Delayed Antibiotic Prescription for Children With Respiratory Infections: A Randomized Trial

Gemma Mas-Dalmau, MD,[a,b] Carmen Villanueva López, PhD,[c] Pedro Gorrotxategi Gorrotxategi, PhD,[d] Emma Argüelles Prendes, MD,[e] Oscar Espinazo Ramos, MD,[f] Teresa Valls Duran, MD,[g] María Encarnación Gonzalo Alonso, MD,[h,i] María Pilar Cortés Viana, PhD,[j] Tatiana Menéndez Bada, MD,[k] Marta Esther Vázquez Fernández, PhD,[l] Ana Isabel Pérez Hernández, MD,[m] Laura Muñoz Ortiz, MD,[n] Paul Little, PhD,[o] Mariam de la Poza Abad, PhD,[p] Pablo Alonso-Coello, PhD,[a,q] ON BEHALF OF THE DAP PEDIATRICS GROUP*

abstract

OBJECTIVES: To assess the effectiveness and safety of delayed antibiotic prescription (DAP) compared to immediate antibiotic prescription (IAP) and no antibiotic prescription (NAP) in children with uncomplicated respiratory infections.

METHODS: Randomized clinical trial comparing 3 antibiotic prescription strategies. The participants were children with acute uncomplicated respiratory infections attended to in 39 primary care centers. Children were randomly assigned into prescription arms as follows: (1) DAP, (2) IAP, or (3) NAP. Primary outcomes were symptom duration and severity. Secondary outcomes were antibiotic use, parental satisfaction, parental beliefs, additional primary care visits, and complications at 30 days.

RESULTS: In total, 436 children were included in the analysis. The mean (SD) duration of severe symptoms was 10.1 (6.3) for IAP, 10.9 (8.5) for NAP, and 12.4 (8.4) for DAP (P = .539), although the differences were not statistically significant. The median (interquartile range) of the greatest severity for any symptom was similar for the 3 arms (median [interquartile range] score of 3 [2–4]; P = .619). Antibiotic use was significantly higher for IAP (n = 142 [96%]) compared to DAP (n = 37 [25.3%]) and NAP (n = 17 [12.0%]) ($P < .001$). Complications, additional visits to primary care, and satisfaction were similar for all strategies. Gastrointestinal adverse effects were higher for IAP.

CONCLUSIONS: There was no statistically significant difference in symptom duration or severity in children with uncomplicated respiratory infections who received DAP compared to NAP or IAP strategies; however, DAP reduced antibiotic use and gastrointestinal adverse effects.

[a]*Iberoamerican Cochrane Center, and* [b]*Nursing Care Reserch Group, Biomedical Research Institute Sant Pau (IIB Sant Pau), Barcelona, Spain;* [c]*Manso Primary Care Center, Barcelona, Spain;* [d]*Pasai San Pedro Primary Care Center, Pasaia, Spain;* [e]*Ribadesella Primary Care Center, Ribadesella, Spain;* [f]*Las Matas Primary Care Center, Las Rozas de Madrid, Spain;* [g]*Val Miñor Primary Care Center, Nigrán, Spain;* [h]*Ugao-Miraballes Primary Care Center, Ugao-Miraballes, Spain;* [i]*Arrigorriaga Primary Care Center, Arrigorriaga, Spain;* [j]*Maragall Primary Care Center, Barcelona, Spain;* [k]*Iruña de Oka Primary Care Center, Nanclares de Oka, Spain;* [l]*Arturo Eyries Primary Care Center, Valladolid, Spain;* [m]*Torrelodones Primary Care Center, Torrelodones, Spain;* [n]*Agency for Health Quality and Assessment of Catalonia, Barcelona, Spain;* [o]*Aldermoor Health Centre, Southampton, United Kingdom;* [p]*Dr Carles Ribas Primary Care Center, Barcelona, Spain; and* [q]*CIBER Epidemiology and Public Health (CIBERESP), Madrid, Spain*

Deidentified individual participant data, the study protocol, the statistical analysis plan, and the informed consent form will be made available after publication. The data will be made available to researchers who provide a methodologically sound proposal for use. Proposals should be submitted to the corresponding author.

WHAT'S KNOWN ON THIS SUBJECT: Delayed antibiotic prescription (DAP) in primary care settings optimizes antibiotic use in adults with acute uncomplicated respiratory infections in high-income–economy countries, such as those in southern Europe, with higher rates of antibiotic use.

WHAT THIS STUDY ADDS: The current study is the largest ever conducted on DAP for children and is the first study of DAP in a pediatric population in a southern Europe country with a high rate of antibiotic use.

