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Real World Evidence (RWE, Real World Data), of the Effectiveness of Amoxicillin-Clavulanate in the Treatment of Children with Upper Respiratory Tract Infections (Tonsillitis, Otitis, Sinusitis)

Maria Gonzalez Yibirin[1], Juan Chirinos[1], David Alberto Rincón Matute[1*], Trinidad Coll[1], Miriam Rosales[1], Yuliana Guevara[1], Kuanlin Doried Guitens Pérez[2], Mauribel Figueroa[3], Rosalía Romero Jurgensen[4], Andrea Rojas[3], Gabriel Jesús Arismendi González[5], Milagros Salcedo[5], Marife Martina Marin Marcano[5], Carolina Mendoza[3], Marycarmen Anuel[6], Maria Morao[7], Raymond Aguilera[2], Diego Ríos[3], Maryenis Rodríguez[7], Loren Sánchez[5], Jennyfer Fernández[7], Rafael González[3], Zaidith Zerpa[3], Nelson Rodríguez[7], Mirluis Rojas[5], Sixtaime Quijada[5], Mariangel Moya[4], Diego Orsini[3], Chris Gómez[5], Hector Gamero[5], José Rodríguez[5]

[1]Laboratorios LETI, S.A.V., Guarenas, Venezuela
[2]Ambulatorio Rural tipo II CPT3, Pampatar, Venezuela
[3]Ambulatorio Los Robles CPT "Dr. Luis Rosas Bravo", Los Robles, Venezuela
[4]Clínica Prevaler, Pampatar, Venezuela
[5]Hospital tipo 1, "Dr. David Espinoza Rojas" en Salamanca, Salamanca, Venezuela
[6]Centro Médico Rotary, El Valle, Venezuela
[7]Ambulatorio Rural Tipo II CPT3 "Dr. Enrique Albornoz Lares", La Asunción, Venezuela
Email: *darinconm@gmail.com

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Abstract

Real-world evidence (RWE) is clinical evidence on a medical product's safety and efficacy that is generated using real-world data (RWD) resulting from routine healthcare delivery. This study evaluates the clinical efficacy of amoxicillin + clavulanic acid in children with pharyngitis, acute otitis, or acute rhinosinusitis with suspected bacterial origin under normal office and home conditions. Methods: This was a real-life, prospective, observational, pharmacovigilance study. It included children of both sexes between 2 and 12 years old, with a diagnosis of Rhinopharyngitis (tonsillitis), Acute Otitis Media and Rhinosinusitis. The main effectiveness variable evaluated was reduction and time to resolution of symptoms. All patients received Amoxicillin/Clavulanic Acid suspension 600 mg/42.9 mg/5 mL at a dose of 90 mg/Kg/day in two doses,

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every 12 hours for 7 days. The evaluations were carried out at the beginning, at 72 hours (3rd day) and at 7 days. All patients underwent culture and antibiogram. Results: The majority of cultures were negative for pathogenic germs, suspecting unidentifiable germs, or viral etiology despite the rigorous selection of subjects following validated scores. The most frequently isolated germ was *Staphylococcus aureus*; growth of gram-negative bacteria was reported in 33.33% of the cultures. There was a significant improvement in symptoms in children with tonsillitis and rhinosinusitis from the first 72 hours of treatment, persisting until the 7 days. In the otitis media group, returning to normal by the tenth day. During the conduction of this investigation, no adverse effects associated with the prescribed therapy were reported.

Keywords

Amoxicillin, Clavulanic Acid, Tonsillitis, Otitis, Sinusitis

1. Introduction

Real-world data (RWD) or Real-world evidence (RWE) is data related to patient health, status, and/or healthcare delivery routinely collected from a variety of sources [1]. This clinical evidence can be the use and potential benefits or risks of a drug or product derived from RWD analysis [1].

RWE studies complement clinical trials by generalizing clinical trial findings to the general population. Additionally, RWE can provide information on other areas, such as the natural history and course of the disease, efficacy studies, outcome studies, and safety surveillance [2].

