Treatment Outcomes of the Uncomplicated Upper Respiratory Tract Infection and Acute Diarrhea in Preschool Children Comparing Those with and without Antibiotic Prescription

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Background: *Upper respiratory tract infection (URI) and acute diarrhea are the two most common reasons for ambulatory visits among young children. Unnecessary use of antibiotics to treat such conditions pose significant financial burden and can result in untoward side effects as well as risk of antimicrobial resistance. On the other hand, inadequate antibiotic treatment in certain cases may increase the risk of suppurative complications and/or invasive infection in this population.*
Objective: *To compare the treatment outcomes between those with and without antibiotic treatment for the uncomplicated upper respiratory tract infection and acute diarrhea in young children.*
Material and Method: *A prospective observational study was conducted in two groups of previously healthy children presenting with acute uncomplicated URI (aged 2 to 5 years) or acute diarrhea (aged 6 months to 5 years). On initial enrolment date, patients were treated by a pediatrician who was not a member of the study investigators. The decision for antibiotic prescription was based entirely on attending physicians' discretion. Data regarding clinical presentations, diagnosis, treatment options, and reasons for antibiotic prescription (if any) were collected. Follow-up phone interviews were conducted on day 3 of enrolment to evaluate treatment outcomes.*
Results: *Two hundred nine cases with symptoms compatible with acute URI, and/or 199 cases with acute diarrhea were enrolled between August and November 2013. Antibiotic prescription rates for URI and diarrhea groups were 30.2% and 13.6%, respectively. Among children presenting with URI symptoms, 80.4% (n = 168) were classified as having upper respiratory tract infection e.g., common cold, acute sinusitis, pharyngitis whereas the other 19.6% were diagnosed with other conditions e.g., lower respiratory tract infection, pneumonia, viral exanthema after evaluation by a pediatrician. Overall improvement rates on day 3 were 92.3% and 86.9% for uncomplicated URI and diarrhea group, respectively. Among URI group, parental satisfaction rates were 100% and 96.6% in those received and did not receive antibiotic, respectively (p = 0.188), whereas in the diarrhea group, there were 100% and 92.7, (p = 0.35), respectively. Univariate analyses indicated that the crude odds ratios (OR) and 95% confidence intervals (CI) of treatment failure comparing those with and without antibiotics were 0.5 (0.2, 1.7) and 1.5 (0.6, 3.7) for URI and diarrhea, respectively. Logistic regression analyses indicated that antibiotic treatment was not significantly associated with better treatment outcomes for both URI and diarrhea cases i.e., adjusted ORs and 95% CI of antibiotic for requirement of additional treatment were 1.06 (0.14, 8.15) for URI cases. Further, adjusted OR and 95% CI of antibiotic for treatment failure was 0.8 (0.2, 2.9) for acute diarrhea cases.*
Conclusion: *Antibiotic did not appear to provide clinical benefit in the management of uncomplicated URI and/or acute diarrhea among previously healthy young children.*

Keywords: *Upper respiratory tract infection, Acute diarrhea, Children, Clinical outcomes, Antibiotics*

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The amount of antibiotic consumption in Thailand has increased steadily over the past decade. Data from the Food and Drug Administration, Thailand, has shown that the estimated expenditure of imported and locally manufactured antibiotics in 2009 was 10,940 million Thai Baht (US$ 365 million) which has been the highest figure since 1997 compared to other types of medication including the treatment of cardiovascular diseases, central nervous system abnormalities, or cancer chemotherapy[1]. Main reasons for the excessive spending were the inappropriate prescription[2], dispensing, and consumption[3], which led to the rapidly intensifying threat of antimicrobial resistance (AMR) globally. To promote the rational use

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of antibiotic, the Antibiotics Smart Use (ASU) Program in Thailand was initiated in 2007[4]. The Program aimed to raise awareness and facilitate behavioral changes regarding antibiotic use among the general public and prescription practice among healthcare workers. This process required multifaceted interventions from various stakeholders. In parallel, to facilitate the adoption of the process, the Program aimed to integrate ASU concepts into national policy and academic collaborations. In parallel, building a new social norm that embrace the rational use of antibiotic as a part of ASU movement is likely to be more effective in sustaining desirable behaviors[4]. During the initial phase, the ASU Program focused on minimizing antibiotic use in three targeted conditions for which antibiotics were frequently inappropriately prescribed: 1) uncomplicated upper respiratory tract infection, 2) acute diarrhea, and 3) fresh traumatic wound. Existing evidence had demonstrated the lack of clinical benefit of antibiotics for these three conditions including studies conducted in both primary care and tertiary centers[4,5]. Nevertheless, a similar evaluation has not been conducted in young children less than 5-years-old in Thailand. This group of children is rather vulnerable and inclined to have frequent upper respiratory tract infection (URI) and/or diarrhea due to their immature immune system especially among those attending childcare services or kindergartens. As a result, they are more likely to be exposed to antibiotics compared to other age groups. Excessive and unnecessary use of antibiotics can result in untoward side effect such as hypersensitivity reaction, adverse drug reactions, and increase risk of antimicrobial resistance in the future[2]. On the other hand, inadequate antibiotic treatment in certain cases may increase the risk of suppurative complications or spreading of infection. Consequently, the effect of antibiotics on outcomes in URI or diarrhea among young children may differ from those of in adults or older children. Pediatricians may be reluctant to adopt the recommendation against antibiotic use in these conditions from Western Countries or adult population in their clinical practice. Therefore, the objective of this study was to compare the treatment outcomes in those treated with and without antibiotic among young children presenting with uncomplicated URI and acute diarrhea.

