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Review

Acinetobacter spp in a Third World Country with Socio-economic and Immigrants Challenges

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Abstract

Introduction: In the last decade, *Acinetobacter* species have taken a major public health concern. This is mainly due the increased resistance to a wide range of antibiotics causing treatment challenges. In view of the constant population mobilization and the economic crisis that Lebanon is currently facing, it becomes a necessity to re-evaluate the real threat of *Acinetobacter* spp and its implication in the one health.

Methodology: This review was conducted through the analysis of 45 research papers and reports pertaining to *Acinetobacter* spp performed in Lebanon. More than 82% of the papers consulted were published in international journals and more than 70 percent of them had received impact factor.

Results: An in depth description of the involvement of this organism in human infection and its role as potential pathogen or simple colonizer was performed. In addition, the different aspects of resistance, mostly to carbapenems and colistin was studied and summarized. While in animals and environment, susceptible strains were mostly isolated, OXA-23/OXA-24 were predominant in humans. Recently, NDM-1 producing *Acinetobacter* spp was detected in a Syrian refugee which then was reported in Lebanese patients. The bacterial identification procedures are non-systematic and not always reliable in the Lebanese studies presenting sometimes discrepancies an inconsistency.

Conclusion: *Acinetobacter* is commonly isolated Lebanon. In view of the spread of resistance among these isolated and their dissemination, Infection control measures attempting to control the spread of this genus in and outside hospitals are lacking and thus require more attention and stewardship activities.

Key words: *Acinetobacter*; bacterial resistance; carbapenems; oxacillinases; epidemiology.

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Introduction

In the last decades, the dissemination of antimicrobial resistance in Gram-negative bacilli (GNB) has caused major public health challenges worldwide [1]. Among others, *Acinetobacter* species are of special interest. This organism constitutes a complex saprophytic genus comprising a group of non-fermentative, facultatively anaerobic, Gram-negative coccobacilli. *Acinetobacter* spp are ubiquitous in nature being widely isolated from soil, wastewater, vegetables as well as humans and animals' skin [2]. The wide distribution of *Acinetobacter* species in different environments is mostly due to their ability to withstand desiccation, starvation and to survive on inanimate surfaces [3]. The *Acinetobacter* genus involves pathogenic and non-pathogenic species with *Acinetobacter baumannii* being the most common one implicated in hospital acquired infections especially in immunocompromised patients and to a lesser extent in community acquired ones [4]. Genotypically speaking, international clones I and II dominate the nosocomial outbreaks caused by this species worldwide [5]. Besides *A. baumannii*, there are increasing reports worldwide, highlighting the clinical relevance of other species such as *Acinetobacter pitii*, *Acinetobacter nosocomialis* and *Acinetobacter calcoaceticus* [4]. These species are difficult to be differentiated using the classical biochemical identification methods [6]. Species of *Acinetobacter* are known for their natural resistance to a wide range of clinically important antibiotics including 1st and 2nd generation cephalosporins and ertapenem [6]. Furthermore, the acquired resistance in these species is complex and involves an inter-play of several mechanisms: a) production of wide spectrum

beta lactamases, notably class D oxacillinases and to a lesser extent class A and B carbapenemases, b) reduced expression of outer membrane proteins such as CarO and OprD and c) over-expression of efflux pumps including AdeABC belonging to the resistance nodulation cell division family; this latter mediates resistance toward beta-lactam and non-beta-lactam antibiotics including fluoroquinolones, aminoglycosides, erythromycin and chloramphenicol [2]. More recently, colistin resistance has also emerged in *A. baumannii* complicating thus further the clinical situation [7]. *Acinetobacter* spp is increasingly implicated in veterinary medicine as an emerging pathogen; cases have been reported in Switzerland and Germany [8]. Asymptomatic carriage of *A. baumannii* was also reported in livestock, companion animals, lice and arthropods [4]. Other clinically important species including *A. pittii, A. nosocomialis, A. calcoaceticus* and *Acinetobacter lwoffii* were detected in vegetables and dairy products [9].