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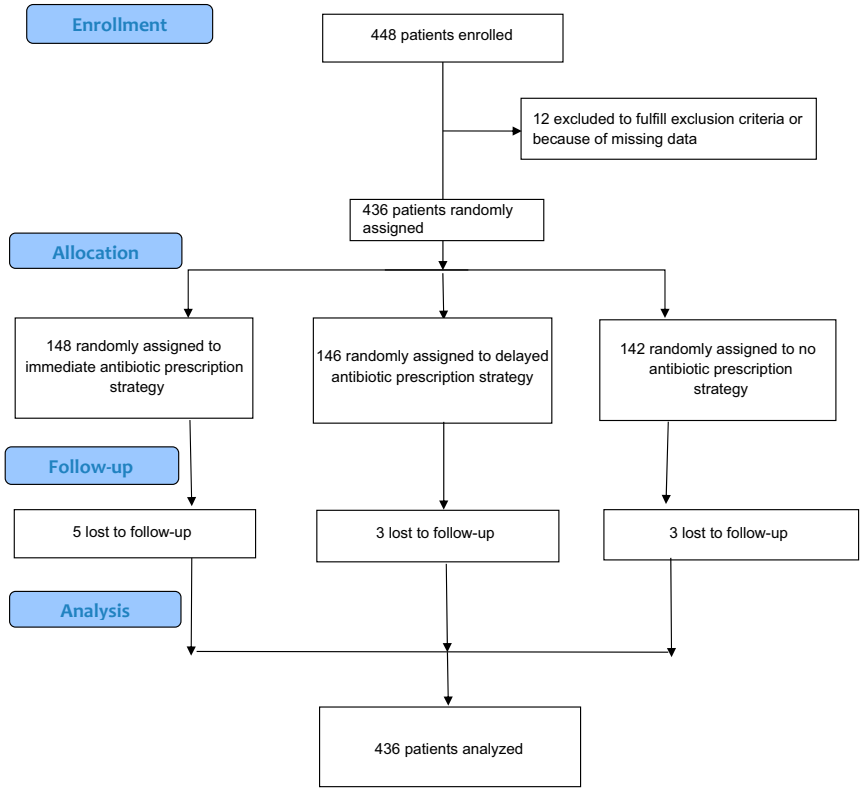

FIGURE 1
Flow diagram. The number of participants enrolled, randomly assigned, followed-up, and included in the analysis are shown in the figure.

Respiratory tract infections (RTIs) are a major reason for medical visits in pediatrics.[1] Most RTIs are self-limiting, and antibiotics hardly alter the course of the condition,[2–4] yet antibiotics are frequently prescribed for these conditions.[5,6] Antibiotic prescription for RTIs in children is especially considered to be inappropriately high.[7,8] The fact that antibiotics are overused is the main reason why resistance to antimicrobial agents has developed[9] to the point of becoming a threat to public health.[10] Use of antibiotics places patients at risk for adverse effects[11] and enhances beliefs to consult for similar episodes.[12]

In primary care, diagnostic methods are often limited, leading to uncertain diagnoses and unclear cases of antibiotic prescription. Antibiotics are also prescribed because of the concern to avoid complications[13] or to meet parental expectations when symptoms persist.[14] Delayed antibiotic prescription (DAP) has been used in primary care when there are reasonable doubts about the need for immediate antibiotic prescription (IAP), which is what happens with some RTIs, conjunctivitis,[15] and urinary tract infections.[16] Some clinical practice guidelines recommend DAP when in doubt that antibiotics may be necessary.[17]

DAP consists of prescribing an antibiotic to take only if the patient's condition worsens or fails to improve a few days after a medical visit. The latest Cochrane systematic review comparing DAP, IAP, and no antibiotic prescription (NAP) in adults and children reported no differences in most symptoms or in complications, whereas antibiotic intake was considerably lower for DAP compared to IAP for similar patient satisfaction levels. Reconsultation rates were also similar for the DAP and IAP strategies.[18]

Randomized clinical trials used to assess DAP for RTIs in children have been conducted for acute otitis media[19–21] and pharyngitis.[22,23] For the otitis media trials, duration of otalgia was slightly shorter[19] and antibiotic use was lower for DAP compared to IAP.[19,20] No differences were observed in otalgia frequency,[20] pain severity, distress, or school absenteeism.[19] As for the pharyngitis trials, only in a single study[22] was the severity of symptoms significantly higher in children allocated to DAP compared to IAP. In both the otitis[19–21] and pharyngitis[22,23] studies, children randomly assigned to IAP experienced more adverse effects.

There is scant evidence about the use of DAP in children, with studies conducted only in the United States,[20,21,23] England,[19] and Jordan.[22] The effects of a DAP strategy in high-income–economy countries with higher rates of antibiotic use, such as those in southern Europe,[24] are still unknown. We therefore conducted a randomized clinical trial to assess the effectiveness of DAP compared to IAP and NAP.

METHODS

Design

We used a multicenter randomized clinical trial to compare 3 treatment strategies for children with acute uncomplicated RTIs: DAP, IAP, and NAP.

