

Carbapenem-resistant *Acinetobacter baumannii* in healthcare settings

8 December 2016

Main conclusions and options for response

Carbapenem-resistant *A. baumannii* poses a significant threat to patients and healthcare systems in all EU/EEA countries. *A. baumannii* is the cause of serious infections in healthcare settings, and carbapenem resistance limits treatment options and increases the risk for adverse outcomes for patients. The epidemiological situation in Europe has worsened in the past years, with a higher number of countries reporting interregional spread or endemicity of carbapenem-resistant *A. baumannii*.

A. baumannii is adapted to persistence in healthcare settings and is difficult to eradicate once it has become endemic. Increased efforts are therefore needed for the detection of cases and the control of outbreaks in order to prevent carbapenem-resistant *A. baumannii* from becoming endemic in further European regions and health facilities.

Options for actions to reduce identified risks

Clinical management

Timely and appropriate laboratory investigation and reporting are essential to avoid delays in appropriate treatment, which are associated with increased morbidity and mortality. Patients with carbapenem-resistant *A. baumannii* infections are likely to benefit from consultations with experts in infectious diseases or clinical microbiology to ensure the best possible outcome considering the limited treatment options.

Prevention of transmission of carbapenem-resistant *A. baumannii* in hospitals and other healthcare settings

Good standard infection control, including environmental cleaning, adequate reprocessing of medical devices, adequate capacity of microbiological laboratories as well as sufficient capacity of healthcare facilities for contact isolation, are the basis for prevention of transmission of highly resistant bacteria, such as carbapenem-resistant *A. baumannii*. Prompt notification of the clinical team and of the infection prevention

Erratum, 10 February 2017: The caption for Figure 2 on p. 8 now reads 'Percentage (%) of invasive *Acinetobacter* spp. isolates with resistance to carbapenems, by country, EU/EEA countries, 2015 (A) and 2014 (B)'.

Suggested citation: European Centre for Disease Prevention and Control. Carbapenem-resistant *Acinetobacter baumannii* in healthcare settings – 8 December 2016. Stockholm: ECDC; 2016.

and control/hospital hygiene team is essential in order to implement infection control precautions in a timely manner.

Targeting patients at high risk for carriage of carbapenem-resistant *A. baumannii*

Early identification of carriers by active screening cultures in epidemic settings is an important tool for outbreak control. In a setting where multidrug-resistant (MDR) *A. baumannii* is not endemic, even two new cases of carbapenem-resistant *A. baumannii* should be considered as a trigger for active surveillance and enhanced infection control measures. Active surveillance cultures should be conducted in accordance with a specified protocol. The factors to be considered in decision-making about active surveillance cultures in endemic settings include the prevalence of *A. baumannii*, the at-risk population, the sensitivity of surveillance cultures, available resources for screening, and the healthcare setting capacity for enhanced control measures. Active surveillance cultures will only be effective in combination with enhanced infection control measures.

Preventing transmission from patients known to carry carbapenem-resistant *A. baumannii*

Hospitals should consider enhanced control measures such as contact precautions, single room isolation or patient cohorting, and dedicated nursing staff for patients who are colonised or infected with carbapenem-resistant *A. baumannii*.

Specific recommendations for outbreak settings

Prompt initiation of an epidemiologic investigation complemented with environmental sampling and molecular typing might establish the source and thus prevent further cases. Potentially effective enhanced measures for outbreak settings include regular active surveillance cultures for patients admitted to affected wards, cohorting of patients with dedicated nursing staff in separate areas, as well as rigorous environmental cleaning and disinfection. Temporary stop of admissions or even complete closure of the ward has been used as a measure of last resort in outbreak situations where other measures failed to control the spread of *A. baumannii*. Education to improve compliance with hand hygiene is important as transmission via the hands of healthcare workers is a frequent mode of transmission in outbreaks. Targeted antimicrobial stewardship interventions may be useful to reduce further selection of resistance.

Antimicrobial stewardship

Antimicrobial stewardship programmes aim to improve clinical efficacy of antimicrobial treatment and limit antimicrobial resistance through reducing selective pressure for the development of resistance to currently effective antibiotics. Although evidence for a specific beneficial effect of antimicrobial stewardship on the emergence and spread of carbapenem-resistant *A. baumannii* is limited, the previous use of broad-spectrum antimicrobials from various groups, and in particular carbapenems, is a known risk factor for carbapenem-resistant *A. baumannii* infection. Therefore, the implementation of comprehensive antimicrobial stewardship programmes, with emphasis on carbapenem use, is recommended for the prevention of emergence and spread of carbapenem-resistant *A. baumannii*. Nevertheless, targeted and appropriate use of antibiotics is not likely to fully reverse the current trends of carbapenem-resistant *A. baumannii* and antimicrobial resistance trends in general, even when combined with enhanced infection control measures. For this reason, there is an urgent public health need for new antibacterial agents (antibiotics) active against prevalent MDR bacteria, including carbapenem-resistant *A. baumannii*.

Prevention of cross-border transmission

Enhanced surveillance and pre-emptive isolation and screening of patients who are transferred from, or had recently been in contact with, hospitals and other healthcare settings in countries with high prevalence of carbapenem-resistant *A. baumannii* are an immediate measure to reduce transmission in healthcare facilities and prevent outbreaks from imported carbapenem-resistant *A. baumannii*. Documentation of known colonisation or infection by carbapenem-resistant *A. baumannii* with cross-border patient transfer would optimise the early and effective implementation of measures to prevent the spread of carbapenem-resistant *A. baumannii*.

Moreover, gathering reliable epidemiological data through notification of cases to public health authorities and exchange of information through electronic early warning platforms, such as the Epidemic Intelligence System (EPIS), are important activities to allow informed and coordinated actions by public health authorities across the EU/EEA.

Improvement of preparedness of EU/EEA Member States

Improvement of laboratory capacity for laboratory characterisation of carbapenem-resistant *A. baumannii*

Identification of isolates at species level within the *A. baumannii* group is recommended when performing microbiological and epidemiological investigations. It is also important to distinguish between the *A. baumannii* group and the *Acinetobacter* spp. outside the *A. baumannii* group as the latter are rarely causing human infections and are usually more susceptible to antimicrobials.

Molecular methods such as PCR and housekeeping genes sequencing, but in particular the wider use of MALDI-ToF technology, will considerably improve the speed and accuracy of the identification of *Acinetobacter baumannii* in clinical settings.

PCR detection of resistance genes could be combined with the detection of other resistance gene targets in multiplex PCR-based assays used for the detection of multi-drug resistance determinants of epidemiological and clinical importance in gram-negative bacteria.

Genotyping methods, including whole-genome sequencing, can also be used for delineation and characterisation of *A. baumannii* outbreak strains and offer additional information about the associated plasmid vector, additional resistance genes, and strain type. In outbreak situations, it can also provide information on the genetic diversity of/within involved clones, their distribution in time and space, their implication in either endemic or epidemic events, the source of acquisition of the infection, and the number of affected patients. All this information supports the implementation of preventive and control measures.

Improvement of surveillance of carbapenem-resistant *A. baumannii*

To gather more information on the extent of the spread and the prevalence of carbapenem-resistant *A. baumannii* in EU/EEA countries, an EU sentinel-based surveillance module for carbapenem-resistant *A. baumannii* and extensively drug-resistant (XDR) *A. baumannii* infections, based on periodically repeated, structured pan-EU surveys following the sampling design of the EuSCAPE project in order to collect strains in European hospitals could be considered.

At the local level, healthcare facilities with sporadic cases or outbreaks of carbapenem-resistant *A. baumannii* and/or XDR *A. baumannii* should consider prospective antimicrobial susceptibility testing, at least on a sentinel basis. This could be followed by PCR characterisation of the carbapenemases to ascertain the introduction of carbapenem-resistant *A. baumannii* and XDR *A. baumannii* into their facility, and to ensure its containment as part of their general efforts to prevent and control MDR bacteria. Testing of patients with recent contact with healthcare facilities in foreign countries for presence of the carbapenem-resistant *A. baumannii* and XDR *A. baumannii* isolates should also be considered, based on available laboratory resources and following current national guidelines.

