of disease complications than young children or elderly individuals,  
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13 297 antimicrobial stewardship should focus on these age groups of patients. In this study,  
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16 298 patient sex of male was also associated with increased antibiotic prescribing. Although a  
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20 299 patient sex difference was observed in another study, the results differed; female patients  
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23 300 were more likely to have high prescribing in the USA.<sup>14</sup> The reason for patient age and  
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26 301 sex difference in antibiotic prescribing remains to be clarified. Patient sex and age-  
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30 302 standardized antibiotic prescription rates need to be assessed in Japan for effective  
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33 303 intervention.

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36 304 Our study has several limitations. First, our results do not represent the entire antibiotic  
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40 305 prescription pattern in Japan because the claims database used in this study was composed  
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43 306 of claims in only one prefecture. Geographical diversity in antibiotic prescribing may be  
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46 307 present, as observed in the previous study from the USA.<sup>14</sup> Second, since we used an  
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50 308 administrative claims database; the accuracy of the diagnosis was not validated. In  
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53 309 addition, we could not link diagnosis and antibiotic prescriptions on a one-to-one level  
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56 310 when patients had multiple infectious diagnoses. Third, there may be other potential

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7 311 confounding factors that were not included in this study. For example, information on  
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10 312 out-of-hours visits,<sup>8</sup> non-specialty physicians,<sup>8, 24, 27</sup> and patient's low-per capita income  
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13 313 or low-education,<sup>14</sup> which have been reported as potential factors associated with  
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16 314 inappropriate antibiotics prescribing, could not be extracted from the claims database in  
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20 315 this study. Fourth, only 65% of antibiotic prescriptions were linked to infectious disease  
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23 316 visits. This may be partly because we could not capture the information concerning  
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26 317 follow-up visits when patients had multiple visits for a single infection (antibiotics were  
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30 318 linked to the infectious diagnoses only when they were prescribed at the first visit of an  
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33 319 illness episode). In addition, approximately 3–5% of medical claims that included  
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36 320 diagnostic codes and 0.1% of pharmacy claims that included prescription (medication)  
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40 321 codes were registered in non-digital format. As non-digital insurance claims were not  
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43 322 included in our database, 3–5% of antibiotic prescriptions were not linked to diagnoses.  
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46 323 Therefore, inappropriate antibiotic prescription might be underestimated rather than  
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50 324 overestimated.

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53 325 In conclusion, this Japanese study demonstrated that third-generation cephalosporins,  
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56 326 macrolides, and quinolones accounted for 88% of oral antibiotic prescription.  
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7 327 Approximately 60% of antibiotic prescription was provided for ARTIs, with viral URI  
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10 328 and pharyngitis being the two ARTI diagnoses with the largest antibiotic prescriptions.  
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13 329 Gastrointestinal infections were the second most common diagnosis for antibiotic  
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16 330 prescribing. The scale of the facilities (clinic or small-scale hospital) and patient age  
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19 331 (adolescents and young adults) were factors associated with antibiotic over-prescription.  
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23 332 Antimicrobial stewardship interventions should focus on targeting antibiotic prescribing  
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26 333 for these infectious diagnoses, patients, and institutions. Further nationwide studies are  
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29 334 needed to support our data, and longitudinal studies using medical claims data are needed  
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33 335 to evaluate the effectiveness of antimicrobial stewardship.  
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7 **336 Authors' contributions**  
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10 337 HH and SH conceived the study, interpreted the data and results, and drafted the  
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13 338 manuscript. HH, HM, YS, and HY collected, organized, analyzed the data, and  
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16 339 performed statistical analyses. KK and RN conceived the study and collected and  
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19 340 interpreted the data. All authors critically revised the manuscript for intellectual content.  
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23 341 All authors read and approved the final manuscript.  
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34  
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40 346 Number 16K09254.  
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43 347  
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46 **348 Competing interests**  
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49 349 None declared.  
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56 **351 Data sharing**  
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7 352 No additional data available.  
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13 354 **Transparency declarations**  
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16 355 The lead author (the manuscript's guarantor) affirms that the manuscript is an honest,  
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20 356 accurate, and transparent account of the study reported; that no important aspects of the  
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23 357 study have been omitted; and that any discrepancies from the study as planned have been  
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26 358 explained.  
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33 360 **Ethical approval**  
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36 361 This study was approved by the Ethics Committee of the Jichi Medical University  
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40 362 (Number 17-002).  
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363 **Table 1.** Frequency of oral antibiotic prescriptions by age and antibiotic groups

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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

365 \*ATC: Anatomical Therapeutic Chemical

366 \*\*Penicillins, J01C; First-generation cephalosporins, J01DB; Second-generation cephalosporins, J01DC; Third-generation cephalosporins, J01DD;

367 Macrolides, J01FA; Quinolones, J01M; Sulfonamides and trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH, J01DI, J01FF,

368 J01G, and J01X

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

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Antibiotic groups coded by ATC** classification***	Number (%) of visits with antibiotic prescription				All facilities
	Free-standing clinic	Small-scale hospital ( $< 200$ beds)-based clinic	Medium-scale hospital (200–499 beds)-based clinic	Large-scale hospital ( $\geq 500$ beds)-based clinic	
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

371 \*13,736 patients with antibiotic prescription were excluded due to missing data about facility scale.

