RAPID RISK ASSESSMENT

Carbapenemase-producing (OXA-48) *Klebsiella pneumoniae* ST392 in travellers previously hospitalised in Gran Canaria, Spain

10 July 2018

Main conclusions and options for response

Conclusions

Between January and April 2018, Sweden and Norway reported a cluster of returning travellers who carried or were infected with carbapenemase (OXA-48)-producing *Klebsiella pneumoniae* ST392. All cases were associated with hospital admissions in Gran Canaria. Isolates from cases showed tight clustering when analysed by whole genome sequencing.

This cluster of 13 patients colonised or infected with OXA-48-producing *K. pneumoniae* ST392 is an example of cross-border spread of carbapenemase-producing Enterobacteriaceae (CPE) in the European Union/European Economic Area (EU/EEA). Cross-border transfers of patients or hospital admissions of patients with previous hospitalisation in another country are a daily occurrence in EU/EEA hospitals.

The risk for individual travellers to acquire OXA-48-producing *K. pneumoniae* ST392 of the Gran Canaria cluster without healthcare contact is very low. However, if carriers of OXA-48-producing *K. pneumoniae* ST392 of the Gran Canaria cluster are admitted to a hospital in their country of origin, there is a high risk of transmission and subsequent outbreaks if OXA-48-producing *K. pneumoniae* ST392 carriage remains undetected and there are no adequate infection control and prevention measures.

This example highlights the benefits of active surveillance (screening) for CPE carriage, including OXA-48-producing *K. pneumoniae* ST392, immediately at hospital admission in patients who are directly transferred from a hospital abroad. It also shows the value of cross-country sharing of epidemiological and whole genome sequencing data as well as the added value of collaborative analyses to determine the origin of this OXA-48-producing *K. pneumoniae* ST392 cluster.

Options for response

Hospitals in EU/EEA countries should consider taking, at hospital admission, a detailed history of travels and hospitalisations for every patient. They should also perform pre-emptive isolation and screening for carriage of CPE, including OXA-48-producing *K. pneumoniae*, at least in patients who were directly transferred or hospitalised in countries with known high prevalence in the 12 months before admission (see ECDC survey of national experts), or in patients who were hospitalised in their own country in the 12 months before admission, but in a region or hospital with known high prevalence of CPE, including OXA-48-producing *K. pneumoniae*. However, as prevalence of CPE, including OXA-48-producing *K. pneumoniae,* is difficult to monitor in some

Suggested citation: European Centre for Disease Prevention and Control. Carbapenemase-producing (OXA-48) *Klebsiella pneumoniae* ST392 in travellers previously hospitalised in Gran Canaria, Spain – 10 July 2018, Stockholm, 2018.

regions and national prevalence might not always reflect the regional or local situation, screening every patient who was hospitalised in a foreign country in the 12 months before admission might be a more suitable option. Microbiological methods suitable for the screening and detection of CPE, including those producing an OXA-48-like carbapenemase, are outlined in the section on laboratory detection below. Detailed actions for the prevention of transmission of CPE in hospitals and other healthcare settings have been described in a prior ECDC Rapid Risk Assessment and in an ECDC guidance document.

Proper transfer letters and good interfacility communication surrounding transfers are key elements of ensuring effective measures to limit the spread of CPE, including OXA-48-producing *K. pneumoniae,* in the receiving hospital. Moreover, gathering reliable epidemiological data, notifying cases to public health authorities, and exchanging information are important activities to enable informed and coordinated actions by public health authorities across the EU/EEA. Public health authorities should issue notifications on the Early Warning and Response System (EWRS) where relevant, as per Article 9 of Decision 1082/2013/EU on serious cross-border threats to health. The use of the Epidemic Intelligence System (EPIS) is encouraged to ensure transparent and timely sharing of information among participating public health authorities in order to detect public health threats at an early stage.

Source and date of request

ECDC internal decision, 28 June 2018.

Public health issue

Sweden and Norway, via the EPIS AMR-HAI platform, reported a cluster of returning travellers who carried or were infected with carbapenemase (OXA-48)-producing *Klebsiella pneumoniae* ST392 during the period from January to April 2018. All cases appeared to have had recent hospital admissions in Gran Canaria prior to admission to a healthcare facility in their home country. This rapid risk assessment evaluates the risk of transmission and further spread of OXA-48-producing *Klebsiella pneumoniae* ST392 from travellers having sought medical care in Gran Canaria to healthcare facilities in their country of origin in the EU/EEA.

