ASSESSMENT

Carbapenem-resistant *Acinetobacter baumannii* related to recent hospitalisation in Ukraine

13 April 2022

Main conclusions and options for response

On 28 March 2022, Denmark reported two patients in EpiPulse with the same new variant of a carbapenem-resistant *Acinetobacter baumannii* (CRAb) strain detected during routine screening upon admission to a Danish healthcare facility. The two patients had been hospitalised in Ukraine in early 2022 before being transferred to Denmark. CRAb is the cause of difficult-to-treat infections, and outbreaks in healthcare facilities have been reported worldwide. Recent data shows high proportions of carbapenem resistance in invasive isolates – mostly from bloodstream infections – of *Acinetobacter* spp. reported from Ukraine and adjacent countries (Belarus, Hungary, Poland, Republic of Moldova, Romania, Russian Federation and Slovakia) compared to considerably lower carbapenem resistance proportions in Central and Northern European countries. While this situation is not new, Russia's invasion of Ukraine has resulted in an increased number of hospital transfers and exchanges of patients with prior healthcare exposure between countries with high and low CRAb prevalence. CRAb infections have especially been reported as associated with trauma and combat injuries, mainly occurring in Afghanistan and Iraq, but also previously in Eastern Ukraine.

Pre-emptive isolation and screening for CRAb carriage of patients who are transferred from, or had recently been in contact with, hospitals and other healthcare settings in countries with high prevalence of CRAb are immediate measures to reduce transmission within healthcare facilities and prevent outbreaks from imported CRAb. In the context of the Russian invasion of Ukraine, this applies to all patients who have a history of hospital admission in Ukraine and adjacent countries in the preceding year. For CRAb-positive patients, 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 CRAb. For further options for response, please see the respective section below.

Event background

On 28 March 2022, Denmark reported two patients in EpiPulse with the same variant of a carbapenem-resistant *Acinetobacter baumannii* (CRAb) strain detected during routine screening upon arrival to a Danish healthcare facility. The two patients had been hospitalised in Ukraine in early 2022 before being transferred to Denmark. The CRAb isolates from both patients belong to the same new sequence type, carry a $bla_{\text{OXA-72}}$ carbapenemase gene conferring resistance to carbapenems and are highly antibiotic-resistant, with only susceptibility to colistin and tigecycline.

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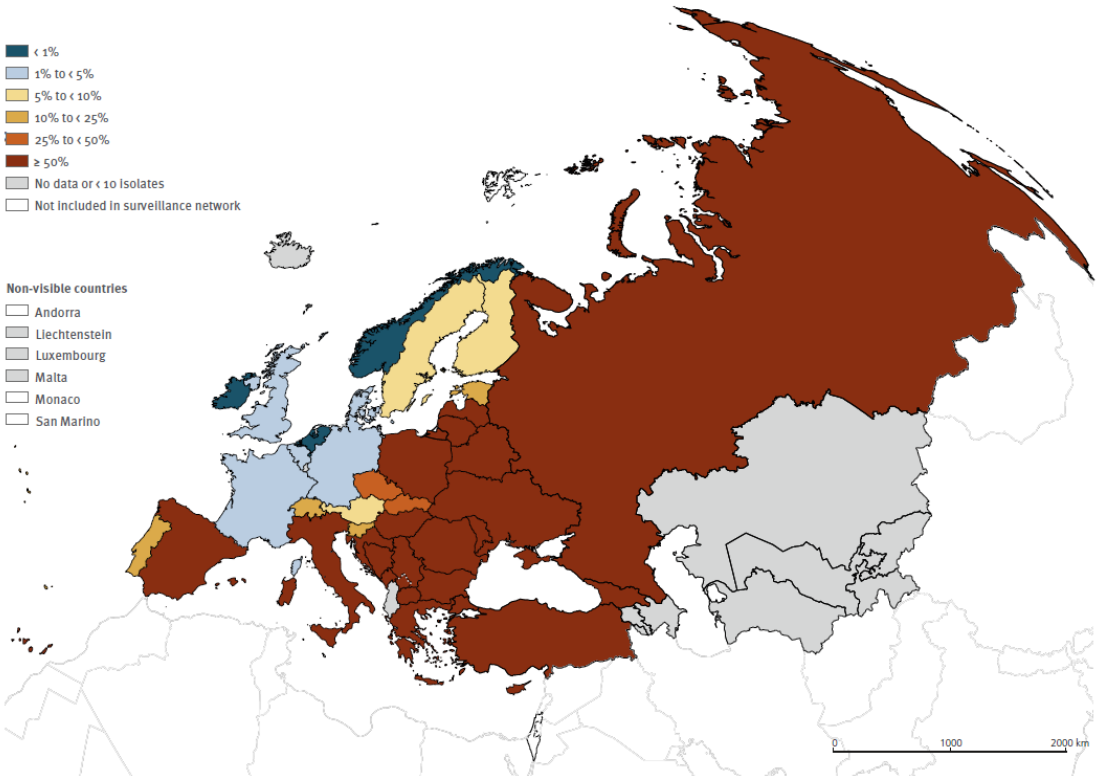
Disease background