At the national level, there is a need for performing prospective testing surveys of the prevalence of carbapenem-resistant *A. baumannii* and XDR *A. baumannii*. Molecular typing of the isolates collected would be valuable to distinguish between the epidemic clones and possibly detect new successful *A. baumannii* lineages associated with hospital outbreaks.

Source and date of request

ECDC internal decision, 15 September 2016.

Public health issue

Acinetobacter baumannii has become a cause of difficult-to-treat infections in healthcare settings in Europe due to an increasing resistance to antimicrobial agents used for the treatment of these infections, especially to carbapenems. Outbreaks of carbapenem-resistant *A. baumannii* in healthcare facilities have occurred worldwide. Increasing carbapenem resistance of *Acinetobacter* spp. in Europe as documented by the European Antimicrobial Resistance Network (EARS-Net) and recent hospital outbreaks highlighted the need for an assessment of the risk for spread of carbapenem-resistant *Acinetobacter baumannii* in healthcare settings in EU/EEA Member States.

Consulted experts

Internal experts consulted (in alphabetical order): Barbara Albiger, Liselotte Diaz Högberg, Anke Kohlenberg, Anna-Pelagia Magiorakos, Dominique Monnet, Diamantis Plachouras, Marc Struelens.

External experts consulted (in alphabetical order): Christian Giske (Karolinska University Hospital, Stockholm, Sweden), Jesús Rodríguez Baño (Hospital Universitario Virgen Macarena, Seville, Spain), Harald Seifert (University of Cologne, Germany), Arjana Tambić (Zagreb University Hospital for Infectious Diseases, Croatia).

Disease background information

Acinetobacter spp. are gram-negative, strictly aerobic non-motile bacteria [1]. The *Acinetobacter* genus consists of over 50 species, most of which are ubiquitous in the environment, have low pathogenicity, but can infect humans as opportunistic pathogens. Of these, *Acinetobacter baumannii*, *Acinetobacter nosocomialis* and *Acinetobacter pittii*, which belong to the *Acinetobacter baumannii* group, are the most clinically relevant species [1]. However, within the *Acinetobacter baumannii* group, *A. baumannii sensu stricto* is responsible for the vast majority (90–95%) of clinical infections and nosocomial outbreaks because of its widespread multi-drug resistance and propensity for clonal spread. *A. nosocomialis* is only rarely resistant to carbapenems but involved in hospital outbreaks in Europe, and the same is true for *A. pittii*, which is a member of the normal human skin microbiota [2–4]. However, due to the difficulty in differentiating these three species in many laboratories, for the remainder of this assessment, these three species will be collectively designated as *A. baumannii sensu lato*, and will hereafter be called '*A. baumannii*'. In the future, with rapidly evolving of technologies (i.e., MALDI-ToF) allowing reliable identification of *Acinetobacter* to species level, the rationale to group these three species *in sensu lato* might become obsolete and should be reconsidered.

The clinical significance of *A. baumannii* is mostly due to its ability to easily acquire resistance to different groups of antimicrobials and to survive for long periods of time on dry surfaces [5], both potentiating its persistence and transmission in healthcare settings. The Infectious Diseases Society of America has therefore included *A. baumannii* in its list of six highly resistant pathogens that are frequently resistant to licensed antimicrobials and for which few new effective drugs are in development. This group has been called the ESKAPE group, an acronym which stands for *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. [6].

The *A. baumannii* population structure is clonal in nature. Three of eight described international clonal lineages (IC1-3) are dominant in Europe and have been found in nearly all European countries. IC1-3 correspond to typical multi-locus sequence typing (MLST) clonal complexes (ST1-3), although in contrast to *K. pneumoniae*, *E. coli* and *P. aeruginosa*, it is more common to use the IC terminology rather than sequence type (ST) [7]. Many outbreaks have been associated with one of these three major European clonal complexes, but IC2 is by far the most prevalent [8–13]. Spread of multidrug-resistant (MDR)-, extensively drug-resistant (XDR) or pandrug-resistant *A. baumannii* has been shown to be associated with distinct epidemic clones, belonging to these international clonal lineages [14].

Antimicrobial resistance

A. baumannii is intrinsically resistant to many antimicrobial agents due to its selective ability to prevent various molecules from penetrating the bacterial outer membrane [15]. The antimicrobial resistance phenotype in *Acinetobacter* spp. varies largely across Europe, with generally high resistance percentages reported from the Baltic countries and from southern and south-eastern Europe [16]. In 2015, combined resistance to fluoroquinolones, aminoglycosides and carbapenems was the most frequently reported resistance phenotype for *Acinetobacter* spp. and accounted for almost half of the blood isolates reported to the European Antimicrobial Resistance Network (EARS-Net) [16]. It should be noted that within EARS-Net it is not mandatory to identify *Acinetobacter* to species level; however, it is well known that carbapenem resistance in *Acinetobacter* spp. in Europe is primarily driven by *A. baumannii sensu stricto*. Over the last decade in Europe and worldwide, *A. baumannii* has become increasingly resistant to carbapenems, a last-line group of beta-lactam antibiotics with very broad activity and an important treatment option for patients infected with multidrug-resistant gram-negative bacteria, including *A. baumannii* [8,17–20].

Diverse mechanisms are responsible for resistance to carbapenems in *A. baumannii*, i.e. decreased permeability to carbapenems, efflux and enzymatic breakdown of the antibiotic by carbapenemases. Of these, carbapenem-hydrolysing class D betalactamases (CHDLs) are of main importance. *A. baumannii* possesses the intrinsic carbapenem-hydrolysing oxacillinase OXA-51 that confers resistance to carbapenems only when over-expressed [21]. The most frequent acquired mechanism leading to carbapenem resistance in *A. baumannii* is the production of one of the following oxacillinases: OXA-23-like, OXA-24/40-like, OXA-58-like, OXA-143-like and OXA-235-like [21]. Metallo-beta-lactamases, such as imipenemase (IMP) or Verona integron-encoded metallo-beta-lactamase (VIM), have only rarely been encountered in *A. baumannii*, although New Delhi metallo-beta-lactamase (NDM)-producing *A. baumannii* isolates are increasingly being reported in Europe [22,23]. Production of *K. pneumoniae* carbapenemase (KPC) and OXA-48 oxacillinase has also been described in *A. baumannii* isolates [24,25]. Sulbactam, a beta-lactamase inhibitor has intrinsic activity against *Acinetobacter* spp. and shows antimicrobial activity against *A. baumannii* [26]. It has been used as targeted therapy for diverse types of infections caused by these microorganisms; unfortunately, most carbapenem-resistant isolates are also resistant to sulbactam.

The increasing number of hospital outbreaks with carbapenem-resistant *A. baumannii* and the lack of new antimicrobial agents active against such highly resistant bacteria, have compelled clinicians to reconsider the use of

colistin (polymyxin E). This 'old' antimicrobial was reintroduced for systemic administration as a last resort for the treatment of healthcare-associated infections due to carbapenem-resistant gram-negative bacteria, including *A. baumannii*, although its efficacy and safety are not yet fully defined [18]. Although still rare, resistance to colistin in *A. baumannii* is increasingly being reported in Europe [27].

Laboratory detection/characterisation and antimicrobial susceptibility testing

It is also important to distinguish between the *A. baumannii* group and the *Acinetobacter* spp. outside the *A. baumannii* group, as the ones that do not belong to the *A. baumannii* group rarely cause human infections and are usually more susceptible to antimicrobials [28].