372 \*\*ATC: Anatomical Therapeutic Chemical

373 \*\*\*Penicillins, J01C; First-generation cephalosporins, J01DB; Second-generation cephalosporins, J01DC; Third-generation cephalosporins, J01DD;

374 Macrolides, J01FA; Quinolones, J01M; Sulfonamides and trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH, J01DI, J01FF,

375 J01G, and J01X

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

377

Diagnoses	All visits	Visits with any antibiotic prescription and prescription rate (%)	Number (%) of visits with antibiotic prescriptions by antibiotic groups*							
			Penicillins	1 <sup>st</sup> /2 <sup>nd</sup> cephem	3 <sup>rd</sup> cephem	Macrolide s	Quinolone s	ST	Tetracyclin es	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 (61.4)	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 (44.4)	37,001 (37.0)	16,941 (16.4)	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

378 1<sup>st</sup>/2<sup>nd</sup> cephem, first/second-generation cephalosporins; 3<sup>rd</sup> cephem, third-generation cephalosporins; ST, Sulfonamides and trimethoprim; STD,  
 379 sexual transmitted diseases; PID, pelvic inflammatory diseases; GI infections, gastrointestinal infections; Skin infections, Skin, cutaneous and  
 380 mucosal infections; COPD, chronic obstructive pulmonary disease; URI, upper respiratory infections

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



384

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

386

Characteristics	Antibiotic prescription, n (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
<b>Patient age</b>			
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
<b>Patient sex</b>			
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
<b>Facility scale</b>			
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

387 CI, confidence interval

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

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

390

Characteristics	Antibiotic prescription, n (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
<b>Patient age</b>			
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
<b>Patient sex</b>			
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
<b>Facility type</b>			
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

391 CI, confidence interval

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1 **Table S1.** Classification of infections by groups with corresponding ICD-10 codes  
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	Diagnosis	ICD-10 codes
<b>Group 1: Infections for which antibiotics are usually indicated</b>		
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)
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### 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)

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5 8 Fever Fever of unknown origin (R50)  
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7 3 \*includes visits in which ICD-10 code for COPD (J41–J44) are present

8 4 \*\*includes visits in which ICD-10 code for COPD (J41–J44) are not present  
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For peer review only

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

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	9
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

Continued on next page

<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	11
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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	
		(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	
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).

# BMJ Open

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

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Manuscripts

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7 **1 Antibiotic prescription among outpatients in a prefecture of Japan, 2012–2013: A**  
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10 **2 retrospective claims database study**

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16 4 Hideki Hashimoto<sup>1</sup>, Hiroki Matsui<sup>2,3</sup>, Yusuke Sasabuchi<sup>2</sup>, Hideo Yasunaga<sup>2,3</sup>, Kazuhiko  
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43 28 **Key words:** antibiotic, antimicrobial stewardship, antimicrobial-resistance, big data,  
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46 29 inappropriate prescribing

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49 30 **Running title:** Antibiotic prescriptions in Japan

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52 31 **Word count for the main text:** 3,002 words

