



Predictive factors of antibiotic prescribing in children with upper respiratory tract infections

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FINAL DEGREE PROJECT

Predictive factors of antibiotic prescribing in children with upper respiratory tract infections

Medical Degree

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ABSTRACT

Introduction: Upper respiratory tract infections (URTIs) are the most common infections in children, their aetiology is mostly viral and their evolution is self-limiting. Antibiotic prescription is still very high in these infections, increasing the risk of resistance and secondary effects. Several studies have shown that certain signs and symptoms, as well as features from the physician, the patient and their family, can influence in antibiotic prescription.

Objectives: To determine if clinical criteria such as high fever or tonsillar exudate increase antibiotic prescription in children. Social and economical factors that could lead to higher prescription will also be assessed.

Participants: Children from 0 to 14 years with an URTI, visited at any Primary Health Care Centre in Tarragona, Spain, from October 2015 to March 2016. Children diagnosed with epiglottitis, or children with either symptoms or a diagnosis of a lower respiratory tract infection will not be included.

Methods: This is a cross-sectional study in which the physician uses a template to fill in the clinical criteria observed on each patient. Other questionnaires are also used, filled in by the child's family and by the own physician.

Expected results: A positive association between high fever, tonsillar exudate and higher antibiotic prescription is expected. Expectation of antibiotics by the child's family and persistence of symptoms are other criteria expected to increase antibiotic prescription.

Key words: Upper respiratory tract infection, antibiotics, antibiotic use, children, paediatrics.

Introducció: Les infeccions de vies respiratòries altes (IVRA) són les infeccions més freqüents en l'edat pediàtrica, d'etiologia majoritàriament vírica i d'evolució autolimitada. La prescripció antibiòtica segueix sent molt elevada en aquest grup d'infeccions, augmentant el risc de resistències i els efectes secundaris. Diversos estudis han mostrat que hi ha certs signes i símptomes,

així com característiques del metge prescriptor o del pacient i la seva família, que poden influir en que s'acabi prescribint un antibiòtic.

Objectius: Determinar si certs criteris clínics com la febre alta o l'exudat amigdal·lar incrementen la prescripció antibiòtica en el pacient pediàtric. També s'analitzaran factors econòmics i socials que poguessin portar a un augment de la prescripció.

Participants: Nens i nenes de 0 a 14 anys que presentin una IVRA, visitats a qualsevol Centre d'Atenció Primària de la ciutat de Tarragona entre octubre de 2015 i març de 2016. No s'inclouran a l'estudi els nens amb símptomes o diagnòstic d'infecció de vies respiratòries inferiors, o els nens amb diagnòstic d'epiglotitis.

Mètodes: Es tracta d'un estudi transversal en el que el metge ha d'omplir una plantilla amb criteris clínics observats en cada pacient. També s'utilitzen un qüestionari pels familiars del nen i pel metge.

Resultats esperats: S'espera trobar una associació positiva entre la febre alta i l'exudat amigdal·lar i l'augment de prescripció d'antibiòtics, així com un augment de prescripció amb altres criteris, com la demanda d'antibiòtic per part dels acompanyants o la persistència dels símptomes.

Introducción: Las infecciones de vías respiratorias altas (IVRA) son las infecciones más frecuentes en la edad pediátrica, de etiología mayoritariamente viral y de evolución autolimitada. La prescripción antibiótica sigue siendo muy elevada en este grupo de infecciones, aumentando el riesgo de resistencias y los efectos secundarios. Varios estudios han mostrado que hay ciertos signos y síntomas, así como características del médico prescriptor o del paciente y su familia, que pueden influir en que se acabe prescribiendo un antibiótico.

Objetivos: Determinar si ciertos criterios clínicos como la fiebre alta o el exudado amigdal·lar incrementan la prescripción antibiótica en el paciente pediátrico. También se analizarán factores económicos y sociales que podrían llevar a un aumento de prescripción.

Participantes: Niños y niñas de 0 a 14 años que presenten una IVRA, visitados en cualquier Centro de Atención Primaria de la ciudad de Tarragona entre octubre de 2015 y marzo de 2016. No se incluirán en el estudio los niños con síntomas o diagnóstico de infección de vías respiratorias inferiores, o los niños con diagnóstico de epiglotitis.

Métodos: Se trata de un estudio transversal en el que el médico ha de rellenar una plantilla con criterios clínicos observados en cada paciente. También se utilizan un cuestionario para los familiares del niño y para el médico.

Resultados esperados: Se espera encontrar una asociación positiva entre la fiebre alta y el exudado amigdalal y el aumento de prescripción antibiótica, así como un aumento de prescripción con otros criterios, como la demanda de antibiótico por parte de los acompañantes o la persistencia de los síntomas.