Material and Method

The authors conducted a prospective observational study in the two groups of previously healthy children presenting with acute uncomplicated URI or diarrhea. Inclusion criteria included less than or equal to five days disease onset, no underlying co-morbidity that might affect the disease severity, and being accessible via telephone contact. Exclusion criteria were presence of symptoms and signs indicating serious illness such as high grade fever $\geq$39°C, respiratory distress, excessive vomiting, feeding intolerance, restlessness, and severe dehydration. For the group of URI, we enrolled children aged between 24-month and 5-year-11-month-old, whereas for acute diarrhea group, we enrolled children aged 6-month to 5-year-11-month-old (6-month to 5-year).

Sample size calculation was based on Blackwelder's equivalency/non-inferiority trial formula[6] and response rates of each treatment arm from previous studies conducted in Thailand[7]. The estimated sample size ranged from 26 to 33 cases/treatment group/condition. However, this formula was originally intended to be used in a randomized control trial, which was not the case in the present study. Therefore, the final sample size was increase to 100 cases per treatment/condition in order to have sufficient number to adjust for potential confounding factors in multivariate analyses. Therefore, the target sample size was 400 cases in URI (n = 200) and acute diarrhea (n = 200) group.

Eligible subjects were invited to participate in the study. After informed consents were provided and the concept of ASU introduced, the phone number and contact information were collected from caregivers. A study specific case record form was added in the out-patient chart to capture data including clinical presentation, diagnosis, treatment options, and reasons for antibiotic prescription (if any). Then, the participants were examined and treated by pediatricians who were not a part of study investigators. Thus, the decision for antibiotic prescription was based on attending physician discretion on enrolment date (day 0). Follow-up phone interviews were conducted on day 3 of enrolment to evaluate clinical outcomes in terms of clinical response, requirement of additional treatments, parental satisfactions, and duration before the child regain his/her daily functioning.

Data were analyzed using both univariate and multivariate analysis to determine whether antibiotic treatment was associated with the clinical outcomes on day 3 after the enrolment including treatment failures, requirement of additional treatment for the same conditions, and caregivers' satisfaction, respectively.

To examine whether antibiotic was an independent factor associated with the primary outcomes i.e., treatment failure on day 3 (no clinical improvement or worsening) and requirement of additional treatments, multivariate logistic regression analysis was employed to control for potential confounding factors. Criteria for variable selection to be included in logistic regression analysis were: 1) predictor of treatment outcomes based on a priori knowledge or existing literature, and/or 2) all correlates from univariate analyses with $p<0.1$. All statistical significant testing were two tails with a significance level of $p<0.05$ and conducted using SPSS Statistics 16 (IBM SPSS, Chicago, IL). Assumptions of logistic regression were checked prior to the analysis including sufficient events per variable, at least 10 "less common event" per number of predictor variable and lack of collinearity between two predictor variables. The model fitting procedure was forward inclusion.

Results

Acute URI

Two hundred nine cases presenting with URI symptoms were screened and enrolled. Overall, antibiotic prescription was 30.2%. While 80% of cases (n = 168) were diagnosed with upper respiratory tract infection, 20% of cases were diagnosed primarily with conditions other than URI e.g., pneumonia or hand-foot-mouth. In parallel, about half of the enrolled cases were diagnosed with common cold/non-specific URI. Associated conditions and/or diagnoses, and reasons for antibiotic prescription are shown in Table 1.

Factors associated with increase the likelihood of antibiotic prescription were being diagnosed with acute sinusitis, otitis media, pharyngitis/tonsillitis (with and without tonsillar exudate), and pneumonia. On the other hand, children who were diagnosed with common cold/non-specific URI were significant less likely to receive antibiotic prescription.

Two hundred one out of 209 enrolled cases (96.2%) were accessible for telephone interview on day 3, 91.5% (n = 184) were improved. Among the URI subgroup (n = 168), the improvement rate and parental satisfaction were comparable between those who received and did not receive antibiotics (Table 2). Detailed treatment outcome and parental satisfaction between the two groups are shown in Table 2.

