PROTOCOL

REVIEW ON DESIGNS AND CHALLENGES TO MONITOR CLINICAL BURDEN OF SELECTED MULTIRESISTANT BACTERIA

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Main output: Review of current research designs and challenges related to the data collection and assessment of the clinical burden of antibiotic resistance as a technical support to prepare future epidemiologic studies with adequate methodologies.

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ABBREVIATIONS

AMR: antimicrobial resistance

BSI: bloodstream infection

CAI: community acquired infection

CAZ: ceftazidime

CDI: *C. difficile* infection

CRAB: Carbapenem resistant *Acinetobacter baumannii*

CR-KP: Carbapenem resistant *Klebsiella pneumoniae*

DALY: disability adjusted life years

DRIVE AB: driving re-investment in R&D and responsible antibiotic use

ESBL: extended spectrum β-lactamases

FQ: fluoroquinolone

GBD: global burden of disease

3GC: third generation cephalosporines

GLASS: global antimicrobial resistance surveillance system

GHE: global health estimates

HALE: health life expectancy

HCAI: healthcare associated infection

HQRL: health related quality of life

LOS: length of hospital stay

LRTI: low respiratory tract infection

LTCF: long term care facilities

MDRO: multidrug resistant organisms

MRSA: methicillin resistant *Staphylococcus aureus*

PPL: priority pathogen list

QALY: quality adjusted life years

STD: sexually transmitted disease

UTI: urinary tract infection

VRSA: vancomycin resistant *Staphylococcus aureus*

BACKGROUND

Comprehensive data on the clinical burden of antimicrobial resistance (AMR) are difficult to obtain. Accurate data is vital for convincing governments of the burden that AMR places on the national health and economy and the need of acting rapidly to prevent the situation worsening steadily. Reliable data will be valuable for campaigns to raise public awareness of AMR and for gaining funding for research and surveillance networks. Most current burden data collected on AMR relates to hospital surveillance retrieved from clinical culture and collected mainly in high-income countries. A comprehensive, homogenous and standardized set of epidemiological data is missing. Patient outcomes, direct costs of the additional treatments, antimicrobial use needed as result of AMR and indirect costs linked not only to AMR but also to the impact of quality of life are all key information to set up a proper and methodologic data collection.

WHO`s AMR Surveillance Unit team has already prioritized in its current Global Antimicrobial Resistance Surveillance System (GLASS) work plan to develop protocols for data collection in sentinel sites allowing the generation of variables to be included in AMR burden calculation models, following the approach of the Global Burden of disease (GBD) Study.

The GBD study has grouped the causes of death into three categories, thus defining communicable, maternal, perinatal and nutritional conditions (Group I), non communicable diseases (Group II) and injuries (Group III). Each disease corresponds to specific definitions in terms of the International Classification of Diseases, Tenth Revision (ICD-10). To assess and quantify the impact on global health of disease burden, injuries and risk factors, the GBD has introduced in 1996 a new metric, the disability –adjusted life year (DALY), a summary measure of population health based on estimates of premature mortality and non fatal health loss (Murray 1996). One DALY can be seen as one lost year of healthy life and the measured disease burden is the gap between a population´s health status and that of a normative reference population. The greater the time lived with a disability, or with the disabling results of illness or the most time lost due to premature death, the greater the burden of the disease is considered to be. DALYs for a specific cause are calculated as the sum of Years Lived with Disability (YLD) and Years of Life Lost due to premature mortality (YLL).

DALY = YLD + YLL

YLD= I (number of incident cases) **x**
DW (disability weight) **x**
L (average duration of the case until remission or death in years)

N (number of deaths at age “x“) **x**
L (standard life expectancy at age “x“ in years)

Another population health summary measure is the Quality Adjusted Life Year (QALY), generally used to analyse the cost – effectiveness of clinical (or public health) interventions and for social welfare

improvement. QALYs are calculated by multiplying the number of years of additional life by a Health related Quality of Life (HQRL) value. HRQL is based on values assigned by individuals about their own state or on values assigned by others about a particular health state.