Acute Respiratory Infections (ARI) are the most common infectious diseases in humans. Many infectious agents, the most frequent being viruses: Respiratory Syncytial Virus (RSV), parainfluenza, adenovirus, rhinovirus, enterovirus, coronavirus, metapneumovirus, bocavirus and mimivirus. Second in frequency are bacteria: Beta hemolytic Streptococcus group A, Mycoplasma pneumoniae and Chlamydia species, Streptococcus pneumoniae, Haemophilus influenzae type b, *Staphylococcus aureus*, predominating in children under five years of age and more prevalent in children under 2 years of age [3].

In Venezuela, the typing of respiratory viruses is made by the National Institute of Hygiene "Rafael Rangel". From week 1 to week 52 of 2016, (last publication available from the Ministry of Popular Power for Health), positive report cases correspond to viruses: RSV (n = 51), Influenza A H1N1 , pdm09 (n = 19), Influenza B, Victoria type (n = 15), Influenza A H3N2 (n = 13), Influenza B, Yamagata type (n = 5), Parainfluenza 2 (n = 2), Influenza A (n = 1), Parainfluenza 1 (n = 1) and Parainfluenza 3 (n = 1). From the point of view of epidemiological surveillance, ARI is defined as all infections of the respiratory system, with an evolution of less than 15 days, caused by both, viruses and bacteria, which present with symptoms related to the respiratory system such as cough, rhinorrhea, nasal

obstruction, odynophagia, dysphonia or respiratory difficulty, whether or not accompanied by fever. They can present clinically at any age, such as flu or influenza, common cold, pharyngitis, tonsillitis, tracheitis and laryngitis, pneumonia and bronchiolitis (in children under 2 years of age) with severe clinical manifestations.

Among the antibiotics used for the treatment of bacterial upper respiratory tract infections are Amoxicillin and Amoxicillin/Clavulanic acid.

Amoxicillin has a broader spectrum against gram-negative microorganisms than other penicillins, maintaining its action against gram-positive germs. Generally sensitive microorganisms other than those indicated: *Clostridium* sp., *Corynebacterium* sp., *Bacillus anthracis*, *Listeria monocytogenes*, *Salmonella* sp., *Shigella* sp., *Bordetella pertussis*, *Brucella* sp., *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pasteurella septica*, *Leptospira* sp., *Vibrio cholerae*, *Fusobacterium* sp. [4].

Amoxicillin/Clavulanic acid is an association of amoxicillin (bactericide, broad spectrum) and β-lactamases inhibitor molecule (clavulanic acid) that makes β-lactamases-producing germs (*Haemophilus influenzae*, *Moraxella catarrhalis*, *Escherichia coli*, *Proteus*, *Klebsiella pneumoniae*) sensible to amoxicillin [5].

2. Acute Upper Respiratory Tract Infections:

Pharyngitis

"Pharyngitis" is a pathology that has different names (tonsillitis, pharyngotonsillitis). Pharyngitis is the inflammation (including erythema, edema, exudate, enanthema, ulcers and vesicles), usually due to infection, of the mucous membranes of the throat.

In tonsil inflammation, signs and symptoms include swollen tonsils, sore throat, fever, difficulty swallowing, and tender lymph nodes on the sides of the neck.

Most cases of tonsillitis are caused by an infection with a common virus, but bacterial infections can also cause tonsillitis.

It must be taken into account to differentiate viral tonsillitis from bacterial tonsillitis since both can have the same signs and symptoms (high fever, odynophagia and pharyngitis with exudates).

The modified Centor criteria (Centor-m) give one point to each of the following signs: temperature above 38˚C, absence of cough, painful lymphadenopathy, exudate and age between 3 - 14 years. If the total is between two and three, then a throat swab for culture is recommended and the decision on antibiotic treatment should be based on the culture results. Patients with a score equal to or greater than four have the highest probability of Group A Streptococcal (GAS) disease, therefore, empirical treatment or sample collection for culture is considered appropriate [6].

With three or more points of the Centor criteria, the patient has a greater chance of benefiting from antibiotics, so we should do a quick test or take a sample for culture and eventually prescribe antibiotics since viruses can also cause high fever and leukocytosis.