The correct laboratory identification of *Acinetobacter* isolates to the species level is complicated by lack of phenotypic standard identification techniques including the semi-automated identification systems and until recently was only possible with molecular methods such as polymerase-chain reaction (PCR) and/or single gene locus or housekeeping gene sequencing. Although molecular methods have improved the speed and accuracy of the identification of *Acinetobacter* isolates, rapid molecular diagnostic tests to easily and rapidly identify carbapenem-resistant *A. baumannii* are not yet commercially available. As a consequence, many laboratories still are unable to reliably identify *Acinetobacter* isolates at the species level. However, with the advent of MALDI-ToF, which allows for the very reliable identification of *Acinetobacter* to species level [29], these difficulties have been overcome, and with the more widespread use of this technology it is expected that the quality of species identification within the genus *Acinetobacter* will considerably improve. Commercially available MALDI-ToF instruments are now able to discriminate between *A. baumannii*, *A. pittii*, *A. nosocomialis*, *A. calcoaceticus* and even novel species, i.e. *A. seifertii* and *A. dikshoornii*, as long as taxonomy reference databases are updated to include these species.

In outbreak situations, classical molecular methods, e.g. pulsed-field gel electrophoresis (PFGE), MLST and PCR-based methods including RAPD, rep-PCR and a recently described modified PCR method called PCR-based open reading frames typing method, allow for the determination of international epidemic clones, bringing down the required time to result from several days to only a few hours. Recently, mass spectrometry has been tested for the rapid diagnostic and identification of isolates that belong to the *A. baumannii* group [30]. Whole genome sequencing can provide an even higher degree of resolution, allowing analysis of transmission events.

To provide the best therapeutic options, clinicians rely on accurate antimicrobial susceptibility testing from the clinical microbiology laboratories. With the updated CLSI breakpoints for imipenem and meropenem, there is now to a large extent consensus between the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical Laboratories Standards Institute (CLSI) for *Acinetobacter* spp. [31]. For doripenem there is still a larger difference between the EUCAST and CLSI breakpoints.

For epidemic settings, implementing a programme of active screening at hospital admission is recommended by the ESCMID guidelines for the management of infection control measures to reduce transmission of multidrug-resistant gram-negative bacteria in hospitalised patients [32]; although methods and frequency of screening (surveillance cultures), as well as the number of samples needed and the location of body sites to be screened for carriage of carbapenem-resistant *A. baumannii*, are not well defined. However, body sites with good sensitivity of surveillance cultures were buccal mucosa, skin, and, to a lesser extent, the rectum in a recent study [33]. More extensive sampling protocols including tracheal aspirates, throat swabs, and samples from insertion sites, wound, groin and rectum have also been used [34].

Event background information

Current situation of carbapenem-resistant *A. baumannii* in EU/EEA Member States

Recent data collected at ECDC from the European survey on carbapenemase-producing *Enterobacteriaceae* (EuSCAPE) project and from the European Antimicrobial Resistance Network (EARS-Net) confirmed that although there is already a high resistance baseline in some countries, there has been an overall increase of carbapenem-resistant *A. baumannii* in Europe, especially in countries with lower prevalence (Figures 1 and 2) [16,19,35].

Data on carbapenem-resistant *A. baumannii* in EU/EEA Member States from the EuSCAPE project (2012–2015)

Interim results from the European survey on carbapenemase-producing *Enterobacteriaceae* (EuSCAPE) project suggested that carbapenem-resistant *A. baumannii* (resistant through the production of carbapenemases) might be more widely disseminated in Europe than carbapenem-resistant *Enterobacteriaceae* (resistant through the production of carbapenemases) [19].

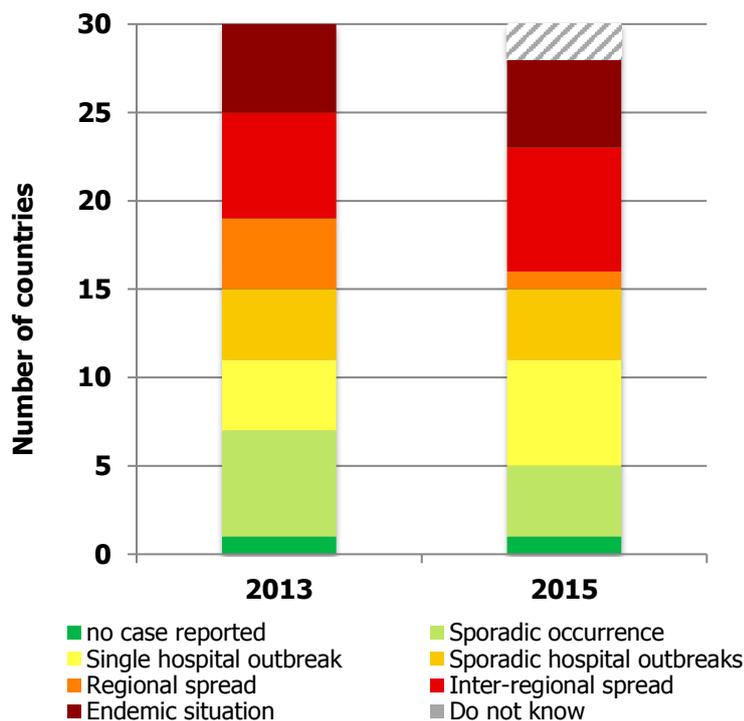
After the completion of the EuSCAPE project, a post-EuSCAPE feedback questionnaire was sent to the 30 participating EU/EEA countries to self-assess whether the occurrence and spread of carbapenem-resistant *A. baumannii* had increased between March 2013 and May 2015 (Figure 1). The national experts completed the questionnaire to the best of their knowledge and, in some cases, based on their knowledge of the national clinical or microbiological data. As only one national expert was selected per country, their answers could represent subjective assessments that may not represent the exact extent of the spread of carbapenem-resistant *A. baumannii*.

The national experts from the participating countries who replied to the questionnaire were asked to describe the nationwide expansion of carbapenem-resistant *A. baumannii* using the same epidemiological scale:

- No cases were found or reported.
- Sporadic occurrence corresponding to epidemiological unrelated single cases.
- Single hospital outbreak, where an outbreak is defined as two or more epidemiologically associated cases with indistinguishable geno- or phenotype in a single institution.
- Sporadic hospital outbreaks being unrelated hospital outbreaks with independent (i.e. epidemiologically unrelated) introduction or different strains and no autochthonous interinstitutional transmission reported.
- Regional spread when more than one epidemiologically related hospital outbreak occurs, with the outbreaks confined to hospitals that are part of the same region or health district, suggestive of regional autochthonous interinstitutional transmission.
- Interregional spread when multiple epidemiologically related outbreaks occur in different health districts, suggesting interregional autochthonous interinstitutional transmission.
- Endemic situation when most hospitals in a country are repeatedly seeing cases admitted from autochthonous sources.

Using this epidemiological scale, it was obvious that according to the experts' assessments, the epidemiological situation of carbapenem-resistant *A. baumannii* worsened in the EU/EEA countries over a period of only two years (Figure 1).

Figure 1. Comparison of the epidemiological stages of the nationwide expansion of carbapenem-resistant *A. baumannii* based on an assessment by 31 national experts in 30 participating EU/EEA countries, March 2013–May 2015



Source: EuSCAPE project (unpublished data)

Note: Two Member States reported a lack of knowledge with regard to an increasing occurrence and spread of carbapenem-resistant *A. baumannii* since February 2013 (shown in hatched grey); in the 2013 survey, one Member States reported a hospital outbreak and another one an endemic situation.