Participants

Patients eligible for inclusion were children aged 2 to 14 years who, with their parent(s), attended a primary care pediatrician's office with the following conditions: pharyngitis,

TABLE 1 Patient Baseline Characteristics

	Prescription Strategy			Total (*N* = 436)
	IAP (*n* = 148)	DAP (*n* = 146)	NAP (*n* = 142)	
Girls	79 (53.4)	68 (46.6)	79 (55.6)	226 (51.8)
Age, y, mean (SD)	6.4 (3.1)	6.4 (3.2)	6.1 (2.8)	6.3 (3.0)
2–5	67 (45.2)	71 (48.6)	73 (51.4)	211 (48.4)
6–10	59 (39.9)	58 (39.7)	57 (40.1)	174 (39.9)
11–14	22 (14.9)	17 (11.7)	12 (8.4)	51 (11.7)
Wt, kg, mean (SD)	25.8 (11.6)	26.1 (12.1)	24.0 (10.0)	25.3 (11.3)
Parental education				
Primary or less	7 (4.7)	3 (2.1)	7 (4.9)	17 (3.9)
Secondary	66 (44.6)	65 (44.5)	61 (43.0)	192 (44.0)
Tertiary	75 (50.7)	78 (53.4)	74 (52.1)	227 (52.1)
Respiratory comorbidity	16 (10.8)	14 (9.6)	11 (7.8)	41 (9.4)
Pulmonary disease	13 (8.8)	13 (8.9)	7 (4.9)	33 (7.6)
Smoker parents	60 (40.5)	57 (39.0)	56 (39.4)	173 (39.7)
Respiratory tract infection				
Rhinosinusitis	9 (6.1)	9 (6.1)	8 (5.6)	26 (6.0)
Pharyngitis	48 (32.4)	49 (33.6)	49 (34.5)	146 (33.5)
Acute bronchitis	14 (9.5)	13 (8.9)	13 (9.2)	40 (9.2)
Acute otitis media	77 (52.0)	75 (51.4)	72 (50.7)	224 (51.4)
Symptom severity score, mean (SD)[a]				
Fever	3.7 (2.0)	3.7 (1.6)	4.1 (1.7)	3.8 (1.8)
Discomfort and/or general pain	3.1 (1.3)	3.0 (1.1)	3.0 (1.3)	3.0 (1.2)
Cough	2.1 (1.9)	2.4 (1.9)	2.5 (2.1)	2.3 (1.9)
Difficulty sleeping	2.6 (1.8)	2.8 (1.8)	3.1 (1.8)	2.8 (1.8)
Everyday routine disruptions	2.8 (1.4)	2.7 (1.3)	2.9 (1.3)	2.8 (1.4)
Irritability	2.6 (1.6)	2.6 (1.5)	2.6 (1.6)	2.6 (1.6)
Symptom duration previsit, d, mean (SD)	2.5 (3.1)	2.8 (5.8)	2.2 (3.2)	2.5 (4.2)
General health status score, mean (SD)[b]	66 (19)	65 (17)	64 (19)	65 (18)
Feverish	32 (36.8)	28 (33.3)	19 (26.0)	79 (32.4)
Fever ≥38°C lasting ≥24 h	51 (34.5)	54 (37.0)	62 (43.7)	167 (38.3)
Parental worry level				
Not at all or only slightly worried	17 (11.5)	25 (17.1)	17 (12.0)	59 (13.5)
A little worried	52 (35.1)	46 (31.5)	47 (33.1)	145 (33.3)
Moderately worried	69 (46.6)	71 (48.6)	73 (51.4)	213 (48.9)
Very or extremely worried	10 (6.8)	4 (2.7)	5 (3.5)	19 (4.4)

Data are reported as frequencies and percentages except where otherwise indicated.

[a] Symptoms, scored on a Likert scale from 0 (no problems) to 6 (as bad as it could be), are those common to the 4 studied pathologies.

[b] Scored at first visit on a visual analog scale from 0 (worst health status) to 100 (best health status).

rhinosinusitis, acute bronchitis, or acute otitis media (Supplemental Information). Children were included if pediatricians had reasonable doubts about the need to prescribe an antibiotic. Pediatricians that had access to rapid streptococcal testing did not include children with pharyngitis but included children with the other 3 infections. Recruitment was conducted in 39 primary care centers in Spain between June 2012 and June 2016. The study was approved by the Clinical Research Ethics Committee of the Institute for Primary Health Care Research Jordi Gol i Gurina, by all other ethics committees involved, and by the Spanish Agency of Medicines and Medical Devices.

Interventions

Children were randomly allocated to one of the DAP, IAP, or NAP arms. Randomization was stratified by pathology and in blocks. Allocation was performed centrally by using an online platform. Children, parents, and health professionals were not blinded.

Parents were advised that regardless of the arm and counting days from the onset of symptoms, their child was likely to feel more or less the same for up to 4 days for acute otitis media, 7 days for pharyngitis, 15 days for rhinosinusitis, and 20 days for acute bronchitis.