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7 **33 Abstract**  
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10 **34 Objectives:** To investigate oral antibiotic prescribing patterns and identify factors  
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13 **35** associated with antibiotic prescriptions, with the aim of guiding future interventions to  
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16 **36** reduce inappropriate prescribing.  
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20 **37 Design:** Retrospective cohort study.  
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23 **38 Setting:** Database of public health insurance claims in Kumamoto prefecture (Japan).  
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26 **39 Participants:** Beneficiaries of the national or late elders' health insurance system  
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30 between April 2012 and March 2013.  
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33 **41 Main outcome measures:** Of 7,770,481 outpatient visits, 682,822 had a code for  
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36 **42** antibiotics (860 antibiotic prescriptions per 1000 population). Third-generation  
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40 **43** cephalosporins (35%), macrolides (32%), and quinolones (21%) were most frequently  
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43 **44** prescribed. Acute respiratory tract infections (ARTIs), including viral upper respiratory  
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46 **45** infections (URI) (22%), pharyngitis (18%), bronchitis (11%), and sinusitis (10%) were  
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50 **46** most frequently diagnosed for antibiotic prescribing, followed by gastrointestinal (9%),  
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53 **47** urinary tract (8%), and skin, cutaneous, and mucosal infections (5%). Antibiotic  
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56 **48** prescribing rates for viral URI, pharyngitis, bronchitis, sinusitis, and gastrointestinal  
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7 49 infections were 35%, 54%, 53%, 57%, and 30%, respectively. In multivariable analysis  
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10 50 for ARTIs and gastrointestinal infections, patient age (10–19 years especially), patient  
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13 51 sex (male), and facility scale (free-standing clinics or small-scale hospital-based clinics)  
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16 52 were associated with increased antibiotic prescribing.  
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20 53 **Conclusions:** Broad-spectrum antibiotics constituted 88% of oral outpatient antibiotic  
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23 54 prescriptions. Approximately 70% of antibiotics were prescribed for ARTIs and  
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26 55 gastroenteritis with modest benefit from antibiotic treatment. The quality of antibiotic  
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29 56 prescribing needs to be improved. Antimicrobial stewardship interventions should target  
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33 57 ARTIs and gastroenteritis, as well as young patients and small-scale institutions.  
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7 **58 Strength and limitations of this study**  
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- 10 • This is the first Japanese study to describe outpatient antibiotic prescription patterns  
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13 60 linked to individual diagnosis data, comprehensively, by use of the public health  
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16 61 insurance claims database.  
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20 62 • This study included patients older than 65 years of age, who have not typically been  
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23 63 included in previous Japanese studies.  
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26 64 • The accuracy of the diagnosis has not been validated due to the nature of the  
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30 65 administrative claims database.  
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33 66 • There are some unmeasured potential confounding factors such as out-of-hours  
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36 67 visits and physician specialty.  
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## 69 Introduction

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

76 Since antimicrobial use is one of the important factors in the emergence of antimicrobial  
77 resistance,<sup>6</sup> it is essential to reduce the inappropriate use of antibiotics. In Japan, a  
78 previous sales data-based study revealed that oral antibiotics account for more than 90%  
79 of total antibiotic consumption and that broad-spectrum antibiotics (third-generation  
80 cephalosporins, macrolides, and fluoroquinolones) account for 77% of oral antibiotic  
81 consumption (daily doses defined per 1000 inhabitants per day).<sup>7</sup> The Japanese national  
82 action plan aims to reduce the total antimicrobial use to two-thirds of current use, and the  
83 use of oral cephalosporins, quinolones, and macrolides to one-half, by 2020. To reduce  
84 inappropriate antimicrobial use, it is important to determine the antimicrobial prescribing

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7 85 patterns and factors associated with antibiotic prescription. However, such information  
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10 86 has been limited in Japan to date. Although a few recent studies<sup>8,9</sup> described the  
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13 87 prescription patterns for upper respiratory tract infections and bronchitis, the prescription  
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16 88 patterns of infections other than acute respiratory tract infections (ARTIs) have not been  
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20 89 clarified. In addition, patients older than 65 years of age have not been commonly  
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23 90 included in these studies, because these studies relied on data from an employee-based  
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26 91 insurance claims database. With the high rate in aging population in Japan, it is important  
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30 92 to describe the prescription patterns in elderly patients.

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33 93 In this study, we described outpatient oral antibiotic prescribing patterns for all  
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36 94 infections and in all ages, using the Japanese administrative claims database. Furthermore,  
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40 95 we aimed to identify factors associated with antibiotic prescriptions for ARTIs and  
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43 96 gastrointestinal infections, the targets of the antimicrobial stewardship guideline  
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46 97 formulated by the government of Japan in 2017.<sup>10</sup>

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7 **99 Methods**  
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10 *Data sources*  
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13 101 The current population of Japan is approximately 127 million. All citizens are enrolled  
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16 102 in a universal health coverage insurance program provided by the social insurance system  
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19 103 (for employees younger than 75 years of age), national health insurance system (for self-  
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23 104 employed or unemployed people younger than 75 years of age), and the late elders' health  
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26 105 insurance system (for those aged 75 years and older). In Japan, patients can visit any  
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29 106 clinic of their choice. All physicians working at any free-standing or hospital-based  
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33 107 clinics can provide primary care and prescribe antibiotics.  
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36 108 We conducted a retrospective analysis using the administrative health insurance claims  
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39 109 database of Kumamoto prefecture, situated in the southwestern region of Japan, with a  
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43 110 population of about 1.7 million. This database covers approximately 780,000 residents of  
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46 111 Kumamoto prefecture (44% of the population) who were beneficiaries of the national  
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49 112 health insurance system,<sup>11</sup> or the late elders' health insurance system.<sup>12</sup> The participants  
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53 113 in this study may be older than the general population of Japan.  
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56 114 The database is composed of medical and pharmacy claims. It provides monthly  
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7 115 information about patient demographics (year and month of birth and sex), diagnoses,  
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10 116 date of diagnoses, medical procedures, medications, scale (number of beds) of the  
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13 117 medical facility, as well as the identification numbers assigned to each individual, medical  
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16 118 facility, and dispensing pharmacy. At the end of each month, claims are registered from  
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20 119 each medical facility. The diagnoses were recorded by physicians of each medical facility  
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23 120 and coded according to the International Classification of Diseases and Related Health  
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26 121 Problems, 10th Revision (ICD-10).  
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33 123 *Data preparation*  
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36 124 We linked the medical and pharmacy claims on the database using an identification  
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40 125 number unique to each patient, medical facility, and dispensing pharmacy. We identified  
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43 126 all newly diagnosed outpatients, with any infectious diseases, between April 2012 and  
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46 127 March 2013. Infectious diseases diagnoses were categorized according to the indication  
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50 128 for antibiotic use (Table S1, available as supplementary data). This categorization was  
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53 129 based on the study by Fleming-Dutra KE *et al.*<sup>13</sup> Bronchitis and bronchiolitis were divided  
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56 130 into two categories based on whether the patients had chronic obstructive pulmonary  
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7 131 disease (COPD) as comorbidity or not, because of differing need of treatment with  
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10 132 antibiotics. If a patient had multiple infectious diagnoses in one month, a single infectious  
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13 133 diagnosis, selected in order from Group 1 (antibiotics are usually indicated) to Group 3  
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16 134 (antibiotics are rarely indicated), and the first-listed diagnosis in alphabetical order of  
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20 135 ICD-10 codes in the selected group was included in the analyses (Table S1).

