ANTIBIOTIC RESISTANCE IN LEBANON

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Over the last 50 years, antibiotics have contributed to one of the greatest advances in medicine. Today, however, the emergence of pathogenic bacteria that have become resistant to antibiotics and their spread in the human population is a public health concern *(1)*. The often inappropriate exposure of the population to antibiotics and the inter-individual transmission of resistant strains are the major determinants of the emergence and increase of bacterial resistance to antibiotics. Thus, overuse and misuse of antibiotics in the veterinary, livestock, agriculture and medical (hospital and community) sectors has led to increasing levels of antimicrobial resistance. This problem is even more important since the numerous factors leading to the emergence and spread of multi-resistant strains remain uncontrollable today, such as the inappropriate use of antibiotics (exaggerated global use, incomplete or incorrect therapeutic strategies, availability of antibiotics without prescription, etc.), the failure of infection control policies in hospitals and the widespread use of antibiotics in agriculture *(2-4)*. This problem is not exclusive to developed countries; developing countries also suffer in a more accentuated way, given the chaotic use of antibiotics at all levels and the presence of suboptimal or falsified medicinal preparation *(5)*.

Lebanon: A state-of-the-art developing country in an epidemiological transition

Lebanon is a developing country, classified as a middle-income country by the World Health Organization (WHO) *(6)* and an upper-middle-income country by the World Bank (WB) *(7)*.

Sociodemographic data

In 2007, the population residing in Lebanon was estimated at 3,759,136 inhabitants, increasing to 4,822,000 in 2013, of which 21% were aged less than 15 years and 12% more than 60 years *(7)*. This dramatic increase was due to the influx of Syrian refugees following the declaration of war in Syria in 2012, which caused a large budget deficit aggravated by the withdrawal of the international organizations that had pledged to participate in the financing *(8)*. Table 1 summarizes some development indicators issued in 2007.

Distribution of diseases

Lebanon is a country with transition in health, i.e., a gradual decline in infectious diseases and an increase in chronic diseases in relation to the ageing of the population. In terms of infectious diseases, 7% of deaths in children aged less than five are related to acute respiratory infections, 2% to diarrhoea and 4% to neonatal sepsis *(9)*. Infectious respiratory diseases occupy the seventh place in terms of mortality (2.6%) *(9)*. At the same time, Lebanon also has quite high levels of resistance to antibiotics, a multifactorial global problem *(11-16)*.

The healthcare system

The majority of the Lebanese healthcare system is private, with conflicting characteristics at several levels *(6, 7)*:

- Social coverage: despite collective solidarity and private insurance, 51.7% of the population has no social security coverage.
- Funding: care is financed through various means (public, semi-public and private); however, households are the major mode of financing *(8)*.
- Public sector: the State, represented by the Ministry of Public Health (MOPH), plays the role of a third-party payer instead of being limited to the regulation of the healthcare system.

However, patients, irrespective of their social status, have access to public and private care *(17)*.

Access to medications

Expensive drugs are distributed by the MOPH *(8)*. As for other medicines, they are available in community pharmacies,

Table 1: **Some indicators of development**

Illiteracy rate	5,2% *(9)*
Mortality rate of children less than 5 years	1% *(10)*
Child mortality rate	0,9% *(10)*
Population living in urban areas	88% *(7)*
Access to drinking water and sanitation	100% *(7)*

distributed throughout the Lebanese territory *(18)* and constituting an essential selling point for medicines in Lebanon, in addition to primary healthcare centres run by the State and various non-governmental organizations (NGOs) *(19)*. Antibiotics constitute an important part of available medications and they are available without medical prescription *(20)*.

Antibiotic resistance and overuse in human clinical practice

Antimicrobial resistance (AMR) is a natural biological phenomenon that has been amplified due to poorly controlled or abusive use of products made available to humans. Resistance reduces the effect of once-life-saving medicines and jeopardizes the protection of future infected individuals.

Community antibiotics consumption

Resistance is established due to the overuse or misuse of antibiotics; the patients sometimes ask for medicines not intended for their medical condition and the health services tend to overprescribe them or are happy to provide them. Not to mention the aggressive commercialization by industries and pharmaceutical companies that sometimes push doctors to prescribe newly marketed powerful antibiotics.

The worsening of AMR is due to social causes that are paradoxically different in different countries. In some cases – especially in poor countries – it is the drug's underutilization that encourages the development of resistance. For example, when patients cannot afford to buy enough medicines for a full course of treatment or rely on counterfeit medicines (including products with little or no active ingredients) obtained on the black market, bacteria are killed but the most resistant succeed in surviving and breeding *(1, 5, 21, 22)*.