For children allocated to DAP, pediatricians handed the antibiotic prescription to parents, recommending them to only consider administering the antibiotic if (1) the child did not start to feel better after 4, 7, 15, or 20 days from symptom onset for acute otitis media, pharyngitis, rhinosinusitis, or acute bronchitis, respectively; (2) the child had a temperature of ≥39°C after 24 hours or a temperature of ≥38°C but <39°C after 48 hours; or (3) the child

TABLE 2 Patient Symptoms at the First Visit

	Prescription Strategy			Total (N = 436), n (%)
	IAP (n = 148), n (%)	DAP (n = 146), n (%)	NAP (n = 142), n (%)	
Moderate symptoms (3 or 4)[a]	120 (81.1)	115 (78.8)	117 (82.4)	352 (80.7)
Severe symptoms (5 or 6)[a]	71 (48.0)	70 (48.0)	75 (52.8)	216 (49.5)
Common symptoms[b]				
Everyday routine disruptions	128 (96.2)	126 (98.4)	125 (98.4)	379 (97.7)
Irritability	100 (91.7)	98 (92.5)	97 (91.5)	295 (91.9)
Pharyngitis symptoms				
Fever	41 (89.1)	45 (100.0)	42 (97.7)	128 (95.5)
Headache	33 (86.8)	29 (96.7)	23 (74.2)	85 (85.9)
Sore throat	46 (95.8)	47 (97.9)	47 (100.0)	140 (97.9)
Difficulty swallowing	43 (91.5)	43 (93.5)	43 (95.6)	129 (93.5)
Acute otitis media symptoms				
Earache	76 (100.0)	70 (97.2)	71 (100.0)	217 (99.1)
Rhinosinusitis and acute bronchitis symptoms				
Breathlessness	16 (80.0)	16 (88.9)	14 (77.8)	46 (82.1)
Chest noises breathing	15 (93.8)	10 (83.3)	14 (93.3)	39 (90.7)
Pharyngitis and acute bronchitis symptoms				
Cough	38 (74.5)	35 (79.6)	31 (75.6)	104 (76.5)
Rhinosinusitis, pharyngitis, and acute bronchitis symptoms				
Discomfort and/or general pain	68 (98.6)	69 (100.0)	66 (100.0)	203 (99.5)
Nasal mucus	46 (82.1)	51 (89.5)	46 (86.8)	143 (86.1)
Difficulty sleeping	45 (90.0)	47 (87.0)	42 (87.5)	134 (88.2)

Statistical significance was calculated per symptom by using Pearson's χ^2 test.

[a] Symptoms are scored on a Likert scale from 0 (no problems) to 6 (as bad as it could be).

[b] Symptoms common to the 4 studied pathologies.

felt much worse. Parents were told to consider returning to the doctor if they felt it was necessary or if the child felt worse even after taking the antibiotic.

For children allocated to NAP, pediatricians did not prescribe antibiotics. For children allocated to IAP, pediatricians prescribed antibiotics to be taken from the day of the consultation. In both strategies, pediatricians recommended that parents consider returning to the doctor if (1) the child did not start to feel better after 4, 7, 15, or 20 days from symptom onset for acute otitis media, pharyngitis, rhinosinusitis, or acute bronchitis, respectively; (2) the child had a temperature of ≥39°C after 24 hours or a temperature of ≥38°C but <39°C after 48 hours; or (3) the child felt much worse, their condition worsened, or the parent(s) deemed it necessary.

All parents were informed that it was normal for a child to feel slightly worse in the first days after the visit. Each pediatrician decided the antibiotic type to be prescribed for both the DAP and IAP strategies.

Outcomes

Primary efficacy outcomes were severity and duration of acute uncomplicated RTI symptoms over 30 days. Symptom severity was scored by parents on a 7-point Likert scale (0 = no problem to 6 = as bad as it could be). Scoring was as follows: 0 = absence of symptoms, 1 to 2 = mild symptoms, 3 to 4 = moderate symptoms, and 5 to 6 = severe symptoms. Symptom duration was calculated to the point when symptoms disappeared.

Secondary efficacy outcomes were antibiotic use over 30 days, parental satisfaction and beliefs regarding antibiotic efficacy, and additional unscheduled visits to primary care over 30 days. Parental satisfaction was scored according to a 6-point Likert scale ("extremely satisfied" to "not at all satisfied"). Both the severity and satisfaction scales have been previously validated[14,25] and used in other studies.[13,14] Beliefs on antibiotic efficacy were evaluated with a 6-point Likert scale ("extremely effective" to "not at all effective").[13,26] Infection-related complications were recorded for the first 30 days (pneumonia, abscesses, cellulitis, visits to the hospital emergency department, and hospital admissions).

Procedures

Previously trained pediatricians informed parents in a structured manner regarding the condition's natural course, self-limiting processes, adverse effects, and marginal benefits of antibiotics. Included children ≥12 years of age and all parents signed an informed consent form. Eligible children were randomly assigned into the different arms, and parents were given the corresponding DAP, NAP, or IAP recommendations. In the baseline