Epidemiological situation in Europe

CRAb is among the three multidrug-resistant bacteria in the category of highest priority for which new antibiotics are urgently needed on the WHO priority pathogen list [1]. It poses a significant threat to patients and healthcare systems in countries of the European Union (EU)/European Economic Area (EEA) with an estimated 2,363 annual attributable deaths in 2015 [2]. However, percentages of carbapenem resistance in *Acinetobacter* spp. vary considerably between European countries, with higher proportions of resistance in Southern and Eastern countries than in Northern and Central European countries (Figure 1) [3]. Ukraine and adjacent countries have high proportions of carbapenem resistance in invasive *Acinetobacter* spp. isolates with 77.1% in Ukraine, 94% in Belarus, 73% in Hungary, 78.2% in Poland, 93.1% in the Republic of Moldova, 93.3% in Romania, 93.9% in the Russian Federation and 30.8 % in Slovakia [3]. Carbapenem resistance in *Acinetobacter* spp. is related to the global spread of high-risk clones of carbapenemase-producing *A. baumannii* in healthcare systems [4-6].

Figure 1. *Acinetobacter* spp.: percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country/area, WHO European Region, 2020 [3]



Assessment

Impact of CRAb on human health

Healthcare-associated infections

Healthcare-associated infections caused by *A. baumannii* in general include pneumonia, bloodstream infections, wound infections, urinary tract infections and meningitis after neurosurgical procedures [7]. *A. baumannii* infections frequently occur in patients with severe underlying diseases, mainly in intensive care units, and are often related to invasive procedures or indwelling devices [8,9]. However, infections in patients admitted to conventional medical and surgical wards are also increasing [10]. Although community-acquired *A. baumannii* infections have been described in tropical settings [11], CRAb infections in Europe seem to be almost exclusively healthcare-associated.

Carbapenems used to be the drug of choice for treatment of *A. baumannii* infections, but carbapenem resistance has been increasing globally [9]. The two CRAb isolates reported by Denmark were still susceptible to colistin and tigecycline. Both antimicrobials are being used to treat CRAb infections, but their clinical efficacy has limitations due to unfavourable pharmacokinetics despite *in vitro* susceptibility [12]. In addition, resistance to colistin and tigecycline has developed related to their use for treatment of CRAb, and pandrug-resistant *A. baumannii* isolates

have been described [13-15]. CRAb infections have been associated with poor patient outcomes [16] with increased mortality for patients with CRAb infections compared to carbapenem-susceptible *A. baumannii* infections [17,18].