INTRODUCTION

Upper respiratory tract infections (URTIs) include common cold, acute rhinitis, acute purulent rhinitis, laryngitis, pharyngitis/tonsillitis, acute rhinosinusitis and acute otitis media(1). URTIs are responsible for 20-30% of total general practitioner (GPs) appointments in Spain, and 61.5% of antibiotic prescriptions to children are the result of diagnosing a respiratory disease(2). Viruses cause most of these infections, their evolution is self-limiting and their complications are rare(1).

When treating **acute pharyngitis**, antimicrobial use is recommended only when the presence of streptococcal (group A Streptococcus, GAS) aetiology has been proven(3), due to its effect on shortening the duration of symptoms and a likely reduction of the bacteria's horizontal transmission(4). GAS is only present in around 20% of acute pharyngitis(5). As it is difficult to distinguish between viral and bacterial aetiologies, scoring systems such as the Centor criteria (6) can contribute to identify the need for a rapid-antigen detection test. For **common cold** (including **acute rhinitis** and **acute purulent rhinitis**), there is no evidence on the benefits from antibiotics; therefore, their routine use is not recommended(7). When treating **acute rhinosinusitis**, the use of antimicrobials depends on the clinical presentation(8): antibiotics should be prescribed to children with severe or worsening symptoms. In case of persistent symptoms (>10 days, with nasal discharge of any quality, cough or both), either medical observation with a close follow-up or antibiotic therapy can be considered. Antibiotics should not be used to treat **Laryngitis** since its aetiology is mostly viral(9). In **acute otitis media**(10) (**AOM**), therapy with antimicrobials is recommended for all children with severe signs or symptoms. Bilateral AOM in children younger than 24 months should also be treated with antibiotics, and observation can be considered in this age group in nonsevere unilateral AOM. Finally, observation is also an option for older children with nonsevere symptoms. Children treated with antibiotics are more likely to achieve clinical success, but most cases are resolved spontaneously and without complications, regardless of treatment. Some guidelines(9) include **epiglottitis** among URTIs. Epiglottitis is mainly caused by type-B *Haemophilus Influenzae* (Hib) and other

bacteria, and it is a severe condition that can potentially lead to death, due to the airway obstruction. Therefore, airway management is the first step to take in unstable patients, and antibiotics are always needed. That is the reason epiglottitis was not assessed in our study.

Although antimicrobial agents do not modify or only change slightly the evolution of most of these infections, they are still being prescribed to U.S. outpatients almost twice as often as expected(11). Its use is associated with increased resistance among bacteria, which implies higher risk both at the individual and at the community level (12,13). Moreover, antibiotics are the main cause of medication-related adverse reactions among children(14), and early exposure to these drugs could lead to long-term undesired effects (asthma, bowel inflammatory disease, obesity...)(4). Antibiotics have been proven to reduce the risk of suppurative complications (such as peritonsillar abscess or secondary OMA) and rheumatic fever(15). Traditionally, antibiotics have been prescribed to prevent these complications, contributing to a decrease in their incidence, so the number of patients one would need to treat nowadays in order to prevent a single case of peritonsillar abscess or rheumatic fever is very high (4,15).

Even though it is difficult to clinically distinguish between viral and bacterial aetiologies, validated clinical criteria can help in both making a diagnosis and restricting antibiotic prescription only to the suspected bacterial cases(4). Some studies (16,17) have focused on learning which criteria currently determine antibiotic prescription to children. These included physician's personal characteristics (sex, years of experience, specialty) and the patient or their parents' characteristics (socioeconomic status, asking for a prescription). They found that children in households with higher incomes were less likely to receive an antibiotic for an URTI. Moreover, emergency physicians were the specialists with the highest prescription of antibiotics for URTIs, when compared with paediatricians and GPs, and paediatricians prescribed more antibiotics than GPs but were more likely to use second-line antibiotics.

Parents' knowledge and expectations towards antibiotics have also been studied (18). The majority of parents considered URTIs to be self-limited. Nevertheless, nearly 75% of them expected their children to receive antibiotics

when this diagnosis was given. Many studies have analysed several physician-targeted interventions to improve antibiotic prescription. But few (19-21) have focused on the clinical factors that have an effect on this prescription. In addition, most of the available studies have not specifically targeted the paediatric population, where these infections are more common, and in some cases the study designs had limitations. Moreover, some of the observed results were not consistent. In the *Llor C et al(19)* study, performed in adults, the symptom that was most strongly associated to antibiotic prescription was the presence of tonsillar exudate, followed by ear discharge and the presence of sputum. Higher patient demand for antibiotics was also found to be associated with higher prescription. This fact was also observed in the *Ong S et al(20)* study, where the sinus tenderness was the most strongly associated symptom. Nevertheless, in the *Safdar N et al(21)* study the duration of the illness was the most determining factor, and the patient's wish of an antibiotic did not influence its prescription. It can be seen so, that some of the results are inconclusive. Therefore, more studies are needed, which should put the focus on paediatrics and on gathering as many clinical criteria as possible.