In Lebanon, studies on Gram negative bacilli (GNB) have shown the wide production of beta lactamases [10]. One study conducted in the north of Lebanon, has shown that in 2009-2012, 28% and 9% of bacteremia episodes in neutropenic patients were caused by 3rd generation cephalosporins and carbapenem resistant GNB respectively [1]. More recently, a countryside study conducted in 11 Lebanese hospitals revealed 1.2%, 41% and 88% of Enterobacteriaceae, *Pseudomonas* spp and *A. baumannii* respectively, were carbapenem non-susceptible [10]. Enterobacteriaceae isolates harbored mainly the OXA-48 gene, whereas VIM-2, IMP-2 and IMP-1 were more prevalent in *Pseudomonas* spp. Among *A. baumannii* strains, OXA-23 and GES-11 were most commonly detected [10]. A recent nationwide study done by the Lebanese Society of Infectious Diseases (LSID) has shown that the rate of imipenem resistance in *Acinetobacter* species have significantly increased from 57.6% in 2011 to 84.5% in 2013 [11]. The identification of *Acinetobacter* species in most of these studies is done using standard microbiological techniques [12]. While in the clinical reports, *A. baumannii* was the most commonly identified specie; in environmental studies that mostly used molecular techniques a wider variety of *Acinetobacter* species was reported [8]. As *Acinetobacter* spp are generally known to originate from the environment, their identification is not as simple as it looks to be. Standard microbiological phenotypic as well as biochemical techniques are not highly reliable in view of the complexity of this genus [6]. This puts a question mark on the accuracy of the numbers and percentages of *Acinetobacter* reported as *A. baumannii*. Subsequently, a false impression about the real occurrence of this specie might be given. In view of the recent demographic and socio-economic challenges imposed on the middle eastern region over the last 10 years, it is expected that the epidemiology of resistant *Acinetobacter* species would suffer significant changes under the pressure of continuous population mobilization and immigration. We attempt in this review to assess the real threat posed by *Acinetobacter* species and its implications on the clinical setting as well as in animals and environment in Lebanon; a Middle Eastern country with variable degrees of healthcare services and a significant burden of refugees.

Acinetobacter baumannii in Lebanon: a real threat or an over-estimated colonizer?

Acinetobacter species has been known since the early 1980s to be among the most common Gram-negative bacilli causing nosocomial infections in Lebanon [13]. In 2004, multi-drug resistant (MDR) *A. baumannii* became a common isolate detected in the microbiology Laboratory of the Saint George Hospital in Beirut, mostly from ICU patients. In this report, molecular typing of isolates revealed one major PFGE pattern suggesting a clonal spread of this bacterium in the clinical setting [14]. *A. baumannii* in Lebanon was mostly implicated in ventilator associated pneumoniae [15,16], urinary tract, intra-abdominal, blood and wound infections [17-19]. Furthermore, unique cases of necrotizing fasciitis caused by multi-drug resistant *A. baumannii* were also reported [20,21]. In one of the aforementioned necrotizing fasciitis cases, the strain was only sensitive to amikacin and polymyxin, challenging therefore the available treatment [21]. Besides *A. baumannii*, other species in this genus such as *A. junii* and *A. lwoffii* were also reported in the Lebanese clinical settings [17]. Kanj *et al.* associated *Acinetobacter anitratus* bacteremia to an early relapse of thrombotic thrombocytopenic purpura in a 58 years old male during plasma exchange therapy in 2003 [22]. On the other hand, *A. pittii* was detected in the urine culture of a four-month-old child as well as from febrile gastroenteritis infected patient [23].