Consulted experts

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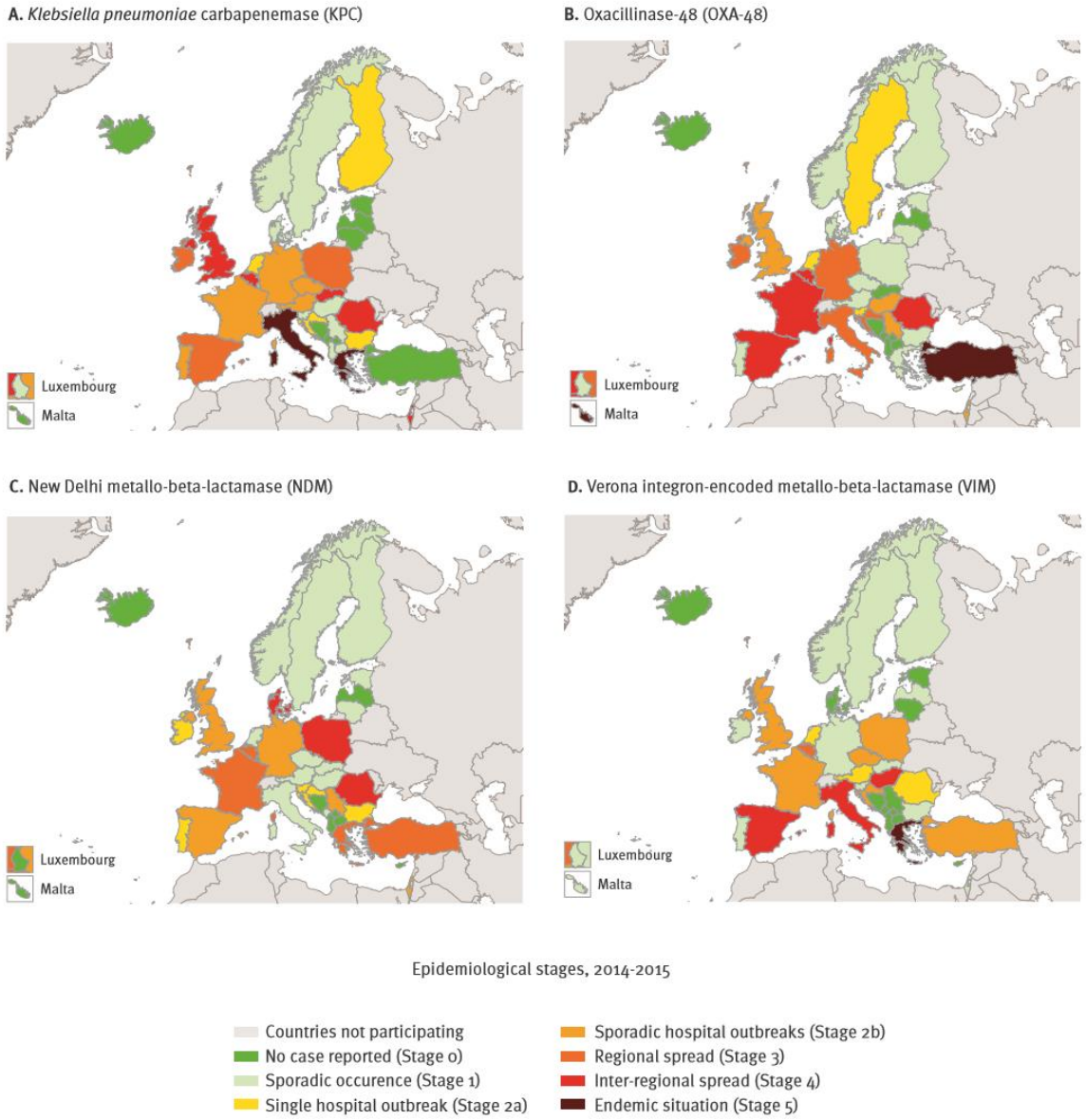
Disease background information

Epidemiology of OXA-48-producing *K. pneumoniae*

Since its first description in 2001 in a Turkish patient [1], OXA-48-producing *K. pneumoniae* strains have caused outbreaks worldwide, particularly in the Mediterranean area (Turkey, North Africa and the Middle East). Sporadic cases or outbreaks of OXA-48-producing *K. pneumoniae* have been described for most European countries [1,2]. According to the European Antimicrobial Resistance Surveillance Network (EARS-Net), the percentage of carbapenem resistance in *K. pneumoniae* isolates from invasive infections in Spain was low (2.1%) in 2016 [3].

