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REVIEW ARTICLE

Rational use of antimicrobials in the treatment of upper airway infections☆

Santiago Alfayate Miguélez [a], **Luis Garcia-Marcos** [b,c,d,*]

[a] *Universidad de Murcia, Hospital Clínico Universitario Virgen de la Arrixaca (HCUVA), Department of Pediatrics, Infections Unit, Murcia, Spain*
[b] *Universidad de Murcia, Hospital Clínico Universitario Virgen de la Arrixaca (HCUVA), Respiratory Medicine and Allergy Units, Murcia, Spain*
[c] *Instituto de Pesquisa em Biomedicina de Murcia (IMIB), Murcia, Spain*
[d] *Rede ARADyAL, Madrid, Spain*

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KEYWORDS
Antibiotic resistance;
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Abstract
Objective: To analyze the main cause of the irresponsible use of antibiotics at the pediatric level in a very frequent, usually self-limited, and typically viral condition: upper airway respiratory infections.
Sources: Different databases were searched using specific terms related to resistance to antibiotics, upper airway respiratory infections, and pediatrics patients.
Summary of the findings: Effectiveness varies depending on the place, the form of intervention, and the resources used. Multiple interventions appear to be more effective. The foundations of treatment are training in technical aspects and in communication skills for the prescribers, and having enough time for each patient; and training through the health clinic and the media for patients/parents. Deferred prescription and the use of rapid diagnostic tests in the primary care setting have been shown to be effective. A fluid relationship based on trust between clinicians and parents/guardians is one of the keystones.
Conclusions: Any project that seeks to be totally effective must include a health authority, which in addition to helping implement these measures, has the firm intention of drastically reducing the use of antibiotics in animals and in the environment, as well as favoring research into new antimicrobials.

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* Corresponding author.
E-mail: lgmatrcos@um.es (L. Garcia-Marcos).

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PALAVRAS-CHAVE
Resistência antibiótica;
Infecções das vias aéreas superiores;
Crianças

Uso racional de antimicrobianos no tratamento de infecções das vias aéreas superiores

Resumo

Objetivo: Analisar a principal causa do uso irresponsável de antibióticos em nível pediátrico de doenças muito frequentes, normalmente autolimitadas e virais: infecções respiratórias das vias aéreas superiores.

Fontes: Diferentes bases de dados foram pesquisadas com termos específicos relacionados à resistência a antibióticos, infecções respiratórias das vias aéreas superiores e pacientes de pediatria.

Resumo dos achados: A eficácia varia, depende do local, da forma e dos recursos usados. As formas de múltiplas intervenções parecem mais eficazes. O treinamento em aspectos técnicos e habilidades de comunicação para médicos e tempo suficiente para cada paciente, além do treinamento por meio da clínica e da mídia para pacientes/pais, são a base da eficácia. Prescrições de uso posterior e testes de diagnóstico rápido no ambiente de cuidado primário mostraram ser eficazes. Uma relação de confiança entre médicos e pais ou responsáveis é uma das pedras angulares.

Conclusões: Qualquer projeto que busque ser completamente eficaz deve incluir uma autoridade em saúde, que, além de ajudar a implantar as medidas nos pacientes, tem a sólida intenção de reduzir drasticamente o uso de antibióticos em animais e no meio ambiente, além de favorecer a pesquisa sobre novos antimicrobianos.

Resistance to antibiotics has become one of the most important public health problems throughout the world in today's society.[1,2] This increase, which has been observed since at least the last years of the 20th century, has caused a movement, which has been generalized at a global level, with the aim of limiting the potentially catastrophic effects that have been forecast. The World Health Organization (WHO) defined antibiotic resistance as the resistance of a microorganism to an antibiotic which it had been previously sensitive to (WHO, 2016).