Based on univariate analyses, no significant differences of the two primary outcomes i.e., treatment failure (not improved/or worsen) and requirement of additional treatment on day 3 after hospital visit were identified between URI cases who received and did not receive antibiotic (Table 3, 4).

According to the aforementioned variable selection criteria for multivariate regression analysis, only the primary outcome of "requirement of additional treatment" was evaluated as none of the predictor variables fulfilled the selection criteria for the "treatment failure" outcome. The result of multivariate analysis did not detect a significant association between antibiotic treatment and the requirement of additional treatment by day 3 of treatment in children presenting with uncomplicated URI (Table 5).

Acute diarrhea

Among the 199 diarrhea cases enrolled in the present study, 191 cases (96%) were accessible

Table 1. Sample characteristic among enrolled cases presenting with upper respiratory tract symptoms

Characteristics	Total (%) n = 209
Male	93 (44.5)
History of fever	174 (83.3)
Mean age in month (SD)	44.5 (13.0)
Diagnosis/associated conditions	
Common cold/non-specific URI	101 (48.3)
Acute sinusitis	11 (5.3)
Acute bronchitis	30 (14.4)
Otitis media	3 (1.4)
Exudative pharyngitis/tonsillitis	22 (10.5)
Non-exudative pharyngitis/tonsillitis	8 (3.8)
Acute undifferentiated fever	17 (8.1)
Pneumonia	5 (2.4)
Hyper-reactive airway	7 (3.3)
Viral exanthema	3 (1.4)
Viral LRTI	1 (0.5)
Others*	7 (3.3)
Antibiotic prescription	63 (30.2)
Amoxicillin	38 (18.2)
Amoxicillin/clavulanate	5 (2.4)
Azithromycin	11 (5.3)
Amoxicillin + Amoxicillin/clavulanate	2 (1.0)
Other	7 (3.3)
Reason for antibiotic treatment	
Failed to improve after symptomatic treatment	25 (12.0)
Severe symptoms affecting daily functioning	21 (10.0)
Safety-net prescription if fail to improve within 48-72 hours	15 (7.2)
At risk for invasive infection	6 (2.9)

URI = upper respiratory tract infection; LRTI = lower respiratory tract infection

* Herpangina, Hand-foot-mouth disease

Table 2. Treatment outcomes and parental satisfaction among children with uncomplicated upper respiratory tract infection with and without antibiotic treatment

Outcomes	Total (%) n = 168	Receipt of antibiotic		*p*-value
		Yes (%), n = 50	No (%), n = 118	
Day 3 treatment outcome (n = 201)				0.300*
Fully recovered	64 (38.1)	22 (44.0)	42 (35.6)	
Improved satisfactorily	77 (45.8)	20 (40.0)	57 (48.3)	
Improved somewhat	14 (8.3)	6 (12.0)	8 (6.8)	
No change	6 (3.6)	0	6 (5.1)	
Worsen	7 (4.2)	2 (4.0)	5 (4.2)	
Overall improvement at day 3	155 (92.3)	48 (96.0)	107 (90.7)	0.238
Required additional treatment	13 (7.7)	3 (6.0)	10 (8.5)	0.583
Types of additional treatment				0.344*
Antibiotics	7 (4.1)	2 (4.0)	5 (4.2)	
Other symptomatic treatment	4 (2.4)	0	4 (3.4)	
Hospitalization	2 (1.2)	1 (2.0)	1 (0.9)	
Parental satisfaction				0.188
Satisfied	164 (97.6)	50 (100.0)	114 (96.6)	
Unsure	4 (2.4)	0	4 (3.4)	

Value were represented as n (%), * *p*-value of Chi-square test (RxC contingency table)

for telephone interview on day 3 after treatment, 86.9% (n = 166) were improved. The clinical characteristics of diarrhea cases are shown in Table 6. The improvement rate and parental satisfaction were comparable between those received and did not receive antibiotics. Detailed treatment outcomes and parental satisfaction between the two groups are shown in Table 7.

Factors associated with increase the likelihood of antibiotic prescription was the presence of dysenteric symptoms or diagnosed with suspected invasive diarrhea. On the other hand, children who were diagnosed as having secretory or non-inflammatory diarrhea were significant less likely to receive antibiotics.

The primary outcomes were defined as treatment failure on day 3 after hospital visit. No significant differences of treatment failure nor of caregivers' satisfaction were identified among those who received and did not receive antibiotic based on univariate analysis (Table 7, 8). Multivariate logistic regression analysis was employed using the similar variable selection criteria as in the URI analysis. The results showed that antibiotic was not associated with treatment failure by day 3 after enrolment (Table 9). However, children presenting with dysenteric symptoms were approximately seven times more likely to experience treatment failure on day 3 than their counterpart.