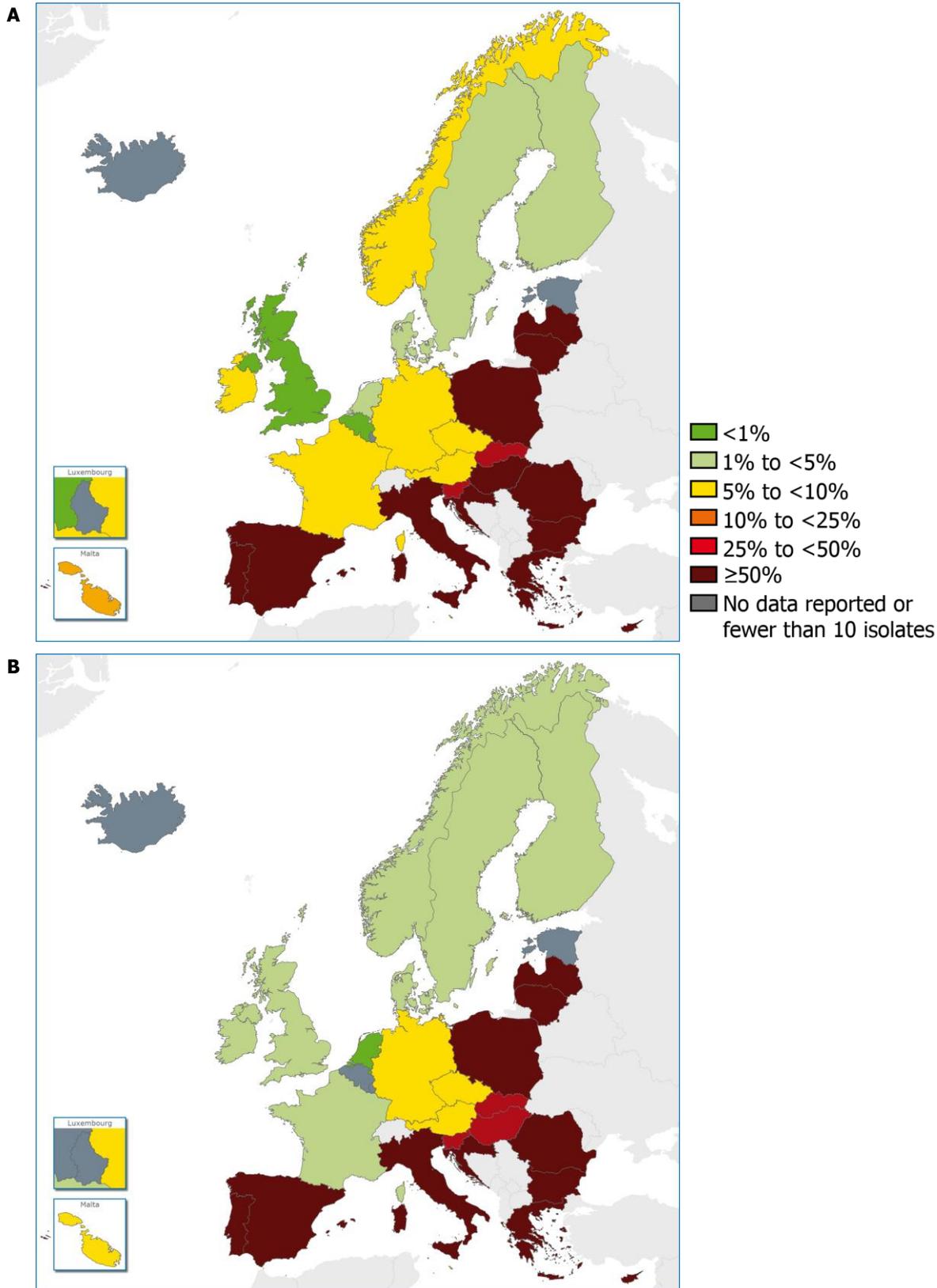
Data on carbapenem-resistant *Acinetobacter* spp. in the EU/EEA Members States from the European Antimicrobial Resistance Surveillance Network (EARS-Net)

After a two-year pilot period (2012–2013), surveillance of *Acinetobacter* spp. was included in the routine EARS-Net protocol in 2014. Surveillance was restricted to genus level (i.e. *Acinetobacter* spp.) due to the difficulties of species identification, and the antibiotics under surveillance were limited to a panel for which there are clear guidelines on susceptibility testing and interpretive criteria [35]. Wide variations in antimicrobial resistance of *Acinetobacter* spp. isolates in EU/EEA Member States were reported, with generally higher resistance percentages observed in countries in the east and south of Europe than in northern Europe [16,35]. Carbapenem resistance is common in invasive *Acinetobacter* spp. isolates and was, in most cases, combined with resistance to fluoroquinolones and aminoglycosides [16,35]. In 2015, 12 out of 27 EU/EEA countries reporting resistance results for 10 or more *Acinetobacter* spp. isolates had percentages of carbapenem resistance of 50% or higher (Figure 2). This is an indication of seriously limited options for the treatment of patients infected with *Acinetobacter* spp. in these countries [16].

In 2015, resistance to colistin was also observed in 4.1% of the carbapenem-resistant *Acinetobacter* spp. isolates and 3.9% of the carbapenem-susceptible *Acinetobacter* spp. isolates reported to EARS-Net, with the vast majority reported from Greece and Italy [16]. These data should, however, be interpreted with caution due to the low number of isolates tested, as data on both carbapenem and polymyxin susceptibility were only available for 58% of the *Acinetobacter* spp. isolates reported to EARS-Net for 2015. Selective testing specifically targeting high-risk patients might also influence the data, as well as the laboratory methodology issues inherent to colistin susceptibility testing. Of note, data on laboratory methods used for determining colistin susceptibility were incomplete in EARS-Net reporting, and the impact of various testing methods on the results is unknown. Also, EUCAST has recently renewed its warning to withdraw the currently available colistin gradient tests from use in the laboratory [36]. Nevertheless, the high levels of resistance to carbapenems, and often multiple other antibiotics including sometimes colistin, reported from several EU/EEA countries is of great concern.

The increasing high levels of carbapenem resistance in *Acinetobacter* spp. reported from many countries in EARS-Net further support the conclusions from the EuSCAPE project that the epidemiological situation of carbapenem-resistant *A. baumannii* is alarming in many EU/EEA countries and worsening in the EU/EEA.

Figure 2. Percentage (%) of invasive *Acinetobacter* spp. isolates with resistance to carbapenems, by country, EU/EEA countries, 2015 (A) and 2014 (B)



Source: EARS-Net, 2016

The number of countries reporting data on *Acinetobacter* spp. to EARS-Net increased from 18 in 2012 to 30 in 2015. Nevertheless, the data on *Acinetobacter* spp. in EARS-Net are still limited and the number of reported isolates varies greatly between countries. This may be partially explained by differences in population size, but could also be attributed to national differences in the prevalence of *Acinetobacter* spp. infections [16].

Most of the countries with high percentages of carbapenem-resistant *Acinetobacter* spp. in EARS-Net also reported a proportionally higher relative frequency of *Acinetobacter* spp. as percentage of all microorganisms associated with healthcare-associated infections in the *ECDC point prevalence survey of healthcare-associated infections in European acute care hospitals 2011–2012*. This suggests that high resistance levels may reflect a generally higher prevalence of *Acinetobacter* spp. infections in these countries [37]. However, to estimate the burden of infection, cases of *A. baumannii* infections per 1 000 patient-days would be a more adequate indicator.

ECDC threat assessment for the EU

Impact on human health

A. baumannii can be a coloniser (resulting in carriage) and a pathogen causing an infection [38]. While *A. baumannii* has been associated with serious infections, the clinical significance of detection of *A. baumannii* is not always easy to determine, e.g. isolation of *A. baumannii* from respiratory or urine samples often represents colonisation rather than infection [39], which makes the ascertainment of the infection status challenging. A careful evaluation should be performed of every patient with isolation of *A. baumannii* from wounds, urine samples or respiratory specimens in order to avoid treatment of patients who are only colonised.

