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summary

Objective: To evaluate the use of antibiotics in primary care centres in Navarre and antimicrobial resistance of the most common bacterias found in frequent infections. Another objective is to find possible areas for improvement. **Material and methods:** Data on consumption and population exposure was obtained from billings on prescriptions in Navarre from 2001 up to 2008. Information on the treatments applied for different infections was extracted from the ISIS program that explores data from the computer based clinical records (OMI) in all primary care centres in Navarra. Pathological data, prevalence of the different microorganisms and resistance was obtained from the microbiology laboratory of the Doctor San Martin Health Clinic, which receives most of the specimens proceeding from primary care centres and covers a population of over 440,000 inhabitants. To respond to the questions raised, consultation was made on Medline and the principal data bases on evidence based medicine with regard to clinical trials, observational studies and systematic reviews. **Results y conclusions:** There is considerable evidence that shows a correlation between the use of antimicrobial therapy and the increase in the prevalence of resistant microorganisms. The global rates in the use of antibiotics in Navarre are similar to the average rate in European countries, but there are great differences between different primary care doctors. Possible improvements in antibiotic prescribing include the use of rapid diagnostic tests for bacterial pharyngitis or tonsillitis, delayed use of antibiotics in case of acute otitis media, no use in viral infections and a correct diagnosis of infections affecting the lower airways with an adequate selection of antimicrobial agents and correct posology.

Cry wolf! The new fable of bad use of antimicrobials and the return of the pre-antibiotic era?

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Introduction

Antimicrobial therapy commenced in 1936 with the development of sulphamides while the posterior discovery of penicillin represented an important milestone in the history of medicine. So much so that some authors refer to it as the "antibiotic revolution". Hence, on examining the historical series, one can appreciate a marked reduction in mortality caused by infections in the USA during the period between 1937 and 1952. Mortality was reduced by 8.2% per year and reductions spanned from 283 deaths to 75 deaths per 100,000 inhabitants per year[1].

Soon, however, resistant strains to the antibiotics were described. First was staphylococcal resistance to penicillin, and in 1953, the first outbreak of multiresistant *Shigella dysenteriae* occured in Japan, and by the end of the 1960´s, the first strains of meticillin-resistant *Staphylococcus aureus* were isolated (MRSA). Later on there was evidence of the worldwide diffusion of *Streptococcus pneumoniae* with lower susceptibility to penicillin, multiresistant strains of *Mycobacterium tuberculosis* or gram-negative bacteria resistant to the majority of antibiotics (*Pseudomonas spp.*, *Acinetobacter spp.,* or enterobacteriaceae).

This problem has continued increasing over the years and poses a serious challenge when treating infections, especially hospital related infections[2], so much so that the Infectious Diseases Society of America has affirmed that this may represent a return to the pre-antibiotic era especially with regard to some infections[3]. To increase awareness on the excessive employment of antibiotics a European Antibiotic Awareness Day takes place every 18 November. Awareness and information campaigns are being carried out in the USA and around Europe[4,5].

In this article we hope to address this problem in the primary care setting of the Navarre Regional Health Service, by investigating the percentage of resistant microorganisms in some of the most frequent infections which may require antimicrobial therapy and by offering some measures that can improve the rational use of antibiotics.

Is there any correlation between the use of antibiotics and the incidence of resistance?

There is a lot of evidence showing a correlation between antimicrobial use and the increase in resistance to these agents. On studying the variability of resistance in the community (ecological studies), it has been observed that there is an important correlation between greater use of antibiotics and a higher rate of resistance. There is an increment in the percentage of strains of *S. pneumoniae* with decreased susceptibility to penicillin and increased resistance to macrolids. More *Streptococcus pyogenes* strains also show macrolid resistance, and *Escherichia coli* resistance to fluoroquinolones or clotrimoxazole has been observed in areas where these agents were previously more widely employed used[6,7].

There is also evidence of resistance at the individual level. Here, prevalence studies[8], prospective cohorts[9] and randomized clinical trials[10] have shown that patients treated with some form of antimicrobial therapy have a greater susceptibility to become carriers of antimicrobial resistant strains.

With the use of antibiotics in humans there are many other factors that influence the dissemination and prevalence of resistant strains to different classes of antibiotics, given that the interactions between microorganisms, different hosts and the environment are very complex[11].

Better employment of antibiotics will not make the problem disappear, but it may improve the incidence of resistance.

How are antibiotics employed in Navarre? What evolution has their employment taken? Is there a problem with antimicrobial resistance?

Data on consumption in Navarre in the last few years in terms of dose per 1000 inhabitants per day (DHD) are shown in figure 1. Currently the use of antibiotics is around 20 DHD, half of the consumption in France and twice that observed in Holland[7].