A national expert assessment in 2015 indicated interregional spread of CPE in Spain, in particular Enterobacteriaceae producing OXA-48 (Figure 1) [4]. In the European Survey of Carbapenemase-Producing Enterobacteriaceae (EuSCAPE), OXA-48-like enzymes were the most frequent carbapenemases detected in carbapenem-resistant *K. pneumoniae* isolates collected in Spain in 2013–2014 [5]. Hospital outbreaks of OXA-48-like-producing *K. pneumoniae* caused by different multilocus sequence types have been described in many countries including Spain [2,6]. The clonal dissemination of OXA-48-producing *K. pneumoniae* has been described in a hospital in the Canary Islands (Tenerife) [7].

Figure 1. Geographic distribution and national dissemination of various carbapenemase-producing Enterobacteriaceae, based on self-assessment by national experts of 38 European countries, May 2015



Source: Eurosurveillance [4]

Laboratory detection of OXA-48-producing *K. pneumoniae*

The OXA-48-like carbapenemase enzymes present a particular problem for laboratory detection because of their weakly hydrolysing capacity of carbapenems. Therefore, OXA-48-producing isolates may be categorised as carbapenem-susceptible according to clinical breakpoints. EUCAST recommends testing clinical isolates with reduced susceptibility ranging between the epidemiological cut-off (ECOFF) and the susceptible breakpoint (screening cut-off: ertapenem or meropenem MIC >0.125 mg/L or equivalent inhibition zone diameter by disc diffusion method) for carbapenemase production [8]. Putative OXA-48-producing isolates identified with the above-mentioned method should be tested by one or a combination of the phenotypic methods available for the detection of carbapenemases (synergistic combination disk testing, colorimetric hydrolysis tests, carbapenem inactivation method, carbapenem hydrolysis detection with MALDI-TOF analysis and specific OXA-48 immunochromatographic lateral flow assays) [8]. Functional biochemical tests may give false-negative results due to slow substrate hydrolysis by OXA-48-producing *K. pneumoniae* isolates, unless the test procedure is modified by prolonging the incubation time. At current, no specific inhibitor is readily available for detecting OXA-48-like enzymes. High-level resistance to temocillin is a non-specific clue to the presumptive production of OXA-48-like enzymes, but requires confirmation [8].

Genotypic detection and identification of genes coding for OXA-48-like enzymes can be performed on isolates following culture or directly on screening and clinical samples by multiplex PCR assays, loop-mediated isothermal amplification (LAMP), or DNA hybridisation assays designed for a pre-defined range of carbapenemase genes [9].

Commercial real-time PCR assays detect different gene variants of OXA-48-like and other types of carbapenemase genes in less than two hours. Some commercial DNA microarray assays and immunochromatographic lateral flow assays designed for the direct detection of carbapenemase genes in blood cultures include probes/antibodies for OXA-48-like genes/enzymes. Whole genome sequencing can be used to identify carbapenemase genes together with providing the full resistome and genome sequence for comparative phylogenetic analysis [9].

Active surveillance (screening) for carriage of patients potentially colonised with carbapenemase-producing Enterobacteriaceae, including OXA-48-producing *K.pneumoniae* or other species of Enterobacteriaceae, can be done by cultivating rectal swabs or stool specimens, either by direct plating or after broth enrichment on selective differential chromogenic agar media, followed by testing the isolate for carbapenemase activity by one of the above mentioned phenotypic tests or by PCR detection of carbapenemase genes [9,10].

