

[REVIEW ARTICLE]

Narrative Review: The Process of Expanding the Manual of Antimicrobial Stewardship by the Government of Japan

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Abstract:

The Ministry of Health, Labour and Welfare has published the Manual of Antimicrobial Stewardship (1st edition) in June 2017 to improve the prescribing practice of antimicrobials for immunocompetent adult and pediatric (both school-aged and older children) patients. Due to the increasing demand for further promoting outpatient antimicrobial stewardship, we conducted a literature and national guideline review to identify the area of need. The results of our review revealed a high antimicrobial prescription rate in the Japanese pediatric population. Furthermore, although the Japanese clinical guidelines/guidance covered the fields of almost all infectious diseases, no system exists to estimate the incidence and treatment patterns of important infectious diseases such as asymptomatic bacteriuria, skin and soft tissue infections, and dental practices in Japan. Therefore, addressing the issues of both establishing surveillance systems and the implementation of guidelines/guidance can be the next step to promote further outpatient antimicrobial stewardship.

Key words: antimicrobial resistance, antimicrobial stewardships, infectious disease guideline, public health

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Introduction/Rationale of this review

Following the publication of Japan's National Action Plan on Antimicrobial Resistance (AMR) 2016-2020 (1), the Japanese Ministry of Health, Labour and Welfare (MHLW) published the "Manual of Antimicrobial Stewardship (1st edition)" (hereinafter referred to as the Manual) to guide the judicious use of antimicrobials in the primary care setting (2). The Manual was developed by the working group on antimicrobial stewardship and approved by the AMR national expert committee and the national advisory board of infectious disease (Figure).

The impetus for the government to issue such a downstream clinical manual was based on the alarming fact that oral antimicrobials accounted for approximately 90% of the total sales of antimicrobials in Japan and the National Action Plan targets to reduce their total use to two-thirds by 2020 using the One Health approach (1, 3-5). Similarly, of all oral antimicrobials, the third-generation cephalosporins,

macrolides, and fluoroquinolones accounted for more than 75% in 2013 and those agents are also targeted to be reduced by half by 2020. Accordingly, the MHLW considered it imperative to reach out to medical providers in the outpatient setting where oral antimicrobials are often prescribed to achieve this goal (6).

The Manual focused on the two commonly experienced infectious disease conditions in the outpatient care: acute respiratory tract infection and acute diarrhea among healthy, immunocompetent adults and pediatric (both school-aged and older children) patients (2). These conditions are often self-limiting and do not require antimicrobial use. Nevertheless, antimicrobial prescription for acute respiratory tract infection is common in Japan as is the case in other developed countries (7). Therefore, the Manual provides a detailed explanation of the rationale behind the necessary and unnecessary antimicrobial prescription and provides practical patients' education materials to facilitate shared decision-making with patients and their parents for busy frontline providers (2, 6). Based on the Manual, a few interventions

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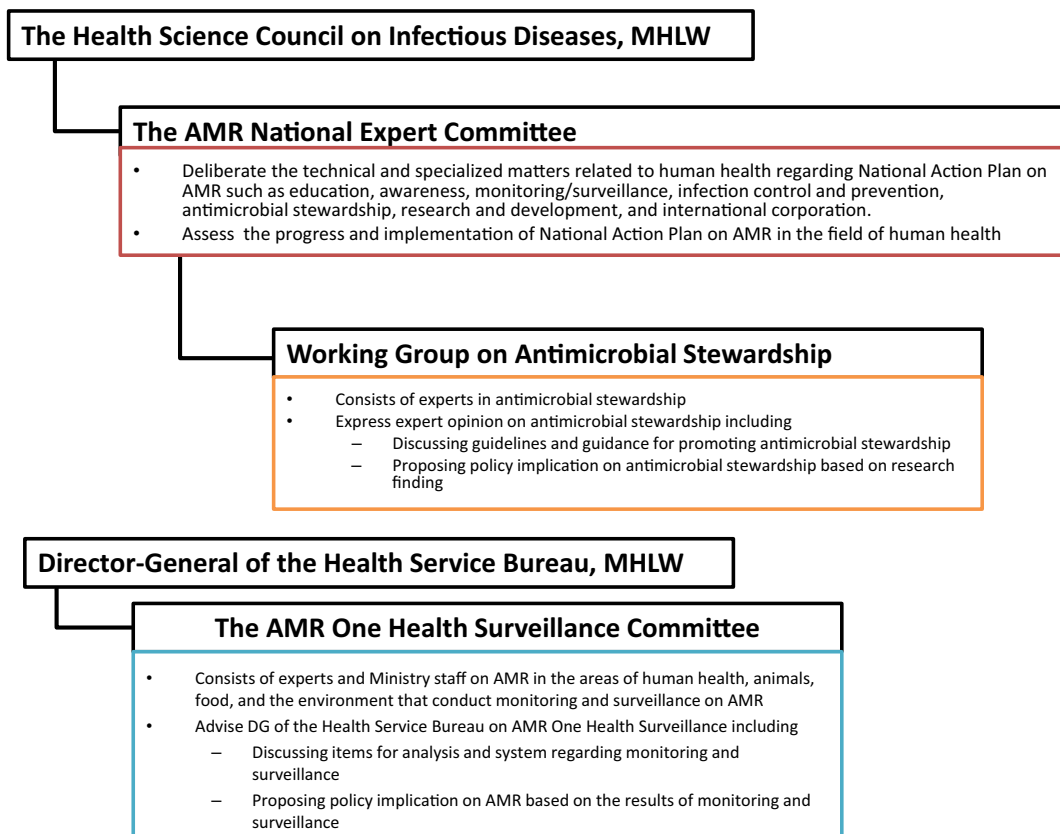