Discussion

During the recent decade, antimicrobial resistance (AMR) has become the global health crisis that can potentially cause breakdown of the entire modern medical system. In Thailand, the annual incidence of 90,000 episodes of nosocomial infection caused by drug resistant pathogens were estimated resulting in extra 3.24 million days of hospital stay and 38,000 deaths attributable to AMR in 2010. One important determinant of AMR is the excessive and unnecessary use of antibiotics within both community and hospital settings[2]. Antibiotics for the treatment of drug resistant pathogen are expensive, for example, in Thailand during January 2014, 15 grams of doripenem (Doribax®) cost approximately 35,000 Thai Baht (THB) or US$ 1,166 whereas 15 grams of gold (0.5 troy ounce) cost 19,350 THB (US$ 645). Moreover, for the same weight of 15 grams, tigycycline (Tygacyl®) was even more expensive, 588,000 THB (US$ 19,600) [8]. Therefore, it is essential that concerted efforts be in place to minimize the unnecessary use of antibiotic, the most important preventable cause of AMR.

The present study was set out to evaluate the applicability of the current recommendation against the use of antibiotics in simple URI and acute diarrhea among young children as proposed by ASU Initiative, Thailand. Young children under 5-year-old are the most vulnerable population commonly affected by these two conditions. Frequent exposure

Table 3. Factors associated with requirement of additional treatment by day 3 after treatment among cases with upper respiratory symptoms

Factors	Receipt of antibiotic		*p*-value	cRR	95% CI
	Yes (%), n = 21	No (%), n = 180			
Antibiotic treatment	6 (28.5)	53 (29.4)	0.934	0.963	0.393-2.360
Presence of fever	18 (85.7)	149 (82.7)	0.734	1.222	0.381-3.917
Common cold/non-specific URI	9 (42.8)	89 (49.4)	0.648	0.788	0.348-1.788
Acute sinusitis	1 (4.7)	10 (5.5)	0.880	0.864	0.127-5.857
Acute bronchitis	2 (9.5)	26 (14.4)	0.538	0.650	0.160-2.641
Otitis media	0 (0)	3 (1.6)	0.551	NA	NA
Exudative pharyngitis/tonsillitis	0 (0)	21 (11.6)	0.098	NA	NA
Non-exudative pharyngitis/tonsillitis	1 (4.7)	6 (3.3)	0.735	1.386	0.215-8.914

URI = upper respiratory tract infection; cRR = crude risk ratio; CI = confidence interval; NA = variable does not calculate risk ratio due to small cell

Table 4. Factors associated with treatment failure at day 3 after treatment among cases with upper respiratory symptoms

Factors	Treatment failure		*p*-value	cRR	95% CI
	Yes (%), n = 17	No (%), n = 184			
Antibiotic treatment	3 (17.6)	56 (30.4)	0.268	0.516	0.154-1.729
Receipt of additional treatment	12 (70.5)	9 (4.8)	<0.001	20.571	8.033-52.678
Presence of fever	14 (82.3)	153 (83.1)	0.933	0.950	0.289-3.127
Common cold/non-specific URI	9 (52.9)	89 (48.3)	0.718	1.182	0.475-2.941
Acute sinusitis	2 (11.7)	9 (4.8)	0.233	2.303	0.606-8.834
Acute bronchitis	1 (5.8)	27 (14.6)	0.317	0.386	0.053-2.798
Otitis media	0 (0)	3 (1.6)	0.596	NA	NA
Exudative pharyngitis/tonsillitis	1 (5.8)	20 (10.8)	0.520	0.536	0.075-3.838
Non-exudative pharyngitis/tonsillitis	0 (0)	7 (3.8)	0.413	NA	NA

URI = upper respiratory tract infection; cRR = crude risk ratio; CI = confidence interval; NA = variable does not calculate risk ratio due to small cell

Table 5. Multivariate analysis to determine independent factors associated with requirement of additional treatment among cases diagnosed with uncomplicated upper respiratory tract infections

Factors	Univariate analysis			Multivariate analysis
	Requirement of additional treatment (n = 168)		cRR (95% CI)	aOR (95% CI)
	Yes (%), n = 13	No (%), n = 155		
Antibiotic treatment	3 (23.1)	47 (30.3)	0.69 (0.18, 2.62)	1.060 (0.14, 8.15)
Presence of fever	10 (76.9)	125 (80.6)	0.80 (0.21, 3.08)	0.693 (0.17, 2.84)

cRR = crude risk ratio; aOR = adjusted odds ratio; CI = confidence interval
Hosmer and Lemeshow goodness of fit test, *p*-value = 0.670
Cox & Snell R Square = 0.024

to unnecessary antibiotics in these groups of children can lead to not only the increase risk of infection caused by drug resistant organisms, but also other long-term health problems such as allergy(9-12), obesity(13-16), for example.