Association of multidrug-resistant A. baumannii *and CRAb with trauma and combat injuries*

Even though data on antimicrobial resistance in war and crisis zones is not easy to gather, combat-associated acquisition of multidrug-resistant *A. baumannii* have frequently been described in injured soldiers repatriated from Afghanistan and Iraq [19,20]. Multidrug-resistant *A. baumannii* caused an outbreak in the US military healthcare system related to military operations in Iraq [19]. CRAb was also isolated from the wounds of civilians injured during the Syrian war [21]. After terrorist attacks in Bali, 19 of 29 patients with severe burn injuries transferred for treatment to a hospital in Australia were found to be colonised with multidrug-resistant *A. baumannii* amongst other multidrug-resistant bacteria [22].

Recent reports have also highlighted the detection of CRAb isolates in patients that were injured in the Eastern Ukrainian conflict in 2014 and 2015 and transferred for medical treatment to Germany [23,24]. Observed clustering of isolates from different receiving hospitals suggested that transmission events occurred during prior medical management in Ukraine or Belarus, or during transport flights [23]. A microbiological survey in four Ukrainian military hospitals in the period 2014-2020 found a proportion of carbapenem resistance of 67.9% in *A. baumannii* isolates from adult servicemen who were treated for war injuries and presented with healthcare-associated infections [25].

Potential for spread of CRAb

Spread in healthcare settings

Most healthcare-associated outbreaks are caused by *A. baumannii sensu stricto* (s.s.), while outbreaks of other closely related species are rare [7]. Transmission occurs mainly via the hands of healthcare workers, contaminated medical equipment and the healthcare environment [26,27]. Factors contributing to outbreaks and the persistence of CRAb in healthcare settings include its antimicrobial resistance as well as resistance to disinfectants and to desiccation resulting in long-term survival on various surfaces [7,28]. *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 [29].

Outbreaks and cross-border transmission

CRAb outbreaks are difficult to control. In Europe, many countries have experienced outbreaks of CRAb in healthcare settings in the past, for example Belgium [30], Bulgaria [31], Croatia [32] Denmark [33], France [34], Italy [35], Germany [36], Greece [37], Latvia [38], Spain [39] and the UK [40]. More recently, outbreaks of CRAb in COVID-19 units were reported worldwide, including in European countries [41]. Some of the outbreaks in European hospitals are documented to have occurred after the introduction of CRAb via cross-border patient transfer. The origin of the index patient has been reported as a European country (e.g. from Greece to Belgium [30], from Spain to Norway [42] and North Macedonia to Switzerland [41]) or a country from another continent (e.g. from Thailand to Germany [36], Iraq to UK [43], and Tahiti to mainland France [34]).

Increased number of patient transfers due to Russia's invasion of Ukraine

High levels of multidrug resistance in healthcare-associated pathogens had been documented in Ukraine and adjacent countries prior to Russia's invasion [3]. Country-to-country patient transfers are also a regular occurrence worldwide with a known risk of introduction of multidrug-resistant strains to new locations [44]. However, these transfers often involve repatriation of single patients while large-scale civil medical evacuations such as after the southeast Asian tsunami and the Bali terrorist attacks have remained rare [44,45]. Still, individual patient transfers between countries have resulted in frequent cross-border import of various multidrug-resistant pathogens into the EU/EEA, including CRAb, and were sometimes followed by outbreaks [30,36,46,47].

More than 100 attacks on healthcare facilities have occurred in Ukraine since the start of Russia's invasion and WHO estimated that, across Ukraine, 1000 facilities are in proximity to conflict areas and in changed areas of control [48]. In addition to direct attacks, shortage of healthcare staff because of flight, injury or killing of healthcare workers, and lack of medical supplies due to disrupted supply chains have further reduced the capacity of the Ukrainian healthcare system [49]. In this situation, healthcare facilities are likely to focus their resources on upholding clinical management of patients in the first place while there will be less capacity and resources for microbiological testing and infection prevention and control (IPC).