TABLE 3 Duration in Days of Patient Symptoms After the First Visit

	Prescription Strategy					Total (N = 436)	
	IAP (n = 148)	DAP (n = 146)		NAP (n = 142)			
	Mean (SD)	Mean (SD)	P[a]	Mean (SD)	P[a]	Mean (SD)	Overall P
Any symptom to disappearance	8.3 (7.8)	8.3 (7.7)	.968	7.9 (9.3)	.593	8.1 (8.2)	.888
Moderate symptoms (3 or 4)[b]	10.2 (7.5)	11.7 (8.7)	.257	10.0 (8.4)	.869	10.7 (8.2)	.435
Severe symptoms (5 or 6)[b]	10.1 (6.3)	12.4 (8.4)	.247	10.9 (8.5)	.682	11.3 (7.9)	.539
Common symptoms[c]							
Everyday routine disruptions	4.2 (3.8)	4.5 (4.0)	.848	4.8 (5.1)	.488	4.6 (4.4)	.837
Irritability	4.6 (4.3)	4.7 (4.1)	.767	4.9 (5.6)	.794	4.9 (4.7)	.965
Pharyngitis symptoms							
Fever	3.6 (2.2)	4.0 (5.2)	.534	4.2 (5.3)	.400	3.9 (4.5)	.824
Headache	5.8 (8.7)	5.5 (7.0)	.867	3.3 (3.0)[d,e]	.052	5.1 (7.0)	.080
Sore throat	5.2 (4.7)	5.0 (4.1)	.824	5.5 (6.2)	.741	5.2 (5.0)	.907
Difficulty swallowing	4.9 (4.8)	4.7 (3.8)	.812	5.0 (5.2)	.952	4.9 (4.6)	.970
Acute otitis media symptoms							
Earache	5.1 (5.3)	4.4 (3.9)	.239	5.2 (6.3)	.893	4.9 (5.2)	.567
Rhinosinusitis and acute bronchitis symptoms							
Breathlessness	7.5 (6.5)	10.2 (9.8)	.321	11.6 (11.1)	.169	9.7 (9.3)	.175
Chest noises breathing	6.2 (4.1)	5.3 (5.2)	.694	10.6 (16.0)[e]	.111	7.6 (10.5)	.101
Pharyngitis and acute bronchitis symptoms							
Cough	7.9 (4.4)	9.5 (7.1)	.295	8.0 (6.6)	.948	8.5 (6.0)	.527
Rhinosinusitis, pharyngitis, and acute bronchitis symptoms							
Discomfort and/or general pain	7.9 (8.2)	6.6 (6.7)	.222	5.6 (5.2)[d]	.023	6.7 (6.8)	.022
Nasal mucus	10.3 (9.0)	10.5 (8.9)	.811	8.3 (7.5)	.260	9.6 (8.5)	.444
Difficulty sleeping	5.8 (7.4)	5.2 (5.2)	.546	5.5 (5.6)	.745	5.5 (6.1)	.890

Only patients who had symptoms for 1 d or more were included. Statistical significance was calculated by adjusting a negative binomial regression model per symptom, with the number of days with the symptom as the dependent variable and prescription strategy and antibiotic use as independent variables.

[a] IAP is the reference category.

[b] Symptoms are scored on a Likert scale from 0 (no problems) to 6 (as bad as it could be).

[c] Symptoms common to the 4 studied pathologies.

[d] $P < .05$ compared to IAP.

[e] $P < .10$ compared to DAP.

visit, pediatricians collected data on the children's health status using a visual analog scale scored from 0 to 100 (0 = worst and 100 = best) and on the severity of their symptoms.

The coordinating center followed-up children by telephoning parents on days 2 and 30 after inclusion, as well as on days 7, 15, and 22 if parents indicated in the previous call that symptoms continued. Data collected in the telephone follow-up were health status, severity and duration of symptoms, use of antibiotics and nonantibiotic medication, and in addition, additional visits to primary care, adverse events, and complications, crosschecked against medical records. Parental satisfaction and belief data were collected only on day 30.

Statistical Analysis

The calculated sample size was 450 children (150 per arm), considering a mean (SD) duration of untreated acute uncomplicated RTI of 12 days.[14] A 2-day reduction in duration was considered a clinically relevant outcome adopting a bilateral approach. The sample size of 450 children was calculated to identify this difference with a type I error of 5% (α = .05) and power of 80% (β = .2). GRANMO sample size calculator software was used.[27] Although the parents and children could interrupt medication at any point in the study, they were still included in follow-up.

Population characteristics were described by using frequencies and percentages for categorical variables and means and SD for quantitative variables. Pearson's χ^2 test was used to compare patient symptoms at the first visit (frequencies and percentages) for the 3 arms. Symptom duration and symptom severity after the first visit were described by using means (SD) and medians and interquartile range (IQR), respectively. For the 3 arms, for each symptom after the first visit, negative binomial regression was used to compare symptom duration, and logistic regression was used to compare symptom severity. Both regression models were adjusted for prescription strategy and informed antibiotic use, and only children with symptoms lasting a day or more were included. Pearson's χ^2 test was used to compare secondary outcomes (frequencies and percentages) for the 3 arms, considering IAP as the reference category. All analyses were guided