Healthcare-associated *A. baumannii* infections

A. baumannii infections frequently occur in patients with severe underlying diseases, mainly in the ICU setting, and are often related to invasive procedures or indwelling devices [15,40]. Frequent healthcare-associated infections caused by *A. baumannii* include pneumonia, bloodstream infections, wound infections, urinary tract infections and meningitis after neurosurgical procedures [1]. A special population at risk of developing infections with *A. baumannii* is burn patients [41]. However, infections in patients admitted to conventional medical and surgical wards are also increasing [42].

In the *ECDC point prevalence survey of healthcare-associated infections in European acute care hospitals 2011–2012*, *Acinetobacter* spp. (data collected only at the genus level, not species level) were the 11th most frequently reported (3.6%) microorganism in microbiologically documented healthcare-associated infections. In this survey, the types of healthcare-associated infections associated with *Acinetobacter* spp. were mainly pneumonia/lower respiratory tract infections (8.7%), bloodstream infections (4.1%) and surgical site infections (2.9%) [37].

Community-acquired *A. baumannii* infections

A. baumannii has rarely been reported as a cause of serious community-acquired pneumonia, mainly in patients with underlying diseases or risk factors. Community-acquired *A. baumannii* isolates are more susceptible to antimicrobials and carbapenem resistance has only rarely been reported [43]. The community-acquired *A. baumannii* infections appear to be associated with warm and humid climate and are limited to tropical regions, with the majority of cases reported from Hong Kong, Singapore, Taiwan, South Korea and northern Australia [43]. Acquisition of *A. baumannii* in the community does not appear relevant for Europe where *A. baumannii* infections are almost exclusively healthcare associated.

Limited treatment options

Carbapenems had traditionally been the drug of choice for empirical treatment of *A. baumannii* infections [28], but carbapenem resistance has been increasing globally [40], leading to increased use of colistin for treatment of highly resistant *A. baumannii* infections. In a study in 21 European countries, colistin was the agent with the highest level of activity against *A. baumannii* in vitro [44], but data on the clinical efficacy of colistin in the treatment of *A. baumannii* infection are limited [18], and colistin treatment is associated with nephrotoxicity and neurotoxicity, although studies have shown that colistin is generally better tolerated than previously expected [45]. In addition, colistin-resistant *A. baumannii* strains have also emerged worldwide since the first report of colistin-resistant *Acinetobacter* spp. from the Czech Republic in 1999 [27,46]. In addition, there were reports of isolates that are XDR or pandrug-resistant and for which there are few or no effective treatment options [47].

Mortality

The extent of mortality attributable to *A. baumannii* infections has been controversial, and there are several published studies which either confirm or refute attributable mortality [48]. The assessment of the mortality truly attributable to *A. baumannii* infections has been hampered by multiple factors, such as heterogeneity in the methodology used, the type of infections included, and confounders, such as the critical clinical status of patients. Differences in mortality might also be partly explained by variability in the virulence of various *A. baumannii* clones [49–51].

It has been suggested that the true virulence of *A. baumannii* might have been underestimated because of the availability of adequate therapy [52]. Receiving effective antibiotic treatment has been shown to lower the mortality of patients with carbapenem-resistant *A. baumannii* bacteraemia [51,53]. In addition, a recent meta-analysis showed an increased mortality of patients with carbapenem-resistant *A. baumannii* infections compared to patients with carbapenem-susceptible *A. baumannii* infections [54].

Potential for spread

Outbreaks and spread in healthcare settings

A. baumannii is known for its propensity to cause outbreaks in healthcare settings [39]. Transmission occurs mainly via the hands of healthcare workers, contaminated medical equipment and the healthcare environment [48,55]. Airborne transmission has also been suggested [56], but the relevance of this route of transmission in healthcare settings is not established.

Factors contributing to outbreaks and the persistence of *A. baumannii* in healthcare settings include its antimicrobial resistance as well as resistance to disinfectants and to desiccation [1]. *A. baumannii* is known for its enhanced capacity to resist dry conditions, resulting in long-term survival on various surfaces [57]. *A. baumannii* has been frequently isolated from the immediate environment of patients carrying *A. baumannii* in hospitals, and even from surfaces in public areas surrounding hospitals [58].

Inadequate environmental disinfection has been reported as a possible cause of an outbreak of carbapenem-resistant *A. baumannii* [59]. In some *A. baumannii* outbreaks, a temporary stop of admissions or even a complete closure of units for enhanced environmental cleaning had to be implemented for outbreak control [60-62].

In addition to the hospital environment, colonised patients may also be important as a reservoir during *A. baumannii* outbreaks; therefore, screening to detect colonised patients should be performed during outbreaks, and contact precautions should be implemented for colonised or infected patients [63].

The risk factors associated with *A. baumannii* acquisition are mainly related to healthcare contact and medical treatment and include nursing home residence, hospital and intensive care unit admission, medical devices and procedures, the local colonisation pressure (defined as patient-days of patients carrying *A. baumannii* divided by total patient days) and exposure to antimicrobial agents, especially the fluoroquinolones, third-generation cephalosporins and carbapenems [38,64,65]. A recent study showed that the risk for acquisition of carbapenem-resistant *A. baumannii* quadrupled with carbapenem exposure [66]. Carbapenem restriction in combination with infection control measures was associated with a reduction of the prevalence of highly resistant *A. baumannii* infections in a Turkish ICU [67].

Cross-border transmission

In Europe, many countries have experienced outbreaks of carbapenem-resistant *A. baumannii* in healthcare settings, including Belgium [68], Bulgaria [10], Croatia [9], Denmark [69], France [70], Italy [71], Germany [72], Greece [73], Latvia [11], Spain [74] and the UK [75]. Some of the outbreaks in European hospitals have occurred after the introduction of carbapenem-resistant *A. baumannii* via transfer of a colonised or infected patient from a country with a higher prevalence to a country with a lower prevalence. The origin of the index patient has been reported as a European country (e.g. from Greece to Belgium [68] or from Spain to Norway [76]), or a country from another continent (e.g. from Thailand to Germany [72], Iraq to UK [77] or Tahiti to mainland France [70]). In addition to European countries with a high prevalence (Figure 2), geographical areas with a high prevalence of carbapenem-resistant *A. baumannii* are south and south-east Asia, South America and the Middle East [78,79]. Cross-border transmission of *A. baumannii* and carbapenem-resistant *A. baumannii* also occurred with the repatriation of war casualties, previously from Iraq and Afghanistan [80,81], and more recently from patients injured in the wars in Syria [82] and Ukraine [83].

Level of preparedness of EU/EEA Member States

Laboratory capacity for characterisation of *A. baumannii* in EU/EEA Member States

In the 2015 post-EuSCAPE feedback self-assessment, 24 out of 30 EU/EEA countries reported having either an officially nominated national reference laboratory for carbapenem-resistant *A. baumannii* or a national expert laboratory that fulfilled a similar role (unpublished data). In 2015, a national recommendation or obligation for reporting (notification) of carbapenem-resistant *A. baumannii*-positive patients to health authorities existed in seven EU/EEA countries. An additional seven EU/EEA countries reported that a national recommendation was under preparation (unpublished data).

Capacity for surveillance and containment of *A. baumannii* in EU/EEA Member States

In 2013, the EuSCAPE project highlighted the fact that surveillance and reporting of carbapenem-resistant *A. baumannii* cases were not routinely performed in all the EU/EEA countries. Many participating countries expressed serious concerns regarding underreporting of carbapenem-resistant *A. baumannii* cases. The EuSCAPE project also showed that, in 2013, only 21 out of 30 EU/EEA countries performed some type of surveillance of carbapenem-resistant *A. baumannii* [19]. This number increased to 24 countries in 2015 (unpublished data).

Between 2012 and 2015, however, the number of countries reporting data on *Acinetobacter* spp. to EARS-Net increased from 18 to 30, i.e. all EU/EEA countries are participating and reporting invasive carbapenem-resistant *Acinetobacter* spp. from blood and cerebrospinal fluid to EARS-Net in 2015 (Figure 2) [16].