All available methods for screening and detection of CPE have specific advantages and limitations in terms of accuracy, turnaround time, logistical and running costs. Clinical accuracy of the different methods/assays has been best documented for KPC enzymes and less well for OXA-48-like enzymes. There is a difference between screening for carbapenem-resistant Enterobacteriaceae and CPE screening, and some of the commercial agars or enrichment broth media with high concentrations of carbapenems may not detect CPE isolates with only decreased susceptibility phenotype.

As emphasised in a recent review of relative performance and practicality of culture-based and molecular methods, the optimal screening approach for CPE should be established in each healthcare facility and for each infection control purpose, given the epidemiologic situation and prevalent carbapenemases [9].

Event background information

Reported cases of OXA-48-producing *K. pneumoniae* ST392 in travellers returning from the Canary Islands

Case definition

Cases: reported cases of OXA-48-producing *K. pneumoniae* ST392 in travellers returning from and having been hospitalised in Gran Canaria in 2018.

Possible cases: cases of OXA-48-producing *K. pneumoniae* ST392 detected before 2018 in travellers returning from the Spanish mainland or the Spanish Canary Islands, with or without information on hospitalisation.

Sweden

Sweden reported eight cases of OXA-48-producing *K. pneumoniae* ST392, six of which meet the case definition, including hospitalisation in Gran Canaria in 2018; two are possible cases detected in 2015 and 2016. The six cases notified between January and April 2018 were all hospitalised in the same hospital (hospital A) in Gran Canaria. Two of these six patients had infections (sputum samples), and the remaining four patients were identified as carriers from screening samples (faeces).

Norway

Norway reported nine cases of OXA-48-producing *K. pneumoniae* and travel history to Gran Canaria in 2018, of which seven have the same multilocus sequence type (ST392) and therefore fulfil the case definition. For the other two cases, typing has not yet been performed. The seven cases with OXA-48-producing *K. pneumoniae* ST392 were hospitalised while abroad. For three of these seven patients, information was available that they had also been admitted to the same hospital (hospital A) as the Swedish cases. Six patients were repatriated via direct hospital transfer to Norway, where they tested positive for OXA-48-producing *K. pneumoniae* ST392 upon hospital admission. Two patients had infections while the other patients were identified as carriers through screening.

Finland

Finland reported two possible cases of OXA-48-producing *K. pneumoniae* ST392 detected in 2015 and 2016, both with a travel history to the Canary Islands. Further information on these cases is currently not available. No cases have been detected in 2018.