This has led us to investigate whether certain clinical and social criteria are linked to an increase in antibiotic prescription. Our hypothesis is that certain signs and symptoms, such as sinus pain or ear discharge, are linked to a higher prescription due to the specific indications of antimicrobial therapy in sinusitis and AOM. We hypothesised that symptoms that can be present in both viral and bacterial URTIs, such as tonsillar exudate and fever, also lead to higher prescription. The duration and severity of symptoms and the patient or parent's demand of an antibiotic are also expected to lead to higher prescription.

The objective of our study is to determine which factors are associated to an increase of antibiotic prescription in children diagnosed with an URTI. A better understanding of the clinical background that influences this prescription could be useful to identify erroneous practices and learning points, and it could provide a framework to help physicians with clinical decision-making. Other factors, such as parents' socioeconomic status, their demand of an antibiotic, or some of the physicians' characteristics, are also assessed.

WORKING HYPOTHESIS

Main hypothesis:

The main hypothesis of this study is that children with an upper respiratory tract infection presenting, either or both, fever $\geq 38.5^{\circ}$ and tonsillar exudate, will receive higher antibiotic prescription rates compared to children with the same diagnosis who are not presenting these signs.

Secondary hypothesis:

Moreover, we hypothesise that the following clinical, social and economical criteria will lead to an increase in antibiotic prescription among children with an URTI:

- Symptoms present for more than 7 days.
- Ear discharge and/or ear pain.
- Sinus symptoms: Frontal headache or sinus pain with sinus tenderness.
- Children younger than 2 years, compared to older children with the same symptoms.
- Expectation or demand of an antibiotic by the child's parents.
- A child's family with an annual household income lower than 15000 €, when compared to families with higher annual incomes.

OBJECTIVES

The main objective of this study is to assess whether certain signs or symptoms are linked to an increase in antibiotic prescription in children diagnosed with an URTI.

The secondary objectives include assessing social and economical criteria surrounding the patients and their families, as well as features related to the physicians attending them, to find out whether they have an impact or not in antibiotic prescription. Also, another secondary objective is to determine whether the clinical criteria that lead to higher antibiotic prescription in our study are based on scientific evidence, and meet the current recommendations that

have been previously stated. Therefore, we expect to contribute to the improvement of clinical decision-making in terms of antibiotic prescription.

METHODS

Study design:

This is an observational, cross-sectional study that will take place in several Primary Health Care centres located in the city of Tarragona (Spain). A template will be used by the physicians to register the clinical presentation (signs, symptoms, clinical diagnosis...) from every patient with an upper respiratory tract infection, and whether antibiotics are prescribed or not in each case. In addition, information on the child's household characteristics and on the physician will also be collected. The data will be obtained from October 2015 to March 2016.

Participants:

Any child younger than 14 years old, attended in any Primary Health Care centre at the city of Tarragona (Spain), that will be diagnosed with an upper respiratory tract infection. Children older than 14 years will not be included in this study since they are not considered paediatric population in these types of centres.

Inclusion and exclusion criteria:

Inclusion criteria:

- Children aged 0 to 14 years, with an upper respiratory tract infection diagnosis. Upper respiratory tract infections include common cold, acute rhinitis, acute purulent rhinitis, laryngitis, pharyngitis/tonsillitis, acute rhinosinusitis and acute otitis media (1).

Exclusion criteria:

- Children with epiglottitis. Epiglottitis is mainly caused by bacteria and it is a very serious disease, therefore antibiotics should always be administered intravenously (9).
- Children with low respiratory tract signs and symptoms (crackles, wheezes, purulent sputum...) even if added to upper respiratory tract ones.
- Children with a diagnosis of a lower respiratory tract infection (bronchiolitis, acute bronchitis, pneumonia...).

Variable definition:

Main variables:

Dependent variable:

- Antibiotic prescription (qualitative, nominal, dichotomous. Answers: Yes, No).

Independent variables:

- Tonsillar exudate (qualitative, nominal, dichotomous. Answers: Yes, No).
- Fever $\geq 38.5^{\circ}$ C (qualitative, nominal, dichotomous. Answers: Yes, No).

