Tender

EMA/329429/2016

Anti-microbial resistance: choice of therapeutic interventions and outcomes for the treatment of infections caused by MDR Gram-negative pathogens

Re-opening of competition no. 7 under a framework contract following procurement procedure EMA/2014/50/RE

September 2016

Background

The global challenge of increasing antibiotic resistance

Antibiotics have been introduced into medical practice more than 60 years ago (1) with a substantial impact on mortality in life-threatening bacterial diseases, such as acute meningococcal meningitis, staphylococcal osteomyelitis, septicaemia and pneumonia (2). The total use of systemic antibiotics in humans has increased much over the last decades, e.g. by 40% in Denmark during 1997-2011 (3). An increase has been documented globally during 2000-2010 (4), with huge international variation related to over-the-counter antibiotic use (5).

Overuse and misuse of antibiotics in both humans and animals has been a main cause of antibiotic or antimicrobial resistance worldwide (6), which is the ability of disease-causing bacteria (i.e. pathogens) to change and resist the effects of drugs, created to destroy pathogens or to stop them from growing and multiplying. Several biochemical mechanisms of resistance exist, including mutational alteration of the target protein, enzymatic inactivation of the antibiotic drug, acquisition of genes for less susceptible target proteins from other species, bypassing of the target or preventing drug access to the target (7). Resistant bacteria do not respect borders. For example, in the Netherlands, with its low antibiotic use in humans, over 10% of community dwelling individuals have recently been shown to carry antibiotic-resistant (extended-spectrum beta-lactamase (ESBL)-producing) Enterobacteriaceae, with a major risk factor being travel to countries outside Europe (8).

All types of bacteria have the ability to become drug-resistant, and occurrence of resistance has been seen for almost all antibiotics that have been introduced (9). During the last decades, several bacterial pathogens have evolved into multidrug-resistant (MDR) forms (i.e. being resistant to several or all antibiotics) both in developed and developing countries (9-11). The World Health Organization (WHO) has recently identified antimicrobial resistance as one of the three most important problems facing human health (12). MDR infections constitute a serious public health problem because they are difficult to treat effectively, leading to longer hospital stays, treatment failures, and adverse outcomes such as complications and death (6;13). The Centers for Disease Control and Prevention (CDC) has estimated that each year in the United States, at least 2 million people become infected with resistant bacteria and at least 23,000 people die as a direct result of antibiotic resistant pathogens (9). Analyses from the European Centre for Disease Prevention and Control (ECDC) in 2009 estimated that infections caused by a subset of resistant bacteria are responsible for about 25,000 deaths in Europe annually (10). The overall crude economic burden of antibiotic resistance in the United States has been estimated at $20 billion in health care costs and $35 billion a year in lost productivity (14) and in Europe, at least 900 million Euro in health care costs and 600 million Euro a year in lost productivity (10;15).

MDR Gram-negative pathogens

Some of the most important MDR pathogens that currently cause infection in hospital and in the community are the so-called "ESKAPE" pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacter* species), emphasizing their capacity to "escape" the effects of routine antibiotics (16;17). Of special concern are several MDR Gram-negative pathogens such as Enterobacteriaceae (mostly *K. pneumoniae*), *P. aeruginosa*, and *Acinetobacter* species (18), which are becoming resistant to almost all antibiotics available, creating situations reminiscent of the pre-antibiotic era (19). Of special importance, the global emergence of extended-spectrum beta-lactamases (ESBLs) (8) in the 1990s led to the widespread use of carbapenems, which are typically used as the "last treatment option" against MDR bacteria (19), followed by the emergence of a pandemic of carbapenem-resistant Enterobacteriaceae (18;20).

