
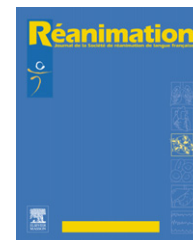




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REVIEWS

Save antibiotics! What can be done to prevent a forecasted disaster? Suggestions to promote the development of new antibiotics^{☆,☆☆}

Sauver les antibiotiques! Que faire pour prévenir un désastre annoncé : propositions pour favoriser le développement de nouveaux antibiotiques

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Summary New antibiotics are needed because of the increasing resistance of bacteria but they will be available in years to come only if drastic changes are implemented in development strategies, evaluation, use, and financing. Over the last decade, various opinions were stated and limited action was undertaken. Optimizing antibiotic use (as the “antibiotic plan” in France) was indispensable, but the process is still on going, and this is only part of the problem. Major questions are recurrently raised such as improvement of development procedures for new antibiotics, optimizing diagnostic methods, innovating financing modalities, or rescue of “old” antibiotics at risk of being withdrawn from the market. The symposium organized in September 2009 by the Swedish EU presidency helped to support previous recommendations. But conclusions remain unspecific. The propositions which are made here, after a work session, have for aim to be more detailed and innovating, even if they can be discussed, or even provocative.

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MOTS CLÉS

Antibiotique ;
Méthode
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Essais clinique

Résumé Les besoins d'antibiotiques nouveaux, rendus nécessaires par l'accroissement des résistances bactériennes, ne seront satisfaits dans les années à venir que si de profonds bouleversements des méthodes de développement, d'évaluation, d'usage et de financement sont mis en place. Depuis dix ans, différentes réflexions et quelques actions ont vu le jour. L'optimisation de l'usage (type « plan antibiotique » en France) était indispensable, elle n'est pas achevée, elle ne représente qu'une partie du problème. Des questions majeures comme les améliorations à envisager dans les procédures de développement de nouveaux antibiotiques, l'optimisation des méthodes diagnostiques, des modalités de financement innovantes, ou le sauvetage de « vieux » antibiotiques menacés, sont régulièrement abordées. La réunion organisée en septembre 2009 par la présidence suédoise de l'UE a permis de conforter des recommandations déjà en place. Mais les conclusions restent encore imprécises. Les propositions qui sont présentées ici, à l'issue d'une réunion de travail, se veulent plus détaillées et innovantes, même si elles sont discutables, voire parfois provocatrices.

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Context

Antibiotics in the early forties changed the history of mankind. Frequent and often deadly diseases became "benign", and for half a century, this revolution was considered as definitely acquired, occulting the extraordinary adaptability of the bacterial world. But, over the last 15 years, bacterial resistances have evolved much faster than innovation, especially concerning Gram-negative bacteria. Hence, infections untreatable by antibiotics are no longer a mere threat but reality [1,2]. At the same time, even if new molecules have been developed, the expected success was not achieved as illustrated by the aborted development of anti-pneumococcal quinolones. Furthermore, we were able to observe the perverse effects of a methodology which was supposed to be more rigorous, but whose inappropriateness to objectives became obvious. For 10 years, our inability to support small progress, minimum development using outdated standards, for various unjustified indications, blocked the availability of new molecules. And during that time we did not understand that modalities of antibiotic prescription were not only to be controlled but also to be completely reviewed [3–5].

This situation was in part linked to a system, or to a positive return on investment greatly conditioned by research axes for innovating molecules, in which thrift was the first concern of payers, or in which the user friendliness replaced reflection on the needs for good use and protection of these "sustainable goods" that are antibiotics.

The conjunction of this deficit in new molecules and of the evolution of bacterial resistance, in both hospitals and in the community (with boundaries increasingly difficult to determine) has become an "emergency situation".

Method

These are the minutes of a symposium organized by the SPILF on October 9, 2009, the main goal of which was to suggest concrete "complementary" propositions to the suggestions made during the Stockholm meeting held under the Swedish EU presidency on September 17, 2009. During that meeting, the title of which was "Innovative incentives for effective antibacterial drugs", we agreed with the "call to narrow

the gap between multidrug-resistant bacteria in the EU, and the development of new antibacterial agents". Three work groups presented axes for reflection to the ministers (or their representatives) of four EU countries, acted by executive representatives of European Medicines Agency (EMA), of the European Commission, and of the European Centre for Disease Prevention and Control (ECDC). Even if they were interesting, these reflections remained too general, and it was concluded that more specific complementary propositions were required.

