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Rates and determinants of antibiotics and probiotics prescription to children in Asia-Pacific countries

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RESEARCH ARTICLE

Abstract

Antibiotic therapy may have important side effects. Guidelines recommend the administration of specific probiotics to reduce the risk of antibiotic-associated diarrhoea (AAD). The rates and determinants of antibiotics and co-prescription of probiotics in children remain poorly known in Asia-Pacific countries, which are very heterogenous in terms of economic development, health care organization and health policies. A survey among general practitioners (GPs) and paediatricians was performed in seven countries of the Asia-Pacific area (Australia, Japan, Indonesia, India, China, Singapore, and South Korea). Physicians completed an online questionnaire that explored their current habits and the determinants for prescribing antibiotics and probiotics. For the 731 physicians who completed the questionnaire (390 paediatricians and 341 GPs), 37% of all consultations for a child led to the prescription of antibiotics (ranging from 17% in Australia to 47% in India). A large majority of physicians (84%) agreed that antibiotics disrupted gut microbiota and considered probiotics an effective intervention to prevent AAD (68%). However, only 33% co-prescribed probiotics with antibiotics (ranging from 13% in Japan to 60% in South Korea). The main reasons for prescribing probiotics were previous episodes of AAD (61%), presence of diarrhoea (55%), prolonged antibiotic treatment (54%) or amoxicillin-clavulanic acid therapy (54%). Although current local guidelines recommend the use of selected probiotics in children receiving antibiotics in Asia-Pacific area, the rates of antibiotics and probiotics prescription significantly vary among countries and are deeply affected by country-related cultural and organisational issues.

Keywords: antibiotic-associated diarrhoea, probiotics, antibiotics resistance, antibiotics prescriptions, microbiota

1. Introduction

Since their discovery, antibiotics have provided great benefits in the treatment of infectious diseases, but nowadays there is a worldwide concern for their excessive use leading to a WHO taskforce action (Center for Disease Control and Prevention, 2019a; Ohl and Luther, 2011; Van Boeckel *et al.*, 2014; World Health Organization, 2014). Indeed, together with the decrease in the development of new antibiotics, there is a simultaneous increase of

the prevalence of drug-resistant pathogens (e.g. resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, *Clostridium difficile*) associated with high morbidity and mortality (Center for Disease Control and Prevention, 2019b; Frieri *et al.*, 2017).

Reduction of unnecessary antibiotic treatment is one of the key factors that can contribute to limit the emergence of resistant bacteria and other serious side effects. Antibiotic treatments, more particularly broad-spectrum antibiotics, disturb the gastrointestinal microflora and are therefore responsible for short-term symptoms like antibiotic-associated diarrhoea (AAD), which occurs in 5 to 40% of patients depending on the antibiotic used (Blaser, 2016; Dominguez-Bello *et al.*, 2019; Kim *et al.*, 2017). Symptoms of AAD are generally mild, but they favour gut colonization by opportunistic pathogens. *C. difficile* infection in children occurs in approximately 20% of AAD (McFarland *et al.*, 2016; Wistrom *et al.*, 2001). This infection can be responsible for a broad spectrum of disorders, from self-limiting diarrhoea to fulminant pseudomembranous colitis or septic shock (Lo Vecchio *et al.*, 2017; McFarland *et al.*, 2016; Surawicz *et al.*, 2013; Yassin *et al.*, 2001). In addition, there is now increasing evidence that dysbiosis persists after antibiotic discontinuation and may contribute to life-long consequences (e.g. allergy, obesity or inflammatory bowel diseases) (Sheehan and Shanahan, 2017; Stephen-Victor and Chatila, 2019; Torres-Fuentes *et al.*, 2017). Long-term persistence of antibiotic resistance genes in the human gut has also been shown with some antibiotics (Jernberg *et al.*, 2010).

Probiotics are defined as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' according to the World Health Organization (FAO/WHO, 2002; Gibson *et al.*, 2017). Various strains of microorganisms are used as probiotics for the treatment of infectious diarrhoea or AAD in children, the most common being strains of lactobacilli and the yeast *Saccharomyces boulardii*. Recent meta-analyses reported that co-administration of selected probiotic strains with antibiotics prevented AAD with relative risk (RR) varying from 0.43 to 0.61 according to trials and might prevent *C. difficile* infection (Guo *et al.*, 2019; Johnston *et al.*, 2018; McFarland, 2006, 2015; Pattani *et al.*, 2013; Szajewska and Kolodziej, 2015). Clinical trials performed in Asia investigated the efficacy of the co-prescription of probiotics with scattered results. Thus, a study performed in China studied the efficacy of *S. boulardii* for the prevention and treatment of diarrhoea in children treated with intravenous antibiotics for lower respiratory infections (Shan *et al.*, 2013). The risk of developing AAD was significantly reduced (RR=0.22; 95% CI: 0.1-0.5). This protective effect of probiotics was however not observed in a Korean retrospective study to evaluate probiotics for the prevention of *C. difficile* infection (Na *et al.*, 2014). However, in this last case, various strains of probiotics were co-prescribed (*Lactobacillus acidophilus, Bacillus subtilis, Streptococcus faecium, S. boulardii*, and *Lactobacillus rhamnosus* being the most frequent).