Antimicrobial resistance phenotype of case isolates

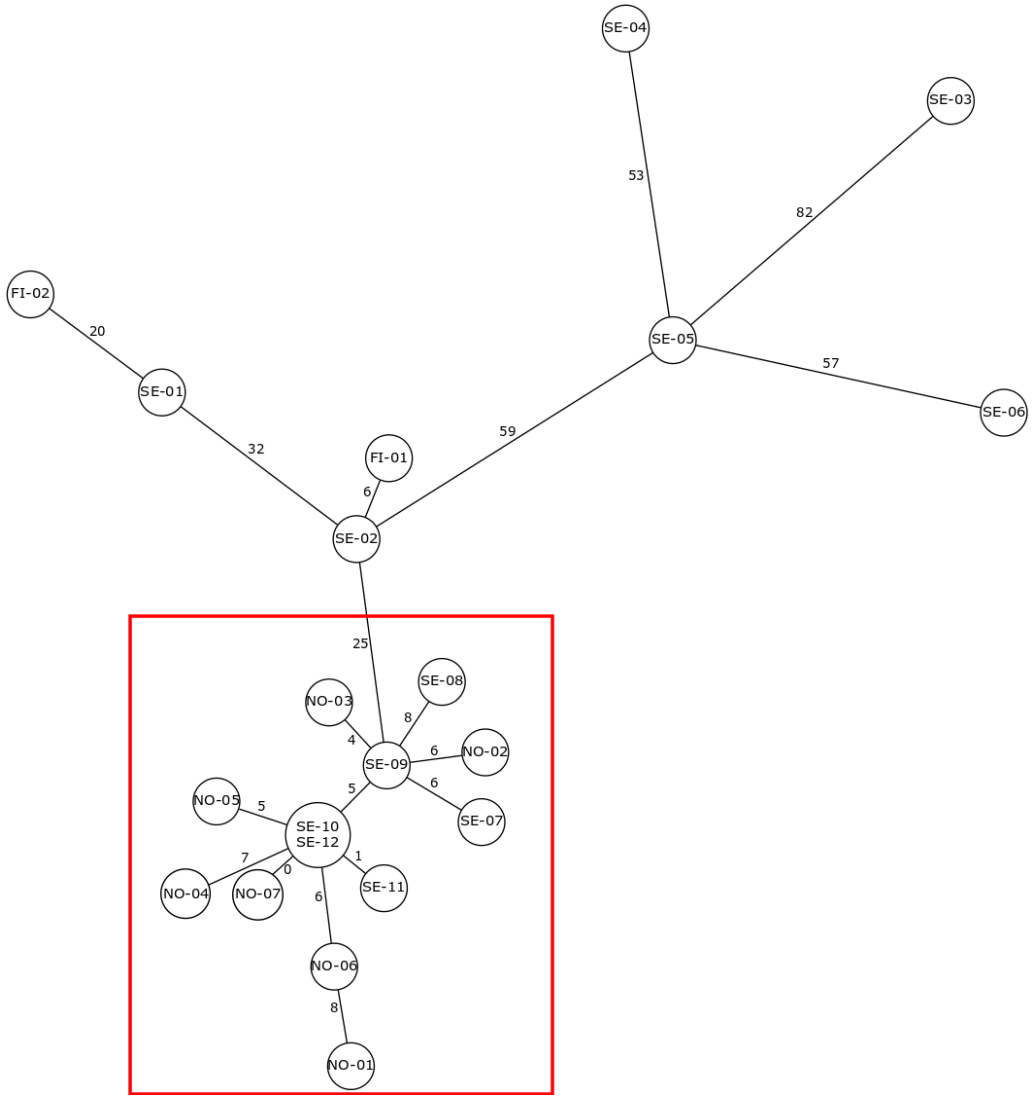
The seven Norwegian and six Swedish OXA-48-producing *K. pneumoniae* ST-392 isolates from the above described case patients all contained the $bla_{\text{CTX-M-15}}$ ESBL gene in addition to the $bla_{\text{OXA-48}}$ gene and expressed the same multidrug resistance profile by broth microdilution (Norway) or gradient diffusion method (Sweden):

- Reduced susceptibility to meropenem (median MIC 1.0 mg/L; range 0.5–2) and to imipenem (median MIC 0.5mg/L; range 0.25–2). These MIC values are below or at the clinical breakpoint for meropenem and imipenem susceptibility (≤2 mg/L).
- Resistance to cefotaxime, ceftazidime, cefepime, aztreonam, piperacillin-tazobactam, ciprofloxacin, trimethoprim or trimethoprim-sulfamethoxazole, gentamicin, tobramycin, and nitrofurantoin.
- Susceptibility to amikacin, tigecycline and colistin. One isolate was colistin resistant (MIC >8 mg/L), but contained no known plasmid-mediated colistin resistance determinants.

Whole genome sequencing results

Whole genome sequencing data on 17 clinical isolates from the cases and possible cases from Sweden, Norway and Finland and four unrelated *K. pneumoniae* ST392 control isolates used as reference were analysed using the bioinformatics pipeline of the Public Health Agency of Sweden [11,12]. The raw sequencing data were mapped to a *K. pneumoniae* ST392 in-house reference genome, and single nucleotide polymorphisms (SNPs) were called, both using CLC Assembly Cell (Qiagen bioinformatics). All isolates from the cases detected in returning Swedish and Norwegian travellers in 2018 were grouped together within eight SNPs differences by single-linkage clustering. The closest related isolates were from the possible cases detected in Finland and Sweden in 2015–2016; their genomes differed from the 2018 outbreak cluster by at least 25 SNPs.