Figure. Regulatory Framework for Combating Antimicrobial Resistance (AMR), The Ministry of Health, Labor and Welfare (MHLW).

have been developed in different levels of healthcare system. For instance, to improve the acceptability and utilization of the Manual by providers, the digest version of the Manual was published by the MHLW (8), and a continuing medical education course using the Manual has been launched in local levels with some success in terms of their readiness to reduce their intention to prescribe unnecessary antimicrobials (9). Furthermore, at the regulatory level, antimicrobial stewardship in the outpatient setting adapting the Manual onto their practices is currently one of the requirements for facilities to claim additional fee through the national reimbursement system (10).

With further demand for expanding the fields and the targeted population of the Manual by professional societies and providers, the AMR national expert committee requested the MHLW-funded research team (11) to make a recommendation for them to discuss further direction of the Manual (12). In other words, the recommendation could assist the committee in making evidence-based decision about prioritizing areas of infectious diseases to optimize the use of antimicrobials in the outpatient setting.

Therefore, our research team investigated the infectious disease fields 1) that had not been covered by the existing national guidelines and 2) wherein unnecessary antimicrobial prescribing was often described (12). In this narrative review, we intended to share the process of analysis and its results with key stakeholders, including primary care providers including internal medicine physicians, professional so-

cieties, and importantly communities, so that we hope that the process can be more transparent and we can promote further discussion and activities to optimize outpatient antimicrobial prescribing trends in various healthcare systems.

Methods

We often ascertain the problematic antimicrobials use as “unnecessary use” or “inappropriate use” (13). The former refers to the use of antimicrobials when they are prescribed unnecessarily. “Inappropriate use,” on the other hand, implies that the selection, dose, and duration of antimicrobials are deviated from standard practice when the clinical situation compels the use of antimicrobials. As such, unnecessary use can be addressed relatively straightforward from the perspective of antimicrobial stewardship, and hence we opted to discuss the unnecessary use of antimicrobials in the current review.

1. Analysis of Japanese Guidelines

We followed the method that the MHLW-funded research report used to analyze the national infectious disease guidelines and to assess their methods, precision, and transparency (14). We explored whether there was any domestic treatment guideline in selected infectious diseases. We selected infectious diseases by referring to the infectious disease practice guidelines published by Swedish and Belgium government (15, 16). In addition to interviewing the area ex-

perts in professional societies, we used the Google Scholar Engine using terms “guideline,” “manual,” and “guidance” and also searched the homepages of Japanese academic societies regarding selected infectious diseases on November 20, 2016 and January 30 and 31, 2019, and additionally on November 28, 2019.