TABLE 4 Severity Scores for Patient Symptoms After the First Visit

	Prescription Strategy			Total	
	IAP, median (IQR)	DAP, median (IQR)	NAP, median (IQR)	Total, median (IQR)	Overall *P*
Maximum severity of any symptom[a]	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	.619
Common symptoms[b]					
Everyday routine disruptions	2 (1–3)	2 (2–3)	2 (2–3)	2 (2–3)	.740
Irritability	2 (1–3)	2 (2–3)	2 (1–3)	2 (2–3)	.556
Pharyngitis symptoms					
Fever	2 (1–3)	2 (2–3)	3 (2–4)[c,d]	2 (2–3)	.090
Headache	2 (1–4)	3 (2–3)	3 (3–4)	3 (2–4)	.926
Sore throat	3 (2–3)	3 (2–5)[c]	3 (2–4)	3 (2–4)	.044
Difficulty swallowing	2 (2–3)	3 (2–4)	2 (2–4)	3 (2–4)	.141
Acute otitis media symptoms					
Earache	2 (1–3)	2 (1–3)	2 (2–3)	2 (1–3)	.543
Rhinosinusitis and acute bronchitis symptoms					
Breathlessness	3 (2–3)	3 (2–3)	2 (2–3)	3 (2–3)	.822
Chest noises on breathing	2 (1–2)	2 (2–3)	2 (2–3)	2 (1–2)	.113
Pharyngitis and acute bronchitis symptoms					
Cough	2 (2–3)	3 (2–3)[c]	2 (1–3)	2 (2–3)	.097
Rhinosinusitis, pharyngitis, and acute bronchitis					
Discomfort and/or general pain	2 (1–3)	2 (2–3)	3 (2–3)[c]	2 (2–3)	.145
Nasal mucus	2 (1–3)	2 (2–3)	3 (2–3)	3 (2–3)	.682
Difficulty sleeping	2 (1–3)	2 (2–3)	2 (2–4)	2 (2–3)	.769

The medians and IQRs for symptom severity were calculated for symptoms lasting >1 consecutive day during the 30-d follow-up. Statistical significance was calculated by adjusting an ordered logistic regression model per symptom, with severity as the dependent variable and prescription strategy and antibiotic use as independent variables.

[a] Symptoms are scored on a Likert scale from 0 (no problems) to 6 (as bad as it could be).

[b] Symptoms common to the 4 studied pathologies.

[c] $P < .05$ compared to IAP.

[d] $P < .10$ compared to DAP.

by an intention-to-treat approach (children randomly allocated to each prescription strategy were included). Children who were lost to follow-up were assigned the average duration and severity of symptoms of the other children included in the same strategy. Significance was set to 5% ($\alpha = .05$). All statistical analyses were performed by using Stata software version 13.1 (Stata Corp, College Station, TX).

RESULTS

Trial Population

A total of 436 children, with mean (SD) age 6.3 (3.0) years, were included in the study and the analysis (Fig 1), 226 (51.8%) of whom were girls; 224 (51.4%) had acute otitis media, 146 (33.5%) had pharyngitis, 40 (9.2%) had acute bronchitis, and 26 (6.0%) had rhinosinusitis. Fever and discomfort and/or general pain were the most frequent symptoms for all 4 conditions and were also the severest symptoms at the first visit (mean scores of 3.8 and 3.0, respectively, on the 7-point Likert scale [0–6]). At the first visit, mean (SD) duration of symptoms was reported as 2.5 (4.2) days, whereas mean (SD) health status was scored as 65 (18) (0–100). Most children (n = 395 [90.6%]) had no respiratory comorbidity. One or both parents of 173 (39.7%) children were smokers, and the parents of 227 (52.1%) children had finished tertiary education. Parents mainly indicated that they were moderately worried (n = 213 [48.9%]) or a little worried (n = 145 [33.3%]) at the first visit (Table 1). Symptoms at the first visit were similar for the 3 arms (Table 2).

Primary Outcomes

Duration in days of any symptom until disappearance was similar for the 3 arms. Mean (SD) duration in days of any symptom until disappearance was DAP 8.3 (7.7) versus IAP 8.3 (7.8) (P = .968) and NAP 7.9 (9.3) versus IAP 8.3 (7.8) (P = .593) ($P_{overall}$ = 0.888). Mean (SD) duration in days of severe symptoms was DAP 12.4 (8.4) versus IAP 10.1 (6.3) (P = .247) and NAP 10.9 (8.5) versus IAP 10.1 (6.3) (P = .682) ($P_{overall}$ = 0.539). Mean (SD) duration in days of moderate symptoms was DAP 11.7 (8.7) versus IAP 10.2 (7.5) (P = .257) and NAP 10.0 (8.4) versus IAP 10.2 (7.5) (P = .869) ($P_{overall}$ = 0.435). Regarding the symptoms common to all 4 conditions, namely, everyday routine disruptions and irritability, mean (SD) duration was similar for the 3 arms (P = .837 and P = .965, respectively) (Table 3).