Instability and insecurity during emergency medical evacuations will further impact the ability to adhere to infection control precautions. In addition, patients may pass through several healthcare facilities on their way – in Ukraine

and/or in adjacent countries - with the risk to acquire locally endemic multidrug-resistant bacteria in these facilities, before reaching their destination. The disruption of Ukraine's healthcare system due to Russia's invasion is resulting in patient transfers into the EU on an unprecedented scale with 10,000 hospital beds being secured for treatment of Ukrainian patients in need of care, including neonates, cancer patients, burn patients and patients requiring intensive care [50].

The patient populations mentioned above are among the high-risk populations for carriage and acquisition of multidrug-resistant bacteria and healthcare-associated infections. It is therefore of high importance that patient transfers and admissions of patients with recent hospitalisation in Ukraine are accompanied by adequate admission screening for multidrug-resistant bacteria, including specifically CRAb, and by appropriate IPC measures during patient transfer as much as possible. Further support to the healthcare facilities in Ukraine and adjacent countries may be needed to uphold IPC measures in difficult conditions with high patient numbers. Improvement of IPC and early detection of multidrug-resistant bacteria such as CRAb will directly benefit Ukrainian patients in need of care as well as patients in recipient healthcare systems.

Options for response

Screening patients at high risk for carriage of CRAb

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 CRAb are an immediate measure to reduce transmission in healthcare facilities and prevent outbreaks from imported CRAb. In the context of the Russian invasion of Ukraine, this applies to all patients with previous hospitalisation in Ukraine and adjacent countries in the past year. The optimal body sites for screening for CRAb have been difficult to determine and a combination of sites may be required to improve sensitivity. In a recent study, sampling of large skin areas (both arms and both legs) with sponges premoistened with phosphate buffer had the highest single site sensitivity for screening for CRAb carriage [51]. However, combinations of different sites for screening for CRAb carriage have been suggested based on other studies [52,53]. In addition, screening upon hospital admission should also include other multidrug-resistant bacteria (such as carbapenemase-producing Enterobacterales and meticillin-resistant *Staphylococcus aureus*) following national protocols. Patients should remain in pre-emptive isolation until availability of screening results.

Preventing transmission from patients known to carry CRAb

Good standard IPC, including hand hygiene, 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 drug-resistant bacteria. Prompt notification of the clinical and IPC teams is essential for the rapid implementation of IPC measures to prevent further spread. In a setting where CRAb is not endemic, each new case of CRAb should be considered as a trigger for further investigation and enhanced IPC measures. For CRAb-positive patients, 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 CRAb.

Specific recommendations for control of CRAb outbreaks

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 IPC 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. A recent study showed that a CRAb outbreak in an intensive care unit was controlled through proactive reinforcement of all routine IPC practices among healthcare workers, starting with hand hygiene; extended screening of patients for CRAb carriage; contact precaution measures for all patients until discharge, independently of CRAb status; environmental sampling using pre-moistened sterile gauze pads; and cycling radical cleaning and disinfection of all rooms, areas and patients, and did not necessitate closure of the unit [54]. Nevertheless, temporary stop of admissions or even complete closure of a unit or ward has been used as a measure of last resort in outbreak situations where other measures failed to control the spread CRAb. 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.

Exchange of information and prevention of cross-border transmission

Documentation of known CRAb carriage or infection at the time of cross-border patient transfer would optimise the early and effective implementation of measures to prevent the spread of CRAb. Standardised patient forms in English and in the language of the referring healthcare facility with information on, e.g., prior microbiological results and antimicrobial treatment, would improve clinical management of patients as well as transfer of information relevant for IPC. Proper IPC measures during transfer of patients should be ensured as much as possible.

Gathering reliable epidemiological data through notification of cases to public health authorities and exchange of information through electronic early warning platforms, such as the EpiPulse and early warning and response system (EWRS), are important activities to allow informed and coordinated actions by public health authorities across the EU/EEA.

Consulted experts

ECDC experts (in alphabetic order): Anke Kohlenberg, Dominique Monnet, Aikaterini Mougkou.

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