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Marie-Cécile Ploy, Antoine Andremont, Bruno Valtier, Claire Le Jeunne, Catherine Dumartin, Didier Guillemot, Alain Bousquet-mélou, Christian Brun-Buisson, Bruno Coignard, Didier Concordet, et al.

THERAPIES

HEADING: GIENS WORKSHOPS 2019 / Translational research

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Antibiotic resistance: tools for effective translational research

Marie-Cécile Ploy[a,*], Antoine Andremont[b,] Bruno Valtier[c], Claire Le Jeunne[d], the participants of Giens XXXV Round Table « Translational research », Catherine Dumartin[e,f], Didier Guillemot[g,h], Alain Bousquet-Melou[i], Christian Brun-Buisson[g], Bruno Coignard[j], Didier Concordet[i], William Couet[k], Romain Guillaumou[l], Cyril Guyard[m], Evelyne Jouvin-Marche[n,o], Solen Kerneis[i,p], Mohamed Khelifa[q], Mourez Michaël[r], Marie-Clémence Verdier[s]

[a] *University Limoges, INSERM, CHU Limoges, RESINFIT, U1092, 87000 Limoges, France*

[b] *INSERM IAME UMR 1137, Paris, France*

[c] *Pfizer, hospital business unit, 75014 Paris, France*

[d] *Service de médecine interne, AP-HP, centre université de Paris, site Cochin, 75014 Paris, France*

[e] *Centre d'appui pour la prévention des infections associées aux soins de Nouvelle Aquitaine (CPias NA), CHU de Bordeaux, 33076 Bordeaux, France*

[f] *Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team Pharmacoepidemiology, UMR 1219, 33000 Bordeaux, France*

[g] *Inserm UMR 1181 « biostastistics, biomathematics, pharmacoepidemiology and infectious diseases » (B2PHI), Institut Pasteur, Univ. Versailles St Quentin, 75015 Paris, France*

[h] *AP-HP, Raymond Poincaré hospital, 92380 Garches, France*

[i] *INTHERES, université de Toulouse, INRA, ENVT, 31000 Toulouse, France*

[j] *Direction des maladies infectieuses, Santé publique France, 94410 Saint Maurice, France*

[k] *Inserm U1070, université de Poitiers, CHU de Poitiers, 86021 Poitiers, France*

[l] *Service de pharmacologie clinique et pharmacovigilance, AP-HM, 13005 Marseille, France*

[m] *Institut de recherche technologique Bioaster,69007 Lyon, France*

[n] *Université Grenoble Alpes, Inserm 1209, CNRS UMR 5309, institute for advanced biosciences, immunologie analytique des pathologies chroniques, site Santé, 38700 La Tronche, France*

[o] *Inserm, 75013 Paris, France*

[p] *Equipe mobile d'infectiologie, AP-HP, centre université de Paris, site Cohin, 75014 Paris, France*

[q] *Sanofi Aventis France, 94250 Gentilly, France*

[r] *Evotec ID Lyon, 1541 Avenue Marcel Mérieux, 69 289 Marcy l'Etoile, France*

[s] *Université Rennes, CHU de Rennes, service de pharmacologie, Inserm, CIC 1414, 35000 Rennes, France*

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*Corresponding author. CHU de Limoges, centre de biologie et de recherche en santé, laboratoire de bactériologie-virologie-hygiène, rue du Pr Bernard Descottes, 87025 Limoges, France.

E-mail adress: marie-cecile.ploy@unilim.fr (M.-C. Ploy)

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Summary

The rising emergence of bacterial resistances has led to a crisis which threatens human, animal and environmental health. The impact of the emergency is enormous in terms of public health and economics. Although there is a global awareness of the warnings and programmes supporting innovative actions to combat fight against antibiotic resistance, it must be admitted that proposed new antibiotics fail to find the economic profitability necessary for them to reach the market and become available for patients and the community. Moreover, it is necessary to develop tools/indicators to define effective interventions against antibiotic resistance. The work of the think-tank reported in this article concentrated on two aspects of translational research: – prevention and the impact on health of the antibiotic resistance issue, and – the specific requirements of clinical research leading to innovation in the fight against antibiotic resistance. This article, which reflects the thoughts of a group of French experts, proposes directly operational solutions which could be rapidly

implemented and radically transform the quality and quantity of our resources available for the combat.