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23 136 We also identified all outpatients with any antibiotic prescriptions. Topical,  
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26 137 intramuscular, and intravenous antibiotics were excluded. Antibiotics were categorized  
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30 138 according to the Anatomical Therapeutic Chemical (ATC) classification system  
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33 139 (<http://www.whooc.no/atcddd/>) as follows: tetracyclines (J01A), penicillins (J01C), first-  
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36 140 and second-generation cephalosporins (J01DB and J01DC), third-generation  
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40 141 cephalosporins (J01DD), sulfonamides and trimethoprim (J01E), macrolides (J01FA),  
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43 142 quinolones (J01M), and others (J01B, J01DH, J01DI, J01FF, J01G, and J01X). We  
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46 143 assumed that third-generation cephalosporins accounted for most of cephalosporins used  
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50 144 in Japan; hence, we divided cephalosporins into two groups: first/second- and third-  
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53 145 generation cephalosporins. Antibiotics were linked to the infectious diagnoses in each  
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56 146 patient's claims when both the code of antibiotics and the code of diagnoses were

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7 147 recorded in the same month.  
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13 149 *Data Analysis*  
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16 150 We calculated the frequency of antibiotic prescription for all visits with infections  
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20 151 (according to diagnosis and antibiotic class). For ARTIs (including pharyngitis, sinusitis,  
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23 152 bronchitis/bronchiolitis, and viral upper respiratory infections [URI]) and gastrointestinal  
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26 153 infections, we performed separate multivariable logistic regression analyses to identify  
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30 154 the factors associated with antibiotic prescriptions. The variables were as follows: age  
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33 155 and sex of patients and scale (number of beds) of the medical facilities. Generalized  
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36 156 estimating equations with exchangeable correlation structure were used to account for the  
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40 157 clustering of the medical facilities.  $P$ -values  $< 0.05$  were considered statistically  
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43 158 significant. All statistical analyses were performed with the statistical package R, v.3.5.0  
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46 159 (<http://cran.r-project.org>).  
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53 161 *Patient involvement*  
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56 162 No patients were involved in the development of the research question or the outcome  
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7 163 measures, nor were they involved in developing plans for design or implementation of  
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10 164 the study. No patients were asked for advice regarding the interpretation or writing of  
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13 165 results. There are no plans to disseminate the study results to the relevant patient  
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17 166 community.

For peer review only

## 168 **Results**

169 In total, there were 7,770,481 outpatient visits between April 2012 and March 2013.  
170 Antibiotics were prescribed in 682,822 visits (860 antibiotic prescriptions per 1000  
171 population). Among these, third-generation cephalosporins were most frequently  
172 prescribed (237,372 visits, 35%), followed by macrolides (215,656 visits, 32%) and  
173 quinolones (145,135 visits, 21%). This trend was observed regardless of age group (Table  
174 1) and scale of the medical facility (Table 2), except for those less than 9 years of age in  
175 whom the systemic use of quinolones is not recommended. Information about facility  
176 scale was available from 669,086 out of 682,822 visits. Of these, antibiotics were  
177 prescribed most frequently at free-standing clinics (530,916 visits, 79%), followed by  
178 small-scale (< 200 beds; 78,546 visits, 12%), medium-scale (200–499 beds; 45,271 visits,  
179 7%), and large-scale (500 beds or more; 14,353 visits, 2%) hospital-based clinics (Table  
180 2).