Recently, recommendations for the usage of probiotics in the Asia-Pacific children were proposed and specific probiotic strains, namely *S. boulardii* CNCM I-745 and *L. rhamnosus* GG, were recommended for prevention of AAD (Cameron *et al.*, 2017). *S. boulardii* CNCM I-745 was also suggested to prevent *C. difficile* diarrhoea. The same probiotic strains are recommended in country-specific guidelines (Chen *et al.*, 2018) and also guidelines from other continents (Cruchet *et al.*, 2015; Guarino *et al.*, 2015; Szajewska *et al.*, 2016). In addition, the same strains are recommended in adjunct to rehydration therapy for acute infectious diarrhoea. However, the decision of co-prescribing probiotics to prevent AAD is left to the physician based on case-by-case evaluation of clinical conditions and risk factors.

The Asia-Pacific countries are very heterogenous in terms of economic development, health care organization and health policies (World Health Organization, 2008). Moreover, different diets, genetic factors and cultures are likely to affect the geographic variations in the composition of the gut microbiota and the prevalence and consequences of AAD. The aim of the present survey was to investigate the current habits of physicians from the Asia-Pacific region in terms of antibiotics use and probiotics prescription in children.

2. Materials and methods

This survey on the medical attitudes towards antibiotics and probiotics co-prescription in children was performed in seven countries of the Asia-Pacific region (Australia, Japan, Indonesia, India, China P.R., Singapore, South Korea) between August and September 2018. The main objectives of the survey were to assess the current habits in terms of antibiotics use in children, to understand the determinants of use of antibiotics, to assess the current use of probiotics co-prescription and to identify the expected effects of probiotics.

No clinical data from patients was recorded in this survey which analysed the opinions and habits of physicians about their clinical practices. Therefore, the approval of an ethics committee was not necessary. The questionnaire included items on antibiotic prescription rates, probiotic co-prescription and medical attitude for a practical clinical case, namely a 4-year-old child with a 2-day history of acute respiratory symptoms and fever. The survey was mainly a web-based interview, but in some countries (Indonesia, India, Singapore, South Korea) a mixed data collection methodology was implemented to enhance fieldwork capabilities. The average duration for completing the

questionnaire was 10 min. Physicians were compensated for their participation (except Chinese physicians and a fraction of Indian physicians who were not compensated).

The questionnaire benefited from the endorsement of the World Gastroenterology Organization. The questionnaire was split into two parts for general practitioners (GPs) or primary care providers and paediatricians. GPs should have at least 25% of children in their patient base to participate to the survey. In Japan, GPs do not see so many children because the latter are managed by paediatricians. To meet the recruitment objective, there was an additional paediatrician recruitment.

The questionnaire was translated and answered by physicians in the following languages: English for Australia, India, and Singapore and in local language for Japan, Indonesia, China, and South Korea. The sample size was determined in order to achieve statistical robustness and reliable analyses both on the total sample and on each country and specialty. Overall, 731 physicians were enrolled including 341 GPs and 390 paediatricians: Australia (50 GPs/50 paediatricians), Japan (20/80), Indonesia (50/50), India (70/70), China (70/70), Singapore (31/20), and South Korea (50/50).

The analysis was essentially descriptive and no formal hypothesis was tested. Categorical variables were summarised by frequencies and proportions and continuous variables were summarised by averages, median and ranges. Results were presented as means of all countries and after comparisons between each country and all countries (country vs total) and between specialties (GPs vs paediatricians). An overall weighting was applied when reading total results (sum of countries and/or specialties) to provide the same weight in results regardless the number of physicians who answered the question. For results on country and specialty level (no sum), results were unweighted. Comparative tests were performed with an alpha risk set at 5%. There was no adjustment for multiple comparisons.