2. Assessment of the impact of unnecessary antimicrobial prescription on health outcomes

We searched the incidence of selected infectious diseases. To assess the impact of unnecessary antimicrobial prescription on health outcomes and the incidence of adverse events (17) derived from antimicrobial prescription, we searched the published literature, conference reports, and white papers to the MHLW in PubMed, Google Scholar, and Ichu-shi (Japan Medical Abstracts Society) (18). We selected acute upper respiratory tract infection, skin and soft tissue infection (SSTI), asymptomatic bacteriuria, and dental infection, and the corresponding Medical Subject Headings terms for English articles and their Japanese translated terms for Japanese articles were used. These infectious diseases were often described as the important clinical areas for antimicrobial stewardship in the outpatient setting (7, 19-21). Similarly, we also searched for the frequency of complications caused by the infectious diseases and the effect of antimicrobials used for preventing such complications. We conducted this search in December 2017 and January 2018 and additionally in November 2019.

Results

1. Analysis of the Japanese Guidelines

We found 21 original guidelines that cover various respiratory tract infections, urogenital tract infections, gastrointestinal tract infections, SSTIs and dental infection, and acute bacterial conjunctivitis (Table). Some guidelines covered more than one area of diseases, and the Japanese Association for Infectious Disease and the Japanese Society of Chemotherapy have published joint guidelines for the management of various infectious diseases extensively (Table); in addition, individual academic societies have developed a guideline. Among all the identified guidelines, eight (38%) required subscription fee or purchase to view the content. Overall, we found such guidelines/guidance covered the areas of major infectious diseases.

2. Assessment of the importance of unnecessary antimicrobial prescription

1. Epidemiology abroad

In the US ambulatory care 2011-2012, among 184,032 sampled visits, 12.6% involved antimicrobial prescription that translated into 506 antimicrobial prescriptions per 1,000 US population annually (7). The annual antimicrobial prescription rate was variable for age categories and geographical locations. For instance, the highest rate was observed

among children aged 0 through 2 years at 1,287 prescriptions per 1,000 population, and the lowest rate was observed among adults aged 20-39 years at 397 prescriptions per 1,000 population. The southern region had the highest annual prescription rate at 553 per 1,000 population versus the western region at 423 per 1,000 population. Sinusitis, suppurative otitis media, and pharyngitis were the major indications for the antimicrobial prescription, followed by SSTIs and urinary tract infections.

SSTIs include a wide spectrum of diseases. Localized mild cellulitis and abscess can be treated in the outpatient setting, whereas severe diseases such as necrotizing fasciitis necessitate critical care and surgical debridement (22, 23). In addition, the 2014 Infectious Disease Society of America guidelines did not recommend routine antimicrobial therapy after incision and drainage for a healthy population with mild diseases (20). Alternatively, recent large randomized control studies suggested a potential benefit of adjunctive antimicrobial therapy in this population (24-26).

Asymptomatic bacteriuria refers to the identification of bacteria in an appropriately collected urine specimen from patients without symptomatic urinary tract infection (27). In addition to special clinical scenarios with pregnant patients and patients undergoing urologic procedures, the majority of patients with asymptomatic bacteriuria do not warrant antimicrobial therapy given its scarce adverse consequences. The prevalence of asymptomatic bacteriuria differs according to age, sex, comorbidities, and pregnancy. For instance, 6-7% of the female population in their 50s and 60s and 8-10% of females in their 60s and 70s were reported to have asymptomatic bacteriuria (28). In the young healthy female population, asymptomatic bacteriuria is transient, although in the elderly, it can be continuous and repetitive phenomena (29). Multicenter studies conducted in the US have revealed that 38% of patients with asymptomatic bacteriuria were treated (30). Unnecessary antimicrobial use is a plausible risk in both ambulatory and inpatient practices (31).

In the UK, dental practitioners accounted for 7-9% of community prescriptions of antimicrobials (32, 33). In Canada, from 1996 to 2013, although the overall antibiotic use declined by 13% and the proportion of physicians prescribing antibiotics declined by 18%, dental prescribing increased by 62% and its proportionate contribution increased from 6.7% to 11.3% of antimicrobial prescription (21). This information implicates the importance of understanding the current situations at both regional and national levels and perhaps require intervention for dental practices with antimicrobial stewardship (34).

According to the guidelines from US and Europe (35, 36), antimicrobial prophylaxis for the prevention of endocarditis is warranted when invasive dental procedures such as tooth extractions are involved in high-risk populations (e.g., adults with prosthetic heart valves). Questionnaire surveys conducted on dentists in Canada showed that the degree of following such guidelines was variable; some dentists may prescribe prophylactic antimicrobials to

Table. Japanese Infectious Disease Guidelines.