Our findings corroborate with several existing evidences including the most recent meta-analysis(17) suggesting that antibiotics do not provide additional benefit for uncomplicated URI and diarrhea in children. Nevertheless, being cognizant of the evidence is

Table 6. Sample characteristic among enrolled cases with diarrhea symptoms

Characteristics	Total (%) n = 199
Male	108 (54.3)
History of fever	121 (60.8)
Mean age in month (SD)	2.04 (1.3)
Stool characteristics	
Watery	98 (49.2)
Loose/semi-solid	82 (41.2)
Mucus	32 (16.1)
Mucus-bloody	7 (3.5)
Other	2 (1.0)
Diagnosis/associated conditions	
Food poisoning	9 (4.5)
Secretory diarrhea/non-inflammatory	159 (79.9)
Dysentery/inflammatory diarrhea	17 (8.5)
Secondary lactase deficiency	5 (2.5)
Herpangina	1 (0.5)
Non-specific fever	2 (1.0)
Pneumonia	1 (0.5)
URI	8 (4.0)
Influenza A	1 (0.5)
Others*	5 (2.5)
Stool exam performed	25 (12.6)
Abnormal	11 (5.5)
Stool culture submission	13 (6.5)
Enteropathogen identified	5 (2.5)
Degree of dehydration	
Mild	94 (47.2)
Moderate	6 (3.0)
Severe	2 (1.0)
Receipt of antibiotic	27 (13.6)
Cefdinir	3 (1.5)
Cefixime	1 (0.5)
Norfloxacin	11 (5.5)
Cotrimoxazole	1 (0.5)
Amoxicillin	4 (2.0)
Ceftriaxone	3 (1.5)
Bactrim	3 (1.5)
Dicloxacillin	1 (0.5)
Reason for antibiotic prescription	
Suspected inflammatory invasive diarrhea	17 (8.5)
At risk for invasive disease	5 (2.5)
Others	5 (2.5)
Additional treatment beside ORS	
Racecadotril	25 (12.6)
Probiotic	4 (2.0)
Smectite	5 (2.5)
Lactose free formula	20 (10.1)
Others	124 (62.3)

ORS = oral rehydration therapy

* Acute appendicitis, Carotene yellow skin, secondary bacteremia, viral infections, dengue fever

unlikely to be sufficient to reduce physicians' prescription rate. Successful reduction of unnecessary use of antibiotic requires good communication that enables patients/parents to understand the risk and benefit of each intervention, and be realistic about their expectation regarding the natural course of their illness. For example, an observational study among preschool children with uncomplicated URI has shown that the average duration of symptoms generally last between 6.6 and 8.9 days in children aged 1- to 2-year-old who were raised at home and children younger than 1-year-old who attended out-of-home childcare service. In addition, 6.5 to 13.1% of these children experienced a protracted course of illness that last more than 15 days prior to uneventful recovery[18]. The communication process can be enhanced by providing information leaflet on the disease condition, warning sign and symptoms, and indication of antibiotic, for example. Further, physicians should be able to provide effective supportive/symptomatic treatment by applying various non-pharmaceutical interventions such as nasal irrigation to remove nasal secretion, inhaling steam or eucalyptus oil to reduce nasal congestion. A recent study has shown that the use of traditional remedy like vapor rub is effective in improving the signs and symptoms of children with URI and significantly reduce sleep difficulty among both affected children and their caregivers[19]. Provision of customized management plan that includes a list of do-it-yourself intervention to relieve the symptoms; advice on what to do when the symptom fail to improve; and warning signs for further medical attention is more likely to increase treatment success and patients' satisfaction.

In parallel, the application of delayed antibiotic prescription approach is also a useful strategy in certain scenarios. For example, acute otitis media/AOM is one of the most common reason for antibiotic prescription in ambulatory setting despite the fact that about 90% of this condition is caused by virus[20] and thus is self-limited in most cases. A recent meta-analysis with total subjects of approximately 5,400 children found that up to 81% of those who did not receive antibiotics recovered uneventfully, whereas those who received antibiotics had approximately 13.7% higher rate of complete resolution by day 7 to 14 after treatment (number needed to treat = 7.2). In other words, only one out of seven children with AOM who receive antibiotic will benefit from it[21]. Therefore, the indiscriminate use of antibiotic especially among the low risk group, not only result in unnecessary expense but also contribute to the increase the risk of adverse

Table 7. Treatment outcomes and parental satisfaction among acute diarrhea cases with and without antibiotic treatment