3. Results

Medical attitudes toward antibiotic treatment in children

For the 731 physicians of the survey, a consultation with a child led to antibiotic prescription in 37% of cases with substantial differences between countries (e.g. only 17% in Australia, but 47% in India) (Table 1). There was a relationship between age and antibiotic prescription rates, although this relationship was different in different countries (Table 1). Overall antibiotics were more frequently prescribed to young children (3-6 years) with some exceptions according to countries: India (0-1 year, 37%), Singapore (12-18 years, 66%), and South Korea (1-3 years, 39%). Moreover, GPs prescribed antibiotics more frequently to older children (24% for 6-12 years and 30% for 12-18 years) whereas paediatricians prescribed them more frequently to younger children (15% to 0-1 year and 28% to 1-3 years).

A specific question was related to the role of antibiotics in perturbating intestinal microbiota. The vast majority of responders agreed on this side effect (Table 1). However, the main risk that detracted from an antibiotic prescription to a child was the risk of antibiotic resistance (36%), possible side effects (26%), lack of efficacy (25%) and a possible alteration of the intestinal microbiota (13%) (Table 2). Some risks were perceived with a higher intensity in some countries: antibiotic resistance in South Korea (59%) and Indonesia

Table 1. Prescription of antibiotics in APAC countries: attitudes of physicians.[1]

	AUS (n=100)	JPN (n=100)	IDN (n=100)	IND (n=140)	CHN (n=140)	SGP (n=51)	KOR (n=100)	Total (n=731)
Consultations leading to AB prescription[2]	17% ↓	23% ↓	42%	47% ↑	43% ↑	46% ↑	38%	37%
Main age group for AB prescription[3,4]	3-6 y, 32%	3-6 y, 35%	3-6 y, 38%	0-1 y, 37%	3-6 y, 31%	12-18 y, 66%	1-3 y, 39%	3-6 y, 27%
Agree about AB disrupting intestinal microbiota[5]	85%	95% ↑	69% ↓	76%	94% ↑	79%	86%	84%

[1] AB = antibiotics; AUS = Australia; JPN = Japan; IDN = Indonesia; IND = India; CHN = China; SGP = Singapore; KOR = South Korea; ↑ = significantly higher ($P<0.05$) than the total (last column); ↓ = significantly lower ($P<0.05$) than the total (last column).

[2] Question C1: 'Over the past year, what was the approximate percentage of all children consultations that had led to antibiotic prescription?'

[3] Question C2: 'In your general practice, to which age group do you prescribe antibiotics more commonly?'

[4] n=99 for Australia and Japan.

[5] Question C4: 'Would you say that you agree or not with the following sentence: prescribing an antibiotic to children is disturbing the intestinal microbiota?'

Table 2. Main risks associated to antibiotics for children according to physicians.[1,2]

	AUS (n=100)	JPN (n=100)	IDN (n=100)	IND (n=140)	CHN (n=140)	SGP (n=51)	KOR (n=100)	Total (n=731)
Antibiotic resistance	30%	19% ↓	52% ↑	16% ↓	34%	41%	59% ↑	36%
Side effects	14% ↓	7% ↓	26%	53% ↑	37% ↑	28%	15% ↓	26%
Lack of efficacy	47% ↑	64% ↑	4% ↓	14% ↓	14% ↓	15% ↓	15% ↓	25%
Alteration of intestinal microbiota	8%	9%	17%	17%	15%	16%	9%	13%
None	1%	1%	1%	0%	0%	0%	2%	1%

[1] Question C3: 'Please choose and rank by importance the potential risks that detract you from prescribing antibiotics to children'.
[2] AUS = Australia; JPN = Japan; IDN = Indonesia; IND = India; CHN = China; SGP = Singapore; KOR = South Korea; ↑ = significantly higher (P<0.05) than the total (last column); ↓ = significantly lower (P<0.05) than the total (last column).

(52%), side effects in India (53%) and China (37%) and lack of efficacy in Japan (64%) and Australia (47%).

Concerns about consequences of antibiotic treatment

The consequences of antibiotic treatment considered the most worrisome were antibiotic resistance (65%), allergic reaction (50%), loss of antibiotic efficacy (42%), antibiotic-associated diarrhoea (50%), long-term consequences of antibiotics (43%) and *C. difficile* diarrhoea (26%) (Figure 1A). Some consequences of antibiotic treatment were perceived as significantly more worrisome in some countries: antibiotic resistance in South Korea (84%) and in China (76%), allergic reactions in India (88%), antibiotic-associated diarrhoea in China (61%) and *C. difficile* diarrhoea in China (36%) and Singapore (57%).