Apparently, the aforementioned studies showed that *A. baumannii* strains are highly prevalent, but endemic in the Lebanese clinical settings. Several issues could be raised here: what about the co-isolation of other Gram-negative bacilli from the site of infection such as *P. aeruginosa* and *E. coli*? Is the threat attributed to *A. baumannii* over-estimated in view of the virulence and

pathogenicity of this genus? What about non-*baumannii Acinetobacter* species? Are identification procedures to the species level reliable? All this raises a big question mark about the real epidemiology of this organism in Lebanon. For instance, in their study, Kanafani *et al.* showed that among the most common organisms causing ventilator associated pneumonia were *A. anitratus* It is the same as A. baumannii but also *Pseudomonas aeruginosa*; the difference between the number of isolates was not significant (11 vs 8 isolates, respectively) [16]. Similarly, Awad *et al.*, reported close prevalence of *P. aeruginosa* (31%) and *A. baumannii* (37%) isolated from ventilator associated pneumoniae affected patients in the intensive care unit [15]. In another study, *Acinetobacter* spp along with *Candida* and *Escherichia coli* predominated in catheter associated urinary tract infections [18]. In intra-abdominal and urinary tract infections, *Acinetobacter* spp was not among the most common causative agents [19]. Indeed, the prevalence of this bacterium was comparable to *P. aeruginosa* [19]. Moreover, Chamoun *et al.* conducted a nationwide study where microbiological data were retrieved from 16 different hospitals across Lebanon from January 2011 till December 2013. This study showed that the most common Gram-negative bacillus causing nosocomial infections was *E. coli* followed by *P. aeruginosa* and *Klebsiella* spp [24], showing a secondary involvement of *A. baumannii.*

As for clinical outcomes, Jurdak *et al.* conducted a study where the mortality rate was assessed in patients with nosocomial pneumoniae admitted to the intensive care unit in a tertiary care center in Lebanon. Statistical analysis showed that the only significant differences between survivals and deceased were the duration of mechanical ventilation and the patient's age [25]. Another study conducted at the American University of Beirut Medical Center showed that multi-drug resistant *A. baumannii* infections resulted in a high mortality rate among ICU patients ranging from 52% to 66% between 2007 and 2014. Although not statistically significant, the complications due to *A. baumannii* infections were more correlated with the resistant strains than the susceptible ones, except for the acute respiratory distress syndrome. Despite all this, the attributable mortality rates could not have been calculated since these latter were more likely seen in older patients i.e. those with invasive device use, trauma, multiple co-morbidities and cancer [17]. One study, addressing patients with neutropenic fever have found that increased in-hospital mortality rate was associated with the duration of neutropenia and treatment modification for clinical deterioration [26]. Moreover, in concordance with previous worldwide studies, Ballouz *et al.* found that prolonged hospital stay that is often associated with a loss of functionality, as well as antibiotic and steroid exposure especially in critically ill patients, increases the risk of exhibiting *A. baumannii* bacteremia with poor outcome [27]. Dahdouh *et al.* conducted a study on ninetyfive *A. baumannii* strains isolated from a tertiary care center in Beirut and showed that their virulence profiles were highly variable and without a specific pattern [28]. In addition, no specific association was observed between resistance patterns in these isolates and their virulence profiles. The relationship between different virulence factors including resistance is highly complex in *A. baumannii* species and requires more investigations [28]. All of this might suggest that the pathogenicity attributed to *A. baumannii* might have been over-estimated over the past years.

Identifying *Acinetobacter* to the specie level is another concern in the Lebanese hospitals. Indeed, the majority of the clinical laboratories perform biochemical identification. This methodology has poor specificity and cannot differentiate between different *Acinetobacter* species including *A. baumannii*, *A. pittii*, *A. nosocomialis* and *A. calcoaceticus* [6]. This is mainly due to their close phenotypic and genetic relatedness [6]. Non *baumannii* species differ from *A. baumannii* in terms of antibiotic susceptibility [29]. Lee *et al.* found that non *baumannii* strains were more resistant to colistin than their counterparts; for instance, *Acinetobacter* genomospecies 14TU are shown to have natural resistance to colistin [29]. One study conducted in Japan, used MALDI-TOF for the identification of *Acinetobacter* spp isolated from blood cultures. In this study, 13 different species of *Acinetobacter* were identified. Surprisingly, the incidence of *A. pittii* exceeded that of *A. baumannii* (34.1% vs 17.9% respectively) [30]. In view of this, the accurate identification of *Acinetobacter* spp is instrumental for the appropriate management of the infection and for a more rational judgement of the real threat imposed by *baumannii* and non *baumannii Acinetobacter* as per the prevalence, clinical outcome and level of antibiotic resistance.