Diseases	Guidelines	Published by	Published year	Link	Subscription required
Overview of the management of infectious diseases	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y
Respiratory airway infections	The Japanese Respiratory Society guidelines for the management of respiratory tract infection	The Japanese Respiratory Society	2003	http://www.jrs.or.jp/modules/guidelines/index.php?content_id=18	N
	JAID/JSC Guidelines for the Treatment of Respiratory Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2014	http://www.chemotherapy.or.jp/publications/publications.html	Y
	The Japanese Respiratory Society guidelines for the management of cough and sputum	The Japanese Respiratory Society	2019	https://www.jrs.or.jp/modules/guidelines/index.php?content_id=121	Y
Otitis media	Clinical practice guidelines for the management of serious otitis media in children	The Oto-Rhino-Laryngological Society of Japan/Japan Society for Pediatric ORL	2015	http://www.otology.gr.jp/guideline/img/guideline_otitis2015.pdf	N
	Clinical practice guidelines for the diagnosis and management of acute otitis media in children in Japan	Japan Otological Society/Japan society for Pediatric ORL/Japan Society for Infection and Aerosol in Otorhinolaryngology	2018	https://www.otology.gr.jp/common/pdf/guideline_otitis2018.pdf	N
	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y
Pneumonia	JAID/JSC Guideline for the Treatment of Respiratory Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2014	http://www.chemotherapy.or.jp/guideline/jaidjsc-kansenshochiryoko_kokyuki.pdf	N
	The Japanese Respiratory Society guidelines for the management of pneumonia in adults	The Japanese Respiratory Society	2017	http://www.jrs.or.jp/modules/guidelines/index.php?content_id=94	Y
	Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan	Japanese Society of Pediatric Pulmonology/Japan Society for Pediatric Infectious Diseases	2017	http://eckyowa.shop16.makeshop.jp/shopdetail/000000000091/	Y
	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y
COPD exacerbation	JAID/JSC Guideline for the Treatment of Respiratory Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2014	http://www.chemotherapy.or.jp/guideline/jaidjsc-kansenshochiryoko_kokyuki.pdf	N
	The Japanese Respiratory Society guidelines for the diagnosis and treatment of COPD (5th edition)	The Japanese Respiratory Society	2018	https://www.jrs.or.jp/modules/guidelines/index.php?content_id=112	Y
	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y
Seasonal influenza infection	JAID/JSC Guideline for the Treatment of Respiratory Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2014	http://www.chemotherapy.or.jp/guideline/jaidjsc-kansenshochiryoko_kokyuki.pdf	N
	Guidance to seasonal influenza infection 2019–2020 season	Japan Pediatric Society	2019	http://www.jpeds.or.jp/uploads/files/2019-2020_influenza_all.pdf	N
	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y
Acute cystitis	JAID/JSC Guide to the Clinical Management of Infectious Diseases - Urinary tract infection/male genital infection	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2015	http://www.chemotherapy.or.jp/guideline/jaidjsc-kansenshochiryoko_nyouro.pdf	N
	Clinical Guideline for the management of Obstetrics and Gynecology - Gynecology clinic setting	Japan Society of Obstetrics and Gynecology	2017	http://www.jsog.or.jp/activity/pdf/gl_fujinka_2017.pdf	N
	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y

Table. Japanese Infectious Disease Guidelines. (Continued)