Keywords: Innovation; Antibio-resistance; Impact; Stewardship; Microbiota

Introduction.

The antibiotic crisis which has followed the emergence of antibiotic resistance is high on the agendas of public health problems and solutions are urgently needed. In the years 2000-2010, serious warnings resulted in an increase in national and international initiatives to deal with the situation. Following these initiatives, translational research in this field was greatly stimulated and a large number of advances were made, as much in terms of new antibacterial candidates as in terms of alternative strategies to fight antibiotic-resistant bacteria [1]. Nevertheless, after a period of renewed interest in these developments, the pharmaceutical industry now shows little interest in this field. They have been discouraged by the poor stock market performances of emergent stakeholders, which culminated in the worst-case scenario of bankruptcy – as for example the case of Achaogen which developed a new antibiotic in accordance with current guidelines. It is for this reason that the director of CARB-X [2], a non-profit partnership of 500 million dollars dedicated to the development of new solutions to combat the antibiotic crisis, appeared pessimistic concerning the future of innovation in this domain unless new rules were defined. Translational research in the field of antibiotic resistance needs to bridge the gap between fundamental, innovative research in diagnosis, therapy, or preventive medicine and the clinical trials leading finally to practical therapeutic implementation. Nevertheless, certain steps in this continuum are currently ineffective, in particular the transition from pre-clinical studies to clinical development and later to market availability, primarily due to the lack of appropriate tools to evaluate the economic impact of these innovations [3].

Given this situation, it was considered timely to gather together French public and private stakeholders specialising in the combat against antibiotic resistance in order to discuss the

implementation of new tools to reverse the trend and enable this research to continue and develop. The methodology of this roundtable focused on the question of translational research by analysing existing data in the international literature on the subject enriched by the complementary experiences of the various participants.

In view of the complexity of this field of research, the roundtable concentrated its analyses on two aspects: i) antibiotic resistance : prevention and impact on health , and ii) the specific requirements of clinical research designed to lead to innovation in the fight against antibiotic resistance (new molecules, therapeutic alternatives).

The issue of antibiotic resistance: prevention and impact on health

Problem statement

To effectively prevent the emergence and spread of resistance genes and resistant bacteria in human and animal health, various measures were identified in the inter ministerial road map for controlling antibiotic resistance, launched in France in 2017 [4]. These included antibiotic stewardship programmes in humans and animals and the supervision of antibiotic consumption and bacterial resistance, in both the community and healthcare establishments, as well as the prevention of infections (including preventive vaccination and prevention of cross-contamination), including healthcare-associated infections in humans, and in animals, improvement in biosecurity to prevent transmission of pathogens, and thus reduce the use of antibiotics.

It is also of prime importance to communicate information on antibiotic resistance to the general population and healthcare personnel to improve awareness and a collective commitment of the general public so that each individual person feels concerned.

The analysis of the literature shows that the evaluation of the impact of these strategies suffers from several pitfalls concerning (i) the methodological quality of the studies and (ii) the indicators used to evaluate the impact of the interventions on human, animal and environmental health, including the

effect on the microbiota. In human, a recent review on the impact of antibiotic stewardship programmes in community and hospital settings thus showed the existence of numerous methodological biases in most published studies [5]: no randomisation, mainly single centre studies , retrospective with few evaluations of the clinical, or medico-economic impact. Moreover, very little attention has been given to the contribution of behavioural change strategies [6, 7] and of the role of artificial intelligence in this domain to date. The use of artificial intelligence tools would enable the development of therapeutic decision support algorithms or, in animals, the supervision of livestock to provide prompt detection of infections and thus reduce the number of animals requiring treatment.

In order to identify the most effective interventions in the combat against antibiotic resistance, it therefore appears essential to establish a database of studies including the assessment of their evidence levels. The definition of methodological standards could be based on the recommendations of consensus conferences [7] or existing checklists, adapted to the context of antibiotic resistance [8, 9]. An initiative along these lines is proposed by the Global AMR R&D HUB, an initiative arising from the G20 [10].