Secondary independent variables:

Child's characteristics:

Variables	Characteristics			Answers
Patient's sex	Qualitative	Nominal	Dichotomous	Male, Female
Age (Date of Birth)	Quantitative	Continuous		Any age ranging from 0 to 14 years
Erythematous pharynx Oropharyngeal examination will be needed	Qualitative	Nominal	Dichotomous	Yes, No

Swollen tonsils Oropharyngeal examination will be needed	Qualitative	Nominal	Dichotomous	Yes, No
Odynophagia (painful swallowing). Will not be measurable in the youngest children	Qualitative	Nominal	Dichotomous	Yes, No
Rhinorrhea	Qualitative	Nominal	Dichotomous	Yes, No
Purulent rhinorrhea	Qualitative	Nominal	Dichotomous	Yes, No
Cough	Qualitative	Nominal	Dichotomous	Yes, No
Stridor A kind of respiratory sound caused by partial upper respiratory tract obstruction	Qualitative	Nominal	Dichotomous	Yes, No
Sinus symptoms Frontal headache or sinus pain with sinus tenderness. Will not be measurable in the youngest children	Qualitative	Nominal	Dichotomous	Yes, No
Swollen anterior cervical nodes Anterior cervical zone palpation will be needed	Qualitative	Nominal	Dichotomous	Yes, No
Ear symptoms and signs: Presents one or more than one of the following: Ear pain, hearing loss, purulent discharge...	Qualitative	Nominal	Dichotomous	Yes, No
Duration of illness	Qualitative	Ordinal		< 7 days, 7 – 14 days, > 14 days)
Antibiotics expected / demanded by the patient or parents	Qualitative	Nominal	Dichotomous	Yes, No
Clinical impression	Qualitative	Nominal	Dichotomous	Bacterial, Viral

Subjective impression according to the signs, symptoms and duration of illness				
Clinical Diagnosis Diagnostic approach, based on clinical presentation	Qualitative	Nominal		Common cold, acute pharyngitis acute tonsillopharyngitis acute rhinosinusitis acute otitis media acute laryngitis

Physician's characteristics:

Variables	Characteristics			Answers
Sex	Qualitative	Nominal	Dichotomous	Male, Female
Age (years)	Quantitative	Continuous		Any age
Medical specialty	Qualitative	Nominal		Paediatrician, General Practitioner, other
Years in practice Years of medical practice, from the start of the specialization until nowadays	Quantitative	Continuous		Any number
MIR specialization	Qualitative	Nominal	Dichotomous	Yes, No

Household's characteristics:

Variable	Characteristics		Answers
Annual household income (€)	Qualitative	Ordinal	< 15000, 15000-25000, 25000-50000, > 50000
Level of education	Qualitative	Ordinal	See annex 3

Measurement instruments:

- A questionnaire (*Annex 1*) to be filled in by each physician that will take part in the study. The questionnaire asks about the sex, age, specialty, years of practice and whether or not they have a MIR specialisation.
- A template (*Annex 2*), adapted from the *Llor C et al. (18)* study, to be filled in by each physician that will take part in the study, during or after every visit that includes a diagnosis of an URTI. The physician has to register data about the signs and symptoms presented, the clinical impression, the clinical diagnosis, the duration of illness, whether there is an antibiotic prescription or not and whether the parents expect or ask for an antibiotic.
- A questionnaire (*Annex 3*) that measures the level of education and the annual household income from every patient's family. This questionnaire has to be filled in by the patient's father or mother.

Data collection:

At first, the protocol should be approved by the local ethics committee. Next, each centre's medical director will be contacted and told about the study, requesting their paediatricians' participation. The data will be collected from all the Primary Health Care centres in Tarragona, Spain (*Annex 4*). All the paediatricians (and other physicians attending children) working in these centres will be recruited to participate voluntarily. They will be given the protocol and they will be told about the aim and methodology of the study. If they agree to take part in the study, they will be given the three questionnaires.

The fieldwork period will last for six months. Every time a patient that meets the inclusion criteria comes to the Primary Health Care centre, the physician will, firstly, inform the child's mother and/or father about the study and give them the informed consent. If they agree to participate, the physician will collect all the data in the template seen in *annex 2*. The patients who return to the consult for a second time or more with a diagnosis of an URTI, will be registered again in the template, but their family's characteristics will not. Finally, the physicians will also have to fill in the questionnaire asking about their own characteristics.

After the recruitment period ends, a field worker will introduce all the collected data in a database and afterwards the data will be cleaned, its quality will be checked and the data analysis will be performed. The results will be compared then to the current scientific evidence of the matter, that is, the Clinical Practice Guidelines used as a reference in our study. Finally, study's publication will be carried out.

Sample:

In order to estimate the needed sample, previous similar studies were analysed. *Pennie R* (15) registered 4344 children visits, in which 2084 respond to a diagnosis of an URTI.

Llor C et al (18) included a total of 16751 visits, including upper and lower respiratory tract infections, registered by the 309 physicians that agreed to take part in the study, throughout a three-week period. 66% of the registers (11066) received a diagnosis of an URTI. Therefore, we assumed that, with approximately 15 times less physicians available (a total of 22), 15 times less registers (≈ 740) could be obtained in the same period of time (3 weeks). Then, **900-1000 registers per month** would be expected.