The greatest severity for any symptom on the 7-point Likert scale was similar for the 3 arms, for a median (IQR) score of 3 (2–4). Severity of both common symptoms and specific symptoms was broadly similar for all 3 arms, with significant differences only between DAP and IAP in 2 of 13 symptoms (sore throat and cough), between IAP and NAP in 2 of 13 symptoms (fever and

TABLE 5 Secondary Outcomes

	Prescription Strategy					Total	
	IAP	DAP		NAP			
	n = 148	*n* = 146	*P*[a]	*n* = 142	*P*[a]	*N* = 436	Overall *P*
Antibiotic used	142 (96.0)	37 (25.3)	<.001	17 (12.0)	<.001	196 (45.0)	<.001
Antibiotic duration, d, mean (SD)	7.9 (2.0)	8.4 (2.3)	.181	7.5 (2.7)	.613	7.9 (2.1)	.316
Type of antibiotic			.475		.092		.108
Amoxicillin	106 (74.7)	30 (81.1)		9 (52.9)		145 (74.0)	
Azithromycin	11 (7.8)	2 (5.4)		2 (11.8)		15 (7.7)	
Amoxicillin-clavulanate	9 (6.3)	4 (10.8)		1 (5.9)		14 (7.1)	
Phenoxymethylpenicillin (penicillin V)	7 (4.9)	1 (2.7)		1 (5.9)		9 (4.6)	
Other[b]	9 (6.3)	0 (0.0)		4 (23.5)		13 (6.6)	
Nonantibiotic medication	108 (73.0)	136 (93.2)	<.001	136 (95.8)	<.001	380 (87.2)	<.001
Unscheduled primary care visits	16 (10.8)	15 (10.3)	.881	17 (12.0)	.756	48 (11.0)	.895
Health status score, mean (SD)[c]	97 (8)	97 (8)	.555	97 (9)	.929	97 (8)	.762
Gastrointestinal adverse effects	13 (8.8)	5 (3.4)	.064	4 (2.8)	.040	22 (5.1)	.037
Complications	2 (1.4)	1 (0.7)	.577	2 (1.4)	.967	5 (1.2)	.813
Parental satisfaction			.352		.373		.389
Not at all or slightly satisfied	2 (1.4)	1 (0.7)		0 (0.0)		3 (0.7)	
Little or moderately satisfied	10 (7.0)	5 (3.6)		10 (7.2)		25 (5.9)	
Very or extremely satisfied	130 (91.2)	135 (95.7)		129 (92.8)		394 (93.4)	
Belief in antibiotic effectiveness			<.001		<.001		<.001
Not at all or slightly effective	3 (2.3)	8 (8.9)		9 (11.4)		20 (6.7)	
Little or moderately effective	21 (16.1)	44 (48.9)		47 (59.5)		112 (37.4)	
Very or extremely effective	106 (81.6)	38 (42.2)		23 (29.1)		167 (55.9)	

Data are reported as frequencies and percentages except where otherwise indicated.

[a] IAP is the reference category.

[b] Antibiotics prescribed to <5 patients: cefuroxime, benzathine benzylpenicillin (benzathine penicillin G), and combinations (amoxicillin with cefuroxime, amoxicillin with phenoxymethylpenicillin [penicillin V]).

[c] Scored on a visual analog scale from 0 (worst health status) to 100 (best health status).

discomfort and/or general pain), and between DAP and NAP in 1 of 13 symptoms (fever) (Table 4).

Secondary Outcomes

Antibiotics were taken in the IAP arm by 142 (96.0%) children compared with 17 (12.0%) children in the NAP arm ($P < .001$) and 37 (25.3%) children in the DAP arm ($P < .001$). Of the 17 children in the NAP arm who took antibiotics, only 7 of these attended an unscheduled visit to primary care, and the mean duration between randomization and antibiotic prescription was 2 days. There were no significant differences in antibiotic treatment duration (P = .316) nor in the type of antibiotic (P = .108) for the 3 arms. Nonantibiotic medication use was similar for DAP (n = 136 [93.2%]) and NAP (n = 136 [95.8%]) and higher than for IAP (n = 108 [73.0%]) ($P < .001$). Belief that antibiotics were very or extremely effective was higher for parents of children in the IAP arm than in the other arms (IAP n = 106 [81.6%] versus DAP n = 38 [42.2%] versus NAP n = 23 [29.1%]; $P < .001$). Gastrointestinal adverse effects were lower in the DAP and NAP arms compared to the IAP arm (P = .037). There were no differences between arms in complications (P = .813) or unscheduled visits to primary care (P = .895), and satisfaction was similarly high for the 3 arms (P = .389). There were 5 complications: perforated eardrum and hospitalization due to dehydration (1 child each) and 3 unscheduled visits to the hospital (Table 5).

DISCUSSION

We report findings for DAP compared to IAP and NAP strategies for children with uncomplicated RTIs as explored in this trial of DAP in children. To our knowledge, this is the largest such study conducted to date. Moderate and severe symptom durations for DAP were slightly greater than for IAP and NAP, although differences were not statistically significant. The greatest severity for any symptom was similar for the 3 arms. Antibiotic use was significantly lower in the DAP and NAP arms than in the IAP arm, and nonantibiotic medication was significantly higher in the DAP and NAP arms. Complications, unscheduled visits to primary care, and emergency hospital visits were similar for all 3 strategies, and likewise, satisfaction was high for all 3 strategies. The IAP arm experienced more gastrointestinal adverse effects than the DAP and NAP arms.