181 We were able to link the individual diagnoses to the antibiotic prescription in 447,232  
182 visits (Table 3). Of these patients, approximately 60% of antibiotics were prescribed for  
183 ARTIs, including viral URI (96,989 visits, 22%), pharyngitis (78,469 visits, 18%),

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7 184 bronchitis without COPD (47,248 visits, 11%), and sinusitis (45,456 visits, 10%). Other  
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10 185 than ARTIs, there were frequent antibiotic prescriptions for gastrointestinal infections  
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13 186 (41,309 visits, 9%), urinary tract infections (37,674 visits, 8%), and skin, cutaneous, and  
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16 187 mucosal infections (23,572 visits, 5%). The antibiotic prescription rates for viral URI,  
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20 188 pharyngitis, bronchitis (without underlying COPD), sinusitis, and gastrointestinal  
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23 189 infections were 35% (96,989 out of 274,441 visits), 54% (78,469 out of 146,508 visits),  
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26 190 53% (47,248 out of 89,479 visits), 57% (45,456 out of 80,078 visits), and 30% (41,309  
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30 191 out of 137,661 visits), respectively (Table 3).

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33 192 Table 4 shows the results of the logistic regression analysis of antibiotic prescription for  
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36 193 ARTIs. Male sex was associated with more antibiotic prescription (adjusted odds ratio  
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40 194 [OR], 1.10; 95% confidence interval [CI], 1.08 to 1.11). With patients aged 65 years or  
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43 195 older as reference, patients aged 10 to 19 years were more likely to be prescribed  
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46 196 antibiotics (adjusted OR, 2.75; 95% CI, 2.69 to 2.82), followed by patients aged 20 to 64  
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50 197 years (adjusted OR, 1.92; 95% CI, 1.89 to 1.94), and patients younger than 10 years  
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53 198 (adjusted OR, 1.48; 95% CI, 1.46 to 1.50). Regarding facility scale, with large-scale (500  
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56 199 beds or more) hospital-based clinics as reference, free-standing clinics (adjusted OR,

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7 200 4.24; 95% CI, 4.03 to 4.45), small-scale (< 200 beds) hospital-based clinics (adjusted OR,  
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10 201 2.07; 95% CI, 1.97 to 2.18), and medium-scale (200–499 beds) hospital-based clinics  
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13 202 (adjusted OR, 1.71; 95% CI, 1.62 to 1.80) were significantly associated with more  
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16 203 frequent antibiotic prescription.

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20 204 Similar results were shown with the logistic regression analysis for gastrointestinal  
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23 205 infections (Table 5). Male sex was associated with slightly more antibiotic prescription  
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26 206 (adjusted OR, 1.04; 95% CI, 1.01 to 1.06) than the female sex. Patients aged 10 to 19  
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30 207 years (adjusted OR, 1.92; 95% CI, 1.83 to 2.00), 20 to 64 years (adjusted OR, 1.55; 95%  
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33 208 CI, 1.51 to 1.60), and younger than 10 years (adjusted OR, 1.76; 95% CI, 1.71 to 1.82)  
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36 209 received more antibiotic prescriptions compared with patients aged 65 years or older.