Epidemiology of carbapenem resistant *Acinetobacter* species in Lebanon

Humans

As mentioned earlier, *Acinetobacter* species are naturally resistant to a variety of clinically important antimicrobial agents. In addition, they have acquired

complex mechanisms of resistance making them resistant to the last resort therapeutic agents available such as carbapenems and colistin. In this context, epidemiological studies, chasing the evolution and dissemination of multi-drug resistant GNB including *Acinetobacter* spp are warranted for appropriate empirical treatment and for the improvement of infection control measures. Multi-locus sequence typing (MLST) and Pulse field gel electrophoresis (PFGE) are the most common molecular tools used for the typing and tracking of multi-drug resistant organisms [6].

In Lebanon, resistance to extended spectrum cephalosporins in *A. baumannii* has been observed since early 1980s with the first report of *Acinetobacter* spp showing a significant increase in a tertiary care center in Beirut following hostilities' outbreak [13]. During the same decade, the isolation of seven hundred thirteen *Acinetobacter* spp over a seven-years period at Makassed General Hospital was reported. The majority of these isolates were multi-drug resistant, including resistance to third generation cephalosporins and aminoglycosides; carbapenems became therefore the treatment of choice for these infections [31]. Few years later, carbapenem resistant *Acinetobacter* species started to emerge in this same hospital [32] as well as other Lebanese hospitals [12-14,33]. Hamouche *et al.* reported the drop of imipenem susceptibility from 95.3% in 2006 to 44.6% in 2009 in *A. baumannii* clinical isolates [34]. A study conducted at a major tertiary care center in Beirut showed that the majority (82/90) of *A. baumannii* isolated from patients with bacteremia were resistant to carbapenem but remained susceptible to tigecycline and colistin [27]. In this study, colistin susceptibility was tested by the Kirby-Bauer technique [27]; this technique is not considered accurate for testing the susceptibility to colistin. On the contrary, MIC determination should be implemented in order to correctly assess the level of colistin resistance [35]. Another study done by Awad *et al.* reported the detection of carbapenem resistant and colistin/tigecycline susceptible *A. baumannii* strains isolated from patients affected by ventilator associated pneumoniae [15].

In 2008, Zarrilli *et al.* described the mechanism of carbapenem resistance in *A. baumannii* isolated from Saint George hospital in Beirut. In fact, resistance was mediated by a plasmid encoded OXA-58 gene flanked by IS*Aba3* and IS*18* elements. The strains belonged to one major PFGE pattern and one sequence type "ST2" [36]. In the following years, OXA-23 genes became predominant in *A. baumannii* strains isolated from the Lebanese hospitals [5]. The PFGE type A'/ST2 prevailed in North Lebanon as well as in Beyrouth suggesting a clonal dissemination of this cluster across the country [5]. In 2011, Hammoudi *et al.* reported the detection of *A. baumannii* co-harboring OXA-23 and GES-11 beta lactamase genes [10]. The co-existence of OXA-23 and GES-11 was further described in *A. baumannii* isolated in nine Lebanese hospitals in 2012 where the insertion sequence IS*Aba1* was detected upstream of the OXA-23 gene in hundred percent of the strains [37]. Furthermore, eighteen different pulsotypes were detected with the pulsotype 17 being predominant in many Lebanese hospitals revealing, again, a clonal dissemination of *Acinetobacter* across the country. On the other hand, the variety of pulsotypes suggests a horizontal transfer of resistance genes between the different clones [37]. At Saint George Hospital-UMC located in Beirut, Dahdouh *et al.* reported the predominance of OXA-23 producing *A. baumannii* strains belonging to the international clone ICII [28]. In this study, carbapenem resistance mediated by the blaOXA−23 gene was positively associated with ICII [28]. It is worth mentioning that in this study, three *A. haemolyticus*, one *Acinetobacter radioresistens*/ *lwoffii* and one *Acinetobacter junii*/*johnsonii* were also reported [28]. Other beta lactamase encoding genes detected in clinical isolates of *A. baumannii* included OXA-24 and hyperproduced ADC genes [7,38]. Similarly, non *baumannii* strains of *Acinetobacter* were detected by Hajjar *et al.* but were not explored further [7]. A study conducted at the American University of Beirut Medical center (AUBMC), a major tertiary care center located in Beirut, revealed an increase of OXA-23 positive *A. baumannii* strains between two outbreaks, the first one described in 2007/2008 and the second one in 2013 [39]. Interestingly, strains isolated in both periods revealed only 22% of genomic relatedness. This suggests on one hand the rapidly changing diversity of this species, and on the other hand the significance of horizontal gene transfer between different clusters over the six years interval [39]. In view of its importance at the national level as a major medical center receiving patients from all over the country, the AUBMC results could be considered as representative of the country.