The golden age of antibiotics, when new molecules appeared every year, has reached its end and the industry is seen as being unable to develop new molecules that can overcome the appearance of new resistances.[3–5]

The consequences of antibiotic resistance are difficult to forecast, but it is estimated that in 2050 it will be the cause of death of around ten million people and assume an enormous economic cost.[6] The European Centre for Disease Prevention Control (ECDC) calculates that it currently causes the death of 25,000 people in Europe every year and has a cost of 1.5 billion euros per year.[7]

The appearance of resistances to antibiotics is a complex problem which is affected by multiple factors:[8] environmental factors, those of the microorganism itself, and those regarding the use of antibiotics in patients and also in animals, especially in the food production chain.[3,9] Chokshi et al.[10] analyzed the contribution to the development of antimicrobial resistances according to the socio-economic and political factors of different countries, extracted from the data of the countries' own health agencies. Their conclusion is that there are many factors involved, and that these differ between developed and developing countries. It should be highlighted that research into new antibiotics is scarce, given the lack of incentives from public administrations.

In the light of the seriousness of this situation, important changes have been occurring in recent years, not only from the health institutions but also from the highest levels of politics.

In 2016, 193 world heads of state at a meeting in the General Assembly of the United Nations committed themselves to adopting a common strategy to tackle the fundamental causes of this problem from a focus of ''One Health''[11] and the WHO included it, in 2019, in its five-year general strategic plan among the ten most important threats to health (https://www.who.int/es/emergencies/ten-threats-to-global-health-in-2019). A ray of hope has appeared, as some studies have communicated that there has been a change in the trend and that consumption has stabilized in recent years.[12] However, there is still a great deal more to be done and the current situation remains unsustainable.

Numerous factors intervene in antibiotic administration to humans, which ultimately condition their inappropriate use. The most important factors include those referring to clinicians, while others refer to the patients, parents/guardians, and even to society itself.[3,13,14] Moreover, when discussing inadequate antibiotic use, the present authors do not only refer to the use of antibiotics in unnecessary situations but also, when required, to the use of broad-spectrum antibiotics instead of the most suitable for each pathology and with a narrower spectrum, as well as the use of incorrect doses and treatment periods.[15] The latter two aspects have been identified as being of great importance in the development of bacterial resistances. The use of sub-doses, as occurs with the use of expired antibiotics or by

incorrect prescription, is related to increased resistances.[9] A prolonged duration of antibiotic treatment gives a false security to the prescriber. However, during recent years it has been shown that, in frequent conditions, short courses of antibiotics are as efficacious, without any effect on the curing or recurrence rates. A short course improves adherence and diminishes side effects and bacterial resistances.[10] The primary care setting accounts for between 70 and 80 % of prescriptions and the majority are for airway infections, in which a viral etiology is predominant.[15]

Among the causes regarding clinicians, the most important are the handling of uncertainty (such as fears, lack of knowledge, diagnostic errors), inadequate communication, undervaluing the disease with respect to that felt by the parents, or the demand perceived from the patients or parents/guardians.[13,14,16]

If we refer to the people as a population as well as when we act as patients, the behavior regarding antibiotics has been established depending on numerous interconnected variables: access to services, adequate medical services and access to medication, knowledge on antibiotics, and social attitudes. In the general population, knowledge on the topic may not be adequate in an important percentage of patients.[1,3,8] Some patients interrupt their treatment once they feel clinically better and self-medicate when faced with a similar clinical picture to another for which they had received antibiotics.[17]

This problem is especially relevant in pediatric ages. Antibiotics are the most used therapeutic agents in this population range,[18] and also, as in the general population, above all in primary care,[19,20] with those indicated in respiratory cases accounting for more than 70 % of the consultations in which antibiotics are prescribed. Upper respiratory tract infections are the most frequent pathologies, including the common cold, pharyngitis, otitis, and sinusitis. These processes are of a viral etiology or in many cases are self-limiting and therefore do not require antibiotic treatment.[20,21]