While in 2013 only two EU/EEA countries reported having national recommendations or guidelines on infection prevention and control measures to control and prevent the spread of carbapenem-resistant *A. baumannii* [19], 12 EU/EEA countries reported in 2015 that they implemented national recommendations or guidelines, either for single cases or in the case of an outbreak, and an additional six countries reported having such recommendations or guidelines under preparation (unpublished data).

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) published guidelines for the control of multidrug-resistant gram-negative bacilli, including *A. baumannii* [32].

References

1. Peleg AY, Seifert H, Paterson DL. *Acinetobacter baumannii*: emergence of a successful pathogen. *Clin Microbiol Rev.* 2008 Jul;21(3):538-82.
2. Seifert H, Dijkshoorn L, Gerner-Smidt P, Pelzer N, Tjernberg I, Vaneechoutte M. Distribution of *Acinetobacter* species on human skin: comparison of phenotypic and genotypic identification methods. *J Clin Microbiol.* 1997 Nov;35(11):2819-25.
3. Yang J, Chen Y, Jia X, Luo Y, Song Q, Zhao W, et al. Dissemination and characterization of NDM-1-producing *Acinetobacter pittii* in an intensive care unit in China. *Clin Microbiol Infect.* 2012 Dec;18(12):E506-13.
4. Schleicher X, Higgins PG, Wisplinghoff H, Korber-Irrgang B, Kresken M, Seifert H. Molecular epidemiology of *Acinetobacter baumannii* and *Acinetobacter nosocomialis* in Germany over a 5-year period (2005-2009). *Clin Microbiol Infect.* 2013 Aug;19(8):737-42.
5. Houang ET, Sormunen RT, Lai L, Chan CY, Leong AS. Effect of desiccation on the ultrastructural appearances of *Acinetobacter baumannii* and *Acinetobacter lwoffii*. *J Clin Pathol.* 1998 Oct;51(10):786-8.
6. Talbot GH, Bradley J, Edwards JE, Jr., Gilbert D, Scheld M, Bartlett JG. Bad bugs need drugs: an update on the development pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America. *Clin Infect Dis.* 2006 Mar 1;42(5):657-68.
7. Diancourt L, Passet V, Nemeč A, Dijkshoorn L, Brisse S. The population structure of *Acinetobacter baumannii*: expanding multiresistant clones from an ancestral susceptible genetic pool. *PLoS One.* 2010 Apr 07;5(4):e10034.
8. Higgins PG, Dammhayn C, Hackel M, Seifert H. Global spread of carbapenem-resistant *Acinetobacter baumannii*. *J Antimicrob Chemother.* 2010 Feb;65(2):233-8.
9. Franolic-Kukina I, Bedenic B, Budimir A, Herljevic Z, Vranes J, Higgins PG. Clonal spread of carbapenem-resistant OXA-72-positive *Acinetobacter baumannii* in a Croatian university hospital. *Int J Infect Dis.* 2011 Oct;15(10):e706-9.
10. Stoeva T, Higgins PG, Bojkova K, Seifert H. Clonal spread of carbapenem-resistant OXA-23-positive *Acinetobacter baumannii* in a Bulgarian university hospital. *Clin Microbiol Infect.* 2008 Jul;14(7):723-7.
11. Saule M, Samuelsen O, Dumpis U, Sundsfjord A, Karlson A, Balode A, et al. Dissemination of a carbapenem-resistant *Acinetobacter baumannii* strain belonging to international clone II/sequence type 2 and harboring a novel AbaR4-like resistance island in Latvia. *Antimicrob Agents Chemother.* 2013 Feb;57(2):1069-72.
12. Tomaschek F, Higgins PG, Stefanik D, Wisplinghoff H, Seifert H. Head-to-Head Comparison of Two Multi-Locus Sequence Typing (MLST) Schemes for Characterization of *Acinetobacter baumannii* Outbreak and Sporadic Isolates. *PLoS One.* 2016;11(4):e0153014.
13. Goic-Barisic I, Towner KJ, Kovacic A, Sisko-Kraljevic K, Tonkic M, Novak A, et al. Outbreak in Croatia caused by a new carbapenem-resistant clone of *Acinetobacter baumannii* producing OXA-72 carbapenemase. *J Hosp Infect.* 2011 Apr;77(4):368-9.
14. Zarrilli R, Pournaras S, Giannouli M, Tsakris A. Global evolution of multidrug-resistant *Acinetobacter baumannii* clonal lineages. *Int J Antimicrob Agents.* 2013 Jan;41(1):11-9.
15. Munoz-Price LS, Weinstein RA. *Acinetobacter* infection. *N Engl J Med.* 2008 Mar 20;358(12):1271-81.
16. European Centre for Disease Prevention and Control. European Antibiotic Awareness Day (EAAD) summary of the latest data on antibiotic resistance in the European Union. EARS-Net surveillance data 2015. Stockholm: ECDC; 2016.
17. Dijkshoorn L, Nemeč A, Seifert H. An increasing threat in hospitals: multidrug-resistant *Acinetobacter baumannii*. *Nat Rev Microbiol.* 2007 Dec;5(12):939-51.
18. Doi Y, Murray GL, Peleg AY. *Acinetobacter baumannii*: evolution of antimicrobial resistance-treatment options. *Semin Respir Crit Care Med.* 2015 Feb;36(1):85-98.
19. European Centre for Disease Prevention and Control. Carbapenemase-producing bacteria in Europe: interim results from the European Survey on carbapenemase-producing Enterobacteriaceae (EuSCAPE) project. 2013.
20. Souli M, Galani I, Giamarellou H. Emergence of extensively drug-resistant and pandrug-resistant Gram-negative bacilli in Europe. *Euro Surveill.* 2008 Nov 20;13(47).
21. Da Silva GJ, Domingues S. Insights on the Horizontal Gene Transfer of Carbapenemase Determinants in the Opportunistic Pathogen *Acinetobacter baumannii*. *Microorganisms.* 2016 Aug 23;4(3).
22. Voulgari E, Politi L, Pitiriga V, Dendrinos J, Poulou A, Georgiadis G, et al. First report of an NDM-1 metallo-beta-lactamase-producing *Acinetobacter baumannii* clinical isolate in Greece. *Int J Antimicrob Agents.* 2016 Sep 29.
23. Decousser JW, Jansen C, Nordmann P, Emirian A, Bonnin RA, Anais L, et al. Outbreak of NDM-1-producing *Acinetobacter baumannii* in France, January to May 2013. *Euro Surveill.* 2013;18(31).
24. Elsharif R, Ismail D, Elawady S, Jastaniah S, Al-Masaudi S, Harakeh S, et al. Boronic acid disk diffusion for the phenotypic detection of polymerase chain reaction-confirmed, carbapenem-resistant, gram-negative bacilli isolates. *BMC Microbiol.* 2016 Jul 01;16(1):135.