In cases of pharyngotonsillitis, the treatment of choice is benzathine penicillin, but amoxicillin, amoxicillin/clavulanic acid, ampicillin/sulbactam, cefadroxil, among others, can also be used as alternatives [7].

Group A Streptococcal disease of the throat responds rapidly (within 48 hours) to the use of amoxicillin.

Rhinosinusitis (RNS)

Acute rhinosinusitis is a frequent health problem both in children and adults. It is most commonly caused by a viral upper respiratory tract infection, whereas bacterial involvement is less frequent, accounting for approximately 0.5% - 2% in adults and 6% - 13% in children. Most cases resolve spontaneously and severe complications are quite rare [8].

Sinusitis is the inflammation and/or infection, associated with the presence of exudate, of the mucous membrane that lines the paranasal sinuses.

In acute RNS, symptoms persist for less than 12 weeks; it can be acute viral (common cold): mild or moderate symptoms that resolve within 10 days. Acute bacterial RNS is characterized by persistence of symptoms for more than 10 days, worsening of symptoms 10 days after the onset of symptoms of the disease or onset of severe symptoms: high fever or purulent rhinorrhea for three consecutive days.

The most frequent bacterial agents are Streptococcus pneumoniae 21% - 33%, non-typeable Haemophilus influenzae 31% - 32%, Moraxella catarrhalis 8% - 11% and Anaerobes 2% - 5% [7].

The treatment recommended in children with suspected bacterial RNS (EG: B)

- Amoxicillin (80 - 90 mg/kg/day BID) – Maximum dose/day: 4g (In primary infection without risk factors, 50 mg/kg/day TID may be indicated)
- Alternatives: (EG: B)
- Amoxicillin/clavulanic acid (90 mg/kg/day BID) – Maximum dose/day: 4 g (it is of choice in cases of suspected resistant Haemophilus influenzae)
- Cefuroxime axetil (30 mg/kg/day BID) – Maximum dose/day: 9 g
- Sultamicillin (40 - 50 mg/kg/day TID) – Maximum daily dose: 8 g
- Ceftriaxone (50 mg/kg IM daily dose - 24 to 48 hours) if the patient does not tolerate the oral route. As tolerance improves complete oral treatment.

Patients allergic to penicillin (immediate hypersensitivity Type I) (EG: B)

- Cefuroxime axetil (30 - 40 mg/kg/day BID PO - –75-150 mg/kg/day TID or QID IV/IM) - Maximum daily dose: 1 g
- Cefixime (8 - 12 mg/kg/day OD/BID PO) Maximum dose/day: 400 mg
- Levofloxacin **(< 5 years of age 20 mg/kg/day BID and in > 5 years 10 mg/kg/day OD) Maximum daily dose: 500 mg
- Cefpodoxime* (10 mg/kg/day BID PO) Maximum dose/day: 800 mg/day [7]

Acute Otitis Media (AOM)

It constitutes a pathology with high morbidity, medical consultations, prescriptions and sequelae. AOM is a disease of infants and young children. It is estimated that by the age of 5 years more than 90% of children have suffered an episode of

AOM and 30% have recurrent AOM. The first episode of AOM before the 6th month of life predisposes to later suffering from AOM, as does artificial breast-feeding in the first months of life.

Among the most feared complications are mastoiditis and meningitis, with the consequences of hearing loss and delay in academic development.

AOM has a high percentage of spontaneous cure, since up to 80% of non-severe cases, in children over 2 years of age, resolve without antimicrobial treatment. Catarrhal and exudative AOM in children over 2 years of age is treated symptomatically during the first 48-72 hours of the clinical course.

Shaikh et al validated a 7-item parent-reported symptom score (Acute Otitis Media Severity of Symptom Scale [AOM-SOS]) for children with AOM, following strict guidelines from the US Food and Drug Administration (FDA) on the development of patient-reported outcomes scales. Symptoms included ear pulling/rubbing/holding, excessive crying, irritability, difficulty sleeping, decreased activity or appetite, and fever. AOM-SOS was correlated with otoscopic diagnoses (AOM, OME, and normal middle ear status). AOM-SOS changed appropriately in response to clinical change. Its daily responsiveness supports its usefulness in monitoring AOM symptoms over time [9]-[11].