Many studies suggest that approximately half of the antibiotics used in pediatrics are incorrect in their indication, choice of molecule, and duration.[3,22] Moreover, they are not innocuous and may provoke side effects such as diarrhea, exanthemas, and vomiting, leading to more than 140,000 visits to emergency services in 2008.[23]

As has been stressed previously, this is particularly true for the first years of life, above all in infants under two years of age,[20] and in the primary care setting, in which the majority of upper airway infections (common cold, pharyngitis) have a viral aetiology.[24] The viral etiology of these infections together with the knowledge that group A *Streptococcus* does not usually cause pharyngitis in patients under 3 years of age make it unnecessary in most cases to use antibiotics in the young infants in such infections. Acute otitis media (AOM), which is frequently diagnosed, is in many cases self-limiting.[25]

The diagnosis that is most associated with antibiotic use is for AOM. It is a disease that is difficult to diagnose, and more so in the first 2 years of life when the clinical data and the difficulty in viewing the timpani offer a great deal of help in some cases. Some authors believe it to be an over-diagnosed disease.[22,26] A study carried out by Alzahrani et al.[21] examined the antibiotics used in AOM and found that broad-spectrum antibiotics were used in up to 41.2 % of cases – the main cause for prescribing them. These figures were similar to those found in another prior study, also conducted in the United States, ten years previously. A similar situation was found with sinusitis, and both diagnoses increased the risk of receiving antibiotics when compared to acute pharyngitis. All of these occurred without observing better clinical results.[27]

However, apart from enhancing the appearance of resistances, antibiotics have a great impact on microbiome. This is formed from birth and its most critical phases occur during childhood, especially during the first months of life. Changes in microbiome produce changes in vital functions and has been related with the appearance, in later stages, of metabolism problems such as obesity[28]; with autoimmune diseases such as diabetes, rheumatoid arthritis, and multiple sclerosis [29]; and with allergic diseases.[30] The association grows closer with lower age and higher number of antibiotic doses.[20] Infancy is a critical period in the immunological and metabolic development; antibiotic use may alter these processes.

Another very important piece of data that shows the wide margin for improvement is the variability that exists among different countries, areas, and professionals when analyzing antibiotic prescription rates, taking into account that this cannot be justified by socio-sanitary factors alone.[20,22,24,25,31] The cause of this variability may also be multiple, linked to different prescription polices, to different health systems, to the pharmaceutical market, to sociocultural and economic factors, but above all linked to the prescribers themselves,[24] which is indeed unacceptable. Youngster et al.[22] found up to a 7.5-fold difference when referring to the 0–2 year-old group, in a study carried out in six countries in Europe, the United States, and Korea in children younger than 18 years, divided into four sub-groups. The present authors' experience in a study performed in their region in 3 year-old children (unpublished data) showed up to a seven-fold difference among the prescribing clinicians, without it being possible to justify this by other factors and without the results being compromised in health terms. These differences are both qualitative and quantitative[24] and usually coincide in lower antibiotic use coupled with a better use of those that are used and with a narrower spectrum.[22,24,32] For example, the United States is among the countries that use the most antibiotics in children, more than double that of countries such as Germany and the Netherlands; despite the existence of clinical guides published by the American Academy of Pediatrics (AAP) or the Infectious Disease Society of America (IDSA), the use of azithromycin is found in second place in certain pathologies in which its use should be far more restricted.[20] It is, therefore, an excellent marker of bad practice and appears as an important area for improvement.[24]

Neutralizing and reverting this enormous and complex problem also requires complex intervention that covers all the factors that are involved, *i.e.*, global access to tools for the prevention, diagnosis, and treatment; ensuring that responsible use is made of existing antibiotics; and favoring the research and development of new molecules.[33] Different entities, organisms, and states, led by the WHO, work to

achieve global access to all the prevention, diagnosis, and treatment tools and to stimulate research into new antibiotics, vaccines, and other drugs.[34,35]

In recent years different interventions have been studied and put into practice to influence the most important agents involved in rational antibiotic use, the clinicians/prescribers, the patients, the parents/guardians, and society in general. Some interventions are carried out acting on a single factor while other do so on multiple factors simultaneously. Some of those that the present authors consider to be the most important are analyzed below.