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40 210 With reference to large-scale ( $\geq$  500 beds) hospital-based clinics, free-standing clinics  
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43 211 (adjusted OR, 1.88; 95% CI, 1.68 to 2.10) and small-scale (< 200 beds) hospital-based  
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46 212 clinics (adjusted OR, 1.17; 95% CI, 1.04 to 1.32) were associated with frequent antibiotic  
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50 213 prescription for gastrointestinal infections.  
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7 **215 Discussion**  
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10 216 We described oral antibiotic prescription patterns in the outpatient care setting in Japan.  
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13 217 To the best of our knowledge, this is the first Japanese study to comprehensively describe  
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16 218 antibiotic prescription patterns linked to individual diagnoses data, using the claims  
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19 219 database. Broad-spectrum antibiotics consisting of third-generation cephalosporins,  
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23 220 macrolides, and quinolones accounted for nearly 90% of antibiotic prescriptions in the  
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26 221 primary care settings. Prescription of penicillin was only 5%. This prescription pattern is  
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29 222 consistent with the results of an analysis of antibiotic sales data in Japan, in which 77%  
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33 223 of oral antibiotics shipped were broad-spectrum.<sup>7</sup> In contrast, the use of cephalosporins,  
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36 224 macrolides, and quinolones in the United States of America (USA) and Europe were  
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39 225 much lower than in Japan. Hicks *et al.*<sup>14</sup> analyzed the sales data of oral antibiotics in the  
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43 226 USA and showed that cephalosporins, macrolides, and quinolones accounted for 48% of  
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46 227 the total oral antibiotics. In their study, penicillin had the largest share of the antibiotics  
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49 228 (23%). Data from the European Surveillance of Antimicrobial Consumption project<sup>15</sup> also  
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53 229 showed that cephalosporins, macrolides, and quinolones accounted for about one third of  
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56 230 the total oral antibiotic consumptions, in Europe. This study demonstrated a rather high  
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6 231 ratio of broad-spectrum to narrow-spectrum oral antibiotics, in Japan; therefore, the  
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10 232 quality of antibiotic prescribing needs to be improved.  
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13 233 Although quinolones are not recommended for children, quinolones were prescribed as  
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16 234 much as penicillins in children aged 0–9 years in our study. This may be because oral  
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20 235 fluoroquinolones such as tosufloxacin are approved for children to treat otitis media and  
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23 236 pneumonia in Japan. Since the approval of quinolones in 2010, despite the  
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27 237 recommendation to prescribe quinolones carefully for children, many physicians  
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30 238 prescribed tosufloxacin to children in expectation of clinical effectiveness.  
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33 239 Among antibiotics linked with individual diagnosis data, over 60% of antibiotics were  
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36 240 prescribed for ARTIs, followed by gastrointestinal infections (9%), urinary tract  
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40 241 infections (8%), and skin, cutaneous, and mucosal infections (5%). Surprisingly, viral  
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43 242 URI (common cold) was the most frequent infection associated with antibiotic  
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47 243 prescription. In the ambulatory care setting in the USA, antibiotics were prescribed most  
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50 244 frequently for acute respiratory conditions (41–44%), followed by skin and mucosal  
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53 245 conditions (15–19%), urinary tract infections (7–8%), and gastrointestinal conditions (5–  
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56 246 6%).<sup>13,16</sup> Another study using primary care data in the United Kingdom (UK)<sup>17</sup>  
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7 247 demonstrated that 46% of antibiotics were prescribed for respiratory tract conditions,  
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10 248 followed by urogenital tract (23%), and skin conditions (10%). Only 1% was prescribed  
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13 249 for gastrointestinal conditions. Our study demonstrated a higher proportion of antibiotic  
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16 250 prescription for ARTIs (approximately 15% higher than those in USA or UK) and  
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20 251 gastrointestinal infections (approximately 5% higher) in Japan.

23 252 Antibiotics were prescribed for 35% of viral URI cases and approximately 50–60% of  
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26 253 pharyngitis, bronchitis, and sinusitis cases in our study. These prescription rates were  
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30 254 approximately similar to those of a USA study,<sup>13</sup> which showed a rate of 30% for viral  
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33 255 URI, 62% for pharyngitis, 65% for bronchitis, and 72% for sinusitis. Medically,  
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36 256 antibiotics are rarely indicated for ARTIs.<sup>18</sup> Antibiotics have no role in the treatment of  
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40 257 either viral URI (common cold) or the majority of acute bronchitis cases, which are  
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43 258 generally caused by viral infection. Only a minority of patients with bronchitis (< 10%),  
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46 259 for example patients who have underlying COPD or whooping cough, may derive any  
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50 260 benefit from antibiotic treatment. With pharyngitis, antibiotics are mainly indicated only  
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53 261 for streptococcal pharyngitis, which accounts for 5–15% of pharyngitis in adults and 20–  
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56 262 30% in children.<sup>19, 20</sup>

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7 263 The antibiotic prescription rate for gastrointestinal infections was three times higher than  
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10 264 the rate reported in the USA (30% vs. 10%).<sup>13</sup> As most acute gastroenteritis is self-  
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13 265 limiting, the Japanese national guideline recommends the non-usage of antibiotics for  
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16 266 gastroenteritis unless symptoms are severe.<sup>10</sup> Based on our study, approximately 70% of  
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20 267 oral antibiotics are prescribed for ARTIs or acute gastroenteritis; however, most (> 80%),  
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23 268 did not require antibiotics. Therefore, there is a need for suitable targets to reduce  
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26 269 unnecessary antibiotic use in accordance with antimicrobial stewardship program.  
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30 270 Previous studies from the UK<sup>21, 22</sup> analyzed reasons for antibiotic prescribing for sore  
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33 271 throats and assessed that patient demand for antibiotics and physician pressure to meet  
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36 272 patient demand are associated with antibiotic prescription. In addition, we suppose that  
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40 273 physicians frequently prescribe antibiotics for URI as prophylaxis for complicating  
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43 274 secondary bacterial infections. Previous qualitative studies identified that additional  
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46 275 factors associated with antibiotic prescription included diagnostic uncertainty,  
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50 276 unawareness of guidelines, time pressure at work, and patient expectations regarding  
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53 277 antibiotics.<sup>23-25</sup>  
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56 278 As for antibiotic prescription for ARTIs and gastrointestinal infections, most  
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7 279 antibiotics prescribed were broad-spectrum. For example, quinolones accounted for 15–  
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10 280 35% of the antibiotics prescribed for ARTIs in this study, although the proportion of  
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13 281 quinolones to whole antibiotics prescribed for ARTIs should be <5% according to the  
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16 282 ESAC disease-specific quality indicators.<sup>26</sup> Accordingly, the quality of antibiotic  
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20 283 prescribing should be improved.