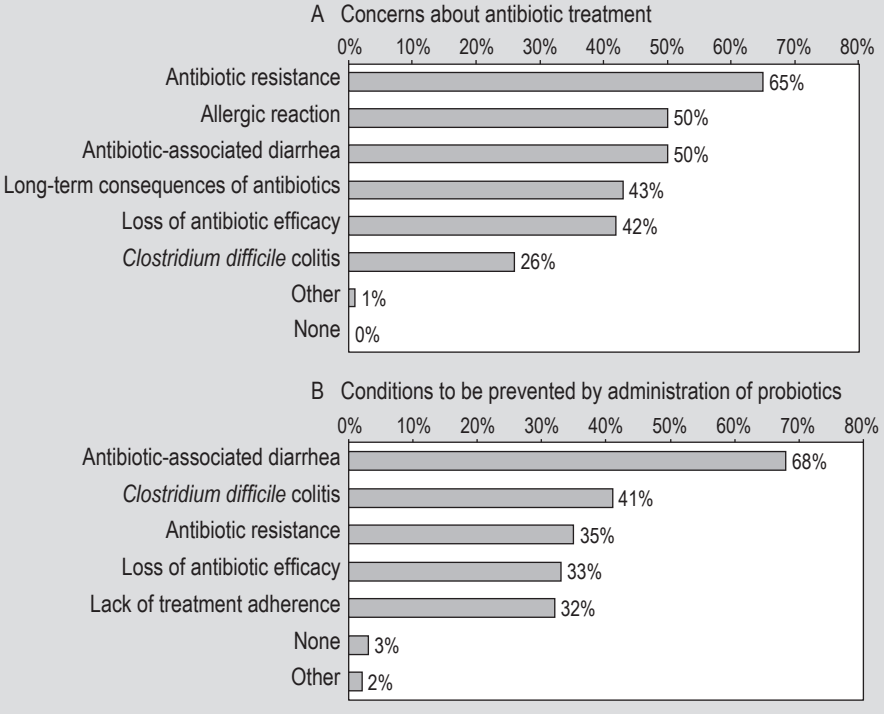

Figure 1. Concerns about antibiotic treatment and conditions considered to be prevented by probiotics. (A) Concerns about antibiotic treatment (Question C5: 'Among the following consequences of antibiotic treatment, which is/are the most worrisome to children in our opinion?') and (B) conditions considered to be prevented by probiotics (Question C6: 'Which of the following conditions, in your opinion, may be prevented by the administration of probiotics to children?').

Among these consequences of antibiotics, a majority of physicians (68%) agreed that AAD (Figure 1B) was the main condition that could be prevented by administration of probiotics (94% in China and 90% in South Korea, but only 19% in Japan); *C. difficile* colitis was quoted by 41% of physicians (only 18% in Japan). Antibiotic resistance was considered to be prevented by administration of probiotics by 35% of physicians (61% in Japan and 58% in India).

Co-prescription of probiotics and their indications

Overall, probiotics were prescribed in 33% of children treated with antibiotics (Table 3). Co-prescription of antibiotics was more frequent in South Korea (60%) and in Singapore (40%) and much less frequent in Australia (13%). Figure 2 presents together antibiotic vs probiotics prescription rates and perceived risk of antibiotic disturbing the intestinal microbiota.

The main determinants of co-prescription of probiotics were mainly children with previous episodes of antibiotic-associated diarrhoea (61%), with diarrhoea (55%), receiving antibiotics with an increased risk of diarrhoea (e.g. amoxicillin/clavulanic acid) (54%), receiving prolonged treatment with antibiotics or broad-spectrum antibiotics (47%) (Table 3). However, the pattern of determinants of probiotic prescription varied significantly according to countries. Thus, almost all Australian physicians (96%) responded they would co-prescribe probiotics in case of prolonged treatment with antibiotics whereas South-Korean physicians were more prone to co-prescribe probiotics in case of previous episodes of antibiotic-associated diarrhoea (83%).

Clinical case: 2-day history of acute respiratory and symptoms and fever

A clinical case was proposed to physicians and their specific prescriptions were recorded. The case was a 4-year-old child with 2-day history of acute respiratory symptoms and fever. The question focused on the preferred initial management. Most physicians would only prescribe medications for symptom relief (62%) and adopt a wait-and-see approach (56%) (Table 4). Antibiotic therapy was prescribed by 26% of physicians. The prescription of medications for symptom relief was much more frequent in India (96%) whereas the wait-and-see approach was more frequent in Australia (77%) and Indonesia (68%). Prescription of antibiotics was more frequent in South Korea (52%) and Singapore (44%).