On prescribers

Some degree of effectiveness has been shown by many strategies, but they are inconsistent over time and, moreover, lose their effectiveness when they are no longer applied.[36]

Wei et al.[37] performed a study in patients aged 2–14 years who attended several hospitals in a province as outpatients. The intervention consisted in educating the clinicians (reviewing guides and training in the prescription), monthly reviews, and brief education given to the care providers in the clinic and previously in the waiting room by means of videos in a group of hospitals, whereas another similar group received no intervention. They achieved a 29 % reduction in prescriptions in just three months in the intervention group compared to the control group.

Gerber et al.[38] studied whether antimicrobial stewardship intervention could reduce the incorrect prescription of broad-spectrum antibiotics for bacterial and viral ARTIs during one year after the interventions. The interventions were carried out in 162 pediatricians and included education on the topic together with audit and feedback of their prescriptions. The main outcomes were changes in the behavior on broad-spectrum prescription for acute sinusitis, streptococcal pharyngitis, and pneumonia, and change in antibiotic use for viral infections. The proportion of children receiving antibiotics was importantly reduced after interventions. This reduction was statistically significant for pneumonia and the same trend (although without reaching statistical significance) was found for acute sinusitis.

Audit and feedback interventions require the least amount of resources to be implemented.[39] They produce a small but statistically significant benefit,[39,40] although with regard to the issue of reducing antibiotics, their benefit is not clear.

On prescribers and parents/guardians

The interaction and good relationship of trust between patient, parents, and clinicians is a basic foundation of the attempts to reduce inappropriate antibiotic use. Different studies have assessed parents' attitudes and knowledge, and although it is true that some parents have the wrong concept regarding which diseases antibiotics are necessary for and in which they are not,[1,11] it is no less true that they only want them when they are really necessary.[41] However, they become unhappy when clinicians minimize the importance of their children's symptoms, do not sympathize with the parents' problems, and fail to offer an alternative.[1,42,43]

In the interaction between parents and prescribers, the latter perceive an unproven pressure from the parents to prescribe antibiotics, and the relationship between both sides deteriorates if this does not happen.[12,13,44] In fact, parents' satisfaction seems to be more related to the quality of the communication than with the fact of using or not using antibiotics in a specific case.[12,13,44]

In the case of children, above all in the youngest, the parents' attitude and their knowledge of antibiotics is one of the most important factors. Bosley et al.[1] carried out a systematic review to understand the factors that may influence the attitude of parents regarding antibiotic use in their children.

Those authors found a great variability in the amount and quality of the knowledge and in the relationship/communication with their pediatricians, and highlighted that a lack of knowledge on their use, the relationship between pediatricians and parents in general, and in each case in particular in the management of each disease and past experiences are very influential factors. A relationship based on trust, with clear messages that can be clearly understood, must exist and the parents must not perceive that their pediatrician undervalues their children's disease.

The knowledge level was greater in developed countries, and antibiotic use was related to the education level received and to the age and anxiety of the parents.[1]

Mangione et al.[44] studied parent satisfaction depending on their communication with their pediatricians. The existence of positive messages (symptomatic medication), plus negative messages (why antibiotics were not used), plus the existence of a contingency plan (follow-up) notably increased the acceptance and satisfaction of parents and facilitated the reduction in unjustified antibiotic use.