The treatment of choice is amoxicillin 80 - 90 mg/kg/day in uncomplicated AOM and without risk factors. The treatment of choice for AOM in patients with risk factors is amoxicillin/clavulanic acid 90 mg/kg/day for 7 to 10 days. Alternative antibiotic treatments include cefuroxime axetil, ceftriaxone (and other cephalosporins) or clarithromycin. (7) Treatments with cephalosporins have demonstrated equal clinical and microbiological efficacy. In one study, the use of cefprozil was significantly associated with a lower risk of adverse effects (mainly gastrointestinal effects), when compared to amoxicillin/clavulanic acid (reduced risk of 48%) [12].

In respiratory conditions in children, the laboratory test for acute respiratory infections is, first, a peripheral blood test. The white blood cell count is normal or low during viral infection and the proportion of lymphocytes increases. In bacterial infections, the white blood cell count increases and the ratio shifts to the left. The second is the pathogenic examination, which is not usually done unless necessary, to determine the type of virus; bacterial culture and drug sensitivity testing are useful for the diagnosis and treatment of bacterial infections. Finally, other ancillary tests may be done, such as a chest X-ray examination.

3. Materials and Methods

Objective:

To evaluate the clinical efficacy of amoxicillin + clavulanic acid in children with pharyngitis, acute otitis, or acute rhinosinusitis with suspected bacterial origin under normal office and home conditions.

This was a real-life, prospective, observational, pharmacovigilance study. It included children of both sexes between 2 and 12 years old, with a diagnosis of:

Rhinopharyngitis: Children with a temperature above 38 ˚C, absence of cough, painful lymphadenopathy, exudates.

Acute Otitis Media: Children with AOM-SOS scale ≥ 3

Rhinosinusitis: Children with at least five of the following seven parameters: nasal obstruction, mucopurulent rhinorrhea, postnasal drip, cough, facial pain, headache and fever; suspected bacterial etiology at the discretion of the treating physician.

The conditions for inclusion were that the patient had not received antibiotics in the previous 15 days. The father or his legal representative understood the study and signed his or her informed consent.

Exclusion criteria: those children with the presence of a peritonsillar abscess, anatomical anomalies (e.g. naso-lip-palatine cleft), presence of uncontrolled bronchial asthma, cystic fibrosis, tuberculosis or known allergic manifestations in the throat and/or mouth were excluded according to the protocol, obstruction in the pharynx due to enlarged tonsils (causing serious sleep disorders, e.g. sleep apnea). Children with severe cardiovascular, kidney or liver disease, as well as gastroesophageal reflux, unstable diabetes mellitus or hyperthyroidism. Children with a history or presence of all types of serious streptococcal complications (rheumatic heart disease, glomerulonephritis, arthralgia, arthritis); previous surgery in the last six months or need for surgery on the nose or paranasal sinuses, adenoids and/or tonsils; evidence of any malignancy during the last two years before enrollment in the trial. Presence of neurological and/or psychiatric diseases.

Other exclusion criteria: cases of children with treatment with systemic antibiotics, glucocorticosteroids or drugs with immunomodulatory activities during the last four weeks. Treatment with antibiotics, glucocorticosteroids or immunomodulators with local action on the tonsils during the last week, before enrollment in the trial. Patients with known or suspected hypersensitivity to penicillin and cephalosporin drugs, as well as those with a history of immunodeficiency.

The main effectiveness variable evaluated was reduction and time to resolution of symptoms. All patients had an admission culture.

All patients received: Amoxicillin/Clavulanic Acid suspension 600 mg/42.9 mg/5 mL at a dose of 90 mg/Kg/day in two doses, every 12 hours for 7 days.

The evaluations were carried out at the beginning, at 72 hours (3rd day) and at 7 days. The in-person evaluations were the initial one, the others could be done by telephone if there was no deterioration in the patient's evolution. Furthermore, if the patient did not show improvement after 72 hours of treatment, the doctor instructed him to return to the office for an in-person reevaluation with a physical examination. All patients underwent culture and antibiogram.

4. Evaluations

Patients with tonsillitis

Score on the Centor scale: Give one point to each of the following signs: temperature above 38˚C, absence of cough, painful lymphadenopathy, and exudates.