To evaluate the impact of strategies, outcome indicators are necessary. Numerous indicators have been proposed to measure, firstly, antibiotic use, and secondly, bacterial resistance. A European consensus was established recently concerning indicators for antibiotic consumption and bacterial resistance in humans and animals [11]. These indicators are very often quantitative, which has the advantage of being easy to collect, but they suffer from a lack of valence, in particular clinimetric, where antibiotic stewardship is concerned. They give a poor assessment of quality and do not allow to evaluate the link with a positive clinical and microbiological result for the individual patient or animal. For example, a count of the quantities of antibiotics used is not enough to evaluate the impact of the stewardship programmes in human medicine. The measurement is generally focused on the community or the hospital setting and the healthcare pathway is not taken into account, nor is the relevance of the treatment (related to the patient's pathology, local ecology, etc.). This data collection

may be completed by an indicator measuring prescriptions, which reflects prescriber behaviour more directly [12]. Moreover, the level of implementation on the ground of the guidelines published by the scientific societies, and also compliance (acceptability of an antibiotic stewardship team in human health, understanding of the relevance of the guidelines) are not always measured, limiting validity of the studies and whether they may be extrapolated. Of course, clinical and qualitative data are more difficult to collect and require cross referencing with different data. The use of IT systems is therefore a prerequisite for effective surveillance requiring interoperability and appropriate tools for the integration of surveillance data. The recent implementation of a Health data hub in France for this purpose could be very useful. The usefulness of combined indicators, used to summarise information concerning resistance and/or the use of antibiotics [9, 11-16], remains to be studied, as does the use of additional indicators as proposed in the report of the European programme Drive-AB [16-19], for example taking into account, both the quantities of antibiotics used and the number of patients treated. To date, very few studies with a methodology providing a high level of evidence have been published. This methodology thus requires developing as much to assess the impact of antibiotic stewardship programmes as to assess the hygiene measures set up to limit transmission of pathogens. This is because the relationship between the use of antibiotics and bacterial resistance is influenced by numerous factors, related, in particular, to the patient and to his pathologies, to the bacteria involved, to the antibiotics used in the patient and in his close contacts, as well as the infection control and prevention measures employed. It is best to use clinical and microbiological results to measure the impact of the interventions and to add secondary criteria concerning determinants and the processes (quantity and quality of antibiotic use, knowledge, compliance, conditions of implementation, etc.) [5]. If the experience of patients is taken into account this could provide additional information [20].

The use of modelling techniques, based on pooled data from previous studies may provide additional understanding of the complex interactions between measurements of prevention and antibiotic resistance, for better consideration of the various risk factors, to simulate the impact of

various scenarios and propose personalised prescribing aids. Lastly, the medico-economic impact has hardly been evaluated.

Recommendations

The working group recommends the following actions:

1. To improve methodology of antibiotic stewardship studies investigations by (i) promoting the conduct of evidence-based impact studies meeting methodological guidelines, (ii) the development of a medico-economic analytical methodology specific to strategies of antibiotic stewardship and prevention of infection and, (iii) the integration of implementation science in evaluation studies.
2. To define indicators of the impact of human, animal and environmental health strategies both in terms of clinical results as in terms of prevention of the emergence/spread of resistance, prescribing quality, compliance with actions and adaptation, basing this on the development of IT systems for automatic data collection/generation.
3. To develop medico-economic studies designed to measure the impact of the implemented actions.
4. To communicate knowledge gained from convincing interventions via evidence-based program registers (from scientific literature and ongoing research projects) on the subject of the combat against the antibiotic crisis.
5. To develop tools for personalised and/or precision prescribing (artificial intelligence, new diagnostics in human and animal health and for livestock).
6. To provide open access databases (including biobanks, omics, data/samples of microbiome and clinical samples), linked to the Health data hub.

Clinical research innovations needed to combat antibiotic resistance

Problem statement

Numerous start-ups have performed significant research work and have developed various therapeutic innovations. Nevertheless, the difficulties related to the requirements of the Agencies which grant marketing authorisations, coupled with the lack of appropriate economic models providing sufficient profitability have led to a series of failures and declining interest of industrials for this sector of bacterial infections. The recent bankruptcy of Achaogen is an eloquent example. The clinical development of a product requires a considerable investment estimated at an average of 850 million dollars [21], and the likelihood of successful marketing remains low: of the antibacterial molecules in pre-clinical testing only 1.5% complete their development [22].