Cantarero et al.[9] carried out a systematic review with the objective of describing the characteristics of parents' knowledge about antibiotic use in respiratory infections, their attitude towards their pediatrician, and their behavior when their child suffers an infection. Its objective was to answer the questions as to whether there is a relationship between the degree of knowledge and judicious antibiotic use, and to analyze the sociodemographic factors linked to antibiotic use in these infections. They found that parental knowledge on antibiotics affects their attitudes and behavior, although said acceptable knowledge does not always impede antibiotic use, because few parents believe that their children receive too many antibiotics. The main problem detected was the lack of a complete physical examination and specific clarifications that could help the child in his/her recovery, more than merely prescribing antibiotics with no further explanation. Once again, good communication and not undervaluing the problem are shown to be instrumental in reducing inadequate antibiotic use.

Lucas et al.[15] conducted research into qualitative studies with the aim of describing the points of view, beliefs, and attitudes of parents, children, and pediatricians that may influence prescribing antibiotics for acute infections in the primary care setting. They highlighted certain points that the present authors' consider to be of utmost importance in understanding this issue and seeking to find effective solutions. Clinicians frequently use antibiotics ''just in case,'' when they do not feel sure of the results at a clinical

and social level or due to a supposed pressure from parents. On the contrary, this can be avoided when parents do not ask for them or resistance or intolerance problems exist. Parents ask for antibiotics when they believe that they will improve their child's disease, but also wish to avoid the antibiotic's side-effects. Finally, something as straightforward as paying careful attention, with a good examination, in itself transmits security to parents. This may create a conflict with clinicians, who seek to finish the consultation quickly on occasions. Parents' anxiety coupled with green nasal mucus were clear indicators for antibiotic prescription. The confidence in the clinician-parent/patient relationship, educating the parents on the evolution of the process, and their satisfaction are essential in not prescribing antibiotics.

Hernández-Díaz et al.[45] studied the beliefs, behavior, and adherence of parents/guardians of children of Latin origin, under the age of 6 years, in the United States with respect to antibiotic use in upper airway respiratory infections, concluding that the knowledge and erroneous beliefs of that group indicate a significant problem, and that this is more so the lower the educational level and age of the parents is.

Van Hecke et al.[46] carried out a qualitative study about the perception of parents on antibiotic use and resistance in children under the age of 5 years; they found them to be very optimistic because they believed that their families would not be affected by resistance since they used few antibiotics, and very few considered that resistance is a problem. Furthermore, they considered that the campaigns about this problem are in line with their behavior and thus they will not be affected, thus those authors concluded that they must be revised.

Kianmehr et al.[47] carried out a systematic review on the expectations patients have when receiving antibiotics for airway infections and concluded that there is a trend to a lower perceived need over the years and that this was global, thus highlighting that this may be a point of support for the prescribers in order to improve antibiotic use.

On informative campaigns

Information campaigns are another of the possible interventions to reduce antibiotic use and, as with other strategies, have also produced contradictory results. Huttner et al.[48] performed a review of campaigns carried out in developed countries which were driven and developed by health authorities at both national as well as regional level. Five of them were specifically directed at the pediatric population. The methods varied greatly: they used written formats such as pamphlets, posters, and notices, as well as audio-visual techniques. These interventions were part of a broader campaign that was usually directed at prescribing clinicians. Those authors concluded that the effects are difficult to assess, but that the data suggest that they may have a positive effect. However, Roope et al.,[49] in a study carried out in the United Kingdom, found that these campaigns can have a paradoxical effect of actually producing an increase in antibiotic demand. Therefore, they recommend that such campaigns must be tested in small areas prior to being generalized. The messages must be clear, simple, impacting, highlighting all the positive aspects, but without omitting the drawbacks and even evoking fear.[48] Authors such as Barriere[50] even believe that the dramatism of the means of communication when talking of the appearance of superbacteria is a positive element, which makes the public more aware of the problem.

A Cochrane review by O'Sullivan[51] analyzed the effectiveness of written information on the reduction of antibiotics in upper airway respiratory infections in pediatric patients, concluding with moderate-to-low level of evidence that this strategy is effective in achieving a significant reduction in antibiotics, without finding significant changes in re-consultations nor in parental satisfaction.