In many countries, especially in the developing world, antibiotics can be purchased without a prescription. In addition, the overuse of antibiotics becomes integrated into the local culture, such as those used to prevent diarrhoea after eating suspected soiled foods or as a prophylaxis for sexually transmitted diseases. Not to mention that the most-used antibiotics, inexpensive and popular in developing countries, are broad-spectrum *(5, 21, 22)*.

A cross-sectional study was conducted in Lebanon to identify the factors that influence the knowledge and practice associated with the use of antibiotics. False ideas and inappropriate practices have been found in parents of school-aged children. For example, 33.9% of parents consider antibiotics to be useful in treating colds in children and 36.2% believe that antibiotics accelerate their recovery. In addition, 37.9% of respondents thought that antibiotics are used to treat viral infections. About 20% of the participants believed they could reduce the dose of antibiotics if the child improved. The low educational and socioeconomic levels of parents were identified as factors significantly associated with poor knowledge and misuse. Despite clear evidence on the limited role of antibiotics in upper respiratory infections, parents in Lebanon continue to misuse them *(23)*.

Another study was conducted in Beirut and its suburbs to assess the determinants of self-medication with antibiotics in the general population among buyers of antibiotics in pharmacies. Of the 319 participants, 42% reported purchasing antibiotics without a prescription, based on the advice of the pharmacist in 18.8% of the cases. The most frequently cited reason was the saving of time (39.7%). Self-medication was significantly higher in men and more common in those with sore throats and unaware of the dangers of using antibiotics. In addition, self-medication was associated with amoxicillin and inversely related to the quinolones, cephalosporins and other classes of antibiotics *(24)*.

Overuse due to inappropriate prescription

The way antibiotics are prescribed is a determining cause of resistance. In hospitals, inadequate antibiotic use is estimated to be the case more than 50% of the time. More than 40% of the antibiotic prescriptions are administered for viral diseases. Stopping antibiotic treatments when the symptoms disappear before the pathogen is eliminated is very common *(25, 26)*.

A study to evaluate the relevance of prescribing antibiotics by doctors not specialized in infectious diseases was carried out in community pharmacies in Lebanon in patients who presented with an antibiotic prescription. The results showed that the most frequently prescribed antibiotics were cephalosporins (82%) and that almost half of the antibiotics were prescribed for respiratory tract infections (41%). The study also showed that the choice of the prescribed antibiotic was appropriate in 61.5% of the cases studied, while the prescribed dose and duration of treatment were inadequate in 52% and 64%, respectively. This study found a high prevalence of inappropriate antibiotic prescriptions in Lebanon *(27)*.

Antibiotic resistance of animal origin

The overuse of antibiotics in the veterinary and zootechnique fields has led to a problem of antibiotic resistance in meat in a context where the interaction of human populations, animal populations in the agricultural sector and the environment has

become more complex *(2)*. Although there is a general consensus that meat consumption is closely correlated with antibiotic resistance, epidemiological evidence is largely lacking *(28-30)*. The relationship between the use of antibiotics and the appearance and spread of resistance is complex, but knowledge accumulates gradually. More advanced analyses will only be possible when data are readily available. It will be required first to monitor the use of antibiotics in farms, slaughterhouses, hospitals and their concentrations in the environment, in addition to rationalizing their use. Unfortunately in Lebanon, the system of importing, distributing, selling and controlling the veterinary medicinal product is under the sole control of the Ministry of Agriculture *(31)*. Thus, the pharmacist and the Lebanese Order of Pharmacists play no role in the circuit of these medicines.

Description of ineffective initiatives

In Lebanon, there is a National Antibiotic Resistance Committee at the MOPH. This committee has been working for more than a decade to develop a national plan of action to combat the emergence of antibiotic resistance. Despite the WHO guidelines in this regard, the plan is yet to emerge. On the other hand, at the hospital level, the application of accreditation standards has made it possible to create Committees for the Control of Nosocomial Infections (CLIN) and to establish policies and procedures to safeguard the most "valuable" antibiotics in the majority of hospitals. However, these measures remain ineffective in curbing antibiotic resistance in Lebanon *(32)*.

Consequences

Bacterial resistance remains a threatening reality for the future, which makes therapeutic choices, both in the hospital and in the community, complex and uncertain *(1)*. Moreover, this resistance seriously compromises the quality of care and the safety of patients and thus leads doctors to prescribe widely the few molecules that are still active, often the most recent and/or wide-spectrum molecules. Finally, antibiotic resistance has its weight in terms of morbidity and mortality and more particularly in frail patients (aged, immunocompromised...) *(1-3, 33)*.

In hospital practice, the increase in antibiotic resistance results in an increase in morbidity, mortality, and hospitalization cost; it often leads to the appearance of microorganisms resistant to all available antibiotics. The fear of a therapeutic "dead end" presupposes the control of this public health problem representing a real challenge for clinicians, microbiologists and health authorities *(34-38)*.