25. Martinez T, Martinez I, Vazquez GJ, Aquino EE, Robledo IE. Genetic environment of the KPC gene in *Acinetobacter baumannii* ST2 clone from Puerto Rico and genomic insights into its drug resistance. *J Med Microbiol*. 2016 Aug;65(8):784-92.
26. Higgins PG, Wisplinghoff H, Stefanik D, Seifert H. In vitro activities of the beta-lactamase inhibitors clavulanic acid, sulbactam, and tazobactam alone or in combination with beta-lactams against epidemiologically characterized multidrug-resistant *Acinetobacter baumannii* strains. *Antimicrob Agents Chemother*. 2004 May;48(5):1586-92.
27. Cai Y, Chai D, Wang R, Liang B, Bai N. Colistin resistance of *Acinetobacter baumannii*: clinical reports, mechanisms and antimicrobial strategies. *J Antimicrob Chemother*. 2012 Jul;67(7):1607-15.
28. Garnacho-Montero J, Dimopoulos G, Poulakou G, Akova M, Cisneros JM, De Waele J, et al. Task force on management and prevention of *Acinetobacter baumannii* infections in the ICU. *Intensive Care Med*. 2015 Dec;41(12):2057-75.
29. Mari-Almirall M, Cosgaya C, Higgins PG, Van Assche A, Telli M, Huys G, et al. MALDI-TOF/MS identification of species from the *Acinetobacter baumannii* (Ab) group revisited: inclusion of the novel *A. seifertii* and *A. dijkshoorniae* species. *Clin Microbiol Infect*. 2016; epub ahead of print.
30. Mencacci A, Monari C, Leli C, Merlini L, De Carolis E, Vella A, et al. Typing of nosocomial outbreaks of *Acinetobacter baumannii* by use of matrix-assisted laser desorption ionization-time of flight mass spectrometry. *J Clin Microbiol*. 2013 Feb;51(2):603-6.
31. European committee on antimicrobial susceptibility testing. Breakpoint tables for interpretation of MICs and zone diameters, Version 6.0 valid from 2016-01-01: EUCAST; 2016. Available from: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_6.0_Breakpoint_table.pdf.
32. Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. *Clin Microbiol Infect*. 2014 Jan;20 Suppl 1:1-55.
33. Nutman A, Lerner A, Schwartz D, Carmeli Y. Evaluation of carriage and environmental contamination by carbapenem-resistant *Acinetobacter baumannii*. *Clin Microbiol Infect*. 2016 Nov;22(11):949.e5-.e7.
34. Molter G, Seifert H, Mandraka F, Kasper G, Weidmann B, Hornei B, et al. Outbreak of carbapenem-resistant *Acinetobacter baumannii* in the intensive care unit: a multi-level strategic management approach. *J Hosp Infect*. 2016 Feb;92(2):194-8.
35. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2014. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) [Internet]. Stockholm: ECDC; 2014. Available from: <http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-europe-2014.pdf>.
36. European committee on antimicrobial susceptibility testing. EUCAST warnings concerning antimicrobial susceptibility testing products or procedures - antimicrobial susceptibility testing of colistin - problems detected with several commercially available products. [internet]. EUCAST; 2016. Available from: http://www.eucast.org/ast_of_bacteria/warnings/#c13111.
37. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals. Available from: <http://ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf>. Stockholm: ECDC; 2013.
38. Fishbain J, Peleg AY. Treatment of *Acinetobacter* infections. *Clin Infect Dis*. 2010 Jul 1;51(1):79-84.
39. Fournier PE, Richet H. The epidemiology and control of *Acinetobacter baumannii* in health care facilities. *Clin Infect Dis*. 2006 Mar 1;42(5):692-9.
40. Perez F, Hujer AM, Hujer KM, Decker BK, Rather PN, Bonomo RA. Global challenge of multidrug-resistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother*. 2007 Oct;51(10):3471-84.
41. Keen EF, 3rd, Robinson BJ, Hospenthal DR, Aldous WK, Wolf SE, Chung KK, et al. Prevalence of multidrug-resistant organisms recovered at a military burn center. *Burns*. 2010 Sep;36(6):819-25.
42. Villar M, Cano ME, Gato E, Garnacho-Montero J, Miguel Cisneros J, Ruiz de Alegria C, et al. Epidemiologic and clinical impact of *Acinetobacter baumannii* colonization and infection: a reappraisal. *Medicine (Baltimore)*. 2014 Jul;93(5):202-10.
43. Dexter C, Murray GL, Paulsen IT, Peleg AY. Community-acquired *Acinetobacter baumannii*: clinical characteristics, epidemiology and pathogenesis. *Expert Rev Anti Infect Ther*. 2015 May;13(5):567-73.
44. Jones RN, Flonta M, Gurler N, Cepparulo M, Mendes RE, Castanheira M. Resistance surveillance program report for selected European nations (2011). *Diagn Microbiol Infect Dis*. 2014 Apr;78(4):429-36.
45. Lim LM, Ly N, Anderson D, Yang JC, Macander L, Jarkowski A, 3rd, et al. Resurgence of colistin: a review of resistance, toxicity, pharmacodynamics, and dosing. *Pharmacotherapy*. 2010 Dec;30(12):1279-91.
46. Qureshi ZA, Hittle LE, O'Hara JA, Rivera JI, Syed A, Shields RK, et al. Colistin-resistant *Acinetobacter baumannii*: beyond carbapenem resistance. *Clin Infect Dis*. 2015 May 1;60(9):1295-303.

47. Tsioutis C, Kritsotakis EI, Karageorgos SA, Stratakou S, Psarologakis C, Kokkini S, et al. Clinical epidemiology, treatment and prognostic factors of extensively drug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia in critically ill patients. *Int J Antimicrob Agents*. 2016 Aug 12.
48. Maragakis LL, Perl TM. *Acinetobacter baumannii*: epidemiology, antimicrobial resistance, and treatment options. *Clin Infect Dis*. 2008 Apr 15;46(8):1254-63.
49. Jones CL, Clancy M, Honnold C, Singh S, Snesrud E, Onmus-Leone F, et al. Fatal outbreak of an emerging clone of extensively drug-resistant *Acinetobacter baumannii* with enhanced virulence. *Clin Infect Dis*. 2015 Jul 15;61(2):145-54.
50. Garnacho-Montero J, Gutierrez-Pizarra A, Diaz-Martin A, Cisneros-Herreros JM, Cano ME, Gato E, et al. *Acinetobacter baumannii* in critically ill patients: Molecular epidemiology, clinical features and predictors of mortality. *Enferm Infecc Microbiol Clin*. 2016 Jan 25.
51. Nutman A, Glick R, Temkin E, Hoshen M, Edgar R, Braun T, et al. A case-control study to identify predictors of 14-day mortality following carbapenem-resistant *Acinetobacter baumannii* bacteraemia. *Clin Microbiol Infect*. 2014 Dec;20(12):O1028-34.
52. Spellberg B, Bonomo RA. The deadly impact of extreme drug resistance in *Acinetobacter baumannii*. *Crit Care Med*. 2014 May;42(5):1289-91.
53. Esterly JS, Griffith M, Qi C, Malczynski M, Postelnick MJ, Scheetz MH. Impact of carbapenem resistance and receipt of active antimicrobial therapy on clinical outcomes of *Acinetobacter baumannii* bloodstream infections. *Antimicrob Agents Chemother*. 2011 Oct;55(10):4844-9.
54. Lemos EV, de la Hoz FP, Einarson TR, McGhan WF, Quevedo E, Castaneda C, et al. Carbapenem resistance and mortality in patients with *Acinetobacter baumannii* infection: systematic review and meta-analysis. *Clin Microbiol Infect*. 2014 May;20(5):416-23.
55. Markogiannakis A, Fildis G, Tsiplakou S, Ikonomidis A, Koutsoukou A, Pournaras S, et al. Cross-transmission of multidrug-resistant *Acinetobacter baumannii* clonal strains causing episodes of sepsis in a trauma intensive care unit. *Infect Control Hosp Epidemiol*. 2008 May;29(5):410-7.
56. Bernards AT, Frenay HM, Lim BT, Hendriks WD, Dijkshoorn L, van Boven CP. Methicillin-resistant *Staphylococcus aureus* and *Acinetobacter baumannii*: an unexpected difference in epidemiologic behavior. *Am J Infect Control*. 1998 Dec;26(6):544-51.
57. Wendt C, Dietze B, Dietz E, Ruden H. Survival of *Acinetobacter baumannii* on dry surfaces. *J Clin Microbiol*. 1997 Jun;35(6):1394-7.
58. Rose M, Landman D, Quale J. Are community environmental surfaces near hospitals reservoirs for gram-negative nosocomial pathogens? *Am J Infect Control*. 2014 Apr;42(4):346-8.
59. Liu WL, Liang HW, Lee MF, Lin HL, Lin YH, Chen CC, et al. The impact of inadequate terminal disinfection on an outbreak of imipenem-resistant *Acinetobacter baumannii* in an intensive care unit. *PLoS One*. 2014;9(9):e107975.
60. Ayraud-Thevenot S, Huart C, Mimos O, Taouqi M, Laland C, Bousseau A, et al. Control of multi-drug-resistant *Acinetobacter baumannii* outbreaks in an intensive care unit: feasibility and economic impact of rapid unit closure. *J Hosp Infect*. 2012 Dec;82(4):290-2.
61. Chmielarczyk A, Higgins PG, Wojkowska-Mach J, Synowiec E, Zander E, Romaniszyn D, et al. Control of an outbreak of *Acinetobacter baumannii* infections using vaporized hydrogen peroxide. *J Hosp Infect*. 2012 Aug;81(4):239-45.
62. Koeleman JG, Parlevliet GA, Dijkshoorn L, Savelkoul PH, Vandenbroucke-Grauls CM. Nosocomial outbreak of multi-resistant *Acinetobacter baumannii* on a surgical ward: epidemiology and risk factors for acquisition. *J Hosp Infect*. 1997 Oct;37(2):113-23.
63. Rodriguez-Bano J, Garcia L, Ramirez E, Martinez-Martinez L, Muniain MA, Fernandez-Cuenca F, et al. Long-term control of hospital-wide, endemic multidrug-resistant *Acinetobacter baumannii* through a comprehensive "bundle" approach. *Am J Infect Control*. 2009 Nov;37(9):715-22.
64. Arvaniti K, Lathyris D, Ruimy R, Haidich AB, Koulourida V, Nikolaidis P, et al. The importance of colonization pressure in multiresistant *Acinetobacter baumannii* acquisition in a Greek intensive care unit. *Crit Care*. 2012;16(3):R102.
65. Chusri S, Silpapojakul K, McNeil E, Singkhamanan K, Chongsuvivatwong V. Impact of antibiotic exposure on occurrence of nosocomial carbapenem-resistant *Acinetobacter baumannii* infection: a case control study. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy*. 2015 Feb;21(2):90-5.
66. Munoz-Price LS, Rosa R, Castro JG, Laowansiri P, Latibeaudiere R, Namias N, et al. Evaluating the Impact of Antibiotic Exposures as Time-Dependent Variables on the Acquisition of Carbapenem-Resistant *Acinetobacter baumannii*. *Crit Care Med*. 2016 Oct;44(10):e949-56.
67. Ogutlu A, Guclu E, Karabay O, Utku AC, Tuna N, Yahyaoglu M. Effects of Carbapenem consumption on the prevalence of *Acinetobacter* infection in intensive care unit patients. *Ann Clin Microbiol Antimicrob*. 2014 Jan 09;13:7.