In order to obtain another sample size estimation, we analysed other data regarding our study setting, the city of Tarragona. According to the total paediatric population in Tarragona (25029, see *Annex 4*), the number of physicians attending them at the primary health care centres (22, see *Annex 4*), the approximate number of visits in a paediatrician consult (a mean of 27 visits/day), and the percentage of visits for URTIs (20-30% from the total (2)), about **600 registers per month** would be expected.

We considered that a very long data collection period would be overloading for the physicians, since URTIs are an extremely common diagnosis and the registers would have to be carried out several times a day. Using a six-month period would imply **5400-6000** registers (if using the first estimation) or **3600** registers (if using the second one), and in both cases would be enough to ensure a sufficient sample size.

In conclusion, we will consider for our study a sample size of 3600 patients, that is a similar n used in the *Pennie R* study (15)

Statistical analysis plan:

The data will be analysed with the IBM SPSS statistical programme. The confidence interval should be calculated based on a confidence level of 95%, which will imply a p-value of <0.05 .

Firstly, a descriptive analysis will be done. A frequency table will be used for qualitative variables, checking their frequency distribution. The Mean and the Standard Deviation will be calculated for quantitative variables.

Then, a bivariate analysis will be performed. We will compare our outcome variable (antibiotic prescription) with each one of the independent variables. The statistical significance of the relationship between antibiotic prescription and all the independent variables will be tested using a chi-square test in the categorical variables, and a T-student test in the quantitative variables.

Next, a multivariate analysis will be performed in order to eliminate possible confounding effects and to identify other potential relationships. To do so, logistic regression will be done including several variables, such as the child's age, duration of symptoms, odynophagia, and ear or sinus symptoms. Also, the prevalence ratio will be calculated.

Schedule arrangement

(See annex 5)

The study will be designed from May to July 2015. Submittal for approval to the local ethics committee will be in August 2015. The recruitment of the different physicians working in the selected primary health care centres is scheduled for September 2015. All the data collection (fieldwork) will last from October 2015 to March 2016. From April to September 2016 all the data will be introduced in the database and cleaned. The data analysis and the posterior study publication will be carried out from October 2016 to March 2017.

ETHICAL CONSIDERATIONS

This project respects what is established by national (Law 14/2007, from July 3, of Biomedical Research) and international (Declaration of Helsinki and Tokyo) laws and regulations on ethical aspects. Each person and their personal data is guaranteed under the Organic Law of Personal Data Protection (15/1999, December 13). All the parents or legal guardians will be verbally and writtenly informed about their child's participation in the study and will have to sign an informed consent. The project will be submitted to the ethics committees of the participating centres.

See annex 6 for the informed consent and the patient's information sheet.

POSSIBLE LIMITATIONS

This study has several limitations. First, it is designed as a cross-sectional study, therefore no cause-effect inferences can be made, since there is a lack of temporality assessing both dependent and independent variables.

Some biases are expected due to the physicians taking part in the study. All the physicians that are willing to participate in it, may naturally be more prone to this subject, and their prescribing criteria may differ from the ones not interested. Also, it is possible that only by deciding to take part in the study, some physicians change their usual prescribing habits, adapting them to more evidence-based criteria.

It must be taken into account that our work focuses on a single city only. Therefore, the results could lack of external validity.

Even though the children sample is planned to be large enough, there will be few paediatricians available, so in order to ensure a sufficient sample size a long data field collection period is needed. It is possible that throughout this period some paediatricians decide to leave the study or stop collecting data, since quite a lot of time needs to be dedicated to data collection every day.

Also, a previous study(22) showed that there was an increase in respiratory hospitalisations and nocturnal cough in children living near the petrochemical site of Tarragona, and that could imply both higher incidence and more severe presentation of URTIs among this population, that could again have an effect on the external validity of this study.

Finally, regarding to the data collection method, missing data could occur when dealing with the household income variable, since a certain level of non-response is expected.

EXPECTED IMPACT

Although no causality can be inferred from the obtained results, they can provide consistent ideas about which criteria are the most related to higher antibiotic prescription rates, therefore they can act as a framework for further actions.

A suitable analysis can be obtained from our results, defining which of them are actually based on scientific evidence and which of them are not. Some clinical criteria (such as purulent tonsillar exudate) have traditionally been linked to a bacterial aetiology even though they do not rely on a scientific basis on their own. This study can properly state if there are some erroneous prescribing habits, so it can help planning interventions to modify them, and therefore promoting a rational use of antibiotics.

One of the strengths of this study is that it gathers many different criteria at the same time, considering most of the factors that have been previously found to have an impact on antibiotic prescription, and adding some new ones. Other studies have not provided such a wide range of possible criteria.