The last GBD 2015 results for DALYs and Healthy Life Expectancy (HALE) 1990-2015 found a reduction in DALYs from Group I diseases with significant declines of total burden, among infectious diseases, of lower respiratory tract infections (LRTI), diarrhoeal disease, tuberculosis, meningitis, malaria, tetanus, measles and HIV/AIDS (Kassebaum, 2016). Despite the inclusion in the global health estimates (GHE) cause categories of almost all main causative agents of infectious diseases (comprehensive of the GLASS target bacteria) and the continuous inclusion of new ones (such as acute hepatitis A and E, cysticercosis, echinococcosis, yellow fever, food-borne trematodosis), categories like health care associated infections (HCAI) and antimicrobial resistant bacteria are not considered yet. Given that these lattern two represent emerging and growing health threats, it has been suggested that they should be analyzed by the GBD like estimates for multidrug resistant tuberculosis, which is already planned for the future rounds of the GBD (Kassebaum 2016; Vos 2016) .

Major obstacles to the calculation of DALYs for antimicrobial resistance are represented by the lack of incidence and epidemiological data gathered through standard and uniform reports around the globe and comprehensive, methodologically sound data on clinical burden of AMR.

AIM OF REVIEW

To perform a comprehensive review of current research designs and challenges related to the adequate data collection and assessment of the clinical AMR burden. The data will contribute to the better understanding of the potential impact of selected antibiotic resistant bacteria and prepare future epidemiologic studies with adequate methodologies, within the GLASS framework.

METHODS

Design: review of literature (no limit – Sept 2016)

Inclusion criteria:

- Published studies on human subjects focusing on the GLASS target bacteria (see table 1) and the following clinical syndromes (included in the GBD) categorized according to the ICD-10 codes (2016 version):
    I. Bloodstream infections (BSI): sepsis due to *Streptococcus pneumoniae* (A40.3), sepsis due to *Staphylococcus aureus* (A41.0), sepsis due to other Gram negative organisms (A41.5), systemic inflammatory response syndrome of infectious origin with or without organ failure (R65.0., R65.1)
    II. Meningitis: bacterial meningitis (G00)
    III. Lower respiratory tract infections (LRTI): pneumonia due to *Streptococcus pneumoniae* (J13), bacterial pneumonia (J15).
    IV. Urinary tract infections (UTI): urinary tract infection (N39).
    V. Intestinal infectious diseases: diarrhoeal diseases such as typhoid and paratyphoid fevers (A01), other Salmonella infections (A02), Shigellosis (A03), other bacterial intestinal infections (A04.0-A04.4).
    VI. Sexually transmitted disease: gonococcal infection (A54)

- Reporting at least one clinical outcome measures

  and / or

- Reporting QALY or DALY as indirect outcome.

Exclusion criteria

- Diagnostic and microbiological studies, reviews and non-clinical studies
- Study protocols
- Studies exclusively focusing on risk factor for acquisition of infections due to antibiotic resistant bacteria (however, risk factors studies providing at least one clinical outcome measure of interest will be included)

Types of studies

- All study design
- Conducted in hospital, community and other healthcare center (including long term care facilities and nursing homes)
- All population with no age limit

Target bacteria

All bacteria included in the GLASS study will be considered for this review.

Bacteria	Resistance type
Escherichia coli	Fluoroquinolones (FQ), third generation cephalosporines (3GC), carbapenems
Klebsiella pneumoniae	3GC, Carbapenems
Acinetobacter baumannii	Carbapenems
Staphylococcus aureus	Methicillin, vancomycin
Streptococcus pneumoniae	Penicillin non susceptible
Salmonella spp	FQ
Shigella spp	FQ
Neisseria gonorrhoeae	FQ, 3GC

Table 1

Sources of data and search strategies

Existing databases (databases from two running projects at UKET)

- **DRIVE-AB project**. A multinational project aiming to gather data from worldwide surveillance systems, antibiotic prescription databases and published literature in order to estimate the present and the future burden of antibiotic resistance from both clinical and economic perspectives. The research results will feed into the development and testing of new alternative economic models to incentivize investment in antibacterial drug research and development. The UKET database contains results from a systematic review and meta-analysis on all published studies analyzing the mortality

and length of stay (LOS) in patients with infections due to the following resistant bacteria*:* ***carbapenem-resistant and carbapenemase producing Enterobacteriaceae (including Klebsiella, E. coli and Proteus spp.), Pseudomonas spp. and Acinetobacter spp*****.** compared with patients with sensitive infections or randomly chosen.

Inclusion criteria: published studies on human subjects studying multidrug resistant organism (MDRO) of interest and reporting at least one of the outcome measures with presence of a comparison group or a subgroup comparison. Studies evaluating colonization, study protocols, diagnostic studies, reviews, non-clinical studies were excluded.

Data sources: MEDLINE, 1950-up to September 2016, In-Process and other non-indexed citations, OvidS.