K. pneumoniae can cause nosocomial pneumonia, bloodstream infections, wound or surgical site infections, and meningitis. *K. pneumoniae* has developed extensive antimicrobial resistance, most recently to carbapenems (20). According to the ECDC Antimicrobial Resistance Surveillance Network (EARS-Net) (10), 22% of all *K. pneumoniae* were resistant in 2011 to at least three antimicrobial classes, and a substantial increase in resistance to carbapenems in *K. pneumoniae* from 8% to 15% has been reported over the period 2005–2010. *P. aeruginosa* infection has evolved into a major nosocomial disease causing pneumonia, bloodstream and urinary tract infections, as well as surgical site infections mainly in patients with compromised immune defense (21). Antimicrobial resistance in *P. aeruginosa* is common in Europe, with a majority of the 29 EARS-Net countries reporting resistance above 10 % for all antimicrobial groups under surveillance (10). In addition, 15% of *P. aeruginosa* were resistant to at least three antimicrobial groups and 6% were resistant to all five antimicrobial groups under regular EARS-Net surveillance (10). CDC has estimated that 6,700 of MDR P. aeruginosa occur annually in United States causing 440 deaths (9). *A. baumannii* is involved in mechanical ventilator-associated pneumonia, central-line-associated bloodstream infections, urinary tract infections, surgical site infections and other types of wound infection (22). Today, *A. baumannii* has extensive resistance to most first-line antibiotics (23). The CDC has estimated that 7,300 of MDR *A. baumannii* infections occur annually in United States, causing 500 deaths (9). *A. baumannii* has also become an issue in war conflict zones and has spread particularly in the United Kingdom and the United States (24).

Available interventions and therapies against MDR Gram-negative infections

Several guidelines regarding MDR Gram-negative infection prevention and control interventions are currently available. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) published guidelines in 2014 based on a systematic review (25) provide recommendations regarding different interventions to prevent the spread of MDR bacteria, including hand hygiene, education, contact precautions, isolation room, environmental cleaning. In 2016, a joint working party comprising of microbiologists, infectious disease physicians, epidemiologists, and patient representatives from the UK published recommendations on specific MDR Gram-negative bacteria, including screening, diagnosis, and infection control precautions including hand hygiene, single-room accommodation, environmental screening and cleaning (26). The WHO global report on antimicrobial resistance published in 2014 (11) identified insufficiency of basic systems to track and monitor the problem of MDR bacteria in many countries as a major barrier to prevention and treatment. The WHO stated that interventions to prevent occurrence of MDR infections are essential, but at the same time invited policymakers and industry to develop new antibiotics.

While in the last 15 years, pharmaceutical industry focused on the development of antibiotics against methicillin- and vancomycin-resistant Gram-positive bacteria, the development of drugs against MDR Gram-negative bacteria got somewhat neglected (18). There is now a strong requirement for the development of novel and effective antibiotics for Gram-negative infections, to overcome the problem of antimicrobial resistance. The Infectious Disease Society of America has taken up a global initiative of 10 × ’20 meaning development of 10 new antibiotics against Gram-negative bacilli by the year 2020 (27).

Currently, a number of older antibiotics have been revived from their previous use in the 1970s–1980s (and subsequent abandonment due to side effects), to combat MDR in Gram-negative bacteria. Important agents include colistin, fosfomycin, temocillin, and rifampicin, as well as the newer antibiotic, tigecycline (18;28). A number of narrative literature reviews have recently been conducted to examine the efficacy of the currently used antibiotics for MDR Gram-negative bacteria (16;18;28-32), focusing on susceptibility and clinical therapy outcomes, yet without being able to offer firm recommendations. Taneja and Kaur summarized the current knowledge on antibiotics approved by the US Food and Drug Administration such as ceftolozane/tazobactam and cetrazidime/avibactam combination therapy, which have been effective against many Enterobacteriaceae and *P. aeruginosa* (18). Available therapies against MDR *Acinetobacter* were reviewed by Poulikakos and colleagues (31) and based on 12 papers published between 2005-2013, the authors did not find sufficient evidence for definitive recommendation regarding specific treatments. Rafailidis and colleagues (32) reviewed 10 clinical trials published during 2013-2014 on current treatment options for carbapenem-resistant

Enterobacteriaeceae, finding that combination treatment might in general be more efficacious than monotherapy, but again, no firm recommendation could be given. Although there are theoretical reasons for using combination treatment in favour of monotherapy, clinical data addressing these considerations are neither overwhelming nor definitive (33;34).