Moreover, this study focuses on clinical features rather than criteria based on diagnostic tests. The latter, though more precise in defining bacterial and viral aetiologies, are not widely implemented in primary health care when diagnosing URTIs, and its use would not be suitable most of the times, since their evolution is acute and self-limiting. Therefore it is important to improve clinical-decision making, which is one of the aims of this study. Also, the obtained results will be compared to current Clinical Practice Guidelines, in order to establish whether the clinical criteria that are being used to prescribe antibiotics adjust to scientific evidence.

Finally, our study could contribute to a more suitable and rational use of antibiotics in children, with potential benefits in terms of bacterial resistance, secondary effects and efficiency.

RESEARCH TEAM COMPOSITION

- Study coordinator: In charge of the study design, literature search, contacting all the selected health centres and their medical directors, recruitment of the selected physicians, presentation of the project to the ethics committee, study's writing and publication.
- Medical directors: The medical director (a total of 8) from each primary care health centre will be asked to coordinate and supervise the whole data collection process taking place in their centres.
- Physicians: A total of 22 physicians attending children in all the selected primary health care centres: patients' selection, delivering of the informed consent and data collection using the templates, as well as filling in a questionnaire with their own features.
- Data manager: Data introduction to a database and their posterior cleaning.
- Graduate in statistics: A graduate in statistics is needed in order to estimate the sample size and perform the statistical analysis plan.
- Economic consultant: Assessment of the costs of the study.

REFERENCES

- (1) NICE Short Clinical Guidelines Technical Team (2008). Respiratory tract infections – antibiotic prescribing. Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. London: National Institute for Health and Clinical Excellence.
- (2) Bryant V., Timoner J., Oliva B., Gil M., Alegre P., De Abajo F.J.. Análisis de la utilización de antibióticos en población pediátrica con patología respiratoria: Estudio en la base de datos BIFAP. Rev Pediatr Aten Primaria 2009 Oct;11(17): 36. Spanish.
- (3) Shulman ST, Bisno AL, Clegg HW, Gerber MA, Kaplan EL, Lee G, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. Clin Infect Dis 2012 Nov 15;55(10):1279-82.
- (4) Hersh AL, Jackson MA, Hicks LA, American Academy of Pediatrics Committee on Infectious Diseases. Principles of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. Pediatrics 2013 Dec;132(6):1146-54.
- (5) Llor C, Hernandez S. Infectious disease in primary care: 1-year prospective study. Enferm Infecc Microbiol Clin 2010 Apr;28(4):222-6. Spanish.
- (6) Fine AM, Nizet V, Mandl KD. Large-scale validation of the Centor and Mclsaac scores to predict group A streptococcal pharyngitis. Arch Intern Med 2012;172(11):847-52.
- (7) Kenealy T, Arroll B. Antibiotics for the common cold and acute purulent rhinitis. Cochrane Database Syst Rev 2013 Jun 4;6:CD000247.
- (8) Wald ER, Applegate KE, Bordley C, Darrow DH, Glode MP, Marcy SM, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. Pediatrics 2013 Jul;132(1):262-80.
- (9) Rodrigo C, Del Castillo F, Martín FG, Pérez DM, Contreras JR. Infección de las vías respiratorias superiores. Protocolos clínicos SEIMC (sociedad española de enfermedades infecciosas y microbiología clínica.[Internet]. [cited 2015 Mar 29] 2012 Oct: 18-22. Spanish. Available from: <http://www.seimc.org/contenidos/documentoscientificos/procedimientosclinicos/seimc-procedimientoclinicoiii.pdf>
- (10) Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. The diagnosis and management of acute otitis media. Pediatrics 2013 Mar;131(3):964-99.