Outcomes	Total (%) n = 191	Receipt of antibiotic		*p*-value
		Yes (%), n = 27	No (%), n = 164	
Day 3 treatment outcome				0.200
Fully recovered	90 (47.1)	8 (29.6)	82 (50.0)	
Improved satisfactorily	60 (31.4)	10 (37.0)	50 (30.5)	
Improved somewhat	16 (8.4)	4 (14.8)	12 (7.3)	
No change	10 (5.2)	3 (11.1)	7 (4.3)	
Worsen	15 (7.9)	2 (7.4)	13 (7.9)	
Overall improvement at day 3	166 (86.9)	22 (81.5)	144 (87.8)	0.361
Required additional treatment	36 (18.8)	5 (18.5)	31 (18.9)	0.962
Types of additional treatment				0.497
Antibiotics	10 (27.8)	1 (20.0)	9 (29.0)	
Other symptomatic treatment	5 (13.9)	0	5 (16.1)	
Hospitalization	21 (58.3)	4 (80.0)	17 (54.8)	
Parental satisfaction				0.349
Satisfied	179 (93.7)	27 (100.0)	152 (92.7)	
Unsure	11 (5.8)	0	11 (6.7)	
Unsatisfied	1 (0.5)	0	1 (0.6)	

Value were represented as n (%), * *p*-value of Chi-square test (RxC contingency table)

Table 8. Factors associated with treatment failure by day 3 after treatment among diarrhea cases

Factors	Treatment failure		*p*-value	cRR	95% CI
	Yes (%), n = 25	No (%), n = 166			
Antibiotic treatment	5 (20.0)	22 (13.3)	0.361	1.519	0.623-3.703
Received additional treatment	17 (68.0)	19 (11.4)	<0.001	9.149	4.287-19.526
Food poisoning	2 (8.0)	6 (3.6)	0.281	1.989	0.564-7.010
Secretory diarrhea/non-inflammatory	17 (68.0)	135 (81.3)	0.180	0.545	0.254-1.170
Dysentery/inflammatory diarrhea	7 (28.0)	10 (6.0)	0.002	3.980	1.943-8.153
Secondary lactase deficiency	1 (4.0)	4 (2.4)	0.508	1.550	0.258-9.306
Herpangina	0	1 (0.6)	0.697	NA	NA
Non-specific fever	0	2 (1.2)	0.581	NA	NA
Pneumonia	0	1 (0.6)	0.697	NA	NA
URI	1 (4.0)	7 (4.2)	0.960	0.953	0.147-6.190
Influenza A	0	1 (0.6)	0.697	NA	NA
Other diagnosis	0	5 (3.0)	0.379	NA	NA

URI = upper respiratory tract infection; cRR = crude risk ratio; CI = confidence interval; NA = variable does not calculate risk ratio due to small cell

Table 9. Multivariate analysis to determine independent factors associated with treatment failure among diarrhea cases

Factors	Univariate analysis			Multivariate analysis
	Treatment failure (n = 191)		cRR (95% CI)	aOR (95% CI)
	Yes (%), n = 25	No (%), n = 166		
Antibiotic treatment	5 (20.0)	22 (13.3)	1.519	0.788 (0.216, 2.876)
Age less than 2 years	14 (56.0)	86 (56.8)	1.158	1.124 (0.468, 2.702)
Dysentery	7 (28.0)	10 (6.0)	3.980	6.675 (1.969, 22.631)

cRR = crude risk ratio; aOR = adjusted odds ratio; CI = confidence interval
Hosmer and Lemeshow goodness of fit test, *p*-value = 0.393
Cox & Snell R Square = 0.049

drug reaction and antimicrobial resistance. As a result, in 2013 American Academy of Pediatrics (AAP) has issued and evidence-base clinical practice guideline for the treatment of AOM by emphasizing the importance of accurate diagnosis. For example, AAP recommend against making a diagnosis of AOM without evidence of middle ear effusion when evaluated by tympanometry and/or pneumatic otoscope[22]. In addition, immediate antibiotic treatment should be preserved for those 6-month-old or older who has severe symptoms (e.g., otorrhea, severe earache, or persistent earache longer than or equal to 48 hours, and fever higher than or equal to 39 Celsius) or bilateral AOM in children younger than 24-month-old. Otherwise, symptomatic treatment or delayed antibiotic or safety-net antibiotic prescription is recommended for those who fail to improve in 48 to 72 hours. Empirical evidence has supported that this approach helped reduce unnecessary antibiotic use while achieving comparable outcomes and parental satisfaction compared to immediate antibiotic prescription in these children[23,24].