Figure 2. Minimum spanning tree of *Klebsiella pneumoniae* ST392 isolates from Sweden, Norway and Finland, 2014–2018



Minimum spanning tree showing the Klebsiella pneumoniae *ST392 isolates from 2015-2018 analysed using SNPs (Public Health Agency of Sweden). 86% of the genome could be included in the analysis. The red box indicates the current outbreak cluster including the 13 Swedish and Norwegian cases. Isolates SE03-06 (top right) are epidemiologically unrelated control isolates of* K. pneumoniae *ST392.*

Table 1. Supplementary data on the *K. pneumoniae* ST392 isolates included in the WGS analysis

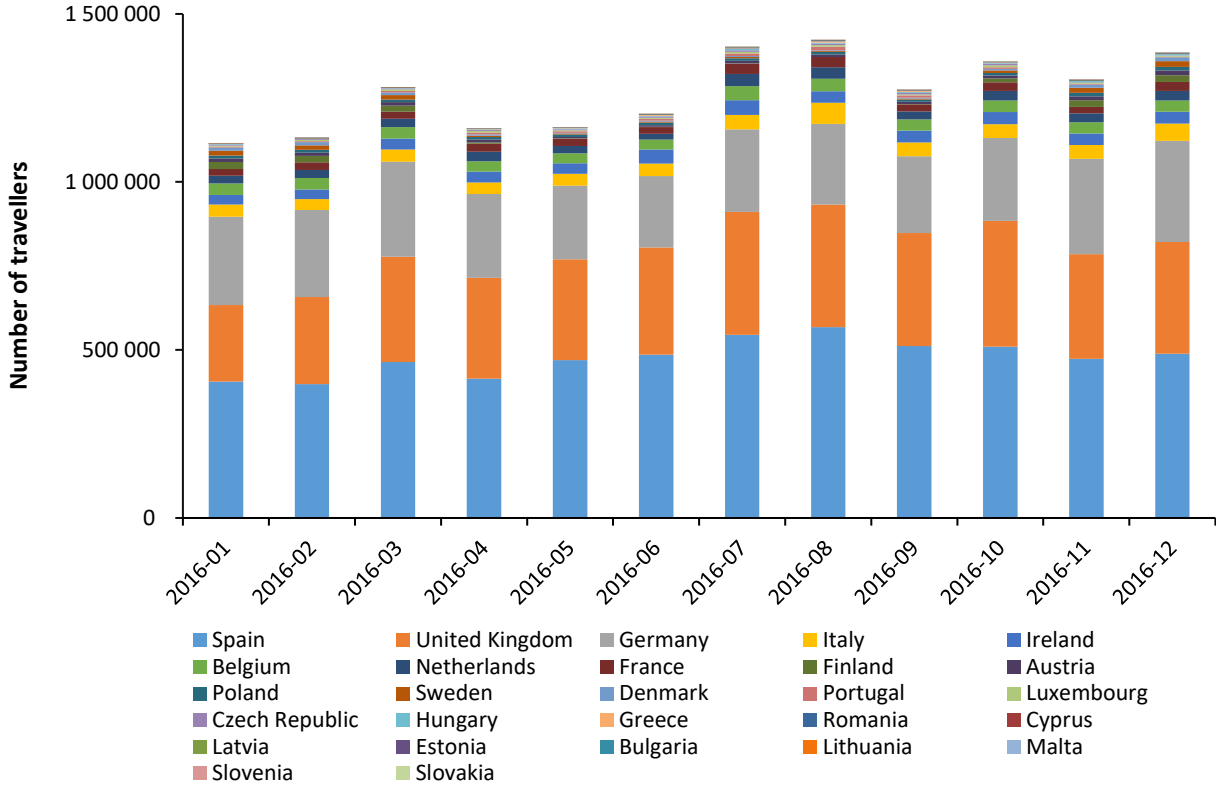
Isolate number	Country	Year	Carbapenemase marker	Travel (returning from)	Hospitalisation during travel (place)
Cases					
SE-07	Sweden	2018	OXA-48	Gran Canaria	Yes (hospital A)
SE-08	Sweden	2018	OXA-48	Gran Canaria	Yes (hospital A)
SE-09	Sweden	2018	OXA-48	Gran Canaria	Yes (hospital A)
SE-10	Sweden	2018	OXA-48	Gran Canaria	Yes (hospital A)
SE-11	Sweden	2018	OXA-48	Gran Canaria	Yes (hospital A)
SE-12	Sweden	2018	OXA-48	Gran Canaria	Yes (hospital A)
NO-01	Norway	2018	OXA-48	Gran Canaria	Yes (hospital A)
NO-02	Norway	2018	OXA-48	Gran Canaria	Yes
NO-03	Norway	2018	OXA-48	Gran Canaria	Yes
NO-04	Norway	2018	OXA-48	Gran Canaria	Yes
NO-05	Norway	2018	OXA-48	Gran Canaria	Yes (hospital A)
NO-06	Norway	2018	OXA-48	Gran Canaria	Yes
NO-07	Norway	2018	OXA-48	Gran Canaria	Yes (hospital A)
Possible cases					
SE-01	Sweden	2015	OXA-48	Gran Canaria	Yes
SE-02	Sweden	2016	OXA-48	Spain	Yes
FI-01	Finland	2015	OXA-48	Canary Islands	Unknown
FI-02	Finland	2016	OXA-48	Canary Islands	Unknown
Control isolates					
SE-03	Sweden	2016	KPC-3	Italy	Yes
SE-04	Sweden	Unknown	OXA-48	Unknown	Unknown
SE-05	Sweden	2017	negative	Unknown	Unknown
SE-06	Sweden	2016	negative	Unknown	Unknown