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23 284 The logistic regression analyses revealed several factors associated with antibiotic  
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26 285 prescriptions for ARTIs and gastrointestinal infections. The smaller the facility scale, the  
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30 286 higher the odds of antibiotic prescribing. Recent studies from Japan<sup>8</sup> and Taiwan<sup>27</sup> have  
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33 287 found similar results. As family practitioners, pediatricians, and internists usually  
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36 288 prescribe a high number of antibiotic courses,<sup>14</sup> greater adherence to treatment guidelines  
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40 289 among physicians in these specialties is particularly important. It has also been reported  
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43 290 that mid- or late-career stage physicians (because the effect of training received during  
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46 291 medical education might have reduced, after this long time) were more likely to prescribe  
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50 292 antibiotics for nonbacterial acute URI.<sup>28</sup>

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53 293 Patient age was another factor associated with antibiotic prescription. In this study,  
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56 294 antibiotic prescription rates for ARTIs and gastrointestinal infections were highest in

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7 295 patients aged 10–19 years, followed by patients aged 20–64 years (ARTIs) or 0–9 years  
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10 296 (gastrointestinal infections). A previous study concerning Dutch primary care showed  
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13 297 similar results of antibiotic over-prescribing for ARTIs in patients aged 31–65 years (i.e.,  
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16 298 not in children or the elderly).<sup>29</sup> As adolescents and young adults generally pose a much  
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20 299 lower risk of disease complications than young children or elderly individuals,  
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23 300 antimicrobial stewardship should focus on these age groups of patients. In this study,  
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26 301 male sex was also associated with increased antibiotic prescribing. Although a patient sex  
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30 302 difference was observed in another study, the results differed; female patients were more  
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33 303 likely to have high prescribing in the USA.<sup>14</sup> The reason for patient age and sex difference  
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36 304 in antibiotic prescribing remains to be clarified. Patient sex and age-standardized  
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40 305 antibiotic prescription rates need to be assessed in Japan for effective intervention.

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43 306 Our study has several limitations. First, our results do not represent the entire antibiotic  
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46 307 prescription pattern in Japan because the claims database used in this study was composed  
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50 308 of claims in only one prefecture. Geographical diversity in antibiotic prescribing may be  
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53 309 present, as observed in the previous study from the USA.<sup>14</sup> Second, since we used an  
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56 310 administrative claims database; the accuracy of the diagnosis was not validated. In

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7 311 addition, we could not link diagnosis and antibiotic prescriptions on a one-to-one level  
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10 312 when patients had multiple infectious diagnoses. Third, there may be other potential  
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13 313 confounding factors that were not included in this study. For example, information on  
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16 314 out-of-hours visits,<sup>8</sup> non-specialty physicians,<sup>8, 27, 30</sup> and patient's low-per capita income  
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20 315 or low-education,<sup>14</sup> which have been reported as potential factors associated with  
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23 316 inappropriate antibiotics prescribing, could not be extracted from the claims database in  
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26 317 this study. Fourth, only 65% of antibiotic prescriptions were linked to infectious disease  
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30 318 visits. This may be partly because we could not capture the information concerning  
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33 319 follow-up visits when patients had multiple visits for a single infection (antibiotics were  
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36 320 linked to the infectious diagnoses only when they were prescribed at the first visit of an  
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40 321 illness episode). In addition, approximately 3–5% of medical claims that included  
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43 322 diagnostic codes and 0.1% of pharmacy claims that included prescription (medication)  
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46 323 codes were registered in non-digital format. As non-digital insurance claims were not  
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50 324 included in our database, 3–5% of antibiotic prescriptions were not linked to diagnoses.  
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53 325 Therefore, inappropriate antibiotic prescription might be underestimated rather than  
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56 326 overestimated.