From a different perspective, the Syrian crisis imposed a socio-economic burden that might have an influence on health and disease including infectious diseases and bacterial resistance in Lebanon. In 2012, Rafei *et al.* reported the first detection of four NDM-1 producing *A. baumannii* strains isolated from Syrian refugees in Tripoli, North of Lebanon. PFGE and

MLST analysis showed that the strains formed one PFGE cluster and belonged to the ST85 [40]. NDM-1 gene was previously described in Lebanon in clinical strains of *Klebsiella pneumoniae* in 2010 isolated from Iraqi patients but not in *Acinetobacter* species [40]. NDM-1 positive ST85 *A. baumannii* clinical isolates were later detected also in Syrian refugees but also in Lebanese patients within the same city [11]. Thereafter, NDM-1 producing *A. baumannii* were isolated from other Lebanese patients, however these latter belonged to a different sequence type "ST25" [41]. Noteworthy, in their study, Rafei *et al.* found that carbapenem resistance was significantly more prevailing among Syrian refugees than Lebanese patients [41]. Salloum *et al.* conducted a genomic analysis on two NDM-1 producing *A. baumannii* isolated in the aforementioned studies and found that NDM-1 was located on a non-conjugative plasmid [42]. The micro-diversity identified between the two isolates emphasizes the role of refugees in reshaping the diversity of multi-drug resistant organisms in Lebanon [42]. As for non-*A. baumannii* strains, a single study reported the first detection of *A. pittii* harboring the blaNDM-1 or the blaOXA-72 gene from a hospital located in the north of Lebanon [23]. This study highlights the importance of non *baumannii* strains in the clinical settings as suggested by other worldwide studies.

Animals and environment

Nowadays, it is widely accepted that multi-drug resistant organisms are no more confined to the hospital settings; rather they are disseminated in animals and environment [1]. A countrywide study conducted in 2012/2013 by Rafei *et al.* in Lebanon reported that *Acinetobacter* species isolated from animals are mainly susceptible to the majority of antibiotics tested and lacked carbapenemase encoding genes [8]. Furthermore, these strains belonged to 36 different STs; twentyfour were of new sequence types [8]. In this study, only one *A. baumannii* isolated from a horse's oral cavity and one *A. pittii* isolated from a rabbit oral cavity were harboring the OXA-143 and OXA-24 genes respectively [8]. Furthermore, OXA-23 with/without OXA-58 carbapenemase encoding gene, were detected in *A. baumannii* strains of livestock origin [43]. Transconjugation experiments suggested that OXA-23 was chromosomally encoded while OXA-58 was plasmid mediated [43]. Furthermore, MLST analysis revealed that isolated strains were of novel sequence types except for ST20 and ST2. ST2 was reported in Lebanon as well as in different outbreaks worldwide [43]. More recently, *A. baumannii* harboring the ADC gene was detected in a fecal sample of poultry origin in the south Lebanon [1] and *A. calcoaceticus* producing the OXA-72 gene was described in vegetables purchased from a local market in Beirut [4,44]. The presence of multi-drug resistant organisms in vegetables could be the result of direct animal contamination or indirect environmental contamination with soil or irrigation water [44].