Travel and tourism in the Canary Islands

Travel data

The EU countries with the largest number of people flying to the Canary Islands are Spain, the UK, Germany, Italy, Ireland, Belgium, the Netherlands and France. According to data provided by IATA, more than 15 million EU/EEA citizens travelled to the Canary Islands in 2016. Spain accounted for 37% of these travellers, the UK for 25% and Germany for 20%. The peak months were July, August, October and December. In 2016, about four million people flew to Gran Canaria.

Figure 3. Estimated number of travellers from EU to the Canary Islands, by month and country of departure, 2016



Source: IATA

ECDC threat assessment for the EU

Hospitalisation abroad and cross-border transfer of patients are well known modes of introduction of carbapenemase-producing *K. pneumoniae* and other Enterobacteriaceae into countries with lower prevalence; they pose a risk for further transmission and hospital outbreaks [13,14]. The described cases of OXA-48-producing *K. pneumoniae* ST392 were detected in several Nordic countries. In these countries, patients who were hospitalised abroad are routinely screened for CPE carriage upon hospital admission, and CPE screening cut-offs according to EUCAST recommendations are used, rather than clinical susceptibility breakpoints. Cases and their travel history are then notified to the national authorities. Such stringent screening policies and sensitive laboratory testing practices are probably only in place in a few EU/EEA countries and even there may not be implemented in all hospitals [4].

According to EARS-Net, Spain still has a low percentage of carbapenem resistance in invasive *K. pneumoniae* isolates [3] and may not be perceived as a high-risk country for carbapenemase-producing Enterobacteriaceae carriage in returning travellers with a history of hospitalisation abroad. However, Spanish experts have acknowledged and reported an interregional spread of OXA-48-producing Enterobacteriaceae in the country [4]. In addition, as stated above, OXA-48-producing *K. pneumoniae* isolates may frequently remain undetected in routine clinical microbiology laboratories as they may be classified as carbapenem-susceptible when clinical breakpoints for carbapenems are applied, which increases the risk that their introduction remains undetected until further spread has occurred.

Carbapenemase-producing *K. pneumoniae* is a resistant bacterium typically acquired in healthcare settings [14]. A whole genome sequencing data analysis of all OXA-48-producing *K. pneumoniae* ST392 isolates available from case patients from Sweden and Norway in 2018 showed a tight clustering (0–8 SNPs difference), indicating a common place of acquisition. Nine cases (six Swedish cases and three Norwegian cases) with admission to hospital A in Gran Canaria were part of this cluster. This supports the hypothesis that hospital A is the most likely place of acquisition.

Controlling the dissemination of antimicrobial-resistant bacteria involving one or more hospitals is primarily the responsibility of local health authorities. However, with a large number of tourists in the area, including elderly persons and persons with underlying diseases, hospitals may become the source of spread to several other European countries when patients are transferred from one country to another. Long-term carriage of CPE has been described in the literature [14]: patients carrying OXA-48-producing *K. pneumoniae* ST392 of the same cluster (as shown by whole genome sequencing analysis) acquired during hospitalisation in Gran Canaria may therefore still introduce this *K. pneumoniae* strain several months after having returned to their country of origin.

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