One of the first hurdles is the design of clinical trials for which the current standard is that of equivalence or non-inferiority. However this standard does not help the marketing of new medicines with truly superior efficacy on an individual level. Although in theory trials showing superiority would be desirable, they would be impossible for industrials to perform because too long and costly, in particular due to the fact of having to include a majority of patients infected with multi-resistant bacteria, and for whom there is no effective standard treatment nor rapid diagnostic tools enabling early inclusion and randomisation. Other models must therefore be invented taking into account alternative outcome criteria or by developing the use of complementary post-marketing studies [23]. Adaptation of the methods for evaluating new therapeutics, diagnostic tests or preventive strategies is urgently needed and should take into account the collective added value of innovations, and this for both human and animal use. These new criteria could include the reduction in the risk of emergence or dissemination of resistance, the impact on the microbiota including the risks of secondary infections linked to dysbiosis, and the impact on the environment [24], with the necessary definition of indicators and outcome criteria. Thus, the impact on the exposed individual would no longer be the sole criterion, the population dimension would become a criteria of interest to gain market access, thus enabling anti-bacterial innovations to be evaluated as eco-evo-drugs according to a principle already evoked in 2011 [25]. However, the pharmacokinetic/pharmacodynamic (PK/PD)

parameters on which marketing authorisations are currently based fail to take into account the impact which new products have on resistance. Modelling tools exist [26] and should be used in the evaluation of innovations. It is therefore necessary to include data on antibiotic exposure and resistance in the results of clinical trials to use these modelling techniques. Lastly, current pre-clinical and clinical development processes are inappropriate for innovations such as modulators of the microbiota, anti-biofilms, or certain medical devices.

Revising the design of clinical trials of products intended to resolve the antibiotic crisis with these new tools/criteria also requires re-structuration and professionalisation of operational clinical research in human health and in animal health. together with regulation Agencies.

Finally, to re-dynamize the industrial sector in this domain, new economic models must also be thought of. Whilst effective and well-funded so-called “Push” incentives have indeed been developed (CARB-X, GARDP, JPIAMR, IMI, Wellcome Trust, Novo REPAIR programmes,…) to finance preliminary research and pre-clinical models as well as supporting the marketing phases (BPI France) [27], there is a lack of “Pull” incentives to help market access and a return on investment for industrials or other innovative economic mechanisms based on new methods of reimbursement such as are being developed in Sweden [28], or in the United Kingdom [29].

Recommendations

The working group recommends the following actions:

1. To reinvent economic models for antibacterial agents at European level by means of Pull financial incentives to complement the numerous Push initiatives currently available and also by measuring and supporting the “ecological medicine” aspect of antibiotics.

2. To improve clinical trial design by promoting population superiority trials which measure the efficacy of interventions and innovations in “real life population”.

3. In the case of non-inferiority trials, evaluate the collective added-value (breaking resistance, impact on the microbiota, impact on the environment with definitions of new indicators and outcome criteria), and all this applied to human, animal and environmental health.

4. To optimise PK/PD (therapeutic and resistance) modelling tools as early as the pre-clinical models and to use the results of this in regulatory development.

5. To organise national clinical research networks (human and animal), already operational in the fight against antibiotic resistance with the aim of having an impact on the European scene, based on existing networks as CLIN-Net, RENARCI, CRICS-TRIGGERSEP [30, 31, 32].

Taken as a whole these recommendations will lead to profound changes in the methods used to combat the antibiotic crisis and to fight antibiotic resistance.

In view of the complexity of the question of antibiotic resistance which must include the 3 domains of life: human, animal, and the environment, it is obvious that translational research cannot be effective until the need to take a multidisciplinary approach is recognised, involving: clinicians, veterinarians, methodologists, microbiologists, chemists, pharmacologists, pharmacists, dentists, biostatisticians/bioinformaticians, the human and social sciences, economists, livestock farmers, patients, citizens.

It is therefore necessary:

- to integrate antibacterial research strategies into a global and coordinated, "One health" initiative, addressing human-animal-environmental challenges;
- to supply the development pipeline with new innovative curative, preventive or diagnostic tools;
- to bring about a paradigm shift and to rethink the clinical development pipeline to facilitate market access for medicines or innovative tools and also to ensure their profitability and accessibility.

Disclosure of interest

AA Co-founder of Da Volterra

Other authors have no conflict of interest to declare linked to this article

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