The scarcity of data on clinical practice and guidelines in Europe

There is currently a scarcity of data on which antibiotics, alone or in combination, are presently guideline-recommended - and used in clinical practice - in Europe for the treatment of infections due to MDR Gram-negative pathogens. Guidelines that are most applicable to Europe may come from those 'Anglo-Saxon' countries that suffer from high MDR problems, such as the United States and Australia (16). For example, University of Washington offers specific detailed recommendations for antibiotic dosage and treatment of e.g. MDR *Pseudomonas* and *Acinetobacter* (i.e., colistin + meropenem, with rifampin or aminoglycoside add-on therapy to consider based on susceptibility patterns, for Acinetobacter furthermore considering minocycline or tigecycline add-on), which can be downloaded from their website (http://depts.washington.edu/idhmc/wp-content/uploads/2015/11/MDR-treatment-algorithm-table-June-2014.pdf). Johns Hopkins offers similar advice at http://www.hopkinsmedicine.org/amp/guidelines/Antibiotic_guidelines.pdf. In Australia, specific antibiotic treatment recommendations for MDR bacteria in urology (35) and for third-generation cephalosporin-resistant Enterobacteriaceae and carbapenem-resistent Enterobacteriaceae (36) are in place. The existence and content of similar guidelines in European centres needs to be fully explored, which is a central aim of our proposal.

In conclusion, current official recommendations suggest different methods to prevent and control MDR Gram-negative infections, but provide little data on new and alternative antibiotic treatment options. In addition, recent systematic reviews summarise current knowledge on the activity of different antibiotics against MDR Gram-negative bacteria, but provide little firm guidance on specific treatment choices and algorithms. We propose a thorough review of this issue in Europe, systematically investigating available literature and guidelines, combined with a cross-sectional survey of infectious disease clinicians and microbiologists in different European countries with low, medium, or high MDR, to capture the current practice for treatment of infections due to MDR Gram-negative pathogens for which limited therapeutic options are available.

Objectives

The service, as proposed by the Agency, which this project will address, includes:

1. A review of relevant published articles and reports providing guidelines on treatment options for MDR Gram-negative infections.

2. A cross-sectional survey of pharmacists or clinicians in a range of selected reference hospitals about therapeutic protocols and/or antibiotics prescribing patterns used to treat infections due to MDR Gram-negative pathogens, irrespective of the body site.

3. As an added value, the collection of patient-level information within hospitals on pattern of prescriptions (e.g. frequency, duration, switching) and relevant outcome data. These data are in place to be analysed in Denmark, and will be pursued in other European countries.

Overall study design

A systematic literature review of all available treatment guidelines and recommendations and the evidence behind them, and a European cross-sectional six-country survey of antibiotic prescribing patterns and algorithms used in clinical practice. As added values, we will include an MDR treatment outcome analysis using existing Danish data and, if accessible, other European individual-level hospital data.

Methodology to be applied, including data to be obtained

1. Review of relevant published articles and reports providing guidelines on treatment options for MDR Gram-negative infections, including the quality of evidence behind these guidelines (study 1)

The aim is to identify all guidelines and underlying literature in the area of MDR Gram-negative infection antibiotic therapy published during the period 2006-2016. The tenderers and their international collaborators, thanks to their scientific and clinical expertise, have knowledge of a large number of these guidelines and articles on a national and international level. Besides, the tenderers have large experience in performing systematic reviews.

We will follow the preferred reporting items for systematic review and meta-analysis (PRISMA) statement on reporting items for systematic reviews and meta-analyses (37) and will develop a detailed search protocol in accordance with the PRISMA-P statement (38). In our search protocol, we will specify study characteristics (such as PICO, length of follow-up) and report characteristics (such as calendar years considered, language, publication status) used as criteria for eligibility.

According to the PICO system, objectives of our review will be to examine, among **People** of all ages with MDR Gram-negative infections, the effectiveness of different antibiotic **Intervention** therapies

(alone or in combination, of specific dose and duration), **Compared** with other available antibiotic therapies, on patient **Outcomes** including adequacy of initial empirical antibiotic therapy, length of hospitalization, clinical complications, and mortality. Our search strategy will be developed together with expert librarians at the Aarhus University, Denmark. An initial PubMed search will use the 'Guideline' publication type and will be expanded to include documents with any of the words; 'Guideline[s]', 'Framework', 'Standards', 'Recommendation[s]', 'Guidance', 'Algorithms', 'Consensus', 'Statement', 'Executive summary', 'Medical guideline', 'Evidence guideline' or 'Practice Guideline' in the title, together with main search terms 'Gram-negative infection' AND 'antibiotic therapy' AND 'bacterial resistance or resistant bacteria' AND 'ESKAPE' 'enterobacteriacea', producing a sensitive search. We will apply no language restrictions upfront, as our consortium and collaborators in different countries can handle different guideline languages. In addition to PubMed, we will search Embase, Scopus, the Cochrane database, Google Scholar, and other databases for antibiotic treatment guidelines issued by local, national or international specialist societies and consortia globally. The search string will be adapted for all specific databases.