The Lebanese Society of Infectious Diseases conducted a retrospective study to describe the antimicrobial susceptibility patterns of bacterial isolates in Lebanon. The data were based on registries extracted from the bacteriological laboratories of 16 Lebanese hospitals between January 2011 and December 2013. The sensitivity results of a total of 20,684 Gram-positive bacteria and 55,594 Gram-negative were analysed. The prevalence of methicillin-resistant *Staphylococcus aureus* was 27.6% and that of *Enterococcus species (spp)* with vancomycin was 1%. *Streptococcus pneumoniae* had susceptibility rates of 46% to oxacillin, 63% to erythromycin and 98% to levofloxacin. *Streptococcus pyogenes* had a sensitivity rate of 94% to erythromycin and 95% to clindamycin. The mean ampicillin sensitivity rate of *Haemophilus influenzae*, *Salmonella spp*, and *Shigella spp* isolates was 79%, 81.3% and 62.2%, respectively. The production rate of extended spectrum beta-lactamase for *Escherichia coli* was 32.3% and for *Klebsiella spp* 29.2%. *Acinetobacter spp* showed high resistance to most antimicrobials, with low colistin resistance (17.1%). The sensitivity of *Pseudomonas spp* to piperacillin-tazobactam and imipenem was less than 80% (79.7% and 72.8%, respectively). This study provided valuable data specific to the Lebanese population that could guide the choice of antimicrobials in Lebanon and assist in establishing an AMR surveillance system following the implementation of national standardization of laboratory methods and data entry *(32)*.

The emergence of carbapenem-resistant strains has also been the subject of numerous Lebanese studies. The prevalence of carbapenem-resistant enterobacterial strains was estimated to be 1.2% and 1.6% *(14, 39)*, the majority of these strains being *E. coli* and *K. pneumoniae*. The molecular characterization of this resistance made it possible to identify that OXA-48 type carbapenemases were the most frequently identified *(39-44)*.

Strategies and control policies of antibiotic resistance

Although the problem of AMR cannot be completely eradicated, the implementation of strategies to limit its threat and minimize its impact on human and animal health is an absolute necessity *(38)*. This strategy could be designed as part of a national plan to fight against antibiotic resistance based on the WHO's regional and global plans. Obviously, it requires the intervention of experts from different disciplines as well as inter-organizational cooperation at the local (hospital or other), national and international levels, all under the aegis of the Ministry of Public Health.

The intervention should be carried out at several levels with the main objective of reducing the development and spread of resistance. In particular, the education and culture of the general population and health personnel (in university and post-graduate training), the application of antibiotic preservation

and hygiene rules in hospitals and other institutions, strengthening the pharmaceutical companies' marketing code of ethics, reinforcing the laws to access antibiotics in human and veterinary medicine and generating regular surveillance data at all levels (bacteria, infections, consumption, morbidity and mortality) *(33, 38, 45-50)*.

Responsibilities are multiple and go from the registration of the antibiotic to its production (pharmaceutical industry), its control, its distribution (pharmacist) and its medical and veterinary use. Accountability of all partners is imperative. It must pass through in respect of the legislation and an awareness of the challenges both for human health and for the livestock. Preventive measures are known and have already shown their effectiveness. This involves combining antibiotic control, good management of the risk of transmission, close monitoring of the evolution of AMR, all thanks to the active knowledge and know-how of the experts in antibiotic resistance (education, training and expertise) *(37, 38, 45-48)*.

Mastering antibiotic therapy

Mastering antibiotic therapy is based on the optimization of prescribing practices by implementing rapid and reliable diagnosis tools and treatment recommendations that derive from local and regional ecology, allowing effective empirical treatment, pending the susceptibility results specific to each identified strain.

- **Diagnostic tools of the resistance.** The clinical microbiology laboratory plays an essential role in antimicrobial management by providing data on patient-specific culture and susceptibility rates to optimize and personalize individual antimicrobial management *(46)*.

  Some Lebanese laboratories have molecular biology tools (mainly by Polymerase Chain Reaction or PCR) in addition to their traditional techniques for the determination of antibiograms, which makes it possible to precisely identify the type of bacterium in question and its microbial load (qualitative and quantitative approach).

- **Rational use of antibiotics.** Promoting the rational use of antimicrobials is an essential part of antimicrobial management. Strategies should thus ensure optimal selection of the antibiotics still available which could induce better clinical outcomes for the treatment or prevention of infection with minimal toxicity to the patient and minimal impact in terms of inducing resistance *(45, 46, 48)*. In order to achieve this, it would be necessary to reduce the overuse of antibiotics on the one hand and to optimize their effectiveness in hospitalized patients on the other. To these strategies, we must add some recommendations related to the administration of antibiotics: dosage and rate of administration, dose adjustment in case of renal or hepatic failure, optimal duration of treatment, undesirable effects and drug interactions *(33)*.