For this symposium we required the participation of experts in clinical, microbiological, and pharmacokinetic practice, from the industry, from the Agence française de sécurité sanitaire des produits de santé (Afsaps = French Drug Agency), the Haute Autorité de santé (HAS = Higher Health Agency), the direction générale de la santé (DGS = Health Ministry Delegation, responsible for antibiotic management), the institut de Veille Sanitaire (InVS = National Epidemiological Surveillance Agency), and the Assurance maladie (health public insurance). Specialists in methodology, chemistry, animal models also participated. The reflection was organized mainly around four workshops, the assignments of which had been prepared by organizers, each responsible for a workshop.

Ten propositions served as a basis for our reflection.

Three have already led to concrete actions in France, with the plan to preserve antibiotic effectiveness and the national program against nosocomial infections:

- improve the good use of antibiotics and their prescription;
- track the evolution of bacterial resistances;
- prevent the transmission of resistant bacteria.

Three deserve to be examined, so that concrete actions must be undertaken:

- set up studies allowing to assess the clinical and therapeutic consequences of bacterial resistance (morbidity and mortality data, recording of therapeutic dead ends, possible substitution strategies);
- updated tracking of antibiotic molecules under development with a predictive estimation of each molecule's value, made independently of the industry;

- develop alternatives to antibiotic treatment (vaccines, nonspecific immunotherapy, inhibitors of virulence, genomics, antibacterial peptides, bacteriophages, etc.).

Four were the major workshop themes for this symposium:

- rescuing “old” molecules at risk of being withdrawn from the market. Which antibiotics would be concerned and according to what criteria?
- suggesting new methods to assess antibiotics for the treatment of severe infections with resistant bacteria;
- optimizing diagnostic procedures (clinical and microbiological) to prevent unnecessary treatments;
- treating the problematics of costs from development to treatment by considering all incitations to boost research and development of new antibiotic molecules.

The three last propositions were the workshop themes of the Stockholm meeting:

- regulatory possibilities to enhance the development, approval procedure, and availability of new antibacterial drugs. Chair: Dr Tomas Salmonson (EMA);
- financial and legislative options. Chair: Dr Richard Laing (WHO);
- research strategies towards new drugs targets and compounds for treating bacterial infections as well as new diagnostic tools. Chair: Dr Ragnar Norrby (Sweden).

Propositions of the work group

Rescuing “old” molecules at risk of being withdrawn from the market. Which antibiotics would be concerned and according to what criteria?

Some molecules, even though on the market for a long time, are still important (amoxicillin, vancomycin, ceftazidim, ceftriaxone), the approval of some others could be withdrawn because they are only used for a few patients even though they are indispensable (streptomycin, cotrimoxazole, aztreonam), finally others which had become obsolete are indispensable again (colimycin, sulbactam). The unpredictable evolution of resistance makes it difficult to forecast which molecules will be indispensable in the years to come.

A preliminary study made under the aegis of the SPILF and the DGS, in 2007, had concluded that 11 molecules were to be protected.

Several questions were raised:

- what criteria should be determined to maintain “old” antibiotics?
- what legal measures should be taken to maintain antibiotics when the firm that markets them wants to withdraw them from the market?
- what is the impact of generic drugs?
- how should “old” antibiotics be promoted?
- what information/training for prescribers?

- what impact on other French speaking countries when the drug is withdrawn from the market?

Proving the indispensable character of an “old” antibiotic is difficult. These are molecules, which were put on the market with levels of proof, which do not correspond to current standards. It is the resistance to recent antibiotic families, which has renewed interest for some of the “older” molecules. The criteria to be taken into account are microbiological (spectrum, mechanism of action), pharmacokinetic, clinical (niche antibiotic and targeted indication even for a few patients, last available molecule of its class, and absence of alternative). Furthermore, it should be kept in mind that the initial “niche” situation may evolve if the frequency of infections due to resistant bacteria increases.

The drug approval agency may veto the withdrawal of a molecule when it is the last available molecule of its class on the market. Nevertheless keeping a drug approval without putting the molecule on the market automatically leads to the administrative abrogation of the approval after 3 years. Then, the question is to find a takeover firm. Public authorities should take part in this endeavor.

It is thus necessary to identify with the utmost reliability molecules, which may become indispensable in the years to come, including for targeted indications.