Diseases	Guidelines	Published by	Published year	Link	Subscription required
Acute pyelonephritis; Asymptomatic bacteriuria; and Prostatitis	JAID/JSC Guide to the Clinical Management of Infectious Diseases - Urinary tract infection/male genital infection	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2015	http://www.chemotherapy.or.jp/guideline/jaidjsc-kansenshochiryonyouro.pdf	N
	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y
Epididymitis	JAID/JSC Guide to the Clinical Management of Infectious Diseases - Urinary tract infection/male genital infection	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2015	http://www.chemotherapy.or.jp/guideline/jaidjsc-kansenshochiryonyouro.pdf	N
	Guideline for the diagnosis and treatment of sexually transmitted diseases	Japanese Society for Sexually Transmitted Infections	2016	http://jssti.umin.jp/pdf/guideline-2016_v2.pdf	N
	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y
Pelvic inflammatory disease	Guideline for the diagnosis and treatment of sexually transmitted diseases	Japanese Society for Sexually Transmitted Infections	2016	http://jssti.umin.jp/pdf/guideline-2016_v2.pdf	N
	Clinical Guideline for the management of Obstetrics and Gynecology - Gynecology clinic setting	Japan Society of Obstetrics and Gynecology	2017	http://www.jsog.or.jp/activity/pdf/gl_fujinka_2017.pdf	N
	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y
Bacterial vaginosis; Candida vulvovaginitis; and Genital herpes simplex virus infection	Guideline for the diagnosis and treatment of sexually transmitted diseases	Japanese Society for Sexually Transmitted Infections	2016	http://jssti.umin.jp/pdf/guideline-2016_v2.pdf	N
	Clinical Guideline for the management of Obstetrics and Gynecology - Gynecology clinic setting	Japan Society of Obstetrics and Gynecology	2017	http://www.jsog.or.jp/activity/pdf/gl_fujinka_2017.pdf	N
	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y
Urethritis	Guideline for the diagnosis and treatment of sexually transmitted diseases	Japanese Society for Sexually Transmitted Infections	2016	http://jssti.umin.jp/pdf/guideline-2016_v2.pdf	N
	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y
Diverticulitis	Guidelines for the management of diverticulosis	Japanese Gastroenterological Association	2017	https://minds.jqhc.or.jp/docs/gl_pdf/G0001033/4/diverticulosis_of_colon.pdf	N
<i>Helicobacter pylori</i> infection	Guidelines for the diagnosis and treatment of <i>H. pylori</i> infection	The Japanese Society for Helicobacter Research	2016	http://www.sentan.com/products/detail.php?product_id=21	Y
Impetigo; cellulitis; erysipelas; and infected leg ulcer	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y
Diabetic foot ulcer and infection	Guideline for the management of wound, pressure ulcer, burn 3: Diabetic foot ulcer and infection	Japan Dermatological Association	2017	https://www.dermatol.or.jp/uploads/uploads/files/3.diabetic_ulcer_GL.pdf	N
	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y
Animal bite	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y

Table. Japanese Infectious Disease Guidelines. (Continued)

Diseases	Guidelines	Published by	Published year	Link	Subscription required
Dental infection	Antimicrobial therapy guideline for patients with periodontal disease	Japan Society of Periodontology	2010	http://www.perio.jp/publication/upload_file/jsp_guideline_antimicrobial_therapy.pdf	N
	JSP Clinical Practice Guideline for Periodontal Treatment	Japan Society of Periodontology	2015	http://www.perio.jp/publication/upload_file/guideline_perio_plan2015.pdf	N
	JAID/JSC Guide to the Clinical Management of Infectious Diseases - Dental Infection	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2016	http://www.chemotherapy.or.jp/guideline/jaidjsc-kansenshochiryu_shisei.pdf	N
	Japanese Clinical Practice Guidelines for antimicrobial prophylaxis in surgery	Japanese Society of Chemotherapy/Japan Society for Surgical Infection	2016	http://www.chemotherapy.or.jp/publications/publications.html#jutugo	Y
	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y
Bacterial conjunctivitis	JAID/JSC Guide to the Clinical Management of Infectious Diseases	The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy	2019	http://lifescience.co.jp/shop2/index_0190.html	Y

JAID: Japanese Association of Infectious Disease, JSC: Japanese Society of Chemotherapy, COPD: Chronic obstructive pulmonary disease, JSP: Japan Society of Periodontology, Y: Yes, N: No

non-high-risk populations, whereas others may not prescribe prophylactic antimicrobials to high-risk populations (37, 38).

2. Epidemiology in Japan

The national claims database (the National Database for Prescription and National Health Check-up) and the sales database are the two major databases that can be used for a retrospective estimation of antimicrobial use in Japan (3, 39, 40). Regarding disease-specific antimicrobial use, we have not developed an on-time surveillance system; therefore, as an alternative, the NDB can be used as a tool to estimate the number of prescribed antimicrobials using the primary and co-diagnosis codes.