Figure 1. Antibiotic use in Navarra

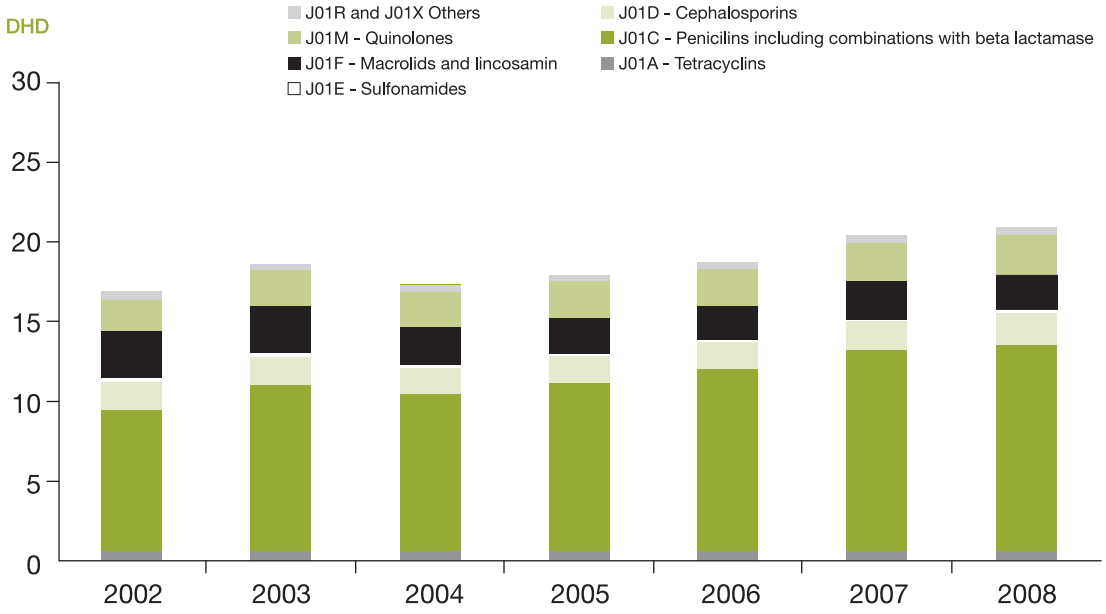


Figure 1 shows that the main agents employed include amoxicillin and amoxicillin combined with clavulanic acid (AMC) (J01C group) that accounts for 62% of all prescribed antibiotics; fluorquinolones represent 12% (mainly ciprofloxacin, levofloxacin and moxifloxacin); macrolids, 10% (claritromycin and azitromycin); and cephalosporins represent 9% (cefuroxime). During the last 5 years there has been an increment in the use of AMC and wide spectrum quinolones (levofloxacin and moxifloxacin).

An assessment was also made of the percentage of the population that received at least one prescription of antimicrobial therapy in a year. In figure 2 it can be observed that the percentage was reduced from an average of 50% between 0 and 2 years to about 20% (1 in 5) up to 65 years of age and later an increase is seen in patients above 65 years. There was however variability when comparing all the doctors prescriptions during all the periods. Thus, in age groups with lower rates of prescriptions (young adults), there are doctors who prescribe 1 antibiotic in 10 patients, while in other cases the rate reached 4 prescriptions out of 10 patients. These differences were not associated to the size of consultancy or setting (urban versus rural).

In our context, resistance of the different microorganisms isolated in the Microbiology laboratory of the Dr. San Martin Clinic is as follows:

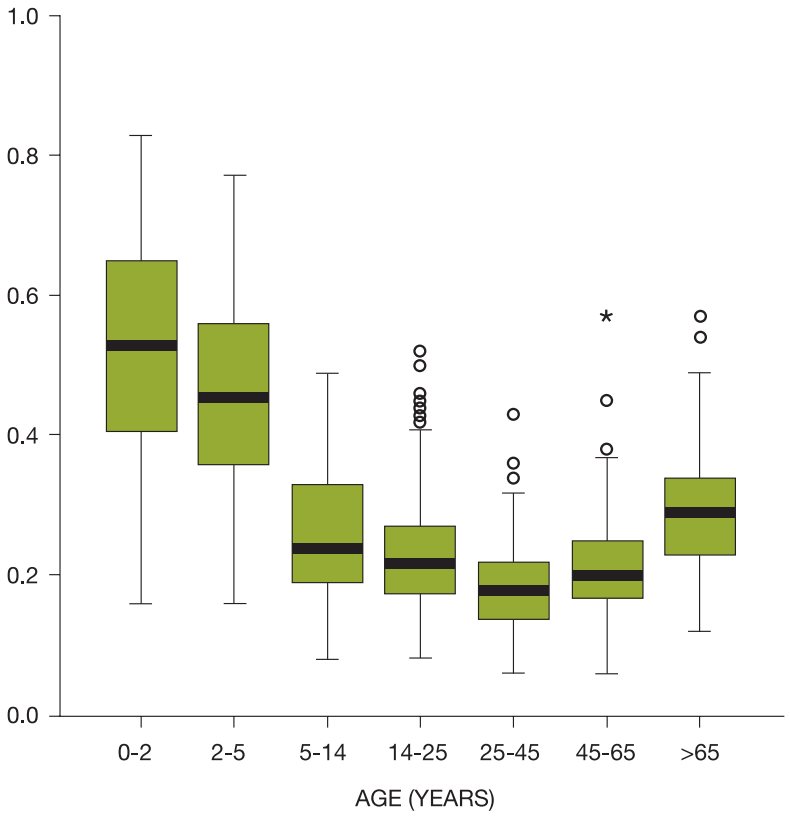
Streptococcus pneumoniae: 3% of resistant strains to amoxicillin and 28% resistant to macrolids.

Streptococcus pyogenes: 12.5% resistant strains to macrolids containing 14 to 15 carbon atoms (eritromycin, claritromycin or azitromycin) and 7.7% resistance to 16 carbon atom macrolids (josamycin and midecamycin).

E. coli: 22.1% resistant strains to quinolones.

The percentage of *S. pyogenes* strains resistant to macrolids has decreased from 35% in 2003 to 12.5%, not so with quinolone-resistant *E. coli* strains that have continued increasing, with a resistance in 2003 of 16% which, as a result, makes these agents no longer recommendable as the elective option for urinary infections.