According to physicians, 42% of parents expect antibiotics for their sick child during a first visit for an acute respiratory

Table 3. Rates of co-prescription of probiotics and their main determinants.[1]

	AUS (n=53)	JPN (n=81)	IDN (n=90)	IND (n=140)	CHN (n=138)	SGP (n=51)	KOR (n=100)	Total (n=653)
Probiotics co-prescription with AB[2]	13% ↓	33%	30%	26% ↓	31%	40% ↑	60% ↑	33%
Determinants of co-prescription[3]								
Previous episodes of AAD	74%	70%	51%	42% ↓	70%	45% ↓	83% ↑	61%
Presence of diarrhoea	62%	64%	50%	30% ↓	64%	39% ↓	83% ↑	55%
Prolonged treatment with antibiotics	96% ↑	42% ↓	28% ↓	61%	65% ↑	37% ↓	64%	54%
AB with increased risk of diarrhoea[4]	66%	67% ↑	34% ↓	52%	55%	29% ↓	82% ↑	54%
Receiving broad-spectrum AB	70% ↑	43%	30% ↓	40%	57%	34% ↓	64% ↑	47%
Underlying condition/comorbidities	68% ↑	12% ↓	28%	66% ↑	41%	25% ↓	30%	37%
Bloody diarrhoea	26%	28%	31%	28%	25%	43% ↑	37%	32%
Clostridum difficile infection	55% ↑	24%	13% ↓	26%	45% ↑	35%	36%	32%
Malnutrition	45% ↑	14% ↓	6% ↓	56% ↑	48% ↑	29%	15% ↓	30%
<3 years of age	26%	30%	17% ↓	16% ↓	36%	27%	51% ↑	29%
Hospitalised children	21%	5%	23%	56% ↑	25%	33%	24%	28%
Children attending day-care	17%	11%	9% ↓	41% ↑	12%	28% ↑	9% ↓	19%
Intravenous AB	13%	4% ↓	4% ↓	38% ↑	24%	19%	18%	18%
Mean number of indications quoted	6.4 ↑	4.1 ↓	3.3 ↓	5.5 ↑	5.7 ↑	4.2 ↓	6.0 ↑	5.0

[1] AAD = antibiotic-associated diarrhoea; AB = antibiotics; AUS = Australia; JPN = Japan; IDN = Indonesia; IND = India; CHN = China; SGP = Singapore; KOR = South Korea; ↑ = significantly higher ($P<0.05$) than the total (last column); ↓ = significantly lower ($P<0.05$) than the total (last column).

[2] Question C7: 'For which percentage of children receiving antibiotics do you co-prescribe probiotics?'.

[3] Question C8: 'In which type of paediatric patients receiving antibiotics, would you consider co-prescribing probiotics?' (base: at least 1% of patients co-prescribed with antibiotics).

[4] e.g. amoxicillin/clavulanic acid.