New methods to assess antibiotics for the treatment of severe infections with resistant bacteria

The current development of antibiotics is based essentially on non-inferiority trials; it is not satisfactory because it is usually meant for indications, which are not those for which it will be used later. Currently, in phase III trials, only a very small number of patients included (a few dozen at most) are infected by resistant pathogens. Thus, this type of file when submitted does not get an “unrestricted” approval for the most resistant bacteria because no extrapolation is possible from non-pertinent clinical trials.

Even if comparative randomized non-inferiority clinical trials on a great number of patients appears reassuring from the statistical point of view, it may often be little contributive for the demonstration of effectiveness on multi-resistant bacteria.

Seeking support and scientific advice from approval authorities (European and/or national) in the early development stages of a new molecule is mandatory. This advice could guide research and development from an early stage, not only for the sake of effectiveness but also for tolerance. Cumulative knowledge on the relationships between structure and activity, structure and toxicity should allow avoiding dead ends of future development.

In the USA, the FDA systematically supports the development of any drug. The project for an early support of European antibiotic development was in the Stockholm meeting propositions. This scientific support is available on two levels. On the European level with the EMA, this must be paid for and is a constraint, which sometimes worries the manufacturer. On the national level with Afssaps, counseling is free. This offers the advantage of flexibility and the drawback of not being on the necessary level of European

collegiality. It is mandatory if a pre-approval marketing is considered.

The synthesis of microbiological, pharmacokinetic, pharmacodynamic, and PK/PD relationship pre-requisites are indispensable to explore as far as possible the presumption of antibiotic effectiveness during a preclinical phase of the approval file. Tissue kinetic data may prove useful in some circumstances. The suggested effectiveness standards reported in the literature must be considered as a minimum and are not always adapted to the most severe cases. Animal models must be developed with three objectives: demonstrate the clinical and microbiological effectiveness on infections with susceptible bacteria, assess and give preliminary data on the *in vivo* effectiveness on infections with resistant bacteria, finally contribute to determining effective doses (which is virtually not possible in the context of clinical trials in man). These two points are essential to determine which clinical trials are not needed because the presumption of effectiveness is sufficient.

The implementation of clinical trials must result from concertation between firms and approval authorities according to the above-mentioned data.

We claim that phase III non-inferiority trials are contraproductive for the development of this type of product, and must no longer be used, except in rare cases. Randomized comparative trials on great number of patients, the cornerstone of drug development to this day, must no longer be mandatory. Trials versus placebo are useless for patients presenting with severe infections due to multi-resistant bacteria. The stringent application of methods for clinical research has for main goal to ensure "confidence" in the quality and pertinence of data presented for analysis.

Thus, some methodologists consider that the study of a few cases or of a cohort may be sufficient, as long as clinical and microbiological diagnoses are proved, evaluation criteria robust, the natural history of the disease severe and documented, and that the irreproachable quality of data provided may be controlled. This is already the case with approval procedures for orphan drugs and could be applied to the development of some antibiotics. It could be of interest to consider a Bayesian method approach integrating all the data collected during the development. Other statistical approaches are possible such as choosing a risk alpha other than 0.05, for example 0.10 (more lenient for the approval of a new treatment); comparison with a "theoretical" effect when calculating the number of patients, even for a comparative trial; using quantitative rather than qualitative criteria for the evaluation.

But carrying on with clinical trials targeting infections difficult to identify because of multiple signs (infections of the skin and soft tissues, intra-abdominal infections) exposes to mixing extremely different diseases of variable severity, a great part of which do not require antibiotherapy but surgery.

Because of the difficulty to find and include these patients rapidly, it is necessary to modify the legislation on the organization of clinical trials to optimize the inclusion of patients concerned by the indication.

In the current epidemiological situation of resistance, these trials will concern mainly hospitalized patients, including in the ICU. But multi-resistant bacteria already

affect extra-hospital population, especially in the case of (still called community acquired) UTIs.

If such modifications are implemented, the evaluation of tolerance will only be possible on much smaller populations. This should lead to a different assessment of the benefit–risk ratio, given the severity of infections studied. In these cases, we should deliver conditional approvals and use a cohort follow-up for effectiveness and tolerance. A risk management plan (RMP) is scheduled with the delivery of approvals.

If a new antibiotic is the only one to be effective on a highly resistant bacterium, it is considered as a salvage antibiotherapy, which justifies a temporary approval for a cohort if possible. Indeed, this temporary approval for a cohort allows collecting information on tolerance. A compassionate use trial would allow collecting data on effectiveness and has the advantage to provide data, which can be used for the approval.