- **WHO Pathogen Priority List (PPL) study**. The major goal of the WHO priority list is to prioritize funding and facilitate global coordination of strategies for the discovery of new antibiotics to treat acute bacterial infections. The UKET database includes the outcomes data for all the DRIVE-AB bacteria plus fluoroquinolones(FQ)-resistant *Campylobacter spp*, ampicillin-resistant *Haemophilus influenza,* clarithromycin-resistant *Helicobacter pylori,* 3GC and FQ -resistant *Neisseria gonorrhoeae*, FQ-resistant *non-Typhoidal Salmonella* and *S.typhi,* FQ-resistant *Shigella spp* and penicillin-non-susceptible *Streptococcus pneumoniae*.

  Inclusion criteria: published studies on human subjects reporting data on mortality/LOS/ and antibiotic resistant bacteria and including a comparison group (either patients with infections due to sensitive bacteria or randomised patients without infections); published studies on human subjects reporting data on recurrence of infections due to resistant bacteria within one year of the first episode.

  Data sources: MEDLINE,1950-up to September 2016, In-Process and other non-indexed citations, OvidS.

Search terms included in the DRIVE AB and WHO PPL projects:

- Mortality: **(mortality[mesh] OR mortality[tw] OR death rate[tw] OR fatality[tw] OR survival rate[tw] OR death[tw] OR died[tw] OR dead[tw]))** plus target resistant bacteria
- Length of stay: **(length of stay[mesh] OR (hospitalisation[tw] AND length[tw]) OR length of hospitalisation[tw] OR length of hospitalization[tw] OR duration of hospitalization[tw] duration of hospitalisation[tw] OR LOS[tw] OR ((period[tw] OR length[tw]) AND (hospital stay[tw] OR hospitalisation[tw] OR hospitalization[tw]) plus target resistant bacteria**
- MRSA: **((("Methicillin resistant"[tw] OR "Methicillin resistance"[tw] OR "Methicillin resistant"[MeSH] OR "Methicillin resistance"[MeSH] OR "Meticillin resistant"[tw] OR "Meticillin resistance"[tw] OR "Meticillin resistant"[MeSH] OR "Meticillin resistance"[MeSH] OR "Meticillin-resistant"[MeSH] OR "Meticillin-resistance"[MeSH] OR "Methicillin-resistant"[MeSH] OR "Methicillin-resistance"[MeSH] OR "Meticillin-resistant"[tw] OR "Meticillin-resistance"[tw] OR "Methicillin-resistant"[tw] OR "Methicillin-resistance"[tw] OR "MRSA"[tw] OR "MRSA"[MeSH]))) AND (Staphylococcus aureus [Mesh] OR Staphylococcus aureus [tw] OR S.aureus[Mesh] OR S.aureus[tw]))))**
- VRSA: **("""vancomycin resistant"""[tw] OR """Vancomycin resistance"""[tw] OR """vancomycin resistant"""[MeSH] OR """Vancomycin resistance"""[MeSH] OR vancomycin-resistan*[mesh] OR vancomycin-resistan*[tw] OR glycopeptide[tw] OR linezolid[tw] OR teicoplanin[tw]) OR ((Drug resistance, Microbial [Mesh]) AND**

Vancomycin/Pharmacology)))) AND **((Staphylococcus aureus[Mesh] OR Staphylococcus aureus[tw] OR S.aureus[Mesh] OR S.aureus[tw])**