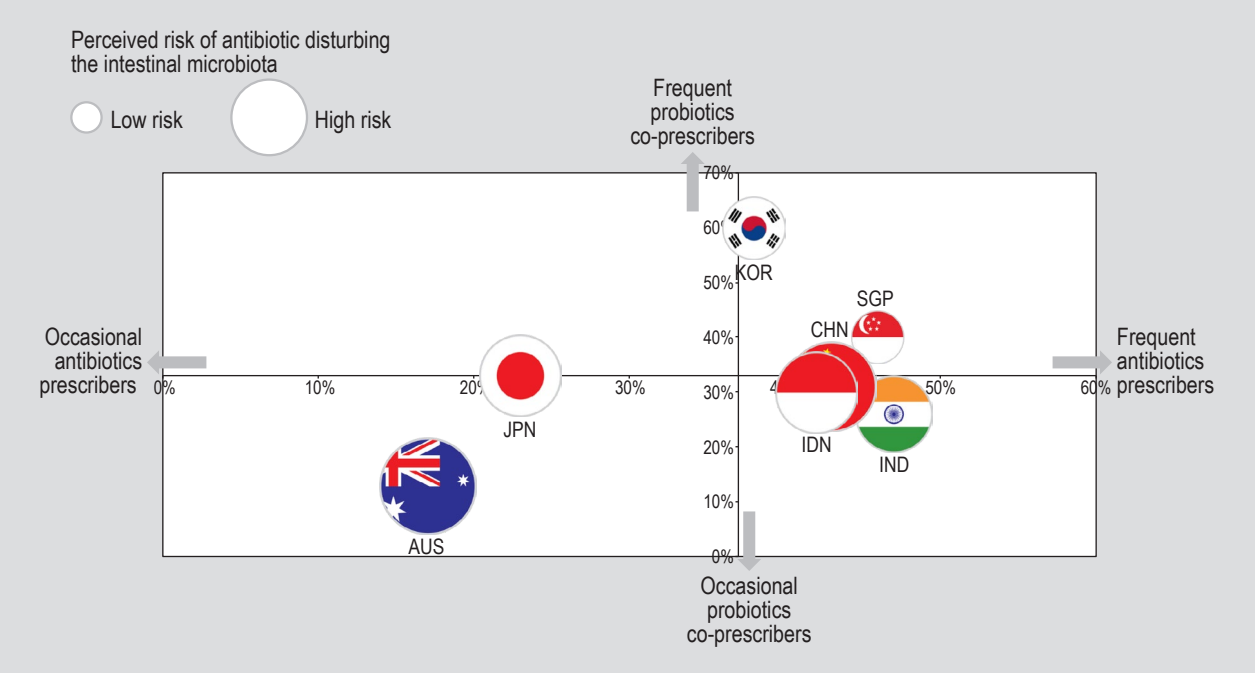

Figure 2. Antibiotic vs probiotics prescription rates in different countries. The flag scheme of data shows a cluster of five countries with frequent antibiotic prescribers whereas two (Japan and Australia) prescribe antibiotics occasionally. Probiotics prescription is also scattered and discrepancies are observed between the perceived risk of antibiotics in disrupting intestinal microbiota (represented here by the magnitude of circular flags) and probiotics prescription.

Table 4. Medical approach to a 4-year-old child with a 2-day history of acute respiratory symptoms and fever.[1]

	AUS (n=100)	JPN (n=100)	IDN (n=100)	IND (n=140)	CHN (n=140)	SGP (n=51)	KOR (n=100)	Total (n=731)
Physician's attitude[2]								
Give medication for symptom relief	42% ↓	51% ↓	69%	96% ↑	65%	62%	51% ↓	62%
Adopt wait-and-see approach	77% ↑	31% ↓	68% ↑	53%	65%	65%	30% ↓	56%
Prescribe antibiotics (AB)	6% ↓	25%	24%	19%	11% ↓	44% ↑	52% ↑	26%
Other	13% ↑	17% ↑	0% ↓	0% ↓	11%	0% ↓	4%	6%
Prescribe nothing	6% ↑	0%	0%	0%	1%	0%	1%	1%
Parents expecting AB prescription for their child[3]	41%	32% ↓	48%	32% ↓	53% ↑	44%	46%	42%

[1] AB = antibiotics; AUS = Australia; JPN = Japan; IDN = Indonesia; IND = India; CHN = China; SGP = Singapore; KOR = South Korea; ↑ = significantly higher ($P<0.05$) than the total (last column); ↓ = significantly lower ($P<0.05$) than the total (last column).
[2] Question C10: 'You see a 4-year old child with a 2-day history of acute respiratory symptoms and fever. The parents request antibiotics. You would...'.
[3] Question C11: 'In your practice, what percentage of parents expect an antibiotic prescription for their child during their first visit for an acute respiratory infection and fever?'.

infection and fever. However, no relationship was detected between the rates of patients expecting antibiotic treatment and the rates of prescription of antibiotics. Thus, although 53% of Chinese parents expect antibiotics for their child, only 11% of physicians reported to prescribe them. In contrast, in South Korea, 46% of parents expect antibiotics for their child and indeed they were prescribed by 52% of physicians.

The severity of specific symptoms was the main determinant for antibiotic prescription as reported by 67% of all responders (78% in Australia and 86% in India) (Table 5). Australian physicians considered mainly clinical conditions and guidelines to take their decision of antibiotic prescription. Singaporean physicians gave more importance to drug cost than the other physicians and less importance

Table 5. Determinants of antibiotic prescription for acute respiratory symptoms with fever.[1,2]