Countrywide studies in Lebanon showed that *Acinetobacter* species isolated from water and soil samples were susceptible to the majority of antibiotics including cephalosporins, carbapenem and non-beta lactam antibiotics [4,8]. Despite the absence of bacterial resistance, the noticeable findings in these studies is the predominance of non *baumannii Acinetobacter* species such as: *A. pittii, A. calcoaceticus, Acinetobacter guillouiae and Acinetobacter bereziniae* [4,8].

Overall, the dissemination of resistant *Acinetobacter* spp in Lebanon appears to be polyclonal and mediated primarily by the diffusion of resistance determinants namely blaOXA-23 in the clinical settings and livestock. Environmentally speaking, although isolated strains are susceptible to the most common antibiotics used in the human medicine; the detection of *Acinetobacter* species with novel sequence types in the environment is of particular importance. These strains with negligible knowledge on their intrinsic resistance, level of pathogenicity, and virulence might be transmitted to humans and animals, acquire resistance determinants, and cause infections of unknown consequences [30]. In the one health concept, this emphasizes that clinical settings, animals, and the surrounding environment form an interconnected chain. The successful control of the spread of bacterial resistance needs to be addressed though national interventions at all levels.

Acinetobacter spread in Lebanon, what needs to be done?

The evolution of resistance and the continuous emergence of new genetic determinants occurs naturally in bacteria [45]. Being intrinsically mediated, this phenomenon cannot be stopped but rather should be slowed down and controlled. Antibiotic stewardship programs aiming to control the misuse and over use of antibiotics in hospitals, community and animals are meant to make this happen. On the other hand, infection control measures that prevent the wide dissemination of multi-drug resistant organisms at the human, animal and environmental interface are also warranted. In Lebanon, the implementation of these measures is challenging due to the difficulty of hospital staff

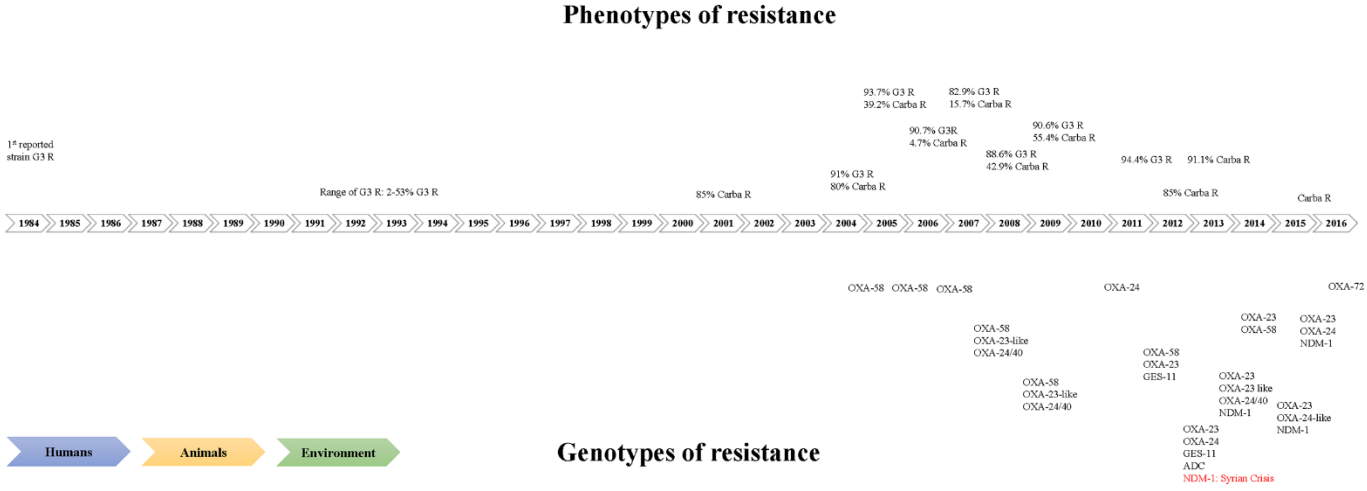
cohorting, especially in staff shortage situations which warrant absolute cooperation from the hospital and nursing administration. Furthermore, patient's isolation imposes psychological well-being and hospital financial costs [46]. Unfortunately, it looks like, infection control measures (if applied) come after the situation has become endemic as it is the case of several hospitals in Beirut and North Lebanon [47].