The use of antibiotic as an empirical treatment for acute diarrhea is another pitfall commonly encountered in pediatric practice whereas existing evidence recommend against it. Specifically, childhood diarrhea is commonly caused by viral pathogens, most importantly rotavirus especially among those with severe dehydration requiring hospitalization[25,26]. In addition, diarrhea caused by bacterial pathogens is generally mild, and self-limiting. There are few enteropathogens for which antibiotic treatment has proven clinical benefit such as *Vibrio cholerae*, *Shigella dysenteriae*, *Campylobacter* spp., and *Entamoeba histolytica*. Whereas those caused by *Escherichia coli*, non-cholera *Vibrio*, *Plesiomonas* spp., or *Yersinia* spp., antibiotic is generally recommended when the symptoms persists and/or fails to improve after adequate supportive therapy only[27]. On the other hand, salmonella gastroenteritis in otherwise healthy children or adults, antibiotics does not have any impact on duration of illness but prolong shedding or carrier stage instead. In addition, its use can cause selection pressure and drive AMR among commensal enteric bacteria colonized in intestinal tract. Recent evidence in Thailand has shown that the rate of extended spectrum beta-lactamase enzyme producing enteric bacteria colonized in gastrointestinal tract of healthy adults living in rural area was as high as 70%[28].

Of note, currently several conjugate vaccines for the prevention of common invasive bacterial infection in children became available and increasingly accessible in industrializing countries especially in private healthcare settings. Nevertheless, existing data indicate that those who are less price sensitive such as those attending private hospital were more likely to receive antibiotics especially the broad spectrum ones[29-32]. Several studies have shown that prior use of broad spectrum cephalosporin pose a significantly higher risk of subsequent infection/colonization by extended spectrum beta-lactamase (ESBL)-producing and/or multidrug resistant bacteria compared to a narrower spectrum antibiotic in penicillin group. In contrast, the latest U.S. National Practice Guideline recommend against routine septic work-up with complete blood count or blood culture in a well-appearing child presenting with fever without localizing signs who have been immunized with pneumococcal conjugate and *Haemophilus influenzae* type B vaccine except for urinary analysis to rule out urinary tract infection[33]. In addition, the current U.S. National Practice Guideline on pediatric community-acquired pneumonia (CAP) published in 2011 also recommends the use of narrow spectrum (penicillin or ampicillin) for empirical antimicrobial therapy in presumed bacterial CAP[34]. A more recent study published in 2013 after this guideline was launched has supported that narrow spectrum antibiotic was effective[35]. Another recent meta-analysis also provides evidence that supports the short duration (3-5 days) of antibiotic treatment in CAP among young children[36].

Conclusion

Antibiotic does not appear to provide clinical benefit in the management of uncomplicated URI and acute diarrhea among otherwise healthy toddlers and preschool children. Our findings support the current ASU recommendation against antibiotic use in these two most prevalent childhood illnesses.

What is already known on this topic?

Existing studies and systematic reviews conducted in industrialized countries have demonstrated the lack of clinical benefit of antibiotic treatment among patients with uncomplicated upper respiratory tract infection and acute diarrhea. The use of empirical antibiotic treatment for these two conditions can lead to excessive health expenditure, untoward drug reactions, and selection of antibiotic resistance among intestinal microbiota. However, children under 5-year-old are generally vulnerable to invasive infection or suppurative complication compared to older children and adults.

What this study adds?

Children with URI and diarrhea generally recover uneventfully by day 3 after seeking medical attention. Antibiotic does not provide clinical benefit in the management of these two conditions among otherwise healthy toddlers and preschool children whose onset was less than or equal to five days. Our findings support the adoption of current ASU Program recommendation against antibiotic use among these two most prevalent childhood illnesses in developing country like Thailand.

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Potential conflicts of interest

None.

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ผลการรักษาโรคติดเชื้อในทางเดินหายใจส่วนต้นและภาวะท้องเสียเฉียบพลันที่ไม่มีภาวะแทรกซ้อน ในเด็กก่อนวัยเรียน เปรียบเทียบระหว่างกลุ่มที่ได้รับและไม่ได้รับยาปฏิชีวนะ

วารุณี พรรณพานิช วานเดอพิทท์, รัชดา ผลทอง, สุชาดา ศรีศรัง

ภูมิหลัง: *การติดเชื้อในทางเดินหายใจส่วนต้นและท้องเสียเฉียบพลันเป็นการเจ็บป่วยที่พบบ่อยในเด็กเล็กที่เข้ารับการรักษาแบบผู้ป่วยนอก การใช้ยาปฏิชีวนะโดยไม่มีข้อบ่งชี้ในทางการแพทย์ก่อให้เกิดความสิ้นเปลืองและอาจส่งผลให้เกิดอาการไม่พึงประสงค์ ในขณะเดียวกันการละเว้นไม่ใช้ยาปฏิชีวนะในผู้ป่วยบางรายอาจเพิ่มความเสี่ยงต่อการเกิดภาวะแทรกซ้อนหรือการติดเชื้อรุกรานในเด็กอายุน้อยได้*

วัตถุประสงค์: *เพื่อเปรียบเทียบผลการรักษาระหว่างกลุ่มที่ได้และไม่ได้รับยาปฏิชีวนะในเด็กก่อนวัยเรียนที่มีอาการของการติดเชื้อในทางเดินหายใจส่วนต้นและท้องเสียเฉียบพลัน*