- Ceftazidime (CAZ)-resistant A*cinetobacter baumanii*: **(((ceftazidime[mesh] OR ceftazidime[tw] OR cephalosporin[tw] OR polymyxin[tw] OR colistin[tw]) AND (Drug resistance[Mesh] OR resistan*[tw]) OR (Drug resistance[Mesh] OR resistan*[tw])) AND (""""""Acinetobacter baumannii"""""[MeSH Terms] OR """""Acinetobacter baumannii"""""[tw] OR """""A.baumannii"""""[tw] OR """""Acinetobacter baumanni"""""[MeSH Terms] OR """""Acinetobacter baumanni"""""[tw]) OR """""A.baumanni"""""[tw]**
- Ciprofloxacin-resistant *Escherichia coli*: **((ciprofloxacin[mesh] OR ciprofloxacin[tw] OR cipro[tw]) AND (Drug resistance[Mesh] OR resistan*[tw]))))** AND **((Escherichia Coli[Mesh] OR E.coli[Mesh] OR Escherichia Coli[tw] OR E.coli[tw])**
- Extended spectrum β-lactamase (ESBL) *Escherichia coli*: **((ESBL[tw] OR ""Extended spectrum beta-lactamase""[tw] OR ESBL[Mesh] OR ""Extended spectrum beta-lactamase"" [Mesh]) OR Extended spectrum ? lactamase[tw] OR Extended spectrum ? lactamase[Mesh])** AND **(Escherichia Coli[Mesh] OR E.coli[Mesh] OR Escherichia Coli[tw] OR E.coli[tw]) AND ("0001/01/01"[PDat] : "2014/12/31"[PDat]))**
- ESBL *Klebsiella pneumoniae*: **((ESBL[tw] OR ""Extended spectrum beta-lactamase""[tw] OR ESBL[Mesh] OR ""Extended spectrum beta-lactamase"" [Mesh]) OR Extended spectrum lactamase[tw] OR Extended spectrum ? lactamase[Mesh]) AND (Klebsiella pneumoniae[Mesh] OR K.Pneumoniae[Mesh] OR Klebsiella pneumoniae[tw] OR K.Pneumoniae[tw]) AND ("0001/01/01"[PDat] : "2014/12/31"[PDat]))**
- Carbapenem-resistant *A.baumanii*, *K.pneumoniae*, *E.coli*: **((((((carbapenem[mesh] OR carbapenem[tw] OR carbapenemase[Mesh] OR carbapenemase[tw])) AND (Drug resistance[Mesh] OR resistan*[tw]))) AND (Drug resistance[Mesh] OR resistan*[tw]) AND ((Klebsiella pneumoniae[Mesh] OR K.Pneumoniae[Mesh] OR Klebsiella pneumoniae[tw] OR K.Pneumoniae[tw])) OR (Drug resistance[Mesh] OR resistan*[tw]) AND (Escherichia Coli[Mesh] OR E.coli[Mesh] OR Escherichia Coli[tw] OR E.coli[tw]) OR ((((""""""Acinetobacter baumannii"""""[MeSH Terms] OR """""Acinetobacter baumannii"""""[tw] OR """""A.baumannii"""""[tw] OR """""Acinetobacter baumanni"""""[MeSH Terms] OR """""Acinetobacter baumanni"""""[tw]) OR """""A.baumanni"""""[tw])))))**

Each term was then coupled with the search term built for the specific bacteria

Search term from the WHO-PPL:

- **microbiology"[MeSH Terms] OR "microbiology"[All Fields] OR "microbiological"[All Fields]) AND failure[All Fields]) OR ("recurrence"[MeSH Terms] OR "recurrence"[All Fields]) OR ("recurrence"[MeSH Terms] OR "recurrence"[All Fields] OR "relapse"[All Fields])** and target resistant bacteria
- *Neisseria gonorrhoeae*: **Neisseria gono*[Mesh] OR Neisseria gono*[tw] OR gonococc*[Mesh] OR gonococc*[tw]**
- *Salmonella* spp.: **((Salmonella[Mesh] OR Salmonella[tw] OR Salmonella spp.[Mesh] OR Salmonella spp.[tw])))**
- *Shigella*: **shigella[Mesh] OR shigella[tw]**
- *Streptococcus pneumoniae*: **((Streptococcus pneumoniae[Mesh] OR Streptococcus pneumoniae[tw] OR S. pneumoniae[Mesh] OR S. pneumoniae[tw] OR pneumococc*[Mesh] OR pneumococc*[tw]))**

Data extraction

All articles included in the DRIVE-AB and the WHO-PPL will be reanalyzed for the relevant variables (quality control of extracted data).Reasons from exclusion from the previous databases will be analyzed to check for possible inclusion in the current research project (other outcomes as mortality and LOS).
Table 2 summarizes the list of variables extracted and included in the existing databases:

Study related variables	**Study population**	**Study design**	**MDRO**	**Outcome**
Author	Population profile	Type of the study	Bacteria	Mortality (definition)
Institute	Setting	Aim of the study	Type of resistance	LOS (defnition)
Country	Clinical syndrome			
Year of publication	Tot no. recruited			
Title of the article				
Journal				
Time of data collection				

Table 2

Outcomes

All outcomes analyzed in the studies will be reported, including but not limited to the following:

- Mortality: all cause mortality, attributable mortality, 30 day mortality, long-term mortality
- Complications: need for surgery/ Intensive care unit (ICU) admission/ super-infection/ *Clostridium difficile* infection (CDI) / need for rehabilitation, admission to LTCFs
- Length of stay (in hospital/ ICU/post-infection)
- Duration of disease
- Hospital readmission
- Days of school lost, absenteeism from work
- QALY and DALY (for the assessment of indirect outcome of disease burden).