(a) Protocols and recommendations (38, 46)

It is clear that the multidisciplinary development of evidence-based guidelines based on microbiology and local and regional resistance data can improve the use of antimicrobials. These recommendations should be inspired by those of the world's leading infectious diseases societies and regularly updated in response to epidemiological evidence of resistance.

(b) Restriction policies/rotation/Association of Antibiotics (49, 51-53)

Some Lebanese institutions have opted for different strategies to control the overuse of antibiotics, including restriction, rotation or combinations of antibiotics. However, in the absence of a national plan, each hospital has adopted its own strategy within the local nosocomial infection control committee. For example, some hospitals have established restrictive lists of antibiotics or classes of antibiotics. These restriction policies concern broad-spectrum antibiotics (such as carbapenems), antibiotics that can induce rapid emergence of resistance (such as fluoroquinolones) or antibiotics of known toxicity (such as aminoglycosides). In addition, the rotation policy consists of proscribing an antibiotic (or class of antibiotics) for a fixed period of time with a subsequent reintroduction, which could lead to a reduction in resistance to antibiotics affected by the rotation. Finally, the combination of antibiotics is of particular interest in certain clinical contexts, particularly in the empirical treatment of immunosuppressed patients or those at risk of carrying multiresistance. Although the results of studies evaluating the impact of these strategies on the reduction of the emergence of resistance are still not completely conclusive, their application in the context of a global approach could be interesting.

(c) Evaluation of antibiotics' indications by specialists

In addition to other measures, some hospitals have adopted the strategy of evaluating indications and prescriptions by specialists requiring a counter-signature of an infectious disease specialist for any dispensation of a broad-spectrum antibiotic. The purpose of this measure is to condition the prescription of certain antibiotics by the advice of an infectious disease specialist. Many studies have shown that inadequate antibiotic therapy is less likely in infected patients treated with an infectious disease agent. In addition, an infectious disease intervention was associated with a reduction in the use of broad-spectrum antibiotics, a more rapid relay by the oral route and, as a part of a multidisciplinary effort, a reduction in

nosocomial infections with multiresistant germs and therefore a reduction in treatment costs.

Adequate management of transmission risk

Adequate infection prevention and control measures are essential to minimize the risk of infection and to limit the occurrence and spread of multidrug-resistant organisms in humans and animals.

Thus, in a strategy to control hospital infections with multiresistant bacteria, the identification of patients carrying these bacteria is essential. For example, many Lebanese hospitals have adopted the systematic search for human multiresistance reservoirs using rectal and nasal swabs when patients are admitted to a hospital centre, in particular in an intensive care unit or intensive medical care. Patients identified as colonized by multidrug-resistant bacteria will be reinforced with technical and geographic isolation measures (with the mention of "Patient to be isolated") and will even be candidates for antibiotic chemo-decontamination.

Surveillance of antibiotic resistance and evaluation of the impact of control policies

In parallel with the development of local strategies for the management of AMR, programmes must establish the means to monitor the measures and policies put in place. The Lebanese system should constitute a database of the evolution of the susceptibility profiles, as well as the emergence of resistant strains. This data bank can be enhanced by integrating data from molecular and epidemiological studies. Indeed, the molecular characterization of resistance gives valuable information regarding bacterial strains circulating in a specific hospital or national environment and above all makes it possible to identify homologies between human, animal and environmental strains, as it has been done by some Lebanese teams *(12, 54-56)*.

Reinforce education and training about antibiotic resistance

Education is an essential element of any programme aimed at influencing prescriptive behaviour and can provide a knowledge base that will improve and increase the acceptance and implementation of antibiotic resistance reduction strategies *(38, 46)*. However, according to international recommendations, education alone, without incorporation of active intervention, is only marginally effective in changing antimicrobial prescribing practices and has no sustained impact *(38, 46)*. Basic and continuing education for the prescription of antibiotics can be carried out through a variety of interventions: presentations by experts inside or outside the institution, audiovisual media, periodic communication of data on the use of antibiotics, development of clinical recommendations, etc.

Conclusions

In Lebanon, many actions have been undertaken both in the surveillance of resistance and in the prevention of transmission of resistant bacteria in Lebanese health institutions. However, much remains to be done in order to promote a better use of antibiotics. Empowering the population to consume and manage antibiotics and reduce their misuse cannot happen overnight. It will take time and goodwill, but above all commitment. Indeed, even if legislations and recommendations exist, they often remain insufficiently applied. The involvement of a wide range of experts (including infectious disease specialists, pharmacists, clinical pharmacologists, clinical microbiologists, hygienists and hospital epidemiologists) and the public as part of a broader action plan to change practises is required. Curbing the resistance of bacteria as a consequence of the application of a national plan in this regard is expected. ■

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