	AUS (n=100)	JPN (n=100)	IDN (n=100)	IND (n=140)	CHN (n=140)	SGP (n=51)	KOR (n=100)	Total (n=731)
Clinical determinants								
Severity of specific symptoms	78% ↑	55% ↓	61%	86% ↑	66%	46% ↓	73%	67%
Underlying condition/comorbidities	74% ↑	37%	35% ↓	58% ↑	45%	33% ↓	41%	46%
Age of patient	66% ↑	25% ↓	45%	14% ↓	63% ↑	53%	39%	44%
Immediate clinical issue	72% ↑	29% ↓	42%	26% ↓	35%	30% ↓	52% ↑	41%
Antibiotic therapy-related determinants								
Safety profile of the antibiotic	52%	26% ↓	43%	71% ↑	79% ↑	46%	26% ↓	49%
History of AAD	35%	19% ↓	30% ↓	68% ↑	58% ↑	38%	45%	42%
Convenient dosing	46% ↑	12% ↓	39% ↑	24%	36%	23%	15% ↓	28%
Cost	13%	3% ↓	12%	9%	16%	26% ↑	7%	12%
Other determinants								
Guidelines/medical literature	72% ↑	45%	27% ↓	74% ↑	44%	31% ↓	57%	50%
Adherence to treatment	26%	5% ↓	24%	28%	32%	35% ↑	27%	25%
Parents' preference	16%	35% ↑	8% ↓	10% ↓	6% ↓	24%	25%	18%
Mean number of determinants quoted	6.0 ↑	3.3 ↓	4.3 ↓	5.0 ↑	5.4 ↑	4.3 ↓	4.4	4.7

[1] AAD = antibiotic-associated diarrhoea; AUS = Australia; JPN = Japan; IDN = Indonesia; IND = India; CHN = China; SGP = Singapore; KOR = South Korea; ↑ = significantly higher (P<0.05) than the total (last column); ↓ = significantly lower (P<0.05) than the total (last column).
[2] Question C12: 'When deciding to prescribe an antibiotic therapy for acute respiratory symptoms with fever, which of the following factor(s) do you consider?'.

to clinical determinants. Japanese physicians considered parents' preference more frequently than physicians from other countries and considered with lower rates clinical determinants and antibiotherapy-related determinants. In China, physicians appeared to be mainly concerned about antibiotherapy-related determinants such as safety and antibiotic resistance.

When considering the prescription of an antibiotic for acute respiratory infection in a child, 68% of physicians most commonly prescribed beta-lactams (e.g. amoxicillin). Macrolides were prescribed by only 18% of physicians. The rate of prescription of beta-lactams increased to 94% in Australia, 81% in Indonesia and 78% in South Korea. In Japan, macrolides (e.g. clarithromycin) and beta-lactams were equally prescribed (46 and 48%, respectively).

4. Discussion

This survey was performed in seven Asia-Pacific countries which are heterogenous in terms of economic development, health care organization and health policies. According to the International Bank for Development and Reconstruction, their level of development varies from low-income (India) or lower middle income (China, Indonesia) to high-income countries (Australia, Japan, South Korea, and Singapore) (WHO, 2008). In addition, India, Indonesia, and China belong to the 15 countries with the highest prevalence of pneumonia and diarrhoea deaths (International Vaccine Access Center, 2018).

Even in the four countries with high income, the habits of physicians about antibiotics and co-prescription of probiotics in children are very heterogenous. A large majority of the Australian physicians reported that their medical attitude was guided by literature and official recommendations. As a consequence, their prescriptions of antibiotics and co-prescription of probiotics to children were not frequent. For the first visit of a child with acute respiratory symptoms, they adopted generally a wait-and-see approach and did not prescribe antibiotics straightaway. The reasons that led them to prescribe antibiotics were mainly clinical determinants such as severity of symptoms, immediate clinical issue, underlying conditions and age of patients.

Japanese physicians also had low rates of prescription of antibiotics and, for a child with acute respiratory symptoms and fever, they rarely prescribed antibiotics immediately. Contrary to the other countries, they considered parents' preferences for antibiotic prescription with relatively high rates, but clinical determinants and antibiotic therapy-related determinants considered for antibiotic prescription were less often quoted than for the other countries. Moreover, in contrast with the physicians from the other countries, only a small percentage of Japanese

physicians considered that AAD could be prevented by the administration of probiotics.

Singaporean physicians had prescription habits very different from other countries: the rates of consultations with antibiotic prescription and co-prescriptions with probiotics were significantly higher than other countries. They tended to prescribe immediately antibiotics for acute respiratory symptoms and fever. Clinical determinants for antibiotic prescription were less frequently quoted, but cost appeared to be a significant factor for decision. The fact that Singaporean physicians may provide medications could explain these features.

In South Korea, physicians adopted less frequently a wait-and-see attitude and prescribed frequently antibiotics for acute respiratory symptoms and fever in a child. Co-prescription of probiotics was very high. Of note, probiotics with drug status are reimbursed in young children under the age of 6 in South Korea by the National Health System which could explain this result.