. The following **new variables** on the study design will also be added:

- Research question
- Demographics (age , sex)
- Duration of the study
- Description on how and when outcomes were measured (including evidence that the tests/instruments used to measure are valid)
- Statistical methods used to compare outcomes (including descriptive statistics on the study sample; control group selection)
- Controlling for confounding (adjustment for LOS, comorbidities, time of antibiotic exposure and effectiveness; multiple population)
- Methods to assess QALY and DALY
- Follow-up time

A second search will be performed to evaluate the studies analyzing the impact of infections due to antibiotic resistant bacteria on the quality of life. Since we expect not to find enough evidence for resistant strains, the search will be extended to severe bacterial infections due to the target bacteria (regardless the susceptibility pattern).

Search terms:

- (independence[tw] OR status[tw] OR deterioration[tw] OR ability[tw] OR QALY OR DALY OR quality of life)
- (school* OR work) AND (absen* OR day)

Quality assessment

Modified EPOC assessment criteria for RCTs, NewCastle Ottawa quality assessment scale for case control studies and cohort studies will be used.

RCTs

- Generation of allocation sequence adequate? (Yes/No/Unclear)
- Allocation concealment adequate? (Yes/No/Unclear)
- Validated and reliable primary outcome measures/systems are used? (Yes/No/Unclear)
- Baseline/primary outcome measurements similar? (Yes/No/Unclear)
- Baseline/primary characteristics similar? (Yes/No/Unclear)
- Adequate addressing of incomplete data outcome? (Yes/No/Unclear)
- Blinding to primary outcome achieved? (Yes/No/Unclear)
- Adequate protection against contamination? (Yes/No/Unclear)

Case Control

- Is the case definition adequate? (yes, no, unclear)
- Representativeness of the cases (consecutive or obviously representative series of cases, potential for selection biases or not stated)
- Selection of Controls (community controls, hospital controls ,no description)
- Definition of Controls (no history of disease (endpoint), no description of source)
- study controls for the most important factor (yes, no, unclear)
- study controls for any additional factor (yes, no, unclear)
- Ascertainment of exposure (secure record (eg surgical records), structured interview where blind to case/control status, interview not blinded to case/control status, written self report or medical record only, no description)
- Same method of ascertainment for cases and controls (Yes/No/Unclear)
- Non-Response rate (same rate, non respondents described, rate different and no designation)

Cohort studies

- Representativeness of the exposed cohort (truly representative, somewhat representative , selected group of users, no description)
- Selection of the non exposed cohort (drawn from the same community as the exposed cohort, drawn from a different source, no description of the derivation of the non exposed cohor

- Ascertainment of exposure (secure record (eg surgical records), structured interview, written self report, no description)
- Demonstration that outcome of interest was not present at start of study(Yes/No/Unclear)
- Comparability of cohorts on the basis of the design or analysis (study controls for the most important factor, study controls for any additional factor)
- Assessment of outcome (independent blind assessment, record linkage, self report, no description)
- Follow-up long enough for outcomes to occur (Yes/No/Unclear)
- Adequacy of follow up of cohorts (complete follow up – all that matters subjects accounted for, subjects lost to follow up unlikely to introduce bias - small number, inadequate numbers but description provided of those lost, inadequate follow up rate and no description of those lost, no statement.

Estimated workload

- Abstracts to be reviewed based on previous searches: 2226
- Papers to be included: around 500 (23%)

	***DRIVE AB* search**	***WHO PPL* search**
Carbapenem resistant *Acinetobacter baumanii* and *Klebsiella pneumoniae*	70	-
ESBL and FQ resistant *Enterobacteriaceae*	800	-
MRSA and VRSA	152	-
Jan-Sept 2016 update (includes ESBL, carbapenem resistant *Enterobacteriaceae*, MRSA and VRSA)	198	-
Salmonella spp	**-**	197
Shigella	-	46
Streptococcus pneumoniae	-	777
Neisseria gonorrhoeae	-	26
TOTAL	**1220**	**1046**

Bibliography

1. Kassebaum, N. J., Arora, M., Barber, et al. (2016). Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematicanalysis for the Global Burden of Disease Study 2015. The Lancet, 388(10053), 1603-1658.

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