68. Bogaerts P, Naas T, Wybo I, Bauraing C, Soetens O, Pierard D, et al. Outbreak of infection by carbapenem-resistant *Acinetobacter baumannii* producing the carbapenemase OXA-58 in Belgium. *J Clin Microbiol*. 2006 Nov;44(11):4189-92.
69. Hammerum AM, Hansen F, Skov MN, Stegger M, Andersen PS, Holm A, et al. Investigation of a possible outbreak of carbapenem-resistant *Acinetobacter baumannii* in Odense, Denmark using PFGE, MLST and whole-genome-based SNPs. *J Antimicrob Chemother*. 2015 Jul;70(7):1965-8.
70. Landelle C, Legrand P, Lesprit P, Cizeau F, Ducellier D, Gouot C, et al. Protracted outbreak of multidrug-resistant *Acinetobacter baumannii* after intercontinental transfer of colonized patients. *Infect Control Hosp Epidemiol*. 2013 Feb;34(2):119-24.
71. Milan A, Furlanis L, Cian F, Bressan R, Luzzati R, Lagatolla C, et al. Epidemic Dissemination of a Carbapenem-Resistant *Acinetobacter baumannii* Clone Carrying armA Two Years After Its First Isolation in an Italian Hospital. *Microbial drug resistance (Larchmont, NY)*. 2016 Mar 18.
72. Kohlenberg A, Brummer S, Higgins PG, Sohr D, Piening BC, de Grahl C, et al. Outbreak of carbapenem-resistant *Acinetobacter baumannii* carrying the carbapenemase OXA-23 in a German university medical centre. *J Med Microbiol*. 2009 Nov;58(Pt 11):1499-507.
73. Tsiatsiou O, Iosifidis E, Katragkou A, Dimou V, Sarafidis K, Karampatakis T, et al. Successful management of an outbreak due to carbapenem-resistant *Acinetobacter baumannii* in a neonatal intensive care unit. *Eur J Pediatr*. 2015 Jan;174(1):65-74.
74. Merino M, Poza M, Roca I, Barba MJ, Sousa MD, Vila J, et al. Nosocomial outbreak of a multiresistant *Acinetobacter baumannii* expressing OXA-23 carbapenemase in Spain. *Microbial drug resistance (Larchmont, NY)*. 2014 Aug;20(4):259-63.
75. Enoch DA, Summers C, Brown NM, Moore L, Gillham MI, Burnstein RM, et al. Investigation and management of an outbreak of multidrug-carbapenem-resistant *Acinetobacter baumannii* in Cambridge, UK. *J Hosp Infect*. 2008 Oct;70(2):109-18.
76. Onarheim H, Hoivik T, Harthug S, Digranes A, Mylvaganam H, Vindenes HA. [Outbreak of multiresistant *Acinetobacter baumannii* infection]. *Tidsskr Nor Laegeforen*. 2000 Mar 30;120(9):1028-33.
77. Turton JF, Kaufmann ME, Gill MJ, Pike R, Scott PT, Fishbain J, et al. Comparison of *Acinetobacter baumannii* isolates from the United Kingdom and the United States that were associated with repatriated casualties of the Iraq conflict. *J Clin Microbiol*. 2006 Jul;44(7):2630-4.
78. Hsu LY, Apisarnthanarak A, Khan E, Suwantarant N, Ghafur A, Tambyah PA. Carbapenem-Resistant *Acinetobacter baumannii* and Enterobacteriaceae in South and Southeast Asia. *Clin Microbiol Rev*. 2017 Jan;30(1):1-22.
79. Clark NM, Zhanel GG, Lynch JP, 3rd. Emergence of antimicrobial resistance among *Acinetobacter* species: a global threat. *Curr Opin Crit Care*. 2016 Oct;22(5):491-9.
80. Hujer KM, Hujer AM, Hulten EA, Bajaksouzian S, Adams JM, Donskey CJ, et al. Analysis of antibiotic resistance genes in multidrug-resistant *Acinetobacter* sp. isolates from military and civilian patients treated at the Walter Reed Army Medical Center. *Antimicrob Agents Chemother*. 2006 Dec;50(12):4114-23.
81. Petersen K, Cannegieter SC, van der Reijden TJ, van Strijen B, You DM, Babel BS, et al. Diversity and clinical impact of *Acinetobacter baumannii* colonization and infection at a military medical center. *J Clin Microbiol*. 2011 Jan;49(1):159-66.
82. Rafei R, Dabboussi F, Hamze M, Eveillard M, Lemarie C, Mallat H, et al. First report of bla_{NDM-1}-producing *Acinetobacter baumannii* isolated in Lebanon from civilians wounded during the Syrian war. *Int J Infect Dis*. 2014 Apr;21:21-3.
83. Granzer H, Hagen RM, Warnke P, Bock W, Baumann T, Schwarz NG, et al. Molecular Epidemiology of Carbapenem-Resistant *Acinetobacter Baumannii* Complex Isolates from Patients that were Injured During the Eastern Ukrainian Conflict. *Eur J Microbiol Immunol (Bp)*. 2016 Jun 24;6(2):109-17.