- (11) Kronman MP, Zhou C, Mangione-Smith R. Bacterial prevalence and antimicrobial prescribing trends for acute respiratory tract infections. *Pediatrics* 2014 Oct;134(4):956-65.
- (12) Chung A, Perera R, Brueggemann AB, Elamin AE, Harnden A, Mayon-White R, et al. Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: prospective cohort study. *BMJ* 2007 Sep 1;335:429.
- (13) Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010 May 18;340:c2096.
- (14) Clavenna A, Bonati M. Adverse drug reactions in childhood: a review of prospective studies and safety alerts. *Arch Dis Child* 2009 Sep;94(9):724-28.
- (15) Llor C, Moragas A, Bayona C. Infecciones del tracto respiratorio superior. *AMF* 2015;11(3):124-31. Spanish.
- (16) Pennie RA. Prospective study of antibiotic prescribing for children. *Can Fam Physician* 1998 Sep;44:1850-56.
- (17) Kozyrskyj AL, Dahl ME, Chateau DG, Mazowita GB, Klassen TP, Law BJ. Evidence-based prescribing of antibiotics for children: role of socioeconomic status and physician characteristics. *CMAJ* 2004 Jul 20;171(2):139-45.
- (18) Panagakou SG, Spyridis N, Papaevangelou V, Theodoridou KM, Goutziana GP, Theodoridou MN, et al. Antibiotic use for upper respiratory tract infections in children: a cross-sectional survey of knowledge, attitudes, and practices (KAP) of parents in Greece. *BMC Pediatr* 2011 Jul 5;11:60
- (19) Llor C, Cots JM, Bjerrum L, Cid M, Guerra G, Arranz X, et al. Antibiotic prescribing in respiratory tract infections and predictive factors for their use. *Aten Primaria* 2010 Jan;42(1):28-35.
- (20) Ong S, Nakase J, Moran GJ, Karras DJ, Kuehnert MJ, Talan DA. Antibiotic use for emergency department patients with upper respiratory infections: prescribing practices, patient expectations, and patient satisfaction. *Ann Emerg Med* 2007;50(3):213-220.
- (21) Safdar N, Tape TG, Fox BC, Svenson JE, Wigton RS. Factors Affecting Antibiotic Prescribing for Acute Respiratory Infection by Emergency Physicians. *Health* 2014;2014.
- (22) Rovira E, Cuadras A, Aguilar X, Esteban L, Borrás-Santos A, Zock JP, et al. Asthma, respiratory symptoms and lung function in children living near a petrochemical site. *Environ Res* 2014 Aug;133:156-163.

ANNEXES

Annex 1

Sexe	Home		Dona	
Data de naixement				
Especialitat mèdica	Pediatria	Medicina Familiar i Comunitària		Altres
Anys de pràctica clínica				
Especialització via MIR	Sí		No	

Annex 2

Altres	Espera o demanda d'un antibiòtic									
	Prescripció antibiòtica	No	Sí							
Durada dels símptomes	>14 dies									
	7- 14 dies									
	< 7 dies									
Impressió clínica	Infecció viral									
	Infecció bacteriana									
Diagnòstic clínic	Laringitis aguda									
	Otitis mitjana aguda									
	Rinosinusitis aguda									
	Faringoamigdalitis aguda									
	Faringitis aguda									
	Refredat comú/Rinitis purulenta aguda									
	Símptomes a l'orella									
	Estridor									
	Adenopaties cervicals anteriors									
	Síptomatologia sinusal									
Signes i símptomes	Tos									
	Rinorrea purulenta									
	Rinorrea									
	Febre (>38.5º)									
	Odinofàgia									
	Amigdales inflamades									
	Exudat amigdalal									
	Faringe eritematosa									
	Data de naixement									
	Sexe	D								
H										
Pacient										
	1									
	2									
	3									
	4									
	5									
	6									
	7									
	8									
	9									
	10									

Other	Expectation/Demand of antibiotic									
	Antibiotic prescription	No	Yes							
Duration of symptoms	>14 days									
	7- 14 days									
Clinical impression	< 7 days									
	Viral									
	Bacterial									
Clinical diagnosis	Acute laryngitis									
	Acute otitis media									
	Acute rhinosinusitis									
	Acute tonsillopharyngitis									
	Acute pharyngitis									
	Common cold / acute purulent rhinitis									
	Ear symptoms									
	Stridor									
	Swollen anterior cervical nodes									
	Sinus symptoms									
Signs and symptoms	Cough									
	Purulent rhinorrhea									
	Rhinorrhea									
	Fever (>38.5°)									
	Odynophagia									
	Swollen tonsils									
	Tonsillar exudate									
Erythematous pharynx										
Date of birth										
Sex	F									
	M									
Patient		1	2	3	4	5	6	7	8	9

Annex 3

Quina és la renda neta anual de casa seva? (comptant tots els ingressos nets aportats per membres de la seva família, incloent-hi prestacions socials)				
Menys de 15000 €	De 15000 a 25000 €	De 25000 a 50000 €	Més de 50000 €	No ho sé / No contesto
Quin és el seu nivell d'estudis? (assenya-li només una opció, la dels últims estudis <u>finalitzats</u>)				
No sé llegir ni escriure	Educació primària no acabada	Educació primària finalitzada		
Educació secundària finalitzada	Formació professional de grau mig	Formació professional de grau superior		
Estudis universitaris o equivalents	No ho sé / No contesto			

These questions were obtained from *Encuesta Nacional de Salud* (Instituto Nacional de Estadística, 2012) and *Encuesta Financiera de las Familias* (Banco de España, 2011).