Figure 2. Diagram showing the percentage distributions of antibiotic prescription by individual consultancies during the last year.



Does the increment in infections caused by antimicrobial resistant bacteria have any importance?

In the hospital environment there exist numerous multiresistant germs that can cause serious problems, especially in critical patients. This problem is increasing in the hospital setting. In the last questionnaire carried out (2009) in intensive care units around Europe, more than half of the physicians had cases of bacterial infections resistant to most if not all available antibiotics[12].

In primary care, the spectrum and incidence is lower. Currently, multiresistant strains that cause the most frequent infections include:

Meticillin-resistant ***Staphylococcus aureus*** (MRSA): 22% of all isolated *S. aureus* (although a good number of the samples were taken at nursing homes).

Extended-spectrum beta-lactamase ***E. coli*** (ESBL): 3.4% of all *E. coli* isolates.

Given their low prevalence of ESBL producing enterobacteriaeceae, they should not be considered when establishing empirical antimicrobial therapy for patients. If necessary though, they should be considered then **when a patient´s clinical course does not improve despite adequate antibiotic treatment and compliance with treatment**. In these cases the recollection of samples and their delivery to the microbiology department laboratory is very important.

What about the individual?

Antimicrobial therapy bears greater risks than was previously believed, and thus careful consideration includes taking into account their risks and benefits and informing patients of these aspects[13]. In the last few years we have witnessed several warnings regarding the safety of some antibiotics[14,15,16]. In addition an increase in the incidence of data from different observational studies has generated new hypothesis with respect to the risk associated with the use of these agents[17,18,19].

This is especially transcendental in infections where the benefits of treatment are not very clear. For example, in the case of upper airway infections, for every 4000 patients treated with antibi-

otics, one severe complication is prevented. On the contrary, there is a probability between 5-25% of presenting diarrhoea, and for every 1000 patients treated[20], one will call on an emergency department due to an adverse effect produced.

Therefore, proposals on new forms of presenting information to patients where they can participate in the decision of taking antibiotics for these infections according to their criteria have been introduced. Patients can start treatment or take a more conservative approach, of waiting and seeing[21].

What can be done? Is there capacity to improve?

To achieve a modification in the use of antibiotics is not an easy task, although some measures have proven effective[22]. Isolated interventions that have been effective include changes in the pharmaceutical guidelines issued by institutions (hospitals, elderly care homes, etc.) or the inclusion/exclusion of publicly funded agents[11]. Multifactorial programmes have also been effective, like in France[23], in which a combination of public information campaigns with activities directed to health care professionals were carried out. As a consequence of this programme, a reduction in resistant *S pneumoniae* strains was observed[24].

It seems clear that it is important to identify areas for improvement. Aggregate data on the consumption of antibiotics (for example, total DHD) are very useful to make comparisons on the consumption between countries and to evaluate tendencies, although they are not very useful in detecting possible areas for improvement. In order to find what areas for improvement exist in primary care in Navarra, an evaluation was made of how adequately certain prevalent infections have been treated with antibiotics.

To facilitate reading, an introduction to the infection has been made, with a description of what could be the most coherent approach given the current knowledge on the subject, and whether this reflects the current situation in the primary care setting under the Navarre Health Services.

Streptotest is useful to identify those patients that may benefit from antibiotic therapy in cases of acute tonsillopharyngitis

Acute tonsillopharyngitis

Ethiology and diagnosis

S. pyogenes or group A beta hemolytic streptococci (GABHS) is responsible for only 10% of the cases of tonsillopharyngitis. In the rest of the cases the majority are of viral origin. Despite this, most patients are treated with antibiotics (up to 80% in Spain[25]). Many of the antibiotics employed are (68%) among the most expensive and of wider spectrum than those recommended in the guidelines[26]. The main objective in the management of these patients with tonsillopharyngitis is the ruling out of GABHS, as it is the main treatable cause and poses a risk of possible complications.

Clinical criteria for diagnosis

Despite the physicians experience, it is difficult to distinguish whether a patient is suffering from a GABHS tonsillopharyngitis. Sensitivity oscillates between 55 and 74% while specificity runs between 58 and 76%[26]. To improve this situation diverse rules of clinical prediction have been elaborated. The most frequently employed are Centor´s criteria:

The Centor criteria are as follows:

- Presence of tonsillar exudate.
- History of fever.
- Presence of tender anterior cervical lymph nodes.
- Absence of cough.

The probability of having a tonsillopharyngitis caused by GABHS is 56% when all four criteria are fulfilled. Given this, if we treat all patients with these criteria then we are over treating 44% of the patients. However, the absence of two of these criteria rules out the streptococcal origin in 85% of the cases[26]. **The presence of one or the absence of all of these criteria rules out the presence of GABHS and there is no need to treat with antibiotics**[27].

Throat cultures have been considered the best test to demonstrate streptococcal presence in tonsillopharyngitis. Its limits are rooted in the response time of 24-48 hours, which make quick decisions impossible. Moreover rural health care clinics do not operate with a daily culture recollection. One solution to these problems could be the employment of a rapid GABHS antigen test.