Regardless of the aforementioned obstacles that face the implementation of preventative measures; these latter are warranted due to the wide dissemination of multi-drug resistant organisms in many ecosystems in Lebanon. According to Kanafani *et al.*, two weeks of additional hospitalization might result from a single central line-associated bloodstream infection or ventilator associated pneumonia episode due to multi-drug resistant *Acinetobacter* species [17]. Knowing that the average cost of one day ICU stay is $1750 [17]. Preventative measures should target equipment/environmental disinfection, hand hygiene program for health care workers, MDRO's screening upon admission and patients' isolations [11]. These latter should be practiced even if in a given hospital, the prevalence of a MDROs is still low. An example of a successful containment of an *A. baumannii* outbreak in Lebanon is at the AUBMC [39]. In this case, on-admission and weekly screening of all respiratory, ICU and high risk patients was performed. The screening included oropharyngeal, umbilical, axillary, perianal and rectal swabbing. Upon the screening results, contact isolation is taken for all infected/colonized patients until discharge. Furthermore, on a daily basis, these patients are bathed with chlorhexidine. This led to the containment of the outbreak in 2013 as compared to 2007-2008 [39].

Another important action to be taken in the country is to upgrade the medical labs and empower the microbiology sections. Clinical microbiologists are the first to encounter and track the evolution and the emergence of new resistance determinants. The fast and correct tracking of bacterial resistance helps on one hand in guiding physicians to the appropriate antibiotic empirical treatment, and on the other hand in alerting the infection control personnel. The clinical microbiology staff should be therefore trained to correctly and appropriately detect and report resistance of a given bacterium to an antibiotic (intrinsic versus acquired resistance) as well as to determine the phenotypic and genotypic mechanism of resistance.

Furthermore, an appropriate and reliable methodology of *Acinetobacter* identification is also needed. This might be expensive for individual hospitals, however, the establishment of a national referee lab for *Acinetobacter* can solve the issue. Such a laboratory can benefit from advanced technology i.e. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). This technique is increasingly used for the reliable identification of microorganisms including Gram positive and Gram-negative bacteria [30]. MALDI-TOF is a cost-effective tool, allowing the fast and simple bacterial identification using a small amount of sample [29]. The monitoring of colistin resistance using MIC determination is also warranted in view of the worldwide emergence and dissemination of colistin resistance in all ecosystems [1].

Figure 1. Emergence of resistance in *Acinetobacter* spp isolated from humans, animals and environment in Lebanon based on the bacterial isolation date.



G3 = third generation cephalosporins, carba = carbapenems, R = resistant.

Conclusion

The dissemination of multi-drug resistant *Acinetobacter* species is a public health concern that needs to be carefully addressed in Lebanon. Although problematic and controversial, the clinical outcome of *A. baumannii* infections are mostly due to the severity of the underlying illness rather than the pathogenicity of the bacterium. More investigations on the risk factors responsible for the acquisition of MDR *Acinetobacter* species and other MDROs in hospitals is therefore warranted. In addition, studies on how to overcome the challenges of implementing antibiotic stewardship and infection control programs are urgently needed. As shown in Figure 1, the big majority of studies in Lebanon addressed the epidemiology of *Acinetobacter* spp in humans; while the investigation of animals and the environment remains very scarce. In the one health concept, this review emphasizes the need of a multi-level cooperative efforts in human, animals and environment in attempt to contain the wide dissemination of MDROs in Lebanon.

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