Annex 4

Primary health care centre	Registered paediatric population	Paediatricians (or other physicians attending children)
CAP Bonavista – La Canonja	2571	2
CAP Jaume I	4379	4
CAP Sant Pere i Sant Pau	3083	3
CAP Sant Salvador	1926	2
CAP Tàrraco	2606	2
CAP Torreforta – La Granja	5111	5
CAP Muralles	2348	2
CAP Llevant	3005	2
TOTAL	25029	22

Annex 5

ACTIONS	MONTHS																								
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23		
Study design	■																								
Presentation to the ethics committee				■																					
Recruitment of physicians					■																				
Fieldwork (data collection)						■																			
Data introduction and cleaning												■													
Data analysis and study publication																		■							
PERIOD	May – July 2015			August 2015	Sept. 2015	October – March 2016						April – September 2016						October – March 2017							

Full d'informació al pacient

Estudi: “Factors predictius de la prescripció d’antibiòtics en nens amb infeccions de vies respiratòries altes”

Benvolgut pare, mare o tutor legal,

L’informem que s’està realitzant un estudi d’investigació als Centres d’Atenció Primària de la ciutat de Tarragona, en la seva població pediàtrica, i que el seu fill/a és candidat a formar-ne part, motiu pel que s’ha sol·licitat la seva col·laboració. Abans de decidir participar és important que llegeixi atentament i entengui el contingut del document següent. En cas que li sorgeixin dubtes o vulgui comunicar qualsevol incidència o queixa pel que fa a l’estudi, pot comunicar-ho al seu metge habitual i aquest el posarà en contacte amb l’equip investigador o la persona pertinent.

L’estudi es denomina “factors predictius de la prescripció d’antibiòtics en nens amb infeccions de vies respiratòries altes”. El seu objectiu principal és determinar si hi ha alguns criteris, ja siguin clínics, és a dir, observats pel propi metge en el pacient, com socials o econòmics, que poden influir en la prescripció d’antibiòtics davant una infecció de via respiratòria alta.

Entenem infecció de via respiratòria alta com aquelles infeccions que afecten la via aèria superior: refredat comú, faringitis aguda, otitis mitjana aguda, sinusitis aguda, etc. En molts casos estan produïdes per virus, en els que els antibiòtics no són efectius. Els tractaments antibiòtics han demostrat ser molt beneficiosos pel tractament d’algunes infeccions, però el seu ús implica també un augment de resistències i la possible aparició d’efectes secundaris, i per això és important utilitzar-los només quan estan indicats. Malgrat tot, la prescripció antibiòtica en les infeccions de vies altes segueix sent molt elevada, i per això ens serà útil a nivell científic conèixer si hi ha criteris que hi poden influir. Un cop els coneguem, podrem dirigir esforços més fàcilment a corregir o reforçar aquests criteris basant-nos en l’evidència científica.

Si accepta participar en aquest estudi, el seu metge omplirà una plantilla amb una sèrie de símptomes observats en el seu fill/a (per exemple, si el nen/a

presenta o no febre o exsudat a les amígdales). També se us demanarà d'omplir un qüestionari sobre característiques socio-econòmiques familiars.

La participació en aquest estudi és de caràcter lliure i voluntari. Com que l'estudi està pensat per fer-se en nens/es menors d'edat, el consentiment es realitzarà a través dels seus pares o tutors legals, preferiblement comptant també amb l'acceptació del participant.

Si vostè decideix que el seu fill/a hi participi i, posteriorment, en el curs de la investigació, decideixen abandonar l'estudi, ho haurà de comunicar al responsable. En cap dels casos l'abandonament de l'estudi tindrà conseqüències en la prestació de l'atenció o en els serveis sanitaris que el seu fill/a requereixi del seu metge o de qualsevol altre professional.

Atentament,

Anna Seguí Grivé

Investigadora coordinadora de l'estudi

CONSENTIMENT INFORMAT

Estudi: “Factors predictius de la prescripció d’antibiòtics en nens amb infeccions de vies respiratòries altes”

Firmant aquest consentiment, vostè autoritza la participació del seu fill/a a l’estudi, així com l’ús i la publicació amb finalitats científiques de les dades que ens faciliti en els procediments de la investigació, sempre de forma anònima.

En cas de disconformitat amb aquests supòsits, no haurien de participar en aquest estudi.

Sr/Sra, amb
DNI....., major d’edat, en ple ús de les meves facultats mentals, i
en qualitat de pare, mare o tutor/a legal del pacient
..... amb DNI
.....

DECLARO,

que he llegit el document amb les explicacions que detallen els objectius i característiques d’aquest estudi, les he comprès i estic conforme amb elles. Per això, dono el meu consentiment per tal que el meu fill/a participi en aquest estudi d’acord amb els termes exposats, i conforme a la legislació espanyola i autonòmica vigent.

Tarragona, a de de

(Firma del pare, mare o tutor/a legal)

Nom i cognoms del metge investigador

Firma de l’investigador