In one good quality study carried out in a similar primary care setting to ours[25], in which a validation of the rapid detection test (OSOMStrepA) in patients with ≥2 Centor criteria concluded that the use of this test could be diffused throughout primary care settings. The following results were obtained:

Sensitivity 95% (88-100%)
Specificity 93% (88-97%)
Predictive Positive Value (PPV) 79% (67-90%)
Negative Predictive Value (VPN) 98.5% (96-100%)
Positive Probability Coefficient (PC+) 13.49 (7.34-24.62)
Negative Probability Coefficient (PC -) 0.05 (0.01-0.21)

This means that, with a similar prevalence found in the study, if the test was negative, only 1% of the episodes of tonsillopharyngitis caused by *S. pyogenes* would be left untreated, while if the test resulted positive then 21% of the cases would be over treated*.

The positive probability coefficient indicates that a person with *S. pyogenes* is 13.5 times more likely to be positive in the test, than a person with an infection not caused by *S. pyogenes.* The inverse, negative probability coefficient (1 / CP-), tells us that a person with no infection is 20 times more likely to give a negative result in the test than a person carrying *S. pyogenes*.

Therefore, the rational use of antibiotics **would improve if patients with two or more of Centor´s criteria and a positive streptotest were treated with antibiotics.**

Expected results of antimicrobial therapy

Tonsillopharyngitis is a disease that remits spontaneously, that is its "cure" is independent of treatment. A Cochrane review has been published evaluating the expected results of treatment with antibiotics in primary care[28]. Patients included in the review were those who came to the consultancy complaining of pharyngeal symptoms. The majority of the studies were carried out in the 1950´s when the rates of severe complications (especially acute rheumatic fever) were more elevated than now.

Acute Glomerulonephritis: cases were observed in the control group, but as the number was very small no significant differences were found; RR = 0.22; (95%CI, 0.02 - 2.08).

Rheumatic fever: Antibiotics reduced the incidence of rheumatic fever; RR = 0.27; (95%CI, 0.12 - 0.60).

Suppurative complications: Antibiotics reduced the incidence of acute otitis media; RR = 0.30; (95%CI, 0.15 – 0.58) and tonsillitis; RR = 0.15; (95%CI: 0.05 - 0.47).

Symptoms: Antimicrobial therapy improved both throat pain and fever. The highest efficacy was observed between days 4 and 5 of treatment. By then symptoms of some 50% of untreated patients had remitted. After a week, almost 90% of both treated and untreated patients had no symptoms.

Of the pharyngeal isolates taken in primary care *(S. pyogenes* was found in 92%, and group C or G betahemolytic streptococcus in 7.7% of the cases) there was no resistant strain to penicillin or amoxicillin, while 12.1% of the strains showed resistance to 14-15 carbon atom macrolids (eritromycin, claritomycin or azitromycin), and 7.1% were resistant to 16 carbon atom macrolids (midecamycin and josamycin).

Elective treatment recommended by different authorities and health professionals[29] continues to be oral penicillin (table 1). In the case of recurrent tonsillopharyngitis, based on indirect evidence (erradication data) some patients could benefit from AMC, first generation cephalosporins (such as cefadroxil) or second generation cephalosporins (such as cefuroxime)[30]. Given the resistance rates shown to macrolids these should not be the elective choice for treatment.

* To increase the sensitivity it is important to correctly recollect the sample. To do so, antibiotics should not be administered previously and on taking the sample vigorous scraping should be performed with the swab in both tonsils and posterior wall of the pharnyx. No samples should be taken from the tongue, hard palate or oral mucosae.

Data regarding the use of elective antibiotics in comparison to the total antibiotics (figure 3) shows considerable variability. Half of the consultancies employed amoxicillin or penicillin in 50% of the episodes of streptococcal tonsillopharyngitis (code R75) and in the remaining 50% of the cases other antibiotics were employed. Only a quarter of the consultancies prescribed first line antibiotics in more than 60% of the cases. There is important margin for improvement in many consultancies.

Management of acute otitis media in children. Delayed use of antibiotics

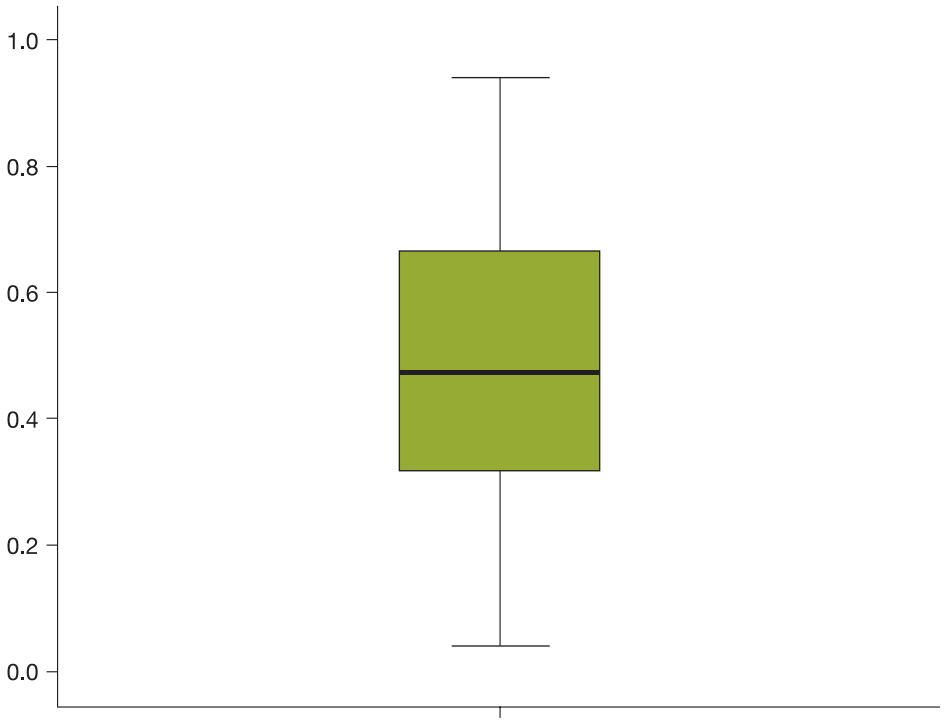
There are three approaches to the management of acute otitis media (AOM): refrain from antibiotics, prescribe immediately, or delay treatment. Immediate prescription consists of starting antibiotics at the moment the patient leaves the consultancy. Delayed treatment refers to deferring the intake of antibiotics for 72 hours and commencing if pain or fever persists or the clinical condition worsens.