On rapid tests that help in the diagnosis in the primary care setting

The use of rapid tests to detect group A beta-hemolytic *Streptococcus* is another of the tools that have been put forward to improve antibiotic use in primary health care. Many studies reflect a positive impact, but some studies have detected a high proportion of incorrectly performed tests, which may minimize that effect. The main cause for considering them inadequate was the presence of clinical data of two or more viral infections.[52] Additionally, the use of rapid influenza diagnostic tests (RIDTs), which have a great sensitivity when used at the point of care, may be useful for improving the diagnosis, reducing the use of antibiotics when not indicated, and supporting antiviral treatment, if warranted.[53]

The use of C-reactive protein (CRP) has been studied with varied results. Some studies have shown a variable, but significant, reduction in the prescription of antibiotics to children with fever, while others, such as a study carried out in Norway in children who attended non-hospital emergency services with fever and respiratory symptoms, have not demonstrated effectiveness in reducing the number of antibiotics nor in the number of patients referred to hospital emergency services.[54] In general, the impact of CRP on more correct antibiotic use is higher in developed countries, also depending on the cut-off point used.[55]

On deferred prescription and shared prescription

Deferred prescription is a strategy that involves prescribing antibiotics to the patient that are only to be taken if certain situations arise, typically a worsening in the infection.

A Cochrane review concluded that, in deferred prescription, the patient's satisfaction is similar to when antibiotic treatment is started immediately and far greater than if treatment is not started. Moreover, when the doctor was not sure whether to use antibiotics or not, deferred prescription significantly reduced antibiotic use.[56]

Couchman et al.[57] found that deferred prescription may be a good method to achieve a reduction in antibiotic use without detriment to parental satisfaction.

Shared decision-making is an important component in patient-centered care. This requires good communication and clinical practice based on the best knowledge. Coxeter et al.[58] carried out a systematic review on the topic

of antibiotic use in upper airway infections, concluding that it is an effective strategy in the short term, without being able to conclude whether its effectiveness is maintained over time.

Multiple interventions

It is difficult to analyze this aspect given that within the multiple interventions there are very different degrees of complexity, but many authors identified them as being the most effective.[48]

Clavenna and Bonati[24] performed a review with the objective of analyzing and comparing the profile of antibiotic prescription in different countries and regions; they found major differences between countries and regions, and at the level of professionals. They concluded that monitoring the consumption and comparing it among different zones and professionals, and the elaboration of local guides, as well as training plans for professionals and educational training for parents, can be effective at reducing antibiotic use.

Lee et al.[59] performed a systematic review analyzing the importance of educating the prescribers and the public in general, including children, on prudent antibiotic use. Medical education programs (training, interactive seminars, mailings, working groups in evidence-based medicine, communication skills workshops, and support visits) achieved a mean 34 % reduction, although this figure is not uniform in the literature and some studies did not find significant reductions. The effectiveness of the combination of these strategies with others such as educating patients and their families, deferred prescription, audits, and feedback showed a greater reduction in antibiotic prescription. In recent years, WHO-supported learning programs have been started to include children from 7 years of age in the training; such initiatives have been shown to increase the knowledge level in that population group.

In a systematic review conducted in patients over the age of 13 years, Köchling et al.[60] found that different actions have a greater impact depending on the characteristics of the country where they are applied: in countries that have a lower prescription rate the most successful actions were those actions directed at improving the communication skills; while in countries with a higher prescription rate, point-of-care testing (POCT) and computerized clinical decision support systems (CDSS) were most successful, although the different trials did show considerable variation. They also observed that an intervention directed at reducing the number of antibiotics prescribed had the collateral effect that those used were used more adequately (better fitting spectrum).

For Goldman and Newland,[19] educating clinicians and adequate and personalized audit and feedback are effective at reducing antibiotic use. However, if the intervention is discontinued the effect disappears, returning to square one.