Patients with rhinosinusitis

They were evaluated using the following scale:

Symptoms	Not at all = 0	Almost nothing = 1	A little = 3	Somewhat = 4	A lot = 5	Extreme = 6
Is your nose stuffy today?						
Do you pour liquid today?						
Do you have a cough today?						
More tired today?						
More irritable today?						
Trouble breathing through the nose today?						
Did you have a cough last night?						
Did you sleep badly last night?						

Patients with acute otitis media

Time to resolution of symptoms will be defined as the time from the start of treatment until a child's AOM-SOS score reaches 0 or 1.

Score	Fever	Pain when pulling the ear	Crying	Irritability	Difficulty sleeping	Decreased activity	Decreased appetite
0	Nothing	Nothing	Nothing	Nothing	Nothing	Nothing	Nothing
1	A little	A little	A little	A little	A little	A little	A little
2	A lot	A lot	A lot	A lot	A lot	A lot	A lot

Parents rated each of the 7 symptoms (ear pulling, irritability, crying, difficulty sleeping, decreased activity, decreased appetite, and fever) as 0, 1, or 2 (not at all, a little, a lot) and reported the scores on Day 1, 2 and 3, then days 4 - 7. The total gave us the AOM-SOS score. The maximum possible score was 14 and the minimum was zero. A score ≥ three was required to enroll in the study.

The results were analyzed through descriptive analysis of the anthropometric variables and the results of the assessment scales, using the non-parametric Wilcoxon Rank test, for a significance level of $P < 0.05$.

5. Results

One hundred sixteen patients met the inclusion criteria, 7 of them were not included for the analysis due to protocol violation or poor data recording. One hundred and eight cultures were performed and in one additional case, the culture could not be processed; however, it was included in the analysis because it had clinical data recorded.

Description of the evaluated population

The patients were included in public and private centers in the state of Nueva Esparta, in Venezuela, the Public Care centers were: Hospital type 1, Dr. David Espinoza Rojas in Salamanca, Rural Outpatient Clinic type II Pampatar, Rural Outpatient Clinic Type II La Asunción, Outpatient Clinic Rural type II Los Robles. The private care centers were Rotary Medical Center and Prevaler Medical Center.

The characteristics of the evaluated population can be seen in Table 1.

Table 1. Description of the evaluated population.

	All (n = 109)	Tonsillitis (n = 65)	Rhinosinusitis (n = 13)	Otitis (n = 31)
Average age in years (range)	5.26 (2 - 11)	5.07 (2 - 11)	5.62 (3 - 7)	5.52 (2 - 11)
Weight in Kg	19.49 ± 6.98	19.51 ± 7.11	19.05 ± 5.03	19.67 ± 7.81
Height in cm	104.25 ± 11.31	103.46 ± 30.75	103.85 ± 34.57	106.62 ± 32.55

Table 2. Distribution of cultures by diagnosis.

Cultures	N	%
Positive	39	36.1%
Negative	69	63.8%

The majority of cultures were negative for pathogenic germs, suspecting unidentifiable germs, or viral etiology despite the rigorous selection of subjects following validated scores (Table 2).

Table 3. Bacteria isolated in positive cultures and sensitivity to the amoxicillin-clavulanic acid association using commercial discs.

Isolated bacteria	N	% Sensitivity to amoxicillin-clavulanic acid
Staphylococcus aureus	26	66,67
Gram negative bacilli	13	33,33%

The most frequently isolated germ was *Staphylococcus aureus*, and 66,67% were sensitive to Amoxicillin/Clavulanic acid; growth of gram-negative bacteria was reported in 33.33% of the cultures (Table 3). Despite resistance of *Staphylococcus aureus* to amoxicillin/clavulanic acid, in vitro, only one patient required a change of antibiotic, as all the others improved clinically.

Table 4. Evolution of symptoms of patients diagnosed with tonsillitis. Centor-m criteria.