Optimizing diagnostic procedures to prevent unnecessary treatments

The difficulty to discriminate between bacterial and viral infections is a frequent cause for inadequate antibiotic prescriptions [6]. Anything, which can contribute to decrease this difficulty, will have a positive impact on antibiotic prescriptions. Thus, writing out guidelines for good practice and especially ensuring their diffusion and appropriation by practitioners is fundamental. Using rapid diagnostic tests (RDT, device labeled CE according to regulation 98/79/CE relative to medical devices for *in vitro* diagnosis) which have been on the market for several years and which are directly available for the practitioners has induced a significant decrease of antibiotic prescription. This was achieved not only with RDT used to screen for group A *streptococcus* already available free of charge for French physicians since 2004, but also with RDT used for flu, and urinary strips to screen for UTIs, not yet refunded by social insurance systems [7,8]. Other tests are also available or under development, both for ambulatory patients (CRP, procalcitonin, etc.) and hospitalized one (urinary *legionella* and *pneumococcus* antigens, PCR specific for the isolation of enterovirus, herpes virus, *meningococcus*, *pertussis bacillus*, etc.). They are far from always being "physician-tests" but the rapidity of results gives them a considerable impact on the number of prescriptions, on the choice of the antibiotic to be used (narrow versus broad spectrum) and/or the length of the antibiotic course prescribed. Usual bacteriological techniques (direct microscopic examination on fresh samples or Gram staining especially) may guide the prescription of antibiotics if they are correctly used (initiation, choice of the antibiotic, duration of course, etc.). The future for hospitalized patients lies in rapid detection techniques of specific and resistant bacteria such as methicillin resistant *Staphylococcus aureus* (MRSA), *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin, or *enterococci* resistant to vancomycin. Mass spectrometry and biochips seem to be promising tests in a close future for the rapid identification of bacteria and specific resistance mechanisms. Nevertheless, it must be kept in mind that no diagnostic test may be a substitute for clinical examination. Biological tests can only

follow clinical examination, they must not come first. The medical decision to prescribe an antibiotic, even in a context of emergency, does not depend on a single test result but on expertise taking into account several criteria to develop a list of diagnostic arguments. Clinical analysis takes into account a number of epidemiological (role of surveillance networks such as the one for flu), anamnestic and clinical parameters to conclude to a pre-test probability which allows to adequately interpret biological test results. Clinical scores such as those for pharyngitis or meningitis are not well enough publicized, and thus little used. An effort should be made to train prescribers focusing on the interpretation of a biological test result (taking into account data such as sensitivity, specificity, predictive values, and especially pre-test probabilities and likelihood ratios) but also parameters which may influence test results such as quality of sampling, respecting procedures, and the notion of pre-test probability. RDT must be integrated in the clinical analysis strategy and their cost included in healthcare management.

The availability of RDT must not prevent from using classical biological tests performed in laboratories where, besides technical facilities, can be found specific competences (logistics for sampling, quality control, continuous care, etc.). RDT used at the patient's bedside have a very useful immediate diagnostic value from a public health standpoint, but are not usually supported by a quality of care policy which allows classifying them as a biological examination. Only an accredited dispatched biological laboratory may reach that standard, especially within hospital wards.

Finally, it should be reminded that the concept of screening or of rapid diagnosis does not rely only on the rapidity of the technique itself, but also in the quality of sampling, the speed of transportation and processing of the sample, and finally the speed of result notification.

Incitations allowing to boost research and development of new antibiotic molecules

The absence of recent findings in research and development of antibiotics, especially for Gram-negative bacteria, appears as a true and imminent risk for a public health crisis. Currently, an estimated 25,000 patients die every year in Europe, from nosocomial infection which no longer responds to any antibiotic treatment [9].

The pharmaceutical industry's lack of interest for research and development of antibiotics is explained by the fact that, in the current system, "antibiotics are not a good investment" when considering the cost of development, with a poor return on investment. There are several reasons for this:

- low volume of prescriptions, for short treatment courses (as opposed to treatments of chronic diseases);
- generic drug legislation and policy;
- legitimate wish to preserve the effectiveness of new molecules by keeping them for the treatment of MRB infections;
- relatively short life expectation of new molecules when confronted to the rapid evolution of resistance;

- price set by regulation agencies which does not take into account the effectiveness of antibiotics on the decrease of infection morbidity and mortality.