There is a Cochrane review evaluating the efficacy of antibiotics in AOM[31]. According to this review, after 24 hours of the onset of symptoms, two-thirds of the patients did not have any pain, while 80% were asymptomatic after 2 to 7 days, independently of whether they took antibiotics or placebo. No differences in hearing between the placebo group and the group under antibiotics were observed. The only complication described was one case of mastoiditis in the group treated with antibiotics.

One article published by Clinical Evidence[32] compared immediate to delayed treatment approaches. Three clinical trials were reviewed that compared immediate and delayed treatments. AOM was defined as otalgia with otoscopic signs of otitis (protrusion of the tympanic membrane, erythema or perforation).

In general, immediate prescription reduced the duration of pain, suppuration, number of days crying, and the number of days of interrupted sleep

Figure 3. Distribution of the proportion of tonsillopharyngitis treated with penicillin or amoxicillin in the different consultancies in primary care.



by one day. There was also greater satisfaction on the part of the parents. However, there was no improvement in the intensity of pain, in the number of daily episodes of suffering or in the number of days of school absence. On the other hand antibiotics produced more adverse effects (most commonly diarrhoea). The quality of evidence was moderate.

Taking into account the number of days, antibiotics are not very useful in the majority of cases and moreover, can produce adverse effects, and even increase antimicrobial resistance. **For all these reasons, a more reasonable approach to management would be delayed treatment with antimicrobial therapy after 72 hours in cases where no clinical improvement is observed**.

In one meta-analysis it was concluded that the delayed approach was the most adequate *except for children under 2 years with bilateral AOM or with AOM associated with otorrhea which represent the cases that most benefit from immediate antimicrobial therapy*[33].

In otic isolates in cases of otitis media, of all the samples derived from primary care, there were no samples obtained from tympanocentesis, only smears from suppurating otitis. From these, H. influenzae (43% of the isolates), S. pneumoniae (28%) and S. pyogenes (23%) were detected. The percentage of global resistance was 6% for amoxicillin, 1% for amoxicillin - clavulanic acid (AMC), 27% to 14-15 carbon atom macrolids (erythromycin, clarithromycin or azithromycin) and 18% to macrolids containing 16 carbon atoms (midecamycin or josamycin).

In a Spanish series obtained from tympanocentesis the most frequent isolate was *S. pneumoniae.* Taking into account resistance rates of *S. pneumoniae* and those of the isolates from otic smears, elective treatment should be amoxicillin at 40 mg/kg three times a day, and in cases of suspicion of strains with reduced sensitivity, the correct dose would be 80-90 mg/kg three times a day (table 1). In cases of failed therapy then an adequate option would be AMC[29].

Data from paediatric consultancies (figure 4) indicate that the majority of the children with AOM (code H71) are treated with either amoxicillin or AMC when antimicrobial therapy is deemed necessary.

Figure 4. Distribution of the proportion of acute otitis media treated with amoxicillin or AMC with respect to the total of otitis media treated with antibiotics in different consultancies in primary care.