Indian physicians reported the highest rates of antibiotic prescriptions; however, for a 2-day history of acute respiratory symptoms and fever they reported a low rate of antibiotic prescription. Moreover, Indian physicians appeared to be more worried about side effects and safety profile of antibiotics than physicians from the other countries.

Chinese physicians were significantly more concerned about safety profile and antibiotic resistance when deciding for antibiotic prescription in acute respiratory symptoms with fever. Indonesian physicians had the highest rates among low- or middle-income countries to adopt a wait-and-see approach.

There were some discrepancies between the knowledge of a risk of resistance to antibiotics and daily practice. Thus, it is interesting to note that the two countries with the lower rates antibiotic resistance as main risks associated to antibiotics were those with the highest rates of antibiotic prescription. Nevertheless, for a 2-day history of acute respiratory symptoms and fever, their attitudes diverged: almost half of Singaporean physicians prescribed immediately antibiotics compared to only one out five Indian physicians. Patient profiles in their daily practice could explain these differences.

Overall, the mean rates of prescription of antibiotics and probiotics and the perceived risks related to antibiotics reported in this survey are not unexpected compared to other countries. However, when we compare antibiotics prescription, probiotics co-prescription and perceived risk of antibiotics disturbing the intestinal microbiota (represented as flag surface area in Figure 2), we observe that countries are distributed in two clusters. The first cluster includes Australia and Japan where the rate of consultations leading to antibiotics prescription is low. The second cluster includes the other countries which are frequent antibiotics prescribers. Although a large majority of physicians from all countries agreed that antibiotics disrupted intestinal microbiota, prescription of probiotics appeared to be unrelated with this knowledge. This was striking for Australia with a high percentage of physicians who agreed about disruption of intestinal microbiota by antibiotics, but probiotics were infrequently co-prescribed. Likewise, almost all Japanese physicians agreed that antibiotics disrupt intestinal microbiota, but only a small percentage considered that AAD was a condition to be prevented by administration of probiotics.

In the second cluster, South Korea is a special case with a high rate of probiotics co-prescriptions. Besides the free reimbursement of probiotics, this difference could be also explained by children profiles. Indeed, compared to other countries, South-Korean physicians reported to see more frequently children less than 3 years of age who had more frequently diarrhoea and had more frequently previous episodes of AAD.

Recommendations for children of the Asia-Pacific region have been recently proposed (Cameron *et al.*, 2017). Indeed, the various preparations of probiotics have not the same efficacy. *S. boulardii* CNCM I-745 and *L. rhamnosus* GG are two strains with evidence of good quality in AAD. Before administration of probiotics for the prevention of AAD, both guidelines for Asia-Pacific region (Cameron *et al.*, 2017) and from the ESPGHAN working group (WHO, 2008) recommended the evaluation of the risk factors for the occurrence and severity of AAD or *C. difficile*-associated diarrhoea (e.g. class of antibiotics, duration of antibiotic treatment, need for hospitalisation, age, comorbidities and previous episodes of AAD and *C. difficile* infection). Some of these determinants are well represented in the response to this questionnaire although with a scattered country-related distribution. Among the determinants to probiotics prescription, the surveyed physicians reported previous episodes of AAD, presence of diarrhoea, prolonged antibiotic treatment and amoxicillin-clavulanic acid treatment. Despite disparities according to countries, the survey responders appeared to adhere quite well to these recommendations since a majority considered that the main condition to be prevented by administration of probiotics was AAD followed by *C. difficile* colitis. These results are encouraging, but the disparities reported between countries suggest that stewardship programs for the correct usage of antibiotics and co-prescription of probiotics remain necessary (Doron and Davidson, 2011). The main goals of such programs are to prevent unnecessary antibiotic treatment and emergence of antimicrobial resistance. To this purpose, physicians should optimize indications,

selection, doses and durations of antibiotic treatments in order to reduce antibiotic-related adverse events including secondary infections (for example, *C. difficile* AAD) and to reduce morbidity and mortality (Ohl and Luther, 2011; Roque *et al.*, 2014).

This study has some limitations which are those of a declarative survey. Data reported are the perception of physicians on their practice and are not an assessment of their real practice. Nevertheless, the responses of physicians reflected their knowledge and attitudes about antibiotics and probiotics.

In conclusion, although current local guidelines recommend the use of selected probiotics in children receiving antibiotics in Asia-Pacific area, the rates of antibiotics and probiotics prescription significantly vary among countries and are affected by cultural and organizational issues.

Conflict of interest

The study was funded by BIOCODEX. H. Hoekstra reports speaker fees from Abbott and Biocodex. The other authors do not report conflict of interest.

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