Symptom	Onset ($\bar{x}$)	72 hours	p	7 days	p	p from base
Fever	1.12	0.21	0.00	0.00	0.01	0.00
Pain	1.03	0.33	0.00	0.00	0.00	0.00
Irritability	0.66	0.09	0.00	0.02	0.05	0.00
No appetite	0.88	0.26	0.00	0.05	0.00	0.00
Trouble sleeping	0.88	0.10	0.00	0.00	0.02	0.00
Totals	4.57	0.98	0.00	0.07	0.00	0.00

p: Wilcoxon rank test.

There was a significant improvement in symptoms in children with tonsillitis, from the first 72 hours of treatment, persisting until the 7 days were completed (Table 4).

Table 5. Evolution of symptoms in patients with rhinosinusitis.

Symptom	Onset	72 hours	P*	7 days	P*	p from base
Is your nose stuffy today?	4.23	2.00	0.02	0.31	0.01	0.01
Do you pour liquid today?	3.77	1.46	0.02	0.15	0.07	0.01
Do you have a cough today?	4.54	2.31	0.01	0.23	0.01	0.01
More tired today?	2.62	0.46	0.02	0.00	0.11	0.02
More irritable today?	1.38	0.15	0.16	0.00	0.04	0.01
Trouble breathing through the nose today?	4.69	1.62	0.02	0.15	0.01	0.01
Did you have a cough last night?	3.77	1.62	0.04	0.23	0.01	0.01
Did you sleep badly last night?	3.08	0.38	0.06	0.00	0.01	0.01

p: Wilcoxon rank test.

The average of the points assigned to each row is taken for the analysis. In patients with rhinosinusitis, improvement occurred in the first 72 hours; at the end of the 7 days, all the measured variables improved significantly (Table 5).

Table 6. Evolution of symptoms in patients with acute otitis media.

Symptom	Onset	72 h	p*	5 days	p*	10 days	p*	p from base
Fever	1.04	0.52	0.06	0.14	0.00	0.00	1.00	0.01
Pain when pulling the ear	1.43	0.78	0.03	0.55	0.08	0.05	0.03	0.01
Crying	0.96	0.26	0.01	0.09	0.16	0.00	1.00	0.02
Irritability	0.91	0.17	0.00	0.09	0.16	0.00	0.32	0.02
Difficulty sleeping	0.87	0.30	0.00	0.14	0.16	0.00	0.32	0.01
Decreased activity	0.78	0.30	0.04	0.14	0.16	0.00	0.32	0.01
Decreased appetite	0.78	0.30	0.01	0.05	0.08	0.00	0.32	0.00

p: Wilcoxon rank test.

Regarding the evaluation of clinical improvement in the otitis media group, once treatment with amoxicillin/clavulanic acid was started, a decrease in symptoms was observed, returning to normal by the tenth day; this variation was statistically significant (Table 6).

During the conduct of this investigation, no adverse effects associated with the prescribed therapy were reported.

6. Discussion

Antimicrobial resistance represents a threat to global public health. Acute respiratory infections are the main reason for antibiotic prescription in the pediatric population.

A case-control study was carried out in September and October 2018, in infants with fever and respiratory symptoms, compared to controls who were children participating in the vaccination program. Viral identification was performed by polymerase chain reaction for 21 different viruses. The bacteria were identified through culture studies. In total, 102 cases and 96 controls were included. Microorganisms were detected in 90.1% of cases and 53.7% of controls ($p < 0.001$). Influenza A virus (including H1N1), influenza B virus, Respiratory Syncytial Virus (RSV), and

Streptococcus pneumoniae were independently associated with acute respiratory tract infections. Co-detection of two or more pathogens was present in 49.5% of cases; 31.7% of cases had pneumonia and 90.2% were treated with antibiotics [13].

In another prospective descriptive monocentric study over a period of one year at the Albert Royer National Children's Hospital in Dakar in which multiplex PCR (protein chain reaction) was performed on nasopharyngeal swabs taken from all patients, 109 patients were included. The hospital prevalence of acute respiratory infections was 3.7%. The mean age was 23.7 months with extremes between 1 month and 144 months. The peaks of consultations were found in the months of August, March and April with 22%, 15.6% and 12.8% respectively. Fever, respiratory distress and pulmonary condensation syndrome were the main signs found in their patients. Bacteriology was positive in 82.6% of the samples and the most frequently found bacteria were Streptococcus pneumoniae in 38.5%, Haemophilus influenza b in 32.1% and Moraxella catarrhalis in 25.7%. Pneumonia was the main diagnosis, found in 61 cases, with a prevalence of 59.9%. The average duration of hospitalization was 10 days. The fatality rate was 1.8% or 2 cases [14].