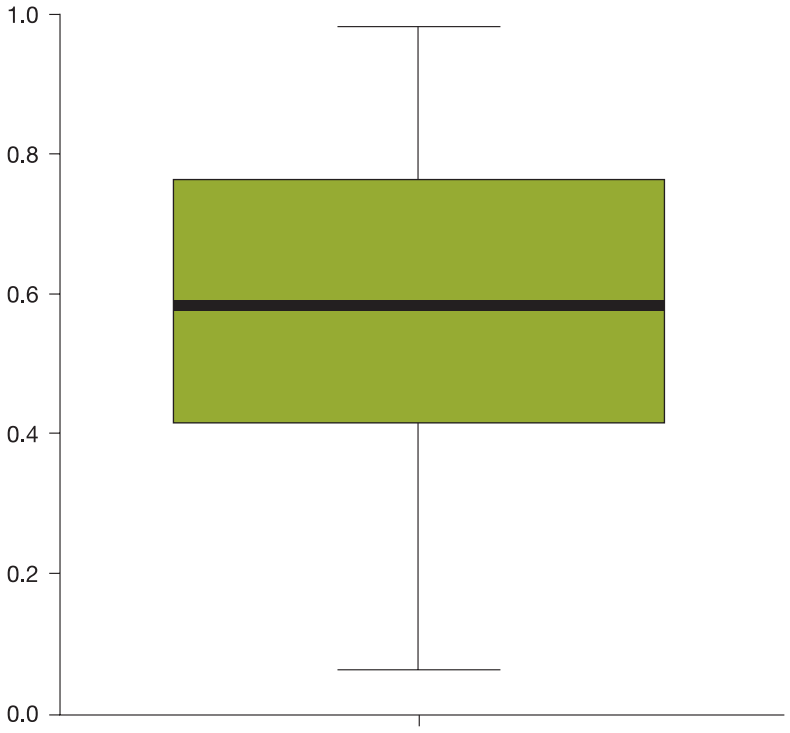
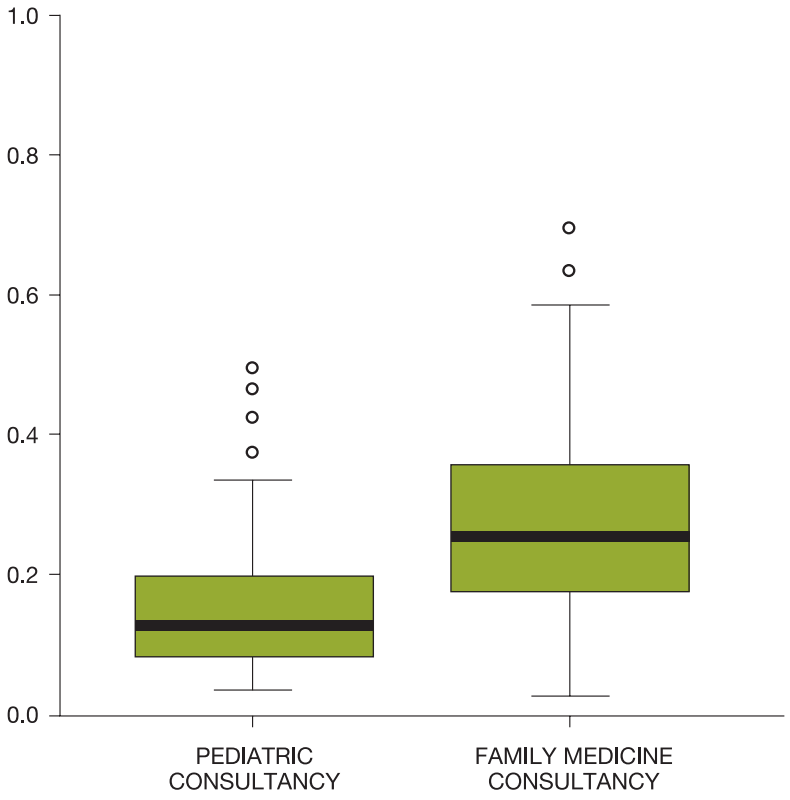


Figure 5. Distribution of the proportion of episodes of viral origin treated with antibiotics.



Viral infections

There is ample consensus, reflected in published guidelines, on the futility of antibiotic treatment in cases of viral infections. We obtained data from the different consultancies in primary care of viral infections treated with antibiotics. In figure 5, one can observe that the majority are not treated with antibiotics, although there is considerable room for improvement in some consultancies, which show wide use of antibiotics, in up to 50% of the episodes.

It is postulated that some diagnostic tools can be useful in daily clinical practice (*point of care diagnostic tests*), for example, antigen tests for influenzae. With respect to this test, studies carried out show that it possesses a high specificity but low to moderate sensitivity. For this reason, it may be useful *in children* with influenzae-like symptoms when the prevalence of influenzae is high[34], whenever the test detects the strains in circulation at that point of time.

It should be taken into account that refraining from prescribing antibiotics or carrying out a delayed approach to treatment should not be applied in some circumstances[35]:

- If the patient is severely sick.
- The patient has symptoms and signs of severe disease and/or complications (mainly pneumonia, tonsilar cellulitis, or intracraneal or intraorbital complications).
- If the patient is at high risk of complications due to a given co-morbidity (immunosuppression, cystic fibrosis, important lung and cardiac disease, liver or renal impairment, neuromuscular disease or premature newborns).
- Patients over 65 years of age with acute cough and 2 or more of the following criteria or those over 80 years and one or more of the following conditions:
  - Hospitalization in the last year
  - Type 1 or 2 diabetes
  - Heart failure
  - Current use of oral corticosteriods

Treatment of lower respiratory tract infections (acute bronchitis, pneumonia, exacerbations in chronic obstructive pulmonary disease, COPD).

There is a clear consensus on the effectiveness of antibiotics in the management of pneumonias and on the importance of early administration of treatment especially in cases of severe pneumonia. A problem may arise when the clinician has to distinguish between pneumonia and acute bronchitis, in which case the benefit of antibiotics in the latter is much lower and the magnitude of the harm due to adverse effects is similar to the benefit expected[36].

The differentiation between these two clinical conditions is not simple[37]. Classically, pneumonias required a chest radiograph and the appearance of a compatible infiltrate in a patient with symptoms of respiratory infection (fever, acute cough, change in characteristics of sputum, etc). This is how pneumonias are described in guidelines on diagnosis and management of community acquired pneumonias[38,39]. The problem is that the sensitivity and specificity of these criteria are not clear[40]. Therefore some guidelines[37,41], consider that with regard **to adults in primary care,** in some cases the diagnosis could be clinical (grade of evidence D).

In a recent clinical trial in primary care in the United Kingdom the combination of both a rapid test for detecting C reactive protein in the consultancy and specialized courses to improve communication skills when treating patients led to a reduction in the prescription of antibiotics. This was achieved with no reduction in the satisfaction on the patients part or with any alteration in the rates of health recovery[42]. Therefore, it has been proposed that the employment of this rapid test in the consultancy could be useful[43], although it is not all that clear[44]. In Sweden, this approach was associated with a worse antibiotic use[45]. The introduction of the test in Navarra would require clinical trials to evaluate its efficacy in our setting beforehand[46].