วัสดุและวิธีการ: *เป็นการศึกษารูปแบบ prospective cohort ในเด็กที่มาด้วยอาการของการติดเชื้อในทางเดินหายใจส่วนต้น (อายุ 2 ถึง 5 ปี) และท้องเสียเฉียบพลัน (อายุ 6 เดือน ถึง 5ปี) ในวันแรกของการศึกษาผู้ป่วยได้รับการตรวจประเมินโดยกุมารแพทย์ที่ห้องตรวจผู้ป่วยนอก โดยการตัดสินใจให้การรักษาด้วยยาปฏิชีวนะจะขึ้นกับแพทย์ที่ดูแลซึ่งไม่ได้เกี่ยวข้องกับคณะผู้นิพนธ์ ข้อมูลที่นำมาประเมินประกอบด้วย อาการแสดงคลินิก ผลการวินิจฉัย การรักษาที่ได้รับ และเหตุผลที่ให้การรักษาด้วยยาปฏิชีวนะ (ในรายที่ได้รับ) ในวันที่ 3 หลังเข้าร่วมโครงการ มีการโทรศัพท์ติดตามอาการผู้ป่วยเพื่อประเมินผลการรักษาและความพึงพอใจของผู้ปกครอง*

ผลการศึกษา: *มีผู้ป่วยเข้าร่วมโครงการทั้งสิ้น 408 ราย เป็นการติดเชื้อในทางเดินหายใจส่วนต้น 209 ราย และท้องเสียเฉียบพลัน 199 ราย ในช่วงเวลาระหว่างเดือนสิงหาคม พ.ศ. 2556 ถึง พฤศจิกายน พ.ศ. 2556 อัตราส่วนยาปฏิชีวนะใน การติดเชื้อในทางเดินหายใจส่วนต้นและท้องเสียเฉียบพลันเท่ากับร้อยละ 30.2 และ 13.6 ตามลำดับ ร้อยละ 80 ของผู้ป่วยที่เข้าร่วมโครงการด้วยอาการของทางเดินหายใจส่วนต้นได้รับการวินิจฉัยว่าเป็นการติดเชื้อของระบบทางเดินหายใจส่วนต้น ในขณะที่ร้อยละ 20 ได้รับการวินิจฉัยเป็นกลุ่มโรคอื่น เช่น ปอดบวม มือเท้าปาก เป็นต้น ผลการรักษาที่ 3 วัน พบว่ามีอาการดีขึ้นร้อยละ 91.5 และ 86.9 ในผู้ป่วยที่มีการติดเชื้อในทางเดินหายใจส่วนต้นและท้องเสียเฉียบพลันตามลำดับ ในกลุ่มเด็กที่มาด้วยอาการการติดเชื้อในทางเดินหายใจส่วนต้นพบว่า ผู้ปกครองมีความพึงพอใจต่อการรักษาร้อยละ 100 และร้อยละ 96.6 ($p = 0.188$) ในกลุ่มที่ได้และไม่ได้ยาปฏิชีวนะตามลำดับ ในขณะที่ในกลุ่มที่มาด้วยอาการท้องเสียเฉียบพลัน ผู้ปกครองมีความพึงพอใจต่อการรักษาร้อยละ 100 และร้อยละ 92.7 ตามลำดับ ($p = 0.35$) การวิเคราะห์โดยวิธี univariate analysis พบว่า odds ratio (OR) และ 95% confidence interval (CI) ของยาปฏิชีวนะต่อการรักษาล้มเหลวเท่ากับ 0.5 (0.2, 1.7) และ 1.5 (0.6, 3.7) ตามลำดับ การวิเคราะห์โดยวิธี logistic regression analysis ไม่พบว่ายาปฏิชีวนะสัมพันธ์กับผลการรักษาในทั้งสองกลุ่มอาการ โดยมี adjusted ORs และ 95% CI ของยาปฏิชีวนะต่ออัตราการได้รับการรักษาเพิ่มเติมเท่ากับ 1.06 (0.14, 8,15) ในเด็กที่มีการติดเชื้อในทางเดินหายใจส่วนต้น และ adjusted ORs และ 95% CI ของยาปฏิชีวนะต่อการรักษาล้มเหลวเท่ากับ 0.8 (0.2, 2.9) ในกลุ่มท้องเสียเฉียบพลัน*

สรุป: *ไม่พบว่ามีหลักฐานที่แสดงให้เห็นถึงประโยชน์ของการใช้ยาปฏิชีวนะในการรักษาเด็กวัยก่อนเรียนสุขภาพแข็งแรงดีมาก่อนที่เจ็บป่วยด้วยอาการของการติดเชื้อในทางเดินหายใจส่วนต้นและท้องเสียเฉียบพลัน*