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7 327 In conclusion, this Japanese study demonstrated that third-generation cephalosporins,  
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10 328 macrolides, and quinolones accounted for 88% of oral antibiotic prescription.  
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13 329 Approximately 60% of antibiotic prescription was provided for ARTIs, with viral URI  
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16 330 and pharyngitis being the two ARTI diagnoses with the largest antibiotic prescriptions.  
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20 331 Gastrointestinal infections were the second most common diagnosis for antibiotic  
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23 332 prescribing. The scale of the facilities (clinic or small-scale hospital) and patient age  
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26 333 (adolescents and young adults) were factors associated with antibiotic over-prescription.  
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30 334 Antimicrobial stewardship interventions should focus on targeting antibiotic prescribing  
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33 335 for these infectious diagnoses, patients, and institutions. Further nationwide studies are  
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36 336 needed to support our data, and longitudinal studies using medical claims data are needed  
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40 337 to evaluate the effectiveness of antimicrobial stewardship.  
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7 **338 Authors' contributions**  
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10 339 HH and SH conceived the study, interpreted the data and results, and drafted the  
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13 340 manuscript. HH, HM, YS, and HY collected, organized, analyzed the data, and  
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15  
16 341 performed statistical analyses. KK and RN conceived the study and collected and  
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18  
19 342 interpreted the data. All authors critically revised the manuscript for intellectual content.  
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23 343 All authors read and approved the final manuscript.  
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43 349  
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46 **350 Competing interests**  
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49 351 None declared.  
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56 **353 Data sharing**  
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7 354 No additional data available.  
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13 356 **Transparency declarations**  
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16 357 The lead author (the manuscript's guarantor) affirms that the manuscript is an honest,  
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20 358 accurate, and transparent account of the study reported; that no important aspects of the  
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23 359 study have been omitted; and that any discrepancies from the study as planned have been  
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26 360 explained.  
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33 362 **Ethical approval**  
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36 363 This study was approved by the Ethics Committee of the Jichi Medical University  
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40 364 (Number 17-002).  
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365 **Table 1.** Frequency of oral antibiotic prescriptions by age and antibiotic groups

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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

367 \*ATC: Anatomical Therapeutic Chemical

368 \*\*Penicillins, J01C; First-generation cephalosporins, J01DB; Second-generation cephalosporins, J01DC; Third-generation cephalosporins, J01DD;

369 Macrolides, J01FA; Quinolones, J01M; Sulfonamides and trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH, J01DI, J01FF,

370 J01G, and J01X

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

372

Antibiotic groups coded by ATC** classification***	Number (%) of visits with antibiotic prescription				All facilities
	Free-standing clinic	Small-scale hospital ( $< 200$ beds)-based clinic	Medium-scale hospital (200–499 beds)-based clinic	Large-scale hospital ( $\geq 500$ beds)-based clinic	
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

373 \*13,736 patients with antibiotic prescription were excluded due to missing data about facility scale.

374 \*\*ATC: Anatomical Therapeutic Chemical

375 \*\*\*Penicillins, J01C; First-generation cephalosporins, J01DB; Second-generation cephalosporins, J01DC; Third-generation cephalosporins, J01DD;

376 Macrolides, J01FA; Quinolones, J01M; Sulfonamides and trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH, J01DI, J01FF,

377 J01G, and J01X



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

379

Diagnoses	All visits	Visits with any antibiotic prescription and prescription rate (%)	Number (%) of visits with antibiotic prescriptions by antibiotic groups*							
			Penicillins	1 <sup>st</sup> /2 <sup>nd</sup> cephem	3 <sup>rd</sup> cephem	Macrolide s	Quinolone s	ST	Tetracyclin es	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 (61.1)	164 (8.9)	167 (9.1)	≤ 10	≤ 10	273 (14.8)

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						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 (44.4)	37,001 (37.0)	16,941 (16.9)	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

380 1<sup>st</sup>/2<sup>nd</sup> cephem, first/second-generation cephalosporins; 3<sup>rd</sup> cephem, third-generation cephalosporins; ST, Sulfonamides and trimethoprim; STD,  
 381 sexual transmitted diseases; PID, pelvic inflammatory diseases; GI infections, gastrointestinal infections; Skin infections, Skin, cutaneous and  
 382 mucosal infections; COPD, chronic obstructive pulmonary disease; URI, upper respiratory infections  
 383 \*Antibiotics were coded according to Anatomical Therapeutic Chemical (ATC) codes: Penicillins, J01C; First-generation cephalosporins, J01DB;  
 384 Second-generation cephalosporins, J01DC; Third-generation cephalosporins, J01DD; Macrolides, J01FA; Quinolones, J01M; Sulfonamides and  
 385 trimethoprim, J01E; Tetracyclines, J01A; Other antibiotics, J01B, J01DH, J01DI, J01FF, J01G, and J01X

386

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

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Characteristics	Antibiotic prescription, n (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
<b>Patient age</b>			
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
<b>Patient sex</b>			
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
<b>Facility scale</b>			
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

389 CI, confidence interval

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

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

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Characteristics	Antibiotic prescription, n (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
<b>Patient age</b>			
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
<b>Patient sex</b>			
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
<b>Facility type</b>			
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

393 CI, confidence interval

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1 **Table S1.** Classification of infections by groups with corresponding ICD-10 codes  
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	Diagnosis	ICD-10 codes
<b>Group 1: Infections for which antibiotics are usually indicated</b>		
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)
<b>Group 2 : Infections for which antibiotics are potentially indicated</b>		
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)
<b>Group 3: Infections for which antibiotics are rarely indicated</b>		
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) **

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COPD		
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

For peer review only

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

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	9
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

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<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	11
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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	
		(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	
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).