Overuse and misuse of antibiotics, as well as self-prescription, are among the most important causes contributing to the growth of antibiotic resistance in humans. A systematic review was conducted describing the phenomenon of antibiotic self-medication (ASM) in children. The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) by searching PubMed, Scopus, and Web of Science through July 2022. Published studies containing information on parental knowledge, attitudes, and behaviors in the self-administration of antibiotics in children were included. Seven hundred and two articles were identified and 57 were selected. A higher prevalence of ASM was found among children in the Middle East (34%), Africa (22%), Asia (20%), and South America (17%), while that the lowest prevalence was found in Europe (8%), which demonstrates that establishing controls on the dispensing of antimicrobials certainly limits the risk of self-medication behavior [15].

In a study that evaluated the epidemiology, clinical and therapeutic profiles, carried out in Mali, in patients (n = 315) who were diagnosed with tonsillitis during one year, it was found that the average age was 14.25 years, predominating in the female sex. The most frequent symptoms were odynophagia (88.63%) and fever (86.27%). In 19.05% of cases there were complications (peritonsillar phlegmon 42.22%, heart disease 33.33%, cervical cellulitis 8.89%, adeno-phlegmon 6.67%, para-pharyngeal abscess 4.44%, and sepsis 4.44%). This is important because appropriate diagnostic criteria and antibiotic treatments must be available to prevent progression to complications [16].

In this study, carried out in real-life conditions (typical routine pediatric medical practice), globally accepted criteria were used for the suspicion of upper respiratory infections of bacterial etiology. We found bacterial growth in a little more than 30% of the patients, being *Staphylococcus aureus* the most frequently isolated germ. This finding is worth highlighting since the majority of reports in the

literature have group A beta-hemolytic Streptococcus as the leading bacteria, giving rise to continued research in the field of bacteriology. In a systematic review and meta-analysis published in April 2024, it was found that the global prevalence of asymptomatic colonization of *Staphylococcus aureus* was 25.1% (3.7% to 48.6%), with the highest prevalence in Portugal (48.6%). followed by Brazil (48.0% and 47.3%), which could explain the presence of *S. aureus* in the population included in our study [17].

A review focused on interactions between *S. aureus* and non-influenza viruses. Clinical data evidenced that rhinovirus infection may increase the *S. aureus* carriage load in humans and its spread. In children, respiratory syncytial virus infection is associated with *S. aureus* carriage. The mechanisms by which some non-influenza respiratory viruses predispose host cells to *S. aureus* superinfection can be summarized in three categories: i) modifying expression levels of cellular patterns involved in *S. aureus* adhesion and/or internalization, ii) inducing *S. aureus* invasion of epithelial cells due to the disruption of tight junctions, and iii) decreasing *S. aureus* clearance by altering the immune response [18].

Finally, considering the limitations of this type of intervention, it is necessary to continue refining those clinical parameters that allow better identification of bacterial processes compared to other etiologies. Even though clinical practice recommendations continue to justify the use of antibiotics empirically and clinical improvement is indeed found in a high percentage of treated patients, bacteriological confirmation is not frequently obtained.

This type of study urges us to promote the development of better clinical criteria, as well as faster and more precise diagnostic methods, in order to reduce the need for antibiotic therapy in patients without bacterial infection, reducing the associated risk of antibiotic resistance.

It is necessary to have an adequate therapeutic arsenal. Amoxicillin/clavulanic acid, and other known molecules, should be kept in the first line of broad-spectrum antibiotic management, since they show successful clinical results in the majority of cases of community-acquired infections. The successful results obtained with these molecules, despite having been approved for use in the pediatric and adult population for many years, reinforce the message of confidence to medical personnel in their early use, supporting the appropriate use of antibiotics in this type of patient.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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