A recent European study evaluated the use of antibiotics in adults with cough and symptoms of lower respiratory infection. Important differences were observed in the use of antibiotics (from 29% to 90% of the populations attended) with no differences in the percentages of clinical recovery[47].

Taking into account the information mentioned up to now, from a clinical point of view, the Scottish guidelines[37] on the management of lower respiratory infections may prove useful:

- In patients **with symptoms of lower respiratory infection**, antibiotic treatment should be initiated as soon as possible and referral should be considered in those who present one of the following (main ones emphasized):

  Tachypnoea (> 30 breaths per minute)
  Low blood pressure (systolic < 90 mmHg or/and dyastolic < 60 mmHg)
  Recent confusional state.
  Age > 50 years.
  Presence of concommitant disease (for example, heart failure, cardiovascular disease, neoplasm, renal or liver impairment, immune system disorders).
  Temperature < 35 ºC or ≥ 40 ºC
  Tachycardia (> 125 beats per minute)

· Patients who were previously healthy with none of the above characteristics and with no abnormalities in lung field examination should not normally receive any antibiotic.

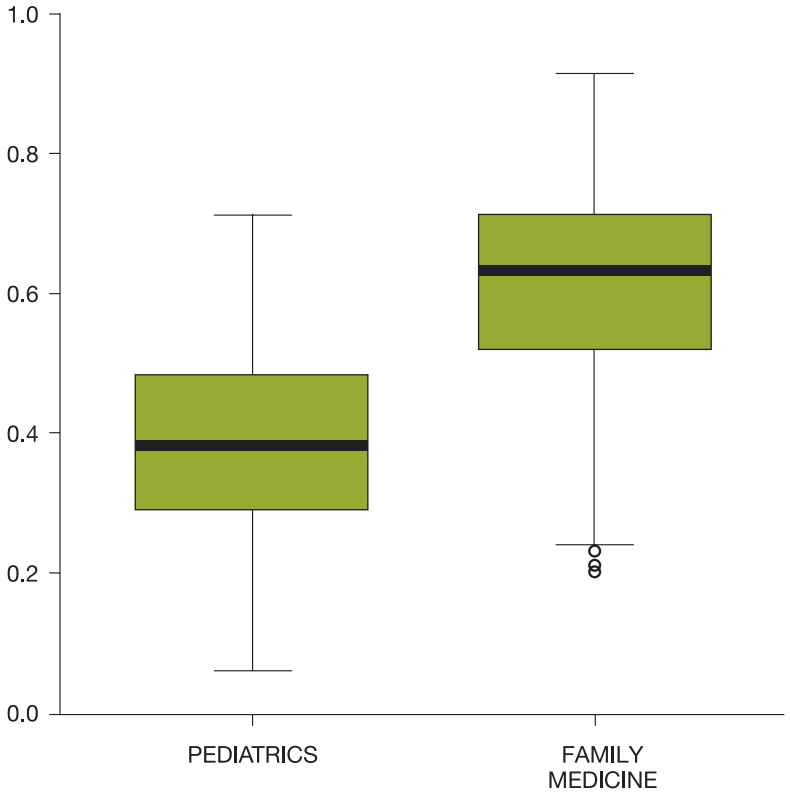
· The appearance of purulent sputum with no other symptom in a previously healthy patient with no chest symptoms, **is NOT an indication for antibiotic treatment**[**].

In the case of acute otitis media, delayed treatment with antibiotics is usually the best option. In bronchitis, the majority of patients do not benefit from antibiotic treatment

An evaluation of the percentage of episodes with code R78 treated with antibiotics (including acute bronchitis and lower respiratory infections excluding pneumonias) (figure 6) shows that the average population receiving antibiotics is a little lower than 40% in children and 60% in adults. Moreover, important differences are observed when comparing consultancies in primary care. This data is similar to that found at the end of the 1990´s[36].

In the management of pneumonias, the review carried out by the Cochrane foundation[48] considers that there is no clear evidence to recommend antibiotic treatment above all other options, and that in individual clinical trials, no clinically significant differences were found among antibiotics. Taking into account the important rates of resistance shown by pneumococcus to macrolids and tetracyclins in our area, elective treatment should be amoxicillin 1 g / 8 h associated or no with macrolids. The addition of a macrolid depends on the suspicion of atypical bacteria where beta-lactamic agents are ineffective (for example, Legionella, Ricketssias, Mycoplasma, etc). Alternative treatment for adults may be ample spectrum quinolones (like levofloxacyn)[29] (table1).

Figure 6. Distribution of the use of antibiotics in acute bronchitis in the different consultancies of primary care.



(**) In a recent study the change of sputum colour provided a diagnostic specificity of 0.46 and a sensitivity of 0.79, with a CP+ = 1.46, and thereby antibiotic treatment is not indicated (Altiner A et al.Sputum colour for diagnosis of a bacterial infection in patients with acute cough. Scandinavian Journal of Primary Health Care 2009;27:70-73).

Table 1. Elective antimicrobial treatment in different infections.