In an earlier study, it was observed that among 691 immunocompetent patients aged 15-64 years with acute respiratory tract infection, excluding influenza, who visited 5 clinics between October 2004 and April 2005, nonspecific respiratory tract infections accounted for 80%, acute rhinosinusitis 2%, acute pharyngitis 13%, and bronchitis accounted for 5% (41). When the researchers followed the ACP guideline (42), 5% of all patients required antimicrobials at the initial visit, and an additional 2% of them needed antimicrobials in the subsequent visits (41). Higashi et al. analyzed NDB data recorded between January and March 2005 and found that oral antimicrobials were prescribed to 60% of patients with nonbacterial upper respiratory tract infection (43). Third-generation cephalosporins were the highest at 46%, followed by macrolides at 27% and fluoroquinolones at 16%. More oral antimicrobial prescriptions were found in the clinics rather than inter hospitals without any significant inter-hospital or interregional differences.

The results of the more recent studies that had analyzed the NDB and an equivalent national claims database regarding outpatient antimicrobial prescribing were similar to or extend those of previous studies. Despite an overall reduc-

tion in its prescription rate, they found that inappropriate antimicrobial prescribing in nonbacterial acute respiratory tract infection and higher antimicrobial prescribing under the diagnosis of infectious diseases such as acute respiratory tract infection and gastrointestinal tract infection for which antimicrobials were rarely indicated (44, 45). Furthermore, in children (aged <15 years), there was no statistically significant change in antimicrobial prescribing between 2013 and 2016, and the antimicrobial prescription rates were the highest among those aged 1-5 years (46). In line with adults, macrolides and third-generation cephalosporins were the most commonly prescribed antimicrobials.

We found no report describing the current practice for SSTIs, including its management and antimicrobial prescribing pattern. Regarding the urogenital infection, the Japanese Association for Infectious Disease and the Japanese Society of Chemotherapy discussed about asymptomatic bacteriuria and they followed the US guideline recommendations (47). However, we found no surveillance or database addressing the burden of asymptomatic bacteriuria in the community and the use of antimicrobials for this condition in Japan.

Regarding Japanese dental practices, we found no data to describe total antimicrobial use. Nagashima et al. monitored antimicrobial use in the 18 privately funded dental university hospitals between 1983 and 2013 and found that the proportion of antimicrobial use among all prescriptions was increased from 22% to 33%, the use of oral cephalosporins was increased from 53% to 67% and that of oral penicillin declined from 33% to 23%, and oral macrolides were often prescribed in the long-term antimicrobial treatment (>7 days) (48). Amari et al. conducted a questionnaire survey on randomly selected 500 dental practitioners working in 500 Japanese urban dental facilities in 2011 (49). They found that among the 252 responders (50.4%), 46% prescribed

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prophylactic antimicrobials for any dental procedure, 90% responded that 3-4 days of prescription was appropriate for prophylactic antimicrobial use, 67.1% reported using antimicrobials after dental procedures but only 12% reported prescribing these prior to procedures, and third-generation cephalosporins, despite the lack of indications by guidelines (36, 50), were the most often prescribed antimicrobials for both prophylaxis and treatment (49). In a more recent survey, despite the fact that >80% of responders understood the indications of antimicrobials for infective endocarditis prophylaxis described in the guidelines, several factors, including a fear of liability, misconception, and culture, directed their unnecessary antimicrobial prescribing practices (51).

3. The frequency of complications and the impact of antimicrobial prescription on the prevention of complications

A multicenter prospective study was conducted in two tertiary and one community hospital in Canada, and among 1,529 adults presenting to the emergency department over a period of 12 months, 184 (12%) were diagnosed with adverse drug events, and the antimicrobial use within 1 week was one of the important variables that was associated with the diagnosis of adverse drug events (52). The calculated excess risk of suppurative complications of respiratory tract infections in children who did not receive an antibiotic was estimated at 3.8 per 10,000 (53). In the systematic review, no evidence of benefit from antimicrobial use was found for the common cold or for persisting acute purulent rhinitis in children or adults (54). Antimicrobials appeared to be ineffective in preventing further bacterial complications following upper respiratory tract infections (55).

Apart from specific patient populations such as pregnant patients and patients undergoing urologic procedures, treatment for asymptomatic bacteriuria does not appear to change the outcome. A prospective study conducted in the US, which followed up 358 elderly subjects for 8 years with urine cultures being analyzed every 6 months, showed no effect on mortality between the patients with asymptomatic bacteriuria who were treated and those who were not treated (31, 56). Similarly, in the randomized controlled study including institutionalized elderly subjects with asymptomatic bacteriuria, the incidence of symptomatic urinary tract infection and death was similar between the treatment group and the nontreatment group (31, 57). Rather, there was an increasing tendency of adverse drug events such as rash, diarrhea, and candidiasis in the treatment group.