However, a multiple intervention that includes communication skills, deferred prescription, implementation of consensus protocols in electronic prescription databases, and quarterly feedback, carried out in the Netherlands by Vervloet et al.[61] in primary care clinicians, achieved a reduction in the patients over the age of 12 years, but surprisingly, not in children under 12.

Bozzella et al.[62] analyzed the different interventions to reduce inadequate antibiotic use in a recent review, suggesting that all the interventions may be beneficial, but that multiple interventions obtain better results.

Conclusions

Clinicians are therefore facing a complex problem that requires complex and personalized interventions depending on the characteristics of the patient population and on the resources available.[3] Multidisciplinary interventions are also necessary in other fields such as the environment and agriculture, not only in those involving people, and these interventions must be prolonged over time and at all levels.

The present authors believe that the first step is involving the corresponding administrations to regulate and minimize antibiotic use in agriculture with the impact that it has at environmental level and directly on humans through foodstuffs. They must also support industry in the research of new molecules and it is a moral obligation of the industry to intensify that research, which can help to resolve this serious problem.

In humans, no single intervention has been shown to be absolutely superior to others and their effectiveness is measured by the sociocultural, economic, and prescription-pattern conditions of each area. Nonetheless, improving antibiotic administration in children in the primary care setting is crucial.

Training and awareness campaigns are important at national or regional level. They must be campaigns delivering clear, direct messages, and they should be impactful. Training parents and guardians is a very important task and must be performed from the very beginning of the relationship with the pediatrician. The pregnancy period is seen as being vital. This is a particularly sensitive period in which messages regarding the health and disease of the unborn child are especially significant. The waiting room of the clinic is also an appropriate setting for health education by means of audio-visual or written messages. Training must cover not only the non-use of antibiotics in pathologies caused by viruses or which are self-limiting, but also in the adequate compliance with them when they are required, in addition to preventing self-medication.

As seen in different studies, good communication with the primary care pediatrician is essential.

A worthwhile option could be the inclusion of health topics in the education of schoolchildren from 7 to 8 years of age with the goal of having a society bearing greater knowledge, but it is essential that students of health professions and all the health professionals involved are fully aware of the seriousness of this issue.

However, ultimately, clinicians must not forget that prescription lies in their hands. Improving it will involve an important effort. There are different scenarios for improvement, namely: elaborating algorithms, protocols, or clinical guides through participation, consensus, and which fit the evidence and the local microbiology, as well as training seminars or sessions. Training in communication skills has been shown, on numerous occasions, to be an essential

aspect; carrying out a thorough physical examination and not undervaluing the child's disease have also been shown to be important in the studies performed. Perhaps pediatricians need to reject the idea that parents are pressuring them and that they leave happier if their child has been prescribed antibiotics, given that the studies do not uphold this idea.

Diagnostic tools based on molecular techniques and the application of these and other rapid techniques outside the hospital setting may help antibiotic use by identifying with greater certainty which patients need antibiotics. Some examples of these tests include the Group A beta-hemolytic *Streptococcus* antigen detection test, above all in infants over the age of 3 years, the CRP test and, in certain cases, the possible use of viral antigenic flu detection tests, *etc*. Additionally, deferred prescription or ''wait and see'' can have a positive impact. Interventions with audit-feedback and assistance by means of computer programs in dispensing may close this circle of help to the prescribing clinician. All these studies indicate that these interventions need to be continual in order to be efficient.

To conclude, it must be recognized that many countries have created tailor-made programs based on the socio-sanitary and economic realities in their countries with the objective of achieving ''One Health'' as called for by the WHO. These projects must include advances in all the fields of development in health, including the control and rational use of antibiotics.

The present authors agree with Barriere[50] when he expresses the opinion that it is a moral obligation of society and of health systems to ensure that these tools that were inherited are available for future generations.

Is there a ray of light at the end of the tunnel?

Conflicts of interest

The authors declare no conflicts of interest.

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