Infection	Elective treatment and posology in adults (children)
Acute bacterial Tonsillopharyngitis	**Elective option:** Penicillin V 500 mg b.i.d. (50 mg/Kg/day) oral for 10 days Alternatives: Amoxicillin 500-1.000 mg b.i.d. (40 mg/kg/día) oral for 7-10 days **If suspected no adherence to treatment:** benzathine penicillin i.m. 1.200.000 units (50.000 units/Kg), single intramuscular dose. **Allergy to beta-lactamic antibiotics:** Josamycin 1 g b.i.d (30-50 mg/kg/day) oral for 7 days. **Recurrent tonsillopharyngitis:** · Cefadroxil 500 mg b.i.d (15 mg/kg/day) oral for 10 days. · Amoxicillin /clavulanic acid 500 mg- 875 mg/125 mg b.i.d) (40 mg/kg/day) oral for 7-10 days
Acute Otitis Media	**Elective option*:** Amoxicillin 500 - 1000 mg / t.i.d. (40-80 mg/Kg/day) p.o for 7 days in < 2 years and 5 days in > 2 years. **Alternative if failed therapy in 3 days:** Amoxicillin/clavulanate 500 mg - 875 mg/125 mg (80-90 mg/kg/día) p.o for 10 days **Allergy to beta lactam antibiotics:** · Clarithromycin 250-500 mg b.i.d. (15 mg/kg/day) p.o for 5-10 days. · Azithromycin 500 mg/day (10 mg/Kg/day) p.o for 3 days
Pneumonia	**Elective:** · Adults Amoxicillin 1 g t.i.d. oral +/- clarithromycin 500 mg b.i.d. oral for 7-10 days** · Children < 5 years: Amoxicillin 80-90 mg/kg/day · Children > 5 years: Clarithromycin 15 mg/kg/day +/- Amoxicillin 80-90 mg/kg/day*** **Alternatives:** Adults: Levofloxacin 500 mg/day oral for 7-10 days Children < 5 years: Amoxicillin/clavulanic acid or macrolides Children > 5 years: Amoxicillin/clavulanic acid
COPD exacerbation with NO risk of Pseudomonas	**Elective:** Amoxicillin-Clavulanic acid 875 mg / 125 mg/t.i.d. oral for 7-10 days **Alternatives:** · Cefuroxime-axetil 500 mg b.i.d. oral for 7-10 days · Levofloxacin 500 mg/day oral for 7-10 days
COPD exacerbation WITH risk of Pseudomonas	**Elective:** Ciprofloxacin 750 mg/b.i.d oral for 10 days **Alternatives:** Patients may requiere hospital admission for treatment.

* The elective option in most children is delayed treatment..

** Evaluate macrolides according to severity of symptoms in the presence of co-morbidity, age and possible cause (*Legionella pneumoniae* or other microorgansims that may cause atypical pneumonia)

*** In children > 5 years, the prevalence of *Mycoplasma pneumoniae* is very high. If *S. pneumoniae* is suspected then amoxicillin should be added.

Criteria for management of COPD exacerbations with antibiotic treatment

The GOLD guidelines[49] recommend treatment with antibiotics in two situations:

· When all three of the following symptoms are present (evidence B): increase in dyspnea, in sputum purulence and in sputum quantity as well.

· Presence of purulence in sputum and moreover one of the following symptoms (evidence C): increase in dyspnea or in the quantity of sputum.

The presence of infection due to *P. aeruginosa* should be suspected in the following situations and adequate coverage with antibiotics should be given (for example ciprofloxacin):

· Recent hospital admission.
· More than 4 antibiotic courses in the last year.
· Severe exacerbations.
· Isolate containing P. aeruginosa both during the stable period or during exacerbation.

More simple antimicrobial regimens

It has been proposed that in some circumstances, for example, children who attend kindergartens or school, the use of dose regimens with longer intervals of administration may be adequate to avoid having to give a dose at lunch hour, which could become complicated in a school. Some of the elective treatments commented previously can be employed, following these regimens. **Nevertheless, we should remember that the evidence that supports this approach is much lower than that for greater frequency in administration.**

Otitis media. 80 or 90 mg/Kg amoxicillin in 2 doses obtains sufficient concentrations in the middle ear for the majority of strains with reduced susceptibility to penicillin[50].

Tonsillopharyngitis: Elective treatment is penicillin V or amoxicillin twice a day, but in cases requiring a simple regimen, an option for children over 3 years could be 750 mg amoxicillin once a day (children < 40 kg) and 1000-1500 mg once a day (children > 40 kg)[51,52]. A review made by the Cochrane foundation[53] concluded that short antibiotic regimens are just as effective as longer ones. Short regimens with macrolids are not recommended in our current situation given high rates of resistance in *S. pyogenes* isolates.

Final reflection. As we have described, the problem of increased antimicrobial resistance is correlated with the inadequate use of antibiotics. It is within our hands to take measures to minimize this problem. We need to avoid repeating Aesop´s fable of the shepherd and the wolf. We cannot be threatened by the wolf without taking any measures. The problem exists and so do the tools to tackle it.

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Conclusions

There is a correlation between the inadequate use of antibiotics and the increment on antimicrobial resistance.

The employment of antibiotics in viral infections carries the risk of increased adverse effects and resistance with no real benefit for the patients.

In tonsillopharyngitis the elective treatment is still either penicillin or amoxicillin. Streptotest could be useful to identify patients that may benefit from antibiotic treatment.

In acute otitis media, the best strategy is delayed antimicrobial treatment and the elective drug is amoxicillin.

With regard to bronchitis, there is considerable variability in the use of antibiotics among different consultancies. The majority of the patients do not benefit from antibiotics.

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