When healthcare providers offered more patient education, patient satisfaction did not appear to be reduced even when antimicrobials were not prescribed to those with a diagnosis of acute respiratory tract infection (41, 58). In a similar manner, the denial of a request for antimicrobials was not associated with lower satisfaction with clinicians (59).

The clinical guidelines and guidance published in Japan have covered the fields of almost all infectious diseases. Research conducted using sales data and NDB were useful for the estimation of total antimicrobial use in Japan, though the estimated quantity of prescribing per diagnosis and its validity may not be reliable due to the nature of the administrative claims database (e.g., lack of validation of diagnostic codes, linkage of other data sets such as microbiology databases, and granularity of clinical data) (45, 60-62). As such, at this stage, the effect of necessary and unnecessary antimicrobial use on the health outcomes can only be estimated through individual-based research.

Outside Japan, acute respiratory tract infection, SSTIs (especially antimicrobial use for localized abscess post drainage), asymptomatic bacteriuria, and dental practice have been the growing areas of focus for optimizing outpatient antimicrobial prescribing (7, 19-21). Similarly, unnecessary antimicrobial use in cases of acute respiratory tract infection and acute gastroenteritis has been well described in Japan over the past decade (41, 43, 63), and the Manual was developed to address this long-standing challenge and to propel outpatient antimicrobial stewardship forward (2). Antimicrobial use in Japan was twice more common in the outpatient setting as in the hospital setting in 2017; and the decline of antimicrobial use between 2016 and 2017 in adults and older children was smaller than that in younger children (64). Therefore, the efforts of implementing antimicrobial stewardship interventions including the Manual should be continued. Of note, the Manual excludes those patients younger than 5 years of age. Among children aged <15 years, the rate of antimicrobial prescribing was the highest among those aged 1-5 years (46). These findings have emphasized the need to address unnecessary antimicrobial use and to develop intervention for providers taking care of children.

There is an ongoing discussion on prescribing antimicrobial post incision and drainage of localized abscess to reduce treatment failure (65). We did not find a study on antimicrobial use for SSTIs in Japan, due to which we were not able to assess the validity and necessity of the prescription. Similarly, we lacked data to assess the incidence of asymptomatic bacteriuria and the frequency of antimicrobial use for this condition. With an aging population in Japan (i.e., those aged ≥ 65 years accounted for 25% in 2013) (66), a high prevalence of asymptomatic bacteriuria likely exists, leading to excessive unnecessary antimicrobial prescribing. Because unnecessary antimicrobial treatment of asymptomatic bacteriuria is recognized as an important contributor to promote the emergence of AMR and *Clostridioides difficile* infection (19), it will be increasingly important for healthcare policies to develop a system to assess the current situation in Japan.

We also lack data describing the current antimicrobial

prescribing in the Japanese dental practices. According to the questionnaire survey administered to dental providers, indications, choices, and the duration of antimicrobial use for both treatment and prophylaxis for endocarditis appear to be variable (48, 49). The Japanese Society of Chemotherapy and Japan Society for Surgical Infection have published a clinical guideline for the prevention of postsurgical infection in dental practice (Table). However, in reality, the Japanese national insurance does not cover the preventive use of antimicrobials, and the degree of implementation of such guidelines is thus questionable.

In conclusion, our findings suggest that the Manual can extend the guidance to immunocompetent children aged <5 years in conjunction with the ongoing emphasis on the judicious antimicrobial use in acute respiratory tract infection and acute diarrhea in healthy adult population commonly seen by internal medicine providers. Further studies are required to develop a national system to capture the burden of SSTIs and asymptomatic bacteriuria in addition to the current antimicrobial prescribing behaviors. We understood that the heterogeneous antimicrobial prescribing behavior in the Japanese dental practices does not align with the clinical guidelines, and intervention for dental practices, such as promoting the use of penicillin in minor surgery, can be launched by implementing guidelines for dental practitioners. As there are extensive infectious disease guidelines, understanding the facilitators and the obstacles of guidelines roll out is also a crucial step for promoting further judicious and necessary use of antimicrobials.

The authors state that they have no Conflict of Interest (COI).

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