Our findings coincide for the most part with the findings of the 2017 Cochrane review[18] on DAP for RTIs, which reported similar symptom durations and no difference in complications for the 3 strategies and lower antibiotic use for DAP and NAP strategies. However, low use of antibiotics observed in clinical trials should be viewed with caution

because the study participants receive structured advice and so are more motivated.[28] In terms of satisfaction, this was high and similar for the 3 arms in our study, contrasting with the Cochrane review,[18] which reported higher satisfaction for IAP than for DAP and NAP. In our study, we found a significant reduction in gastrointestinal adverse events for DAP and NAP compared to IAP, corroborating previous studies in which authors have evaluated DAP for RTIs in children.[19,20]

Our findings are broadly similar to those of a previous trial in an adult population in Spain conducted by our group.[26] In that study, moderate and severe symptom durations were higher for DAP than for IAP but lower than for NAP, whereas in our study in children, symptom duration was slightly greater for DAP than for either IAP or NAP. As for antibiotic use, findings for DAP in children were more favorable than in adults: 32.6% of adults compared with 25.3% of children allocated to DAP took antibiotics. The lower use of antibiotics in our pediatrics study compared to our adult study may be related to 2 factors: greater concern of parents about the adverse effects of antibiotics and more medical consultations for milder episodes. Parents have been reported to be cautious about using antibiotics for RTIs in children on the basis of concerns about adverse effects[29] and past experiences,[30] whereas adults tended not to recall serious consequences of antibiotic treatment.[30] As for medical consultations, parents visited the doctor on behalf of children 3.5 days sooner than adults, and milder episodes led to a higher proportion of doctor visits on behalf of children (the median value of the highest severity score [any symptom] was 2 points lower for children than for adults). The reasons for an earlier medical visit may be fears of the condition worsening or major complications in children or differences in perceptions of the antibiotic risk/benefit equation.[30]

Our findings need to be considered in relation to some limitations. A first main limitation was the open-label design of the study, with outcomes reported by children.[31] However, to reduce the possible placebo effect caused by the open-label nature of the study, all the children received structured information about respiratory diseases and the use of nonantibiotic medication. The second limitation was related to the inferred results for acute bronchitis and rhinosinusitis, as 85% of the included children had acute media otitis or pharyngitis. Nevertheless, strengths of the study are its pragmatic design and the fact that it is the largest ever conducted on DAP for children in southern Europe, in a country with a high rate of antibiotic use.

DAP is an efficacious and safe strategy for reducing inappropriate antibiotic treatment of uncomplicated RTIs in children when the doctor has reasonable doubts regarding the indication. DAP is therefore a useful tool for addressing the public health issue of bacterial resistance.[10] However, NAP remains the recommended strategy when it is clear that antibiotics are not indicated like in most cases of acute bronchitis.[32]

We suggest that the results of this study will enable recommendations to be made for DAP for specific RTIs in children given that as yet there are no guidelines that draw distinctions according to age groups.[33] There is a need, however, for further studies in which authors explore patient profiles for which DAP would be not appropriate, as well as studies in which authors assess DAP-related educational interventions for physicians and parents and children with acute uncomplicated RTIs.[34]

CONCLUSIONS

In this randomized clinical trial of antibiotic treatment strategies for acute, uncomplicated RTIs in children, there was no statistically significant difference in symptom duration or severity who received DAP compared to NAP and IAP strategies. DAP compared to IAP led to greatly reduced antibiotic use and fewer gastrointestinal adverse effects associated with antibiotic intake.

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ABBREVIATIONS

DAP: delayed antibiotic prescription
IAP: immediate antibiotic prescription
IQR: interquartile range
NAP: no antibiotic prescription
RTI: respiratory tract infection

Dr Alonso-Coello conceptualized and designed the study, contributed to drafting of the manuscript, obtained funding, made administrative, technical, and material support, conducted study supervision and had full access to all the data in the study, and assumed responsibility for the integrity of the data and the accuracy of the data analysis; Ms Mas-Dalmau conceptualized and designed the study, contributed to drafting of the manuscript, made administrative, technical, and material support, and conducted study supervision; Drs Villanueva López and Gorrotxategi Gorrotxategi conceptualized and designed the study, conducted the acquisition and interpretation of data, and critically reviewed the manuscript for important intellectual content; Ms Argüelles Prendes, Mr Espinazo Ramos, Ms Valls Duran, Ms Gonzalo Alonso, Dr Cortés Viana, Ms Menéndez Bada, Dr Vázquez Fernández, and Ms Pérez Hernández conducted the acquisition and interpretation of data and critically reviewed the manuscript for important intellectual content; Dr de la Poza Abad conceptualized and designed the study, obtained funding, conducted the interpretation of data, and critically reviewed the manuscript for important intellectual content; Ms Muñoz Ortiz conducted the statistical analysis and critically reviewed the manuscript for important intellectual content; Dr Little conceptualized and designed the study and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Address correspondence to Pablo Alonso-Coello, Iberoamerian Cochrane Center, Biomedical Research Institute Sant Pau (IIB Sant Pau), Sant Antoni Maria Claret, 167, 08025 Barcelona, Spain. E-mail: palonso@santpau.cat

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Delayed Antibiotic Prescription for Children With Respiratory Infections: A Randomized Trial

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