Antibiotherapy seems to be a domain where the "policy of generic drugs" has reached its limits. The principle was to decrease the cost of a drug to enhance its use. For antibiotics, supporting the use of generic drugs is contradictory with the wish to control their use which must no longer be systematic. The excessive availability of generic antibiotic drugs (3 years ago around 25 generic oral first generation cephalosporins were available on the market) and the "all generic" policy may have a perverse effect by trivializing the use of antibiotics. For the industry, this policy has probably played a negative role on research for true innovations, whereas today's research should focus on antibiotics targeting bacteria developing resistance in the future [10].

With this evidence, it is possible to suggest a number of incitations to boost research and development of antibiotic drugs. No single proposition will suffice to make the situation evolve. A selection and "a combination of these various propositions are needed". The development (and the marketing) of drugs has become a worldwide issue; the problem must be dealt with in a global way with concentration between European, North American, and South-East Asian authorities (and political powers).

The corner stone of these incitations is based on a "decrease of development and approval costs" for new molecules. New methods for the evaluation of antibiotics and propositions for the support of development by agencies (suggested in paragraph B) should limit this cost, as well as risks taken by manufacturers.

"Increasing the price of antibiotics" seems to be the easiest solution, especially for "niche" molecules. This proposition with which paying organisms cannot agree, could rapidly become a political choice, when faced with a large scale increase of mortality due to bacterial diseases.

It is currently difficult for a manufacturer to negotiate a high price if the one set by the drug used as comparator in a phase III study is low. The price of a new molecule could vary according to the real need for its use. This issue is especially true for "niche" molecules, the cost of which should evolve according to epidemiological needs. In the same manner to prevent a possible "over-charge", the price should be different whether marketing comes after the purchase of a patent or not.

Normalization of the price on the lowest European one after 5 years of use, for molecules in hospital retrocession to patients, should be reconsidered to preserve this antibiotic patrimony.

The cost of "old molecules" should be re-evaluated, especially for those deemed indispensables. A price renegotiation for molecules with a negative margin is also necessary and an increase of the price should be allowed for "essential" antibiotics and for those for which approval suppression was refused. The price of "old" molecules should also be adjusted when ecological circumstances impose their increased use.

On a national scale, the evaluation of medical service offered and its improvement should take into account the situations of need due to the severity of patients' infections. The "legislation" needs to be "modified" too. It seems

indispensable to extend the patent duration and the protection of approval indications. This prolonged protection could vary according to the planned volume of sales and/or time (for example, an initially "niche" molecule which would have new indications or whose use would become important because of an ecological issue).

Another possibility would be to give antibiotics "a special status" like the one attributed to orphan drugs (exclusive commercial rights for a given number of years, specific modalities of evaluation and price-setting).

Other incitations may be suggested in two other domains, "developing a grant system" and modifying "taxes".

The implementation of grants targeted on antibiotic treatments could support the development of academic research and biotechnology. These grants should become permanently available in time. They could also support the development of public or private partnerships (public or private hospital clinical research programs are often refused as a matter of principle, because of the notion that the manufacturer should pay).

Within the scope of support measures suggested during the development of a molecule, financial advances granted on results at the end of phases I and II could support the further development initiated in academic and/or biotechnological settings.

The possibility of government grant support should be studied on a broader scale.

It could be useful to create free access libraries, grouping molecules with a strong antibacterial potential, coming from academic, biotechnological, or even industrial research.

Tax reductions or credit could be awarded to laboratories investing in research for antibiotherapy. To prevent any "marketing temptation", these would be awarded before the approval rather than after. They could depend on the potential revenues, and be progressive if results allow progressing from phase I to phase II, and then phase III. They could vary according to the ecological context and the molecule's spectrum of activity. Finally, they could be re-evaluated if the new molecule is related to a rapid emergence of resistance.

Conclusion

The current European awareness of the issue works in favor of the elaboration of propositions, all the more as, on the political level, a legislative proposition with recommendations from European Union Council for antibiotherapy is being studied, and as, on the scientific level, a revision of European guidelines for the development of antibiotics is currently discussed at the EMEA.

Conflict of interest

None.

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Appendix A. Supplementary data

A French version of this article is available as a multimedia component. Supplementary material (pdf file) associated with this article can be found at <http://www.sciencedirect.com>, at [doi:10.1016/j.medmal.2010.01.007](https://doi.org/10.1016/j.medmal.2010.01.007) or online at the site [infectiologie.com](http://www.infectiologie.com) at the address below: <http://www.infectiologie.com/site/medias/documents/ATB/SauvegardeATB-SPLIF-09102009.pdf>.

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