A few examples upfront would include the Infectious Diseases Society of America guidelines on intra-abdominal infection in adult and children (39); the European Society of Cardiology guidelines for infective endocarditis (40); the European Guidelines for empirical antibacterial therapy for febrile neutropenic patients (41); the Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock (42); or the German guidelines for diagnosis and treatment of adult patients with nosocomial pneumonia (43). Moreover, we will search for various public or governmental guidelines, such as Public Health England's Guidance on Carbapenemase-producing Enterobacteriaceae as an example (see: https://www.gov.uk/government/publications/carbapenemase-producing-enterobacteriaceae-non-acute-and-community-toolkit), books and decision support resources like UpToDate® and similar. It is well-known that some of these guidelines, in particular international ones, provide treatment guidance in rather broad terms, with a list of potential antibiotics to consider, rather than providing concrete treatment algorithms. An example from the Surviving Sepsis Campaign Guidelines: "Empiric therapy should attempt to provide antimicrobial activity against the most likely pathogens based upon each patient's presenting illness and local patterns of infection. We suggest combination empiric therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, MDR bacterial pathogens such as Acinetobacter and Pseudomonas spp. (grade 2B)." (42). Other national guidelines in contrast, e.g. the German guidelines on nosocomial pneumonia, may offer more detailed guidance on recommended drug choice and dosage (43). We therefore consider

it important to scrutinize local and national guidelines throughout Europe (see planned survey below).

Our review aims are thus twofold: to describe and compare the existing clinical practice MDR treatment guidelines throughout Europe, including a comparison with similar non-European guidelines; and to conduct a systematic review of the quality of evidence behind these guidelines. For the latter aim, we will consider meta-analyses, randomized clinical trials, and observational cohort studies on PubMed, Embase, and the Cochrane database, using a more specific search strategy with key words including 'Acinetobacter', 'Klebsiella', 'Pseudomonas', 'Enterobacteriaceae', 'Gram-negative infection', 'bacterial resistance or resistant bacteria', 'MDR', 'extended drug-resistant (XDR)', 'pan drug resistant (PDR)', 'antibiotic therapy', 'treatment', 'outcomes' and 'mortality'. Thus, we will systematically review the evidence on comparative effectiveness of different antibiotic therapies on MDR Gram-negative infected patient outcomes. In accordance with the PRISMA statement, we will explicitly state the process for selecting studies in our review, and we will assess risk of bias in the individual studies included (including selection bias, information bias, uncontrolled confounding, statistical chance, and publication bias). We will also try to quantify effect measures in a weighted formal meta-analysis. Meta-regression technique can be applied to explore potential sources of heterogeneity. The tenderers have experience with network meta-analyses, which may be considered as well, depending on the final data structure.

2. Cross-sectional survey of clinicians about antibiotic prescribing patterns and clinical practice guidelines for MDR Gram-negative infections (study 2)

The aim of this survey is to identify existing local and national guidelines and prescription habits in everyday clinical practice for MDR Gram-negative infection antibiotic therapy that are not captured by published guidelines and recommendations.

We will conduct this survey in six European countries, with different levels of resistance among important nosocomial pathogens: Denmark and the Netherlands (low MDR), the UK and France (medium MDR), and Romania and Greece (high MDR). In each of these six EU countries, through our consortium network, we have identified collaborators who are specialized in infections and microbial resistance. Our collaborators have offered help and advice in the local national surveys of clinicians and microbiologists in a range of reference hospitals about their therapeutic protocols and/or antibiotics prescribing patterns used to treat infections due to MDR Gram-negative pathogens.

Local cooperation partners and coordinators with expertise in microbiology & infectious diseases within the different EU countries include the following experts:

Greece: Professor Matthew E. Falagas, Alfa Institute of Biomedical Sciences (AIBS), Marousi, Athens, Greece; Department of Internal Medicine, Infectious Diseases, Mitera Hospital, Hygeia Group, Athens, and Tufts University School of Medicine, Boston, Massachusetts, USA.
Romania: Associate professor Irina Brumboiu, Epidemiology and Primary Health Care, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania.
France: Professor Claire Andrejak, Respiratory Disease Unit, University Hospital CHU Amiens-Picardie - Site Sud, Amiens, France
UK: Clinical Lecturer Laura J Shallcross, UCL Centre for Infectious Disease Informatics, Farr Institute of Health Informatics Research, London
The Netherlands: Professor Christina M. J. E. Vandenbroucke-Grauls, Medical Microbiology and Infection Control, VU University Medical Center, Amsterdam, The Netherlands and Dr. Mark G.J. de Boer, Internal Medicine & Infectious diseases, Leiden University Medical Center, Leiden, The Netherlands
Denmark: Professor Thomas Benfield, Department of Infectious Diseases, Copenhagen University Hospital, Amager and Hvidovre Hospital, Copenhagen, Denmark and Professor Henrik C. Schønheyder, Department of Clinical Microbiology, Aalborg University Hospital, Aalborg, Denmark

A standard questionnaire and data collection methodology addressing existing clinical practice in antibiotic treatment of MDR Gram-negative bacteria will be developed by the principal applicant together with local cooperation partners and coordinators following a good practice in the conduct and reporting of survey research (44). Detailed instructions about purpose of survey, length of survey, confidentiality, anonymous presentation of the results, deadline for survey end, contact information, and how to fill in questionnaire will be included.
Questionnaire will be primarily written in English language, but translation into Greek, French and Romanian language will be considered, if evaluated as necessary by local cooperation partners and coordinators. The questionnaire will be primarily multiple-choice closed ended items, and several open ended items will also be included. Multiple-choice questions are quicker and easier to answer and the answers are easier to analyze; those will be set up after the thorough literature review proposed in study 1 of this tender (45). Open-ended questions are important to allow participants to report more information than is possible with a discrete list of answers, and to freely elaborate on questions. Questions will be clear and specific, simple and neutral, avoiding “loaded” words and stereotypes that suggest a desirable answer. Questions will be grouped together and introduced by headings or short descriptive statements concerning treatment of each specific MDR Gram-negative

bacteria. Both questions regarding antibiotic treatment (first, second and third treatment options), doses, length of treatment will be included.

A minimum of three hospitals / centers from each country (thus, at least 18 hospitals) specialized in treating MDR infectious diseases as suggested by local cooperation partners and coordinators will be invited to participate in our survey. More than three hospitals can be suggested by local partners if relevant. The invitation will be sent to the chief consultant at the hospital. The survey will be administered online using REDCap, a Web-based data management platform developed by a Vanderbilt University consortium (46) which is cost-saving, secure, easy to use and has high response rates. Reminders will be sent in case that the questionnaire has not been filled in within 4 weeks.

Thorough statistical methods for analyzing the survey results will be developed and agreed on before starting the survey. A pilot test will be performed at four hospital departments in Denmark, Romanian, Greece and France in order to evaluate the specific questions, format, question sequence and instructions prior to use in the main survey. The pilot test will provide answers if each question measures what is intended to measure, if questions are interpreted in the same way by all participants, if questions are clear and understandable etc.

3. Patient-level information on MDR infections and their hospital treatment and relevant clinical outcome data (study 3)

As an added value, we will conduct a cohort study in Denmark (population = 5.6 million persons) based on existing prospectively collected data from population-based medical and administrative registries. The Danish National Health Service provides tax-supported healthcare to all Danish residents, guaranteeing universal access to primary and secondary medical care. We aim to include a prescription pattern and treatment outcome analysis of specific MDR bacterial infections.

Data sources

We will use data from the from the unique microbiological Laboratory Information System database of the North Denmark Region, linked with the Danish National Patient Registry (DNPR), the Danish Civil Registration System (DCRS), and the Danish National Health Service Prescription Database (DNHSPD). Data sources are available for analysis for the period 2004-2015.

The Department of Clinical Microbiology, Aalborg University Hospital, provides bacteriological services for hospitals and general practitioners from the entire study/catchment area (47). The department's Laboratory Information System database (based on a microbiological database system ADBakt, Autonik AB; Ramsta, Sköldinge, Sweden) holds information on all microbiological specimens

submitted to the department including information on date of culture, bacterial species, and antibiotic susceptibility.

The DNPR (48) includes information of all hospitalized patients since 1977 and outpatient hospital contact since 1995. The register contains information about the date of admission, discharge, type of admissions, diagnosis codes and surgical procedures. From 1977 to 1993 diagnosis codes were coded with reference to the *International Classification of Diseases* [*Eight Revision* (ICD-8) and from 1994 onward diagnoses have been coded with reference to *Tenth Revision* (ICD-10).

The DCRS, established in 1968, assigns a unique ten-digit personal identification number, encoding age, sex and date of birth, to all Danish residents at birth or upon immigration, enabling individual-level linkage across all registries (49). The DCRS also tracks' migrations, residence, and vital status.

The DNHSPD (50) has maintained information on all prescriptions for reimbursed drugs dispensed by community pharmacies in Denmark since 2004, recorded according to the Anatomical Therapeutic Chemical classification system (ATC codes). Additional variables in the DNHSPD include drug name, package identifier (permitting identification of brand, quantity, and drug formulation), date of refill, code identifying the prescribing physician, and code identifying the dispensing pharmacy.

Patients exposed to MDR Gram-negative bacterial infection and comparisons

MDR exposed cohort: All adult patients with MDR Gram-negative bacterial infection in the North Denmark region during the period 2004-2015 will be ascertained from the microbiological Laboratory Information System. For example, we plan to identify all persons with a first diagnosis of ESBL Gram-negative bacterial UTI from 2007 to 2014, and no diagnoses of MDR bacterial Gram-negative infection from 2004 to 2006, ensuring 3 years lookback period. The date of the urine sample (or blood culture, etc.) will be defined as the index date for MDR Gram-negative infection exposed patients.

Comparison cohort: To examine the impact of MDR infection per se, for each MDR infection exposed patient, we will identify 5 matched non-MDR infection patients. In the above example, for each patient with a first diagnosis of ESBL Gram-negative bacterial UTI, we will sample at random 5 controls with non-ESBL Gram-negative bacterial UTI residing in the region. Each control is required to have a UTI diagnosis within one week of the MDR UTI exposed patient index date.

General comparison cohort: For each patient included in the MDR exposed cohort, we will also identify 5 age- and gender-matched persons from the general population using the DCRS who were alive at the infection index date and never were tested positive for any MDR bacteria within one week of the index date for MDR case.

Antibiotic therapy and relevant clinical outcomes

We will ascertain antibiotic therapy given before and after the index date for the MDR and non-MDR infected patient cohorts using the DNHSPD, to examine treatment outcomes associated with given antibiotic therapies, and any effect modification of the MDR/non-MDR – outcome associations by therapy.

We will ascertain morbidity (acute hospitalization, ICU therapy, renal and other organ complications, ventilator therapy, length of stay), short-term mortality (0-30 days post index date), and subsequent long-term mortality (31-365 days post index date) comparing person included in the three cohorts.

Statistical analyses

All patients will be followed from the index date until death, hospitalization, emigration or December 31, 2015, whichever comes first. We will calculate mortality rates (MRs) for all three cohorts and express MRs per 1000 person years. We will use Cox regression analyses to calculate mortality rate ratios (MRR= hazard ratio) with 95% confidence intervals comparing the MDR positive cohort with the two matched comparison cohorts. We will adjust for age, gender, and preexisting comorbidity. We will use the DNPR to obtain a complete medical history for all persons in the study cohorts from 1977 until the index date. As a measure of comorbidity, we will compute the Charlson Comorbidity Index (CCI) score (51;52) for each person at the index date and define three comorbidity levels: a score of 0 (low), given to patients with no previous record of conditions included in the CCI; a score of 1-2 (medium); and a score of 3 or more (high) (53). To study potential differences in the association between exposure to MDR bacteria and mortality risk in subgroups of patients, we will repeat the above analyses (MR and MRR) stratifying on gender, age groups, and calendar year of Index date. Next, we will examine within the MDR and non-MDR infection cohorts the association between type of antibiotic therapy given and clinical outcomes, using a similar analytic strategy as above.

All statistical analyses will be performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Tenderer's capabilities and expertise

Each partner of the Tenderer's consortium is an academic institution with full administrative and research infrastructure. All investigators are doctoral-level epidemiologists with expertise or access to expertise in the relevant clinical subject area. Statisticians in each institution are at Master's level or higher with long-term experience analysing the respective data. As academic institutions, all consortium partners have motivation, mandate and obligation to publish results of all investigations.

The Department of Clinical Epidemiology, Aarhus University Hospital (DCE/AUH) is a large academic department, with more than 15 years' experience conducting epidemiologic research based on registry data, including several successfully fulfilled calls from the EMA. The DCE/AUH strategic aim is to improve clinical care by working in global partnership to produce high-quality clinical epidemiological research, promote education, and strengthen translation of knowledge into clinical practice. One of the DCE/AUH key interest is research addressing the management and prevention of diseases in individuals and population in areas which are of priority to the health of the public, including research within clinical infectious disease epidemiology and pharmacoepidemiology.
The team at KEA/AUH has a long track record of publications based on analyses of electronic health records, particularly the DNPR and DNHSPD data, and is one of the internationally leading centers for epidemiological analysis on such data.

The team leader at the DCE/AUH, who is assigned to this project, is associate professor, MD, PhD and senior epidemiologist with specific and considerable expertise in the field of clinical infectious disease epidemiology. This includes studies of time trends, risk factors and clinical outcomes of patients with bacteraemia, sepsis, pneumonia, urinary tract infections, tuberculosis, pneumococcal, staphylococcal, and Gram-negative infections (54-64), as well as pharmacoepidemiological studies on antibiotic use (65-67), as evidenced by more than 75 peer-reviewed publications within the field of infectious disease epidemiology and more than 175 publications in total. The post-doc investigator, who will be assigned to this project, will be a senior researcher with specific interest in infectious diseases and with expertise in designing and performing epidemiological research, including systematic reviewers and meta-analyses. DCE/AUH has specific expertise working with unique Danish microbiological research databases, which includes a longstanding collaboration with the Danish international-level experts in microbiology and infectious diseases named above (47;68-70).
The Institute of Epidemiology and Health Care at UCL has a long track record of analysis of electronic health records and is one of the internationally leading centres for epidemiological analysis on such data, including pharmacoepidemiology. The local cooperation partner at the UCL Centre for Infectious Disease Informatics has long-standing experience within infectious diseases and antimicrobial resistance (71-73).
The Department of Clinical Epidemiology at the Leiden University Medical Center has a long track record in designing and conducting large clinical studies in several designs (case-control: LETS (Leiden Thrombophilia Study, n=1,000); MEGA (Multiple Environmental and Genetic Assessment, n=10,000). Cohort: NEO (Netherlands Epidemiology of Obesity, n=8,000) and randomised controlled trials: POT-(K) CAST trials (Prevention Of Thrombosis for Knee ArThroScopy or plaster CAST, n=3,000)). The

Department, the staff of which consists of epidemiologists, statisticians, clinicians and data managers, is considered an international leader in clinical epidemiology. The local cooperation partners at the Department of Medical Microbiology and Infection Control, VU University Medical Center, Amsterdam and Department of Internal Medicine & Infectious diseases, Leiden University Medical Center, Leiden have a long track record in designing and conducting studies within infectious diseases and antimicrobial resistance. Our cooperation partner from Amsterdam is leader of the Department of Medical Microbiology and Infection Control at the VU University Medical Center, and considered one of Europe's top experts in MDR infections and antibiotic resistance, as evidenced by numerous peer-reviewed publications (74-79).

The LSHTM is a world-leading centre for research in public and global health and infectious diseases and will provide expertise as needed for the duration of the study.

Our clinical collaborator from Greece is a top-class expert in the very core of this tender - antibiotic therapies of MDR infections - and arguably one of the persons in the world knowing most about this specific topic (80-82). Our collaborators from Romania (83;84) and France (54;85) as well have documented expertise within infectious diseases and antimicrobial resistance.

Person-time of staff spent on project tasks

Work package	Person-months
	Total
WP1 Project coordination and management	3
WP2 Ethical approvals	2
WP2 A preliminary report and initial study plan drafting study 1,2,3	2
WP2 A draft protocol for study 1, including development of methods for systematic review and analyses plan	2
WP2 A draft protocol for study 2, including development of questionnaire for survey, pilot testing, and analyses plan	2
WP2 A draft protocol for study 3, including analyses plan	1
WP2 A final protocol for study 1,2, 3 with response to Agency's comments	1
WP3 Systematic review (study 1), including extraction of data, analyses, and interpretation	4
WP4 Survey (study 2), including data collection, analyses, and interpretation	3
WP5 Patient-level information (study 3)- Data collection	2
WP5 Patient-level information (study 3)-Data analyses and interpretation	2
WP6 Preparation of study report	2
WP7 Preparation of manuscript	3
Total	**29**

Milestones for submission of deliverables with proposed timelines

Months and milestones	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15
Start of project															
WP1 Day-to-day management and communication															
WP2 Ethical approvals															
WP2 A preliminary report and initial study plan drafting study 1,2,3															
WP2 A draft protocol for study 1, including development of methods for systematic review and analyses plan															
WP2 A draft protocol for study 2, including development of questionnaire for survey, pilot testing, and analyses plan															
WP2 A draft protocol for study 3, including analyses plan															
WP2 A final protocol for study 1,2, 3 with response to Agency's comments															
WP3 Systematic review (study 1), including extraction of data, analyses, and interpretation															
WP4 Survey (study 2), including data collection, analyses, and interpretation															

WP5 Patient-level information (study 3)- Data collection															
WP5 Patient-level information (study 3)- data analyses and interpretation															
WP6 Preparation of study report															
WP7 Preparation of manuscript															
Deliverables*:		1, 3	4									2,5			6

*Deliverables, as defined by the Agency:

1. A preliminary report with a literature review of relevant published articles and reports providing guidelines on treatment options for MDR Gram-negative infections.

2. A final report with a literature review of relevant published articles and reports providing guidelines on treatment options for MDR Gram-negative infections.

3. A draft protocol describing the approach that would be employed to address the above research question. This protocol is to be submitted to the Agency for consultation.

4. A final protocol for the study taking into consideration comments provided by the Agency.

5. A study report with full description of results and their interpretation.

6. A manuscript describing the design, main results and conclusions of the study suitable for submission to a peer-reviewed medical journal.

Organisation of the work and quality control measures

One consortium member will contribute with data and expertise. Two other consortium members will contribute with expertise and advice. AUH will coordinate the study and lead the writing of the protocol and publications. AUH will obtain permission and access to the relevant linked data from the Danish Registries. The analyses will be conducted according to the common protocol, approved by the Agency. Each institution will appoint a coordinating epidemiologist to ensure expertise and advice in the study. Data from the literature review, the international survey, and Danish health care data will be analysed locally at AUH by a local statistician with relevant data expertise. Data management and analyses will be conducted according to AUH's standard procedures. At a minimum, all study documents (protocol, report, publications) will be reviewed by the entire research team, and a senior epidemiologist in each institution will review the report before submission to the EMA. Clinical expertise is available in all 6 EU member states participating in the survey for appropriate interpretation of results (see above). At the start of the project, we will establish internal timelines for the work packages to be completed in time to allow review and quality control before submitting each deliverable to the Agency. AUH will serve as the consortium contact point with the Agency.

AUH will ensure the necessary compliance with local data protection, storage and archiving, and patient privacy laws and regulations and will obtain all permission necessary to conduct this study. Permission from the Danish Data Protection Agency will be obtained in order to perform study 3.

Outline of the Study Report

The report will follow the current standards of scientific reporting. Full descriptions of all methods used, data sources, variables and detailed outputs from statistical models will be included.

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European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Anti-microbial resistance: choice of therapeutic interventions and outcomes for the treatment of infections caused by MDR Gram-negative pathogens

Study reference number: EMA/329429/2016

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☒	☐	☐	
1.1.4 Interim progress report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS register	☐	☒	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	Page 6
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	Page 6
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	Page 6
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	Page 12
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	Page 12
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	Page 12

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.2 Age and sex?	☐	☒	☐	
4.2.3 Country of origin?	☒	☐	☐	
4.2.4 Disease/indication?	☒	☐	☐	
4.2.5 Duration of follow-up?	☐	☒	☐	Page 10
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	Page 10

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	Page 12
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	Page 12
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☒	☐	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☒	
7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☐	☒	
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☐	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	Page 10
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	Page 10
9.1.3 Covariates?	☐	☒	☐	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Page 11
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☐	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates?	☐	☒	☐	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	Page 10

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	Page 12
10.2 Are descriptive analyses included?	☒	☐	☐	Page 12
10.3 Are stratified analyses included?	☐	☒	☐	
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	Page 12
10.5 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.6 Is sample size and/or statistical power estimated?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☐	☒	☐	
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☐	☒	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	Page 10, 12, 18

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☒	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	Page 9,10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☐	☒	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	Page 16, 17
15.2 Are plans described for disseminating study results externally, including publication?	☐	☒	☐	

Comments:

